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Section in a book: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine. 2nd ed. St Louis: Mosby; 1974. p.273-85.

Book with single author: Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

Editor(s) as author: Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

Article presented at a meeting: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. P. 1561-5.

Scientific or technical report: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHSIGOE 169200860.

Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

Manuscript in electronic format

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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Case Reports

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Evaluation of the Serum Visfatin and Adiponectin Levels Related with the Activity of Juvenile Idiopathic Arthritis

Oktay Çalışkan[1], Zeynep Banu Güngör[1], Özlem Balcı Ekmekçi[1], Hakan Ekmekçi[1], Kenan Barut[2], Sezgin Şahin[2], Amra Adroviç Yıldız[2], Şeyma Dümür[1], Özgür Kasapçopur[2], Mine Kucur[1]

[1]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Medical Biochemistry, İstanbul, Turkey
[2]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pediatric Rheumatology, İstanbul, Turkey

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ABSTRACT

Objective: This study aimed to investigate the possible relationship of serum adiponectin and visfatin levels that are derived from the adipose tissue in patients with juvenile idiopathic arthritis (JIA), in accordance with the routinely used biochemical parameters, to evaluate the management of therapy and assessment of disease activity.

Methods: According to the Wallace criteria, the study population was divided into active, remission and control groups. Serum adiponectin and visfatin levels were measured by the enzyme-linked immunosorbent assay method. Complete blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were routinely measured. Neutrophil/lymphocyte ratio (NLR) was calculated.

Results: Significant differences were found in serum visfatin levels between the active and the control groups ($p<0.05$) and in serum adiponectin levels between the active and remission groups ($p<0.05$). Significant differences were also observed in routinely used parameters, namely; ESR, CRP and platelet count ($p<0.05$), among the active, remission and control groups, whereas the leukocyte and neutrophil counts together with the percentage of neutrophils, lymphocytes and NLR established significant differences only between the active and control groups ($p<0.05$).

Conclusion: The results suggest that serum visfatin levels may be useful to indicate disease activity in accordance with the correlation between ESR and CRP in patients with JIA. Unlike visfatin, serum adiponectin levels may be utilised in the management of treatment rather than as a diagnostic parameter on the onset of JIA. Although this study included a small sample of patients with JIA, it highlights the potential of the two adipose tissue-derived parameters as new biochemical parameters in JIA, both in the assessment of disease activity and the management of treatment, which are essential to improve the life quality of these patients.

Keywords: Adipocytokine, adiponectin, inflammation, juvenile idiopathic arthritis, visfatin

ORCID IDs of the authors: O.Ç. 0000-0002-1522-9823; Z.B.G. 0000-0002-0649-844X; Ö.B.E. 0000-0001-7432-9915; H.E. 0000-0002-5605-2980; K.B. 0000-0001-8459-2872; S.Ş. 0000-0002-5365-3457; A.A.Y. 0000-0002-2400-6955; Ş.D. 0000-0001-8893-2926; Ö.K. 0000-0002-1125-7720; M.K. 0000-0002-6579-1996.

Corresponding Author: Mine Kucur,
E-mail: mkucur@hotmail.com

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INTRODUCTION

Juvenile idiopathic arthritis (JIA), formerly known as juvenile rheumatoid arthritis, is characterised by idiopathic permanent arthritis lasting at least 6 weeks and onset before age 16 years after the exclusion of other inflammatory diseases, such as reactive arthritis, inflammatory bowel disease and systemic lupus erythematosus. JIA progresses to childhood arthritis in which prolonged synovial inflammation may result in growth impairment, joint destruction, osteoporosis and chronic pain as long-term consequences (1).

Wallace et al. (2) suggested specific criteria for determining the disease activity of children with JIA. To be considered having inactive disease, patients should not have active arthritic joints, fever, rash, serositis, splenomegaly or generalised lymphadenopathy and active uveitis, and normal values of both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Clinical remission with medication is considered inactive for a period minimum of six consecutive months under medication, whereas clinical remission without medication is proposed as 12 consecutive months without anti-arthritis and anti-uveitis medications.

JIA is an inflammatory disease accompanied with innate and adaptive immune system disorders. A dysregulation of the alternative secretory pathway leads to loss of monocytes, macrophages and neutrophils with aberrant activation of phagocytes and plays a role in the release of interleukin (IL)-1, IL-6, IL-8 and proinflammatory S-100 proteins. Eventually, this contributes to multisystem inflammation of JIA (3,4).

Recent studies involving laboratory parameters aimed to determine inflammation, clarify the pathogenesis of the disease and monitor side effects of treatment. Complete blood count (CBC) rheumatoid factor as well as other inflammatory markers, such as ESR and CRP, are commonly used laboratory parameters in the management of JIA. The treatment goal is disease remission. ESR and CRP, which are acute-phase proteins, are used in the diagnosis and monitoring of both active and remission periods (2,3,5,6).

Many inflammatory mediators including cytokines [such as IL-1, IL-6, IL-8 and tumour necrosis factor-alpha (TNF-α)] and adipokines (such as leptin, adiponectin, resistin and visfatin) are released from the adipose tissue (4,7). Adipokines participate in the pathogenesis of various pathologies, mainly inflammation, obesity, insulin resistance, metabolic syndrome and autoimmune diseases such as rheumatoid arthritis (5,6,8,9).

Research studies have recently shown that both adiponectin and visfatin may have critical roles in the pathogenesis of JIA, but this has not yet been clarified. Although the aetiology of JIA is unknown, the immunological predisposition is emphasised and JIA is considered an antigen-dependent T-lymphocyte-mediated autoimmune disease (7,10).

Recent studies have indicated that extracellular matrix degradation and joint destruction induced both the infiltration of adiponectin and migration of monocytes towards the synovium, acting as a proinflammatory mediator in joint diseases (8,11).

Conversely, visfatin enhances the release of CD54 (ICAM), CD40 and CD80 molecules that are effective in activating T-cells and CD14+, and CD19+ chemotaxic molecules for monocytes and B cells (9,12). Additionally, studies have shown that the expression of ICAM-1 and VCAM-1 as a response to reactive oxygen species production is enhanced by visfatin (10,13).

In this study, serum adiponectin and visfatin levels were measured in both active and remission periods of a group of patients with JIA in comparison with a control group. Thus, this study aimed to investigate the predictive roles of these two adipose tissue-derived parameters in monitoring disease activity and management of the treatment of JIA.

METHODS

A total of 87 patients with JIA undergoing follow-up in Cerrahpaşa Medical Faculty Department of Pediatric Rheumatology, İstanbul University Cerrahpaşa, and 50 control subjects were enrolled in this study.

Patients with JIA were diagnosed according to 2001 International League of Associations For Rheumatology classification criteria (11,14). Fifty healthy children whose age and sex were similar to the patient groups, did not receive any medication and had no infection and other any systemic diseases (such as malignancy, chronic inflammatory disease, endocrine disorder, malabsorption, liver disease and obesity) were included in this study. Patients were categorised according to the validated Wallace criteria for patients with JIA dependent of the active or remission period (12,15).

Written informed consent was obtained from all patients. The study protocol was approved by Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 02-107694, approval date: 07.04.2015).

Sample Collection

In this study, 5 mL of blood was collected into gel tubes without anticoagulants for adiponectin and visfatin analysis and left for 30 min for coagulation. After centrifugation at 4,000 rpm for 7 min, serum was collected into separate tubes and stored at -20 °C until analysis. Serum adiponectin and visfatin levels were measured by enzyme-linked immunoabsorbent assay kits (eBioscience Inc. San Diego, CA 92121 United States BMS2032/2 and SunRed, 201-12-0026, respectively) according to the manufacturer's instructions. CBC (Beckman Coulter LH780), ESR (Therma NE Linear) and CRP (Roche Cobas C 501) were also analysed. Neutrophil/lymphocyte ratio (NLR) was calculated by dividing neutrophil count by lymphocyte count in CBC.

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Statistical Analysis

SPSS Statistics for Windows v. 20 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis of the study variables. Analysis of variance test was performed to analyse differences among variables between the subgroups. Student's t-test (homogeneous groups) was performed for binary comparisons. The Pearson test was used to analyse correlation. A value of $p<0.05$ was considered significant. Numerical values obtained were expressed as mean ± standard deviation or standard error of the mean.

RESULTS

The population of this study consisted of 87 children (n=37, 42.5% male; n=50, 57.5% female) with JIA and 50 healthy controls (n=27, 54% male; n=23, 46% female).

Demographic Data

The gender and age distribution of the study population is shown in Table 1. No significant difference was found between the patient group and the control group in terms of gender and age ($p>0.05$).

Patients with JIA were divided into active and remission groups. In the last 6 months, patients with no active arthritis or with no rash and clinical inactive disease were included in the remission group.

Routine Laboratory Parameters

Significant differences were found in routinely used parameters, including ESR, CRP and platelet count ($p<0.05$) among the active, remission and control groups, whereas significant differences were observed only between the active and control groups in terms of the leukocyte and neutrophil counts, along with the percentage of neutrophils, lymphocytes and NLR ($p<0.05$). Routine laboratory parameters of the study groups are detailed in Table 2.

Serum Adiponectin and Visfatin Levels

Serum adiponectin levels were decreased in both the remission group and control group when compared with the active group (Figure 1). However, a significant decline was observed only between the active and remission groups ($p<0.05$). Markedly low adiponectin values are observed in the remission period than in the control group. Although serum visfatin levels were also lower in both the remission and control groups than in the active group, significant difference was found only between the active and control groups ($p<0.05$) (Figure 2). A subsequent decline was observed in visfatin values among the study groups. These results are illustrated in Table 3. A positive correlation was found between visfatin and CRP ($r=0.459$, $p=0.007$) and ESR values ($r=0.409$, $p=0.018$) (Figure 3).

Table 1. Gender and age distribution in the active, remission and control groups

	Active n=54	Remission n=33	Control n=50	p value
Male	25 (46.3%)	12 (36.4%)	27 (54%)	0.992
Female	29 (53.7%)	21 (63.6%)	23 (46%)	0.992
Age (year)	9.4±3.9	9.1±4.1	9.3±4.6	0.972

DISCUSSION

Although adipose tissue was initially thought to store only triglycerides and participate in thermogenesis, adipose tissue also acts as an active endocrine gland and secretes many bioactive peptides and hormones. Adipocytes generally affect both metabolism and immunity; the latter is mediated by various inflammatory and proinflammatory molecules derived from the adipose tissue (16).

Both the adaptive and innate immune system are primarily involved in the inflammatory process (17). Neutrophils are major components of the immune response against inflammation or infection, playing a key role in both the activation and migration

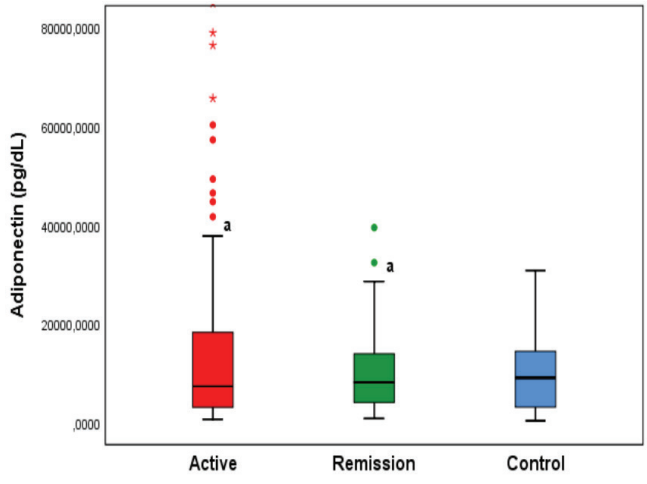

Figure 1. Serum adiponectin (pg/dL) levels in the active, remission and control groups
a: comparison of active group and remission group ($p<0.05$)

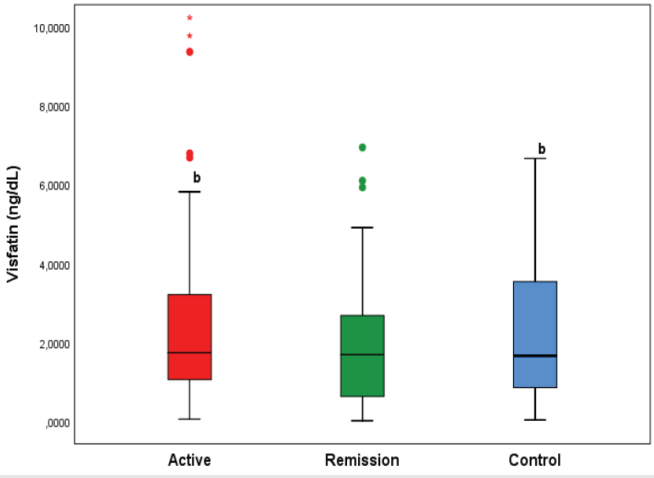

Figure 2. Serum visfatin (ng/dL) levels in the active, remission and control groups
b: comparison of active group and control group ($p<0.05$)

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Table 2. Routine laboratory parameters of the study groups

	Active n=52	Remission n=33	Control n=50	p value
Leukocyte (10^3/mm^3)	9.46±2.73[b]	8.67±2.30	7.77±2.10[b]	0.002
Neutrophil (10^3/mm^3)	5.74±2.42[b]	4.68±2.09	4.04±1.39[b]	0.000
Lymphocyte (10^3/mm^3)	2.80±1.24	2.98±1.22	2.84±1.08	0.798
Monocyte (10^3/mm^3)	0.72±0.30	0.69±0.21	0.61±0.25	0.107
Neutrophil (%)	59.14±12.05[b]	53.01±13.13	52.06±10.11	0.008
Lymphocyte (%)	30.34±10.99[b]	34.95±11.38	36.88±9.64	0.007
Platelet (10^3/mm^3)	375.11±97.08[b]	301.45±88.85[a]	314.26±75.98	0.001
MPV (fL)	7.80±0.78	8.07±1.10	8.01±0.81	0.314
PDW (%)	16.43±0.52	16.63±0.57	16.43±0.52	0.181
NLR	2.50±1.89[b]	1.83±1.09	1.58±0.69[b]	0.003
ESR (mm/saat)	31.00±21.07[b]	12.66±10.73[a]	7.32±3.49	0.000
CRP (mg/dL)	2.71±4.09[b]	0.43±0.80[a]	0.19±0.21	0.000

[a]comparison of active and remission groups, [b]comparison of active and control groups. After the logarithm of the parameters that do not comply with the normal distribution was made suitable for the normal distribution, the groups were compared with each other by using analysis of variance test.
ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, MPV: mean platelet volume, NLR: neutrophil-lymphocyte ratio, PDW: platelet distribution width

Table 3. Comparison of active, remission and control groups in terms of adiponectin and visfatin

	Active n=52	Remission n=33	Control n=46	p value
Visfatin (ng/dL)	2.89±2.65[b]	2.10±1.81	1.74±1.28[b]	0.021
Adiponectin (pg/dL)	20.14±24.10	8.48±6.25[a]	17.17±21.28	0.046

After the logarithm of the parameters that do not comply with the normal distribution was made suitable for the normal distribution, the groups were compared with each other by using analysis of variance test. [a]comparison of active and remission groups, [b]comparison of active and control groups

of antigen-presenting cells. Neutrophil chemotaxis promotes the migration of monocytes to the inflammation site. They are also involved in monocyte differentiation into pro- or anti-inflammatory macrophages. Both reactive oxygen species and lytic enzymes that are released from the neutrophils lead to tissue injury (18,19).

Adipokines that have proinflammatory properties did not directly participate in inflammation, but they are involved in the initiation and termination of the inflammation phase (20).

In our study, we investigated the possible relationship between adiponectin and visfatin with CBC parameters (mainly leukocytes, neutrophils, lymphocytes, monocytes and platelets), ESR and CRP that are considered routine biochemical parameters that manage the inflammatory process in JIA. Leukocyte [white blood cells (WBC)] counts are strikingly elevated in children with JIA. Since JIA is an inflammatory disease, significant difference was found in WBC values during the active and remission periods when compared with the control group. Conversely, Güneş et al. (21) reported no significant difference in WBC between the active and remission periods, whereas Punzi et al. (22) reported higher WBC levels in patients with JIA than in those without JIA, which is

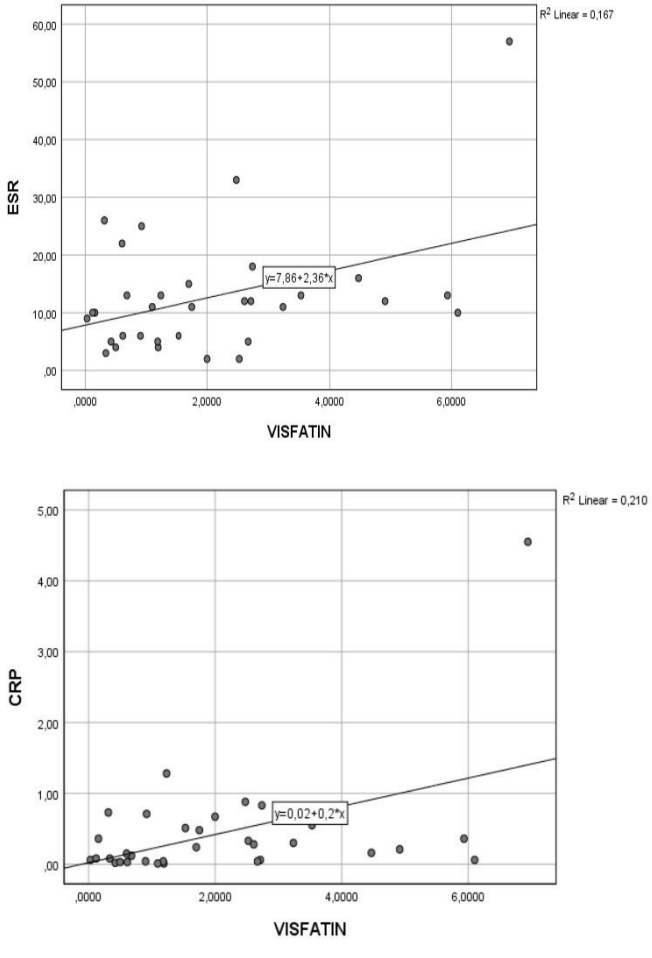

Figure 3. Relationship between visfatin and serum levels of C-reactive protein and erythrocyte sedimentation rate
ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

similar to the results of the present study. Furthermore, neutrophil counts were higher in both active and remission groups than in the control group. Possible reason is that neutrophils are activated by TNF-α, a cytokine that is involved in both tissue damage and repair process. We can assume that neutrophils activate the macrophage-based immune response, and this may trigger the conversion of proinflammatory process into anti-inflammatory and proliferative processes in damaged tissues. This assumption may explain the high neutrophil counts in both active and remission periods (23).

Although lymphocytes are not part of adipose tissues, there is a physical proximity between the lymph nodes and pericapsular adipose tissue surrounding them. Thus, a probable paracrine effect may be observed between adipocytes and lymphocytes (24,25). Directing the lymphocyte transport through the lymph nodes to the spleen is mutually controlled by the regulation of the neutrophil production rate during haematopoiesis. Apoptotic neutrophils on the area of tissue destruction are phagocytised by the migration of macrophages to the region by chemotaxic agents derived from neutrophils (21,26). Therefore, while the neutrophil counts increase in the active period, the NLR subsequently shifts in favour of the lymphocytes in the remission period. Based on this data, in our study, NLR was also evaluated in patients with JIA. NLR was significantly higher in the active group than in the control group, with elevated neutrophil counts related to disease activity. However, this ratio decreased in the remission period. NLR is an acceptable inflammation marker, and it may be useful in the management of disease activity. A recent study by Güneş et al. (21) reported significantly high NLR in both active and inactive (remission subjects) groups in comparison with that in the control group, although no significant difference was found in NLR between the active and remission groups. Although NLR may not be useful in distinguishing active and remission periods, it may be a reliable marker to evaluate disease activity at JIA onset.

Thus far, no reliable, sensitive and specific biochemical parameters have been established to define the diagnosis, prognosis and follow-up of JIA (27). ESR and CRP are used as routine clinical laboratory parameters in evaluating disease activity (28). ESR depends on the concentration of plasma fibrinogen and indirectly reflects the concentration of acute-phase proteins. The analysis of ESR demonstrates the disease activity both at onset and follow-up of patients with JIA. Similarly, CRP is an inflammatory parameter, i.e. an acute-phase protein (29). During active disease, high ESR and CRP values are related to immunologic response, particularly innate immune phase. In the present study, we demonstrated higher ESR and CRP values in the active group than in the control group, supported by similar results in the literature (30).

In vitro, activated platelets release proinflammatory cytokine IL-1β. This cytokine plays a major role in vascular inflammation, taking place in the centre of the cytokine cascade. Activated platelets induce the release of IL-6 and IL-8 from the vascular smooth muscles through IL-1. In turn, IL-1 accelerates neutrophil adhesion to endothelial cells (31). Güneş et al. (32) reported high platelet counts in patients with active JIA compared with individuals without JIA. Ece et al. (33) showed that platelet counts decreased as a response towards therapy in the remission group. Our results also correlated with these recently published results. We found high platelet counts in both the active and remission groups when compared with control subjects. Furthermore, platelet counts positively correlated with the neutrophil counts and CRP.

In the present study, both adiponectin and visfatin levels were evaluated in patients with JIA during the active and remission periods. We demonstrated a significant decrease in visfatin levels in the control group when compared with that in the active group, indicating visfatin as a reliable parameter for the determination of disease activity, exhibiting a correlation between inflammatory parameters ESR and CRP. By contrast, a significant difference was observed in adiponectin levels between the active and remission groups. A marked decline was noted in adiponectin levels in the remission period compared with that in the control group, indicating that it may be useful in the management of the JIA treatment. In a study reported by Aranda-Valera et al. (34), alterations of adipokines function might be exhibited with chronic inflammation, even under remission conditions, and this inflammatory process might promote the anti-inflammatory response related with the adipose tissue in patients with JIA.

Study Limitations

This study has some limitations including the small sample size and unequal distribution in the subgroups.

CONCLUSION

The adipose tissue plays an essential role in the inflammatory process, particularly with adipokines. However, JIA is a common rheumatological problem in the paediatric population and considered an inflammatory disease accompanied with immune response disorder. The present study highlights the concentrations of both visfatin and adiponectin in JIA, and these two adipose tissue-derived biochemical parameters may play a role in the management of disease activity and monitoring of treatment. Moreover, this study emphasised that NLR, a very simple and useful test to predict anti-inflammatory response, may be a reliable marker of disease activity. Further studies with a large sample size and detailed characterisation of subgroups are warranted to validate the role of adiponectin and visfatin in the evaluation of disease activity. This will provide appropriate management strategy of the disease and improve the quality of life in patients with JIA.

Ethics Committee Approval: The study protocol was approved by Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 02-107694, approval date: 07.04.2015).

Informed Consent: A written informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - K.B., A.A.Y., S.Ş., Ş.D., Ö.K.; Concept - O.Ç., H.E., Z.B.G., K.B., A.A.Y., S.Ş., Ö.K.; Design - O.Ç., Ö.B.E., K.B., A.A.Y., S.Ş., Ö.K., M.K.; Data Collection and/or Processing - O.Ç., Ö.B.E., H.E., Z.B.G., K.B., Ş.D.; Analysis and/or

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Interpretation - O.Ç., Ö.B.E., Z.B.G., K.B., Ş.D., M.K.; Literature Search - O.Ç., Ş.D., M.K.; Writing - O.Ç., Ş.D., M.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Barut K, Adrovic A, Şahin S, Kasapçopur Ö. Juvenile idiopathic arthritis. Balkan Med J 2017; 34: 90-101.
2. Wallace CA, Huang B, Bandeira M, Ravelli A, Giannini EH. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. Arthritis Rheum 2005; 52: 3554-62.
3. Kessel C, Holzinger D, Foell D. Phagocyte-derived S100 proteins in autoinflammation: putative role in pathogenesis and usefulness as biomarkers. Clin Immunol 2013; 147: 229-41.
4. Frizinsky S, Haj-Yahia S, Machnes Maayan D, Lifshitz Y, Maoz-Segal R, Offengenden I, et al. The innate immune perspective of autoimmune and autoinflammatory conditions. Rheumatology (Oxford) 2019; 58(Suppl 6): vi1-8.
5. Shoop-Worrall SJW, Kearsley-Fleet L, Thomson W, Verstappen SMM, Hyrich KL. How common is remission in juvenile idiopathic arthritis: a systematic review. Semin Arthritis Rheum 2017; 47: 331-7.
6. Naz S, Aslam R, Ullah E, Shahzad F, Mushtaq A, Ahmad TM, et al. Association of erythrocyte sedimentation rate and c-reactive proteins with active disease in Juvenile Rheumatoid Arthritis. Pak Pediatr J 2014; 38: 24-30.
7. Żółkiewicz J, Stochmal A, Rudnicka L. The role of adipokines in systemic sclerosis: a missing link? Arch Dermatol Res 2019; 311: 251-63.
8. Landecho MF, Tuero C, Valentí V, Bilbao I, de la Higuera M, Frühbeck G. Relevance of leptin and other adipokines in obesity-associated cardiovascular risk. Nutrients 2019; 11: 2664.
9. Fatel ECS, Rosa FT, Simão ANC, Dichi I. Adipokines in rheumatoid arthritis. Adv Rheumatol 2018; 58: 25.
10. Scotece M, Conde J, López V, Lago F, Pino J, Gómez-Reino JJ, et al. Adiponectin and leptin: new targets in inflammation. Basic Clin Pharmacol Toxicol 2014; 114: 97-102.
11. Abella V, Scotece M, Conde J, López V, Lazzaro V, Pino J, et al. Adipokines, metabolic syndrome and rheumatic diseases. J Immunol Res 2014; 2014: 343746. doi: 10.1155/2014/343746.
12. Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H, et al. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. J Immunol 2007; 178: 1748-58.
13. Kim SR, Bae YH, Bae SK, Choi KS, Yoon KH, Koo TH, et al. Visfatin enhances ICAM-1 and VCAM-1 expression through ROS-dependent NF-KB activation in endothelial cells. Biochim Biophys Acta 2008; 1783: 886-95.
14. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004; 31: 390-2.
15. Wallace CA, Huang B, Bandeira M, Ravelli A, Giannini EH. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. Arthritis Rheum 2005; 52: 3554-62.
16. Corrêa LH, Heyn GS, Magalhaes KG. The ımpact of the adipose organ plasticity on ınflammation and cancer progression. Cells 2019; 8: 662.
17. Fandiño Vargas MC. (June 3rd 2020). İnnate immunity and autoimmune diseases [Online First], Intech Open 2020: June 3. doi: 10.5772/intechopen.91366. (Online ahead of print)
18. Lawrence SM, Corriden R, Nizet V. How Neutrophils Meet Their End. Trends Immunol 2020; 41: 531-44.
19. de Oliveira S, Rosowski EE, Huttenlocher A. Neutrophil migration in infection and wound repair: going forward in reverse. Nat Rev Immunol 2016; 16: 378-91.
20. Mancuso P. The role of adipokines in chronic inflammation. Immunotargets Ther 2016;5:47-56.
21. Güneş A, Ece A, Şen V, Uluca Ü, Aktar F, Tan İ, et al. Correlation of mean platelet volume, neutrophil-to-lymphocyte ratio, and disease activity in children with juvenile idiopathic arthritis. Int J Clin Exp Med 2015; 8: 11337-41.
22. Punzi L, Ramonda R, Glorioso S, Schiavon F, Mariuz S, Gambari PF. Predictive value of synovial fluid analysis in juvenile chronic arthritis. Ann Rheum Dis 1992; 51: 522-4.
23. Brown RA, Henderlight M, Do T, Yasin S, Grom AA, DeLay M, et al. Neutrophils from children with systemic juvenile ıdiopathic arthritis exhibit persistent proinflammatory activation despite long-standing clinically inactive disease. Front Immunol 2018; 9: 2995.
24. Cousin B, Munoz O, Andre M, Fontanilles AM, Dani C, Cousin JL, et al. A role for preadipocytes as macrophage-like cells. FASEB J 1999; 13: 305-12.
25. Robker RL, Collins RG, Beaudet AL, Mersmann HJ, Smith CW. Leukocyte migration in adipose tissue of mice null for ICAM-1 and Mac-1 adhesion receptors. Obes Res 2004; 12: 936-40.
26. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med 2012; 5: 2.
27. Akay Tekelı A, Oner A. Clınıcal and laboratory fındıngs of chıldren wıth ıdentıfıed ıdıopathıc arthrıtıs, ınvestıgatıon on treatment and prognosıs - seven years experıence. Pediatr Dimensions 2017; 2: 1-7.
28. Bray C, Bell LN, Liang H, Haykal R, Kaiksow F, Mazza JJ, et al. Erythrocyte sedimentation rate and c-reactive protein measurements and their relevance in clinical medicine. WMJ 2016; 115: 317-21.
29. Sarkar S, Alam MM, Das G, Datta S. Inflammatory markers and disease activity in juvenile ıdiopathic arthritis. Indian J Pediatr 2017; 84: 349-56.
30. Gorczyca D, Postępski J, Czajkowska A, Paściak M, Prescha A, Olesińska E, et al. The profile of polyunsaturated fatty acids in juvenile idiopathic arthritis and association with disease activity. Clin Rheumatol 2017; 36: 1269-79.
31. Thomas MR, Storey RF. The role of platelets in inflammation. Thromb Haemost 2015; 114: 449-58.
32. Güneş A, Ece A, Şen V, Uluca Ü, Aktar F, Tan İ, et al. Correlation of mean platelet volume, neutrophil-to-lymphocyte ratio, and disease activity in children with juvenile idiopathic arthritis. Int J Clin Exp Med 2015; 8: 11337-41.
33. Ece A, Şen V, Yel S, Güneş A, Uluca Ü, Tan İ, et al. Clinical and laboratory characteristics and follow up results of 121 children with juvenile ıdiopathic arthritis. Eur J Gen Med 2015; 10: 136-41.
34. Aranda-Valera IC, Arias de la Rosa I, Roldán-Molina R, Ábalos-Aguilera MDC, Torres-Granados C, Patiño-Trives A, et al. Subclinical cardiovascular risk signs in adults with juvenile idiopathic arthritis in sustained remission. Pediatr Rheumatol Online J 2020; 18: 59.

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Test-Retest Reliability of Electroglottography Measurement

Mehmet Emrah Cangi, Göksu Yılmaz

Üsküdar University Faculty of Health Sciences, Department of Speech and Language Therapy, İstanbul, Turkey

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ABSTRACT

Objective: Electroglottography (EGG) is an instrumental measurement technique that provides a relative measure of the contact area between vocal folds. It is important to examine whether this measurement provides reliable data in Turkish. The aim of this study is to determine the level of reliability of EGG measurements made at different times related to some sustained vowel vocalizations.

Methods: Seventy participants, 35 women and 35 men, aged between 18-25 and who have healthy voice, participated in the study. The Kay-PENTAX Electroglottograph model 6130 was used to study participants' production of /i/, /u/, /ɛ/ and /ʌ/ vowels. Data were collected from participants at four different time points: (1M) first week in the morning, (1E) first week in the evening, (2M) second week in the morning, and (2E) second week in the evening. The data obtained from all these measurements were matched in terms of time points; 1M-1E, 2M-2E, 1M-2E and 1E-2E. The consistency between measurements of these time points was studied by the inter-class correlation coefficient (ICC), a two-way mixed model. The gender differences of the parameters were analyzed with independent samples t-test.

Results: According to repeated test results of all parameters obtained for the /ɛ/ vowel for both sexes and the /i/ vowel for men only, ICC values were statistically significant at levels ranging from moderate to excellent. In addition, when closed and open phase data were examined, values of all vowels did not differ according to gender during phonations. The frequency periodicity parameter of /ʌ/, /ɛ/ and /i/ vowels differs statistically significant in this respect. When the averages were examined, it was found that the measurements of women were higher than those of men in all parameters where significant differences were found.

Conclusion: As a result of repeated measurements with EGG, regardless of the recording time, measurements of the /ɛ/ vowel showed more reliable results compared to other vowels.

Keywords: Test-retest reliability, electroglottography, voice evaluation

INTRODUCTION

Voice disorders can be evaluated in many ways, including acoustic and glottographic techniques. In this context, electroglottography (EGG) method, which is a non-invasive and direct evaluation battery of the glottal cycle, is often used. EGG is based on the electrical conductivity of the vocal fold and surrounding tissues as a measurement principle. Measurements are performed through two electrodes placed on the surface of the laryngeal region. During the measurement, the person is asked to make a phonation, and a very low-amp current is passed through the electrodes by the device. As a result, a certain number of current passes through the folds that open and close during phonation. The value of this current measured by the electrodes, on the other hand, shows differentiation due to impedance, which is constantly variable depending on vocal fold movements. The electroglottographic wave form (Lx) obtained at the end of the measurement is an impedance change wave that reflects the movement of the vocal folds (1,2).

ORCID IDs of the authors: M.E.C. 0000-0001-8149-3254; G.Y. 0000-0001-6123-8395.

Sorumlu Yazar/Corresponding Author: Mehmet Emrah Cangi,
E-mail: mehmetemrah.cangi@uskudar.edu.tr

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In voice evaluations, continuous vowel phonation is often used. Because during vowel phonation, many mixing factors such as accent, intonation, dialect are excluded, and these measurements are mostly performed with continuous vowel phonations, which are phonetically defined by /a/, /i/, and /u/ representations (3). In this context, it was defined by the International Phonetic Alphabet and the productions of all vowels available in terms of phonetics are classified in terms of tongue, lip and jaw movements. The production of different vowels, on the other hand, is due to these differences, which occur according to the place of articulation. Sustained vowel phonations, mostly used for voice evaluation, can alter laryngeal position and vocal tract acoustics due to differences occurring relative to the place of articulation (3,4). In this case, acoustic and/or electroglottographic evaluation parameters can affect the evaluation and therapy process of voice disorders, resulting in different values in different vowel phonations.

Different hypotheses have been proposed to explain the effect of different vowels, often used in voice evaluation procedures, on acoustic perturbation and fundamental frequency values. According to the acoustic coupling (source-filter) hypothesis, perturbation parameters should not be affected by the filter change that occurs during the articulation of different vowels because the source retains its existence without any structural change (5,6). The physical connection hypothesis, on the other hand, is studied in three separate subheadings: tongue pull, tongue compression, and horizontal-vertical pull. The hypothesis holds that there is a physiological-anatomical relationship between the vocal tract and the larynx, which changes acoustically during vowel phonations that differ according to their place of articulation. Research conducted in this context has shown that differences in tongue position or hyoid-larynx complex are related to basic frequency and perturbation parameters (7,8). In short, the configuration of the vocal path filter during different vowel phonation varies based on the differentiation of their placement relative to each other, and it has been determined that these differences in the vocal path affect the acoustic perturbation parameters of the voice analyzed (7,9).

In clinical use, if observed changes in electroglottographic parameters (effectiveness of therapy, degree of pathology progression, etc.) are to be used as an objective predictor of voice quality, knowing under what conditions the reliability between measurements is most optimal within the framework of variations created in terms of time and vowel type of people with normal voice will provide a great advantage for clinical use. In this context, there are a number of studies in the literature examining the reliability levels of aerodynamic and/or electroglottographic parameters of repeated measurements (10-16).

The aim of the current research is to determine the degree of reliability of EGG values obtained from different vowel phonations and measurements made at different times in terms of parameters determined as a result of repeated tests and to compare the obtained parameters in terms of gender.

METHODS

Participants

The study included 70 participants, 35 women and 35 men, between the ages of 18 and 25. Due to the fact that the participant population is university-level students, the age range of participants is 18 to 25 years. The power analysis was calculated using version G-Power 3.1 based on the gender variable. It was found appropriate to include at least 58 participants, including at least 29 in each group, in the power analysis performed by Awan et al. (14) considering the effect size in the analysis in which the differentiation of mean F0 according to gender was examined, with a power of 95% in the 95% confidence interval. In the study, 70 participants were reached and the required sample size was provided. For the purposes of the study, some participant exclusion criteria were determined. Individuals with any structural abnormalities in the head and neck region or a history of surgery, chronic larynx disease, taking a drug that requires constant use, smoking, long-term voice disorders, and hearing disorders were not included in the study. In addition, individuals with lower or upper respiratory infections, seasonal allergies, or complaints about their voice during the measurement were not included in the study. Professional voice users and individuals who had previously received singing or voice therapy were also not included in the study. For female participants, the criteria for not being in the menstrual cycle was determined during the measurement.

It is based on the statements and anamnesis of the participants in the exclusion criteria in which they have a normal voice, but on the perceptual assessment of the researcher conducting the recording process. Accordingly, the authors conducted preliminary evaluations of the participants and participants who met the criteria for the frequency periodicity value for EGG measurement to be less than 20 were included in the study.

This study is planned in accordance with the International Declaration of Helsinki. A written consent form was obtained from all of the individuals who agreed to participate in the study, and the participants were informed about the content of the study. For the study, Ethics Committee approval was obtained from Üsküdar University Non-interventional Research Evaluation Board (decision no: 61351342-/2019-216, date: 25.04.2019).

Recording Procedures

First, the purpose of the study was explained to the participants and written consent was obtained from them. Then, socio-demographic information was taken with the personal information form and information about the participant criteria was provided. In the directive presented to the participants, they were asked to specifically avoid behaviors that may negatively affect vocal hygiene at least 24 hours before each measurement, while they were asked to pay particular attention to the vocal hygiene rules presented at the beginning of the study as part of the research process.

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EGG measurement was performed with Kay-PENTAX Electroglottograph model 6103 (Lincoln Park, NJ, USA), and a pair of electrodes with EGG velcro belts were placed by palpating the thyroid notch in the neck areas of the participants. The system is set to 44.100 sampling rate. In this context, the (17) /ʌ/, /ɛ/, /i/ and /u/ vowels in the phonetic inventory of Turkish were recorded consecutively, each with a minimum of five seconds. For the correct placement of EGG electrodes and adaptation of the person to the process, the person was first asked for sustained phonation of /ʌ/ to last a minimum of five seconds. In this way, the clinician confirmed both the accuracy of the electrode placement with the morphology (1,2) of the Lx wave appearing on the screen and allowed the person to adapt to the recording procedures. The recording order of the vowels was randomly changed for each participant and each registration session. Two minutes of absolute voice rest and hydration intervals were given between recordings. Recordings were taken once for each vowel, recorded in ".nsp" format, and then the three-second segment in the middle of each recorded vowel phonation was analyzed.

A specific calendar was determined for the measurements in the study: 1. When the measurement was taken between 10:00 and 11:00 in the morning (1M), 2. the measurement was taken between 16:00 and 17:00 (1E) in the evening, and sessions 1M and 1E were performed on the same day. The third and fourth measurement sessions were held 1 week after the day of 1M and 1E measurements. The third measurement was taken again between 10:00 and 11:00 in the morning (2M), and the fourth measurement was taken again between 16:00 and 17:00 in the evening (2E), and the 2M and 2E sessions were also performed on the same day. In this context, measurements were completed in a total of 4 different sessions, provided that they were taken at different times for each participant.

During the recording, the person was asked to sit in an upright position and to perform the vowel phonation requested from him in the same tone and volume used in daily life, without interruption. The parameters to be evaluated in EGG-frequency measurement are mean F0, minimum F0, maximum F0, F0 standard deviation, mean jitter and frequency periodicity (periodicity) measurement parameters. The mean, minimum and maximum parameter values of the glottal closure phase (closed phase-CP) and the mean, minimum and maximum parameter values of the glottal opening phase (open phase-OP) were examined. All recording and analysis processes were carried out in Üsküdar University Phonetics Laboratory.

Statistical Analysis

The SPSS 22.0 package program was used to evaluate the data. While using the intraclass correlation coefficient (ICC), the two-way mixed model was preferred because the participants were randomly selected and the person taking the measurement was fixed. This method is calculated with the formula ICC (3,1) (18). For the normality assumption, the skewness-kurtosis coefficients and Shapiro-Wilks test results were evaluated together. In order to determine whether the measurement parameters differ by gender, independent samples t-test were used because the data showed a normal distribution. In both measurements, the significance level was considered $p<0.05$. According to ICC classification criteria, the reliability of ICC values less than 0.5 is low, values between 0.5 and 0.75 are moderately reliable, values between 0.75 and 0.9 are well reliable, and values greater than 0.9 are perfectly reliable (19). In this context, the current ranges are referenced in the ICC classification to be used during the reporting.

RESULTS

In order to calculate the test-retest results of parameters 1E, 1M, 2M and 2E of the /ʌ/ vowel, the correlation coefficient in the class was calculated. Results for women are presented in Table 1.

For women, all ICCs calculated except for the frequency periodicity parameter obtained from the /ʌ/ vowel in accordance with morning (1M) and evening (1E) records on the same day are statistically significant ($p<0.05$). By examining the ICC values obtained for all other parameters, repeated measurements were found to be reliable at moderate and good levels.

One week after the first measurement, all intraclass correlation coefficients were found to be statistically significant except for minimum-CP, maximum-OP and maximum F0 measurements obtained from the /ʌ/ vowel, based on the recordings taken in the morning (2M) and evening (2E) on the same day for women. ($p<0.05$). When the ICC values obtained for all other parameters were examined, repeated measurements were obtained with moderate, good and excellent levels of reliability. All ICCs calculated except the frequency periodicity obtained from the /ʌ/ vowel in accordance with the records received in the morning (1M) on the first day and in the morning (2M) a week later are statistically significant ($p<0.05$). When the ICC values obtained for all other parameters were examined, repeated measurements were obtained reliably at moderate, good and excellent levels. All ICCs calculated except the maximum F0 and frequency periodicity obtained from the /ʌ/ vowel were statistically significant according to the records obtained in the evening (1E) on the first day and in the evening (2E) a week later ($p<0.05$). When examining the ICC values obtained for all other parameters, repeated measurements were obtained reliably at moderate, good and excellent levels (Table 1).

In order to calculate the test-retest results of parameters 1E, 1E, 2M and 2E of the /ʌ/ vowel, the correlation coefficient in the class was calculated. Results for men are presented in Table 2.

For males, all ICCs were found to be statistically significant except mean-OP, minimum-OP and maximum-OP obtained from the /ʌ/ vowel based on the morning (1M) and evening (1E) recordings on the same day ($p<0.05$). When the ICC values obtained for all other parameters are examined, it can be said that repeated measurements are reliable at moderate, good and excellent levels.

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One week after the first measurement, all ICCs were statistically significant (p<0.05), except for the average jitter and frequency periodicity obtained in the /ʌ/ vowel, according to the recordings taken in the morning (2M) and evening (2E) on the same day for men.

When the ICC values obtained for all other parameters were examined, repeated measurements were reliable at low, moderate and good levels. Based on the recordings taken in the morning (1M) on the first day and in the morning (2M) a week later, the whole class calculated except the minimum-CP, maximum-CP, average-OP, minimum-OP, maximum-OP, Average jitter obtained from the /ʌ/ intra-correlation coefficients were found to be statistically significant (p<0.05). By examining the ICC values obtained for all other parameters, repeated measurements were obtained reliably at moderate, good and excellent levels. All ICCs obtained from the /ʌ/ vowel by making evening (1E) on the first day and evening (2E) a week later are statistically significant (p<0.05). Repeated measurements were reliably obtained at low, moderate and good levels when examining the ICC values obtained for all other parameters (Table 2).

In order to calculate the test-retest results of 1M, 1E, 2M and 2E parameters of the /ɛ/ vowel, the ICC was calculated. Results for women are presented in Table 3.

In addition to the morning (1M) and evening (1E) recordings on the same day for women, and the morning (2M) and evening (2E) measurements for women one week after the first measurement, on the same day, morning (1M) and one-week measurements were made. According to the repeated test results of all parameters obtained from the /ɛ/ vowel, the intraclass correlation coefficients were found to be statistically significant (p<0.05). In this context, when examining the ICC values obtained for all parameters, repeated measurements were obtained reliably at moderate, good and excellent levels (Table 3).

Table 1. Test-retest results of measurements of the /ʌ/ vowel for women

	1M-1E	2M-2E	1M-2M	1E-2E
Mean-CP	0.706* (95% CI: 00.393-0.859)	0.511* (95% CI: -0.018-0.766)	0.489* (95% CI: -0.055-0.755)	0.717* (95% CI: 0.416-0.864)
Minimum-CP	0.511* (95% CI: 0.013-0.763)	0.172 (95% CI: -0.705-0.602)	0.567* (95% CI: 0.122-0.791)	0.502*(95% CI: -0.027-0.761)
Maximum-CP	0.744* (95% CI: 0.460-0.879	0.529* (95% CI: -0.006-0.777)	0.568* (95% CI: 0.082-0.795)	0.525* (95% CI: -0.015-0.776)
Mean-OP	0.709* (95% CI: 0.395-0.861)	0.511* (95% CI: -0.018-0.766)	0.486* (95% CI: -0.061-0.753)	0.697* (95% CI: 0.377-0.855)
Minimum-OP	0.721* (95% CI: 0.408-0.868)	0.529* (95% CI: -0.006-0.777)	0.562* (95% CI: 0.068-0.793)	0.514* (95% CI: -0.041-0.771)
Maximum-OP	0.559* (95% CI: 0.099-0.787)	0.172 (95% CI: -0.705-0.602)	0.574* (95% CI: 0.133-0.794)	0.504* (95% CI: -0.017-0.761)
Mean F0	0.881* (95% CI: 00.752-00.943)	0.930* (95% CI: 0.844-0.967)	0.901* (95% CI: 0.794-0.953)	0.931* (95% CI: 0.855-0.967)
Minimum F0	0.871* (95% CI:0.730-00.938)	0.818* (95% CI:0.617-0.914)	0.893* (95% CI:0.777-0.949)	0.792* (95% CI:0.568-0.900)
Maximum F0	0.856* (95% CI:0.696-0.932)	-0.024 (95% CI:-1.150-0.513)	0.891* (95% CI:0.766-0.949)	0.033 (95% CI:-0.937-0.529)
Mean jitter	0.647* (95% CI:0.258-0.832)	0.876* (95% CI:0.738-0.941)	0.503* (95% CI:-0.062-0.765)	0.816* (95% CI:0.617-0.912)
Frequency periodicity	0.218 (95% CI:-0.672-0.631)	0.632* (95% CI: 0.232-0.824)	0.444 (95% CI:-0.136-0.732)	0.264 (95% CI:-0.491-0.643)

*p<0.05, CI: confidence interval, CP: closed phase, OP: open phase, F0: basic frequency, 1M: 1st week in the morning, 1E: 1st week in the evening, 2M: 2nd week in the morning, 3E: 3rd week in the evening

Table 2. Test-retest results of measurements of the /ʌ/ vowel for men

	1M-1E	2M-2E	1M-2M	1E-2E
Mean-CP	0.837* (95% CI: 0.656-0.922)	0.672* (95% CI: 0.311-0.844)	0.620* (95% CI: 0.190-0.820)	0.773* (95% CI: 0.523-0.892)
Minimum-CP	0.545* (95% CI: 0.048-0.783)	0.498* (95% CI:-0.068-0.763)	0.341 (95% CI:-0.419-0.690)	0.706* (95% CI: 0.395-0.859)
Maximum-CP	0.596* (95% CI: 0.152-0.808)	0.716* (95% CI: 0.414-0.864)	0.352 (95% CI:-0.368-0.693)	0.755* (95% CI: 0.493-0.882)
Mean-OP	0.307 (95% CI:-0.469-0.672)	0.754* (95% CI: 0.491-0.882)	0.009 (95% CI:-1.119-0.532)	0.768* (95% CI: 0.520-0.889)
Minimum-OP	0.374 (95% CI:-0.282-0.698)	0.770* (95% CI: 0.509-0.891)	0.079 (95% CI:-0.900-0.558)	0.775* (95% CI: 0.512-0.894)
Maximum-OP	-0.225 (95% CI:-1.697-0.430)	0.645* (95% CI: 0.245-0.832)	-0.478 (95% CI:-2.232-0.310)	0.683* (95% CI: 0.335-0.849)
Mean F0	0.932* (95% CI: 0.773-0.974)	0.895* (95% CI: 0.779-0.950)	0.907* (95% CI:0.807-0.956)	0.858* (95% CI: 0.702-0.932)
Minimum F0	0.882* (95% CI: 0.658-0.951)	0.878* (95% CI: 0.746-0.942)	0.844* (95% CI: 0.675-0.926)	0.850* (95% CI: 0.684-0.929)
Maximum F0	0.839* (95% CI: 0.663-0.923)	0.892* (95% CI: 0.773-0.949)	0.802* (95% CI: 0.580-0.906)	0.843* (95% CI: 0.673-0.925)
Mean jitter	0.752* (95% CI: 0.488-0.881)	0.170 (95% CI:-0.722-0.603)	0.140 (95% CI:-0.832-0.593)	0.595* (95% CI: 0.146-0.807)
Frequency periodicity	0.857* (95% CI: 0.699-0.932)	0.448 (95% CI:-0.180-0.740)	0.673* (95% CI: 0.311-0.845)	0.462* (95% CI:-0.107-0.742)

*p<0.05, CI: confidence interval, CP: closed phase, OP: open phase, F0: basic frequency, 1M: 1st week in the morning, 1E: 1st week in the evening, 2M: 2nd week in the morning, 3E: 3rd week in the evening

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In order to calculate the test-retest results of 1M, 1E, 2M and 2E parameters of the /ε/ vowel, the ICC was calculated. Results for men are presented in Table 4.

In addition to the morning (1M) and evening (1E) recordings on the same day for men, and the morning (2M) and evening (2E) recordings one week after the first measurement for women, on the same day for women, the first day morning (1M) and ICCs were statistically significant (p<0.05), according to the repeated test results of all parameters obtained from the /ε/ vowel, according to the recordings taken in the morning (2M) after a week, in the evening (1E) on the first day, and in the evening (2E) one week later. In this context, when examining the ICC values obtained for all parameters, repeated measurements were obtained reliably at moderate, good and excellent levels (Table 4).

In order to calculate the test-retest results of 1M, 1E, 2M and 2E parameters of the /i/ vowel, the ICC was calculated. Results for women are presented in Table 5.

For women, all ICCs calculated except maximum-CP and minimum-OP obtained from the /i/ vowel in accordance with morning (1M) and evening (2E) records on the same day are statistically significant (p<0.05). By examining the ICC values obtained for all other parameters, repeated measurements were obtained reliably at moderate and good levels. One week after the first measurement, all ICCs, except minimum-CP and maximum-OP obtained in the /i/ vowel, were statistically significant, based on the recordings taken in the morning (2M) and evening (2E) on the same day for women. When the ICC values obtained for all other parameters were examined, repeated measurements were obtained with moderate and excellent levels of reliability. All ICCs obtained from the /i/ vowel are statistically significant according to the records taken in the morning (1M) on the first day and in the morning (2M) a week later (p<0.05). By examining the ICC values obtained for all parameters, repeated measurements were obtained reliably at moderate and excellent levels. It can be said that the measurements obtained for these parameters are reliable.

Table 3. Test-retest results of measurements of the /ε/ vowel for women

	1M-1E	2M-2E	1M-2M	1E-2E
Mean-CP	0.735* (95% CI:0.449-0.873)	0.776* (95% CI:0.533-0.893)	0.740* (95% CI:0.455-0.876)	0.676* (95% CI:0.318-0.846)
Minimum-CP	0.759* (95% CI:0.501-0.884)	0.658* (95% CI:0.280-0.838)	0.744* (95% CI:0.472-0.877)	0.538* (95% CI:0.030-0.780)
Maximum-CP	0.641* (95% CI:0.240-0.830)	0.724* (95% CI:0.429-0.868)	0.736* (95% CI:0.443-0.874)	0.707* (95% CI:0.395-0.859)
Mean-OP	0.747* (95% CI:0.466-0.880)	0.813* (95% CI:0.607-0.911)	0.772* (95% CI:0.528-0.891)	0.633* (95% CI:0.239-0.824)
Minimum-OP	0.649* (95% CI:0.265-0.832)	0.768* (95% CI:0.518-0.889)	0.772* (95% CI:0.519-0.892)	0.673* (95% CI:0.329-0.843)
Maximum-OP	0.788* (95% CI:0.559-0.898)	0.647* (95% CI:0.249-0.833)	0.749* (95% CI:0.475-0.880)	0.538* (95% CI:0.038-0.779)
Mean F0	0.881* (95% CI:0.751-0.943)	0.923* (95% CI:0.839-0.963)	0.868* (95% CI:0.726-0.937)	0.915* (95% CI:0.824-0.960)
Minimum F0	0.723* (95% CI:0.427-0.867)	0.918* (95% CI:0.829-0.961)	0.862* (95% CI:0.713-0.934)	0.688* (95% CI:0.359-0.850)
Maximum F0	0.869* (95% CI:0.727-0.937)	0.909* (95% CI:0.811-0.957)	0.856* (95% CI:0.701-0.931)	0.908* (95% CI:0.809-0.956)
Mean jitter	0.924* (95% CI:0.842-0.964)	0.868* (95% CI:0.723-0.937)	0.717* (95% CI:0.398-0.866)	0.788* (95% CI:0.551-0.899)
Frequency periodicity	0.787* (95% CI:0.631-0.849)	0.711* (95% CI:0.596-0.824)	0.563* (95% CI:0.415-0.743)	0.483* (95% CI:0.308-0.598)

*p<0.05, CI: confidence interval, CP: closed phase, OP: open phase, F0: basic frequency, 1M: 1st week in the morning, 1E: 1st week in the evening, 2M: 2nd week in the morning, 3E: 3rd week in the evening

Table 4. Test-retest results of measurements of the /ε/ vowel for men

	1M-1E	2M-2E	1M-2M	1E-2E
Mean-CP	0.812* (95% CI:0.607-0.911)	0.754* (95% CI:0.485-0.883)	0.728* (95% CI:0.430-0.870)	0.511* (95% CI:-0.039-0.769)
Minimum-CP	0.743* (95% CI:0.458-0.878)	0.665* (95% CI:0.288-0.842)	0.525* (95% CI:0.018-0.772)	0.474* (95% CI:-0.115-0.750)
Maximum-CP	0.855* (95% CI:0.696-0.931)	0.701* (95% CI:0.382-0.857)	0.742* (95% CI:0.459-0.877)	0.549* (95% CI:0.051-0.785)
Mean-OP	0.689* (95% CI:0.339-0.853)	0.838* (95% CI:0.657-0.923)	0.728* (95% CI:0.431-0.870)	0.645* (95% CI:0.255-0.831)
Minimum-OP	0.723* (95% CI:0.414-0.869)	0.782* (95% CI:0.544-0.896)	0.742* (95% CI:0.459-0.877)	0.667* (95% CI:0.294-0.842)
Maximum-OP	0.617* (95% CI:0.185-0.819)	0.745* (95% CI:0.469-0.878)	0.527* (95% CI:0.023-0.773)	0.628* (95% CI:0.237-0.821)
Mean F0	0.902* (95% CI:0.796-0.953)	0.909* (95% CI: 0.808-0.957)	0.865* (95% CI:0.716-0.936)	0.869* (95% CI:0.727-0.937)
Minimum F0	0.893* (95% CI:0.777-0.949)	0.899* (95% CI: 0.786-0.952)	0.860* (95% CI:0.704-0.933)	0.856* (95% CI:0.699-0.931)
Maximum F0	0.908* (95% CI:0.807-0.956)	0.909* (95% CI: 0.808-0.957)	0.870* (95% CI:0.726-0.938)	0.875* (95% CI:0.740-0.940)
Mean jitter	0.864* (95% CI:0.715-0.935)	0.892* (95% CI: 0.720-0.918)	0.734* (95% CI: 0.691-0.882)	0.714* (95% CI:0.410-0.863)
Frequency periodicity	0.585* (95% CI:0.117-0.803)	0.616* (95% CI: 0.187-0.818)	0.678* (95% CI:0.331-0.846)	0.715* (95% CI:0.412-0.863)

*p<0.05, CI: confidence interval, CP: closed phase, OP: open phase, F0: basic frequency, 1M: 1st week in the morning, 1E: 1st week in the evening, 2M: 2nd week in the morning, 3E: 3rd week in the evening

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All ICCs calculated except minimum-CP and maximum-OP obtained from the /i/ vowel in accordance with the records obtained in the evening (1E) on the first day and evening (2E) a week later are statistically significant (p<0.05). When examining the ICC values obtained for all other parameters, repeated measurements were obtained reliably at moderate and good levels (Table 5).

In order to calculate the test-retest results of 1M, 1E, 2M and 2E parameters of the /i/ vowel, the ICC was calculated. Results for men are presented in Table 6.

In addition to the morning (1M) and evening (1E) recordings on the same day for men, and the morning (2M) and evening (2E) recordings for women one week after the first measurement, on the same day, in the morning (1M) and one week ICCs were statistically significant (p<0.05), according to the repeated test results of all parameters obtained from the /ε/ vowel, according to the recordings taken in the morning (2M) after the first day and in the evening (1E) on the first day and in the evening (2E) one week later. In this context, when examining the ICC values obtained for all parameters, repeated measurements were obtained reliably at moderate, good and excellent levels (Table 6).

In order to calculate the test-retest results of 1M, 1E, 2M and 2E parameters of the /u/ vowel, the ICC was calculated. Results for women are presented in Table 7.

All ICCs calculated for women, except frequency periodicity obtained from /u/ vowel, were statistically significant (p<0.05), based on the recordings taken in the morning (1M) and evening (1E) on the same day. When the ICC values obtained for all other parameters were examined, repeated measurements were obtained with a good level of reliability. All ICCs calculated for women one week after the first measurement, except for the average jitter obtained from the /u/ vowel in accordance with morning (2M) and evening (2E) records on the same day, are statistically significant (p<0.05). By examining the ICC values

Table 5. Test-retest results of measurements of the /i/ vowel for women

	1M-1E	2M-2E	1M-2M	1E-2E
Mean-CP	0.754* (95% CI:0.479-0.883)	0.683* (95% CI:0.325-0.850)	0.774* (95% CI:0.521-0.893)	0.641* (95% CI:0.239-0.830)
Minimum-CP	0.652* (95% CI:0.260-0.835)	0.441 (95% CI:-0.180-0.734)	0.639* (95% CI:0.250-0.827)	0.418 (95% CI:-0.250-0.726)
Maximum-CP	0.445 (95% CI:-0.165-0.736)	0.742* (95% CI:0.456-0.877)	0.872* (95% CI:0.733-0.939)	0.504* (95% CI:-0.041-0.764)
Mean-OP	0.754* (95% CI:0.478-0.883)	0.690* (95% CI:0.340-0.853)	0.774* (95% CI:0.522-0.893)	0.636* (95% CI:0.224-0.828)
Minimum-OP	0.444 (95% CI:-0.168-0.736)	0.743* (95% CI:0.457-0.878)	0.874* (95% CI:0.736-0.940)	0.497* (95% CI:-0.060-0.761)
Maximum-OP	0.652* (95% CI:0.260-0.835)	0.445 (95% CI:-0.165-0.736)	0.639* (95% CI:0.250-0.827)	0.424 (95% CI:-0.237-0.729)
Mean F0	0.810* (95% CI:0.597-0.910)	0.951* (95% CI:0.897-0.977)	0.842* (95% CI:0.666-0.925)	0.874* (95% CI:0.734-0.940)
Minimum F0	0.662* (95% CI:0.290-0.839)	0.944* (95% CI:0.881-0.973)	0.856* (95% CI:0.697-0.932)	0.653* (95% CI:0.270-0.835)
Maximum F0	0.790* (95% CI:0.556-0.900)	0.944* (95% CI:0.884-0.973)	0.820* (95% CI:0.619-0.914)	0.854* (95% CI:0.694-0.930)
Mean jitter	0.656* (95% CI:0.294-0.834)	0.615* (95% CI:0.211-0.814)	0.745* (95% CI:0.468-0.878)	0.824* (95% CI:0.631-0.916)
Frequency periodicity	0.787* (95% CI:0.558-0.898)	0.711* (95% CI:0.391-0.862)	0.560* (95% CI:-0.063-0.734)	0.583* (95% CI:-0.029-0.747)

*p<0.05; CI: confidence interval, CP: closed phase, OP: open phase, F0: basic frequency, 1M: 1st week in the morning, 1E: 1st week in the evening, 2M: 2nd week in the morning, 3E: 3rd week in the evening

Table 6. Test-retest results of measurements of the /i/ vowel for men

	1M-1E	2M-2E	1M-2M	1E-2E
Mean-CP	0.876* (95% CI:0.741-0.941)	0.827* (95% CI:0.635-0.918)	0.675* (95% CI:0.327-0.844)	0.751* (95% CI:0.474-0.882)
Minimum-CP	0.836* (95% CI:0.653-0.922)	0.823* (95% CI:0.627-0.916)	0.568* (95% CI:0.125-0.790)	0.758* (95% CI:0.477-0.886)
Maximum-CP	0.860* (95% CI:0.708-0.933)	0.828* (95% CI:0.637-0.918)	0.736* (95% CI:0.447-0.874)	0.770* (95% CI:0.512-0.891)
Mean-OP	0.838* (95% CI:0.661-0.923)	0.828* (95% CI:0.635-0.918)	0.627* (95% CI:0.219-0.822)	0.752* (95% CI:0.475-0.882)
Minimum-OP	0.827* (95% CI:0.636-0.918)	0.828* (95% CI:0.637-0.918)	0.706* (95% CI:0.380-0.860)	0.770* (95% CI:0.512-0.891)
Maximum-OP	0.828* (95% CI:0.637-0.918)	0.823* (95% CI:0.627-0.916)	0.567* (95% CI:0.119-0.791)	0.758* (95% CI:0.477-0.886)
Mean F0	0.920* (95% CI:0.832-0.962)	0.905* (95% CI:0.801-0.955)	0.893* (95% CI:0.775-0.949)	0.863* (95% CI:0.712-0.935)
Minimum F0	0.923* (95% CI:0.838-0.963)	0.902* (95% CI:0.794-0.953)	0.891* (95% CI:0.771-0.948)	0.855* (95% CI:0.697-0.931)
Maximum F0	0.920* (95% CI:0.834-0.962)	0.911* (95% CI:0.814-0.958)	0.900* (95% CI:0.790-0.953)	0.870* (95% CI:0.728-0.938)
Mean jitter	0.901* (95% CI:0.792-0.953)	0.825* (95% CI:0.630-0.917)	0.866* (95% CI:0.721-0.936)	0.802* (95% CI:0.588-0.905)
Frequency periodicity	0.687* (95% CI:0.335-0.852)	0.651* (95% CI:0.266-0.834)	0.650* (95% CI:0.263-0.833)	0.526* (95% CI:0.036-0.771)

*p<0.05; CI: confidence interval, CP: closed phase, OP: open phase, F0: basic frequency, 1M: 1st week in the morning, 1E: 1st week in the evening, 2M: 2nd week in the morning, 3E: 3rd week in the evening

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obtained for all other parameters, repeated measurements were obtained with low, moderate, good and excellent reliability. All ICCs calculated except mean-OP, minimum-OP and frequency periodicity obtained from /u/ vowel in accordance with the records taken in the morning (1M) on the first day and in the morning (2M) a week later are statistically significant (p<0.05). By examining the ICC values obtained for all other parameters, repeated measurements were obtained with low, moderate and good reliability. All ICCs calculated except the average jitter obtained from the /u/ vowel in accordance with the records taken in the evening (1E) on the first day and in the evening (2E) a week later are statistically significant (p<0.05). When examining the ICC values obtained for all other parameters, repeated measurements were obtained as moderate and good reliable (Table 7).

To calculate the test-retest results of 1M, 1E, 2M and 2E parameters of the /u/ vowel, the ICC was calculated. Results for men are presented in Table 8.

For men, all ICCs calculated except minimum-CP, maximum-OP and average Jitter obtained in /u/ vowel according to morning (1M) and evening (1E) records on the same day are statistically significant (p<0.05). By examining the ICC values obtained for all other parameters, repeated measurements were obtained with moderate and good reliability. All ICCs obtained from the /u/ vowel are statistically significant according to the records taken in the morning (2M) and evening (2E) on the same day for men one week after the first measurement (p<0.05). By examining the ICC values obtained for all parameters, it can be said that repeated measurements are moderately and well reliable. All ICCs calculated except the average jitter obtained from the /u/ vowel in accordance with the records taken in the morning (1M) on the first day and in the morning (2M) a week later are statistically significant (p<0.05). When the ICC values obtained for all other parameters were examined, repeated measurements were obtained with moderate and good reliability. All ICCs, except maximum F0

Table 7. Test-retest results of measurements of the /u/ vowel for women

	1M-1E	2M-2E	1M-2M	1E-2E
Mean-CP	0.857* (95% CI:0.701-0.932)	0.841* (95% CI:0.661-0.925)	0.827* (95% CI:0.640-0.917)	0.889* (95% CI:0.770-0.947)
Minimum-CP	0.798* (95% CI:0.573-0.904)	0.767* (95% CI:0.516-0.889)	0.780* (95% CI:0.535-0.896)	0.842* (95% CI:0.671-0.924)
Maximum-CP	0.734* (95% CI:0.441-0.873)	0.761* (95% CI:0.506-0.885)	0.723* (95% CI:0.428-0.867)	0.807* (95% CI:0.596-0.908)
Mean-OP	0.843* (95% CI:0.670-0.925)	0.492* (95% CI:-0.019-0.753)	0.300 (95% CI:-0.418-0.661)	0.884* (95% CI:0.758-0.944)
Minimum-OP	0.741* (95% CI:0.456-0.877)	0.459* (95% CI:-0.093-0.737)	0.243 (95% CI:-0.529-0.633)	0.786* (95% CI:0.551-0.898)
Maximum-OP	0.759* (95% CI:0.492-0.886)	0.473* (95% CI:-0.085-0.747)	0.468* (95% CI:-0.111-0.746)	0.849* (95% CI:0.686-0.928)
Mean F0	0.888* (95% CI:0.763-0.947)	0.938* (95% CI:0.870-0.971)	0.880* (95% CI:0.746-0.943)	0.857* (95% CI:0.698-0.932)
Minimum F0	0.885* (95% CI:0.758-0.946)	0.941* (95% CI:0.876-0.972)	0.880* (95% CI:0.747-0.943)	0.861* (95% CI:0.706-0.934)
Maximum F0	0.885* (95% CI:0.756-0.945)	0.937* (95% CI:0.866-0.970)	0.889* (95% CI:0.765-0.947)	0.857* (95% CI:0.697-0.932)
Mean jitter	0.722* (95% CI:0.422-0.867)	0.415 (95% CI:-0.229-0.722)	0.859* (95% CI:0.703-0.933)	0.232 (95% CI:-0.497-0.621)
Frequency periodicity	0.437 (95% CI:-0.133-0.726)	0.576* (95% CI:0.094-0.800)	0.325 (95% CI:-0.338-0.669)	0.507* (95% CI:-0.053-0.767)

*p<0.05; CI: confidence interval, CP: closed phase, OP: open phase, F0: basic frequency, 1M: 1st week in the morning, 1E: 1st week in the evening, 2M: 2nd week in the morning, 3E: 3rd week in the evening

Table 8. Test retest results of measurements of the /u/ vowel for men

	1M-1E	2M-2E	1M-2M	1E-2E
Mean-CP	0.857* (95% CI:0.701-0.932)	0.841* (95% CI:0.661-0.925)	0.827* (95% CI:0.640-0.917)	0.889* (95% CI:0.770-0.947)
Minimum-CP	0.798* (95% CI:0.573-0.904)	0.767* (95% CI:0.516-0.889)	0.780* (95% CI:0.535-0.896)	0.842* (95% CI:0.671-0.924)
Maximum-CP	0.734* (95% CI:0.441-0.873)	0.761* (95% CI:0.506-0.885)	0.723* (95% CI:0.428-0.867)	0.807* (95% CI:0.596-0.908)
Mean-OP	0.843* (95% CI:0.670-0.925)	0.492* (95% CI:-0.019-0.753)	0.300 (95% CI:-0.418-0.661)	0.884* (95% CI:0.758-0.944)
Minimum-OP	0.741* (95% CI:0.456-0.877)	0.459* (95% CI:-0.093-0.737)	0.243 (95% CI:-0.529-0.633)	0.786* (95% CI:0.551-0.898)
Maximum-OP	0.759* (95% CI:0.492-0.886)	0.473* (95% CI:-0.085-0.747)	0.468* (95% CI:-0.111-0.746)	0.849* (95% CI:0.686-0.928)
Mean F0	0.888* (95% CI:0.763-0.947)	0.938* (95% CI:0.870-0.971)	0.880* (95% CI:0.746-0.943)	0.857* (95% CI:0.698-0.932)
Minimum F0	0.885* (95% CI:0.758-0.946)	0.941* (95% CI:0.876-0.972)	0.880* (95% CI:0.747-0.943)	0.861* (95% CI:0.706-0.934)
Maximum F0	0.885* (95% CI:0.756-0.945)	0.937* (95% CI:0.866-0.970)	0.889* (95% CI:0.765-0.947)	0.857* (95% CI:0.697-0.932)
Mean jitter	0.722* (95% CI:0.422-0.867)	0.415 (95% CI:-0.229-0.722)	0.859* (95% CI:0.703-0.933)	0.232 (95% CI:-0.497-0.621)
Frequency periodicity	0.437 (95% CI:-0.133-0.726)	0.576* (95% CI:0.094-0.800)	0.325 (95% CI:-0.338-0.669)	0.507* (95% CI:-0.053-0.767)

*p<0.05; CI: coefficient interval, CP: closed phase, OP: open phase, F0: basic frequency, 1M: 1st week in the morning, 1E: 1st week in the evening, 2M: 2nd week in the morning, 3E: 3rd week in the evening

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obtained from /u/ vowel, were statistically significant (p<0.05), based on the recordings taken in the evening (1E) on the first day and in the evening (2E) one week later. When ICC values obtained for all other parameters were examined, repeated measurements were obtained with moderate and good reliability (Table 8).

During the phonations, only the frequency periodicity parameter of the vowels /ʌ/, /ɛ/ and /i/ differs statistically significantly (p=0.09; p=0.00 and p=0.002, respectively) according to gender. When the averages were examined, it was determined that the measurements of women were higher than men in all parameters with significant differences. No statistically significant difference was found according to gender in other parameters of the measurement (Table 9).

DISCUSSION

If the studies examining the measurement reliability of acoustic-aerodynamic parameters obtained at the end of repeated tests are examined in more detail; Leeper and Graves (10) measured translaryngeal airflow, air pressure, and laryngeal airway resistance twice a day (morning and evening) for two consecutive days in 15 female participants through repeated tests and found no significant difference between days or within days. Wilson and Leeper (11), in their study including 15 male and 15 female participants, reported that there was no significant difference in the test-retest results for laryngeal resistance, mean airflow and subglottal pressure parameters as a result of the measurements they made on two consecutive days. Lee et al. (12), reported test-retest data (28 days apart) for various acoustic and aerodynamic measurements such as volume, airflow rate, and maximum phonation time and showed no significant difference between the measurements. Garrison (13) evaluated the test-retest reliability of various aerodynamic measurements as a result of tests performed at intervals of ten minutes and one week and stated that there was no significant test-retest difference between the parameters measured at different times. In another study, 30 female and 30 male participants stated that the aerodynamic parameters obtained with the Kay-PENTAX Phonatory Aerodynamic System device were good and excellent in the reliability of repeated tests measured one week apart (14).

Table 9. Comparison of EGG parameters obtained from /i/, /u/,/ɛ/ and /ʌ/ vowel phonation by gender (Based on 1M measurement)

	Female	Male		
	$\overline{X}$±ss	$\overline{X}$±ss	[a]t	p
Mean-CP/ʌ/	46.48±2.88	45.18±4.07	1.419	0.162
Mean-OP/ʌ/	53.52±2.89	53.89±4.98	0.355	0.724
Mean jitter/ʌ/	0.45±0.27	0.43±0.33	0.209	0.835
Frequency periodicity/ʌ/	31.72±8.30	25.16±10.28	2.719*	0.009*
Mean-CP/ɛ/	46.21±4.18	45.45±3.97	0.722	0.473
Mean-OP/ɛ/	53.79±4.19	54.55±3.98	0.717	0.476
Mean jitter/ɛ/	0.45±0.20	0.38±0.28	1.070	0.289
Frequency periodicity/ɛ/	35.01±8.55	24.81±7.91	4.797*	0.000*
Mean-CP/i/	45.70±4.38	46.88±4.70	1.007	0.318
Mean-OP/i/	54.30±4.38	53.43±4.47	0.757	0.452
Mean jitter/i/	0.45±0.21	0.33±0.32	1.706	0.093
Frequency periodicity/i/	33.65±7.43	24.44±7.74	3.171*	0.002*
Mean-CP/u/	45.27±3.47	47.03±4.54	1.684	0.097
Mean-OP/u/	54.87±3.43	52.99±4.55	1.804	0.076
Mean jitter/u/	0.37±0.17	0.29±0.19	1.886	0.064
Frequency periodicity/u/	27.84±8.35	25.48±8.22	1.100	0.276

p<0.05 SD: standard deviation, $\overline{X}$: average, [a]:T-test values, CP: closed phase, OP: open phase, F0: basic frequency, 1M: 1st week in the morning, EGG: electroglottography

Unlike the studies mentioned above to prove test-retest reliability, Higgins et al. (15) examined aerodynamic and electroglottographic reliability through variation coefficients among 21 participants (11 male and 10 female) recorded over four non-consecutive days. As a result, the authors noted that there may be no respiratory control in individuals whose subglottal pressures vary by more than 15% between repeated measurements. In addition, 10% more than the abduction and fundamental frequency that vary with the rate of 25% (for syllable repetition) showing more variability caused by tissue damage or a possible situations of glottal air flow may reflect a disorder of vocal fold neuropathology stated that. In this context, the researchers stated that the open phase ratio studied as a result of repeated measurements made at different times was one of the parameters that showed the least change, while the average phonatory airflow was one of the parameters that showed the most change (15). On the other hand, some researchers stated that values related to the contact area of the vocal fold gave more reliable results (1,16).

Frequency perturbation parameters such as percent jitter (Jitt), relative average perturbation, pitch perturbation coefficient (PPQ), amplitude perturbation coefficient (Shim), and amplitude perturbation coefficient (APQ), which are different techniques, are often used for pathological voice identification. The EGG technique used in this context measures the motion phases of the vocal fold based on the principle of electrical conductivity of the tissues. It shows the data in the form of a Lx wave reflected on the screen, while it can also express the percentage of available glottal phases in this wave in numerical numbers. It also offers clinicians basic frequency and frequency-dependent perturbation values, as it electrically measures the movement of the vocal fold. In contrast, an acoustic measurement is performed only through a microphone and software that will analyze the voice. But in this case, the information about the movement and/or movement regularity of the vocal fold is measured in-directly, as in the EGG measurement. Because the voice recorded through the microphone for analysis is affected by the different resonance properties of the vocal tract (20-23). In the light of this information,

some researchers have suggested that EGG measurements may be more efficient in detecting voice disorders and monitoring the therapy/treatment process (23-25). As the reason for this, the researchers stated that the information on vocal fold contact rates to be obtained at the end of EGG measurements could be an effective method in the classification of voice disorders, and they also showed that perturbation parameters related to vocal stability can also be obtained using EGG (24).

EGG studies show that young adult males tend to exhibit higher rates of vocal contact than young adult females (26-28). In addition, in the study conducted by Paul et al. (29), it was reported that a similar situation is in question in Indian young adult men compared to women. This coincides with the notion that a decrease in fundamental frequency may result in an increase in the off-phase ratio. In contrast, Orlikoff et al. (30) reported similar closed-phase values for males and females with healthy voices during prolonged vowel production. Similarly, in a study conducted by Faria et al. (31), it was reported that there was no significant difference between men and women in the Brazilian Portuguese speaking population. In our study, when we compared the vowels /i/, /u/, /ɛ/ and /ʌ/ by gender, there was no significant difference between the sexes in any vowel phonation in terms of mean OP and CP values in accordance with the literature. In other words, similar mean CP and OP values were obtained for both genders.

The periodicity factor determines the periodicity of the voice, and in general, a value greater than 20 indicates a high periodicity; a value less than 20 indicates a low degree of periodicity and thus a potential problem with the evaluation with continuous vowel phonation (32). In this context, a statistically significant difference between men and women was obtained in all other continuous vowel phonations except /u/ vowel. When the average values of this parameter were examined, women showed a high level of frequency periodicity values compared to men.

In addition, when looking at the mean values of frequency periodicity for women, regardless of statistical significance, there is an order of /ɛ/, /i/, /ʌ/, /u/, respectively, from largest to smallest; For men, again, when the average values of frequency periodicity were examined without making any significant difference, it was seen that the values of all vowels were very close to each other.

When the periodicity parameters of the participants were examined individually within the mean value and standard deviation data, no frequency periodicity value of the participants was found below the limit of 20. This is actually an expected result, given the criteria for participants to have a healthy voice, while it can also be interpreted as a parameter that confirms the voice health of participants.

It is noteworthy that the frequency periodicity value of /ɛ/, /ʌ/ and /i/ phonations in female individuals was significantly higher than in men when the values were examined. In addition, it was observed that the periodicity value of the front vowels in female individuals was obtained as the average value of the back vowels, and the voice with the most periodicity was obtained as the /ɛ/ vowel.

By examining the ICC values in the parameters of repeated measurements at different times over four different vowel phonations, there are statistically significant and non-significant parameters. Statistically significant parameters show that EGG measurements that repeat at different times are reliable, not affected by variations of voice that are likely to be observed during the day, but are not pathological, while parameters that are not statistically significant show that EGG measurements that repeat at different times are not reliable. In this context, in our study, all parameters of the /ɛ/ vowel obtained by EGG measurement and mapped as 1M-1E, 2M-2E, 1M-2M and 1E-2E in terms of time for men and women, and the /i/ vowel as a situation observed only in males. When the repeated measurement results of all EGG parameters were examined, ICC values were obtained as statistically significant. In summary, when the ICC values obtained for all parameters were examined in this study, it was found that repeated measurements were reliable at moderate, good and excellent levels for /ɛ/ vowel in common for both genders.

In order for a measurement to be reliable in the clinical area, the results of the soon-repeated test should not be affected by daily non-pathological variations (14). In this context, vowels that gave statistically significant levels of moderate, good and excellent ICC results in each parameter in all repeated measurements were found to be /ɛ/ vowels for women and /ɛ/ and /i/ vowels for men. In addition, EGG's repeated measurements eventually gave the most frequently non-significant ICC values, while the vowel vowel with the lowest reliability rates was determined as /ʌ/ vowel in both genders.

The reason for the low level of reliability in the /ʌ/ vowel may be due to the fact that the tongue was positioned low and backward in the production of this vowel. EGG measurement is performed by fastening a pair of superficial electrodes to both laminae of the thyroid cartilage, which is palpable in the neck region, with a Velcro strap, and according to the physical connection hypothesis, the tongue, hyoid bone and larynx are interconnected by muscle and connective tissue. While the forward movement of the tongue indirectly causes the hyoid bone to move forward, pulling the larynx upward, it also increases in F0 with increasing tension in the vocal folds, and vice versa (7). In this context, while the forward movement of the hyoid bone in the vowels where the tongue is positioned forward may have caused the larynx to be positioned anteriorly and upwards, acting within the framework of the physical connection hypothesis, while the vowel vowels in which the tongue is positioned behind may pull the larynx down and backward, reducing its prominence in the neck region. As a result, it can help us conclude that the test-retest reliability of vowel vowels with the front and/or high position of the tongue is higher than vowel vowels with the back and/or low position of the tongue, as it causes EGG electrodes to better grasp the

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surface of the larynx. According to the ROC analysis results of EGG parameters obtained from different vowel phonations, the researchers found that mean jitter and periodicity parameters showed higher differential diagnosis performance in front vowels (/ɛ/ and /i/) compared to back vowels (/ʌ/ and /u/) (33) and this is a finding that confirms our research. In our study, the periodicity parameter of the /ɛ/ vowel resulted in the highest value compared to the other vowels in terms of mean value; at the same time, the vowels obtained by placing the tongue in the anterior position of the periodicity parameter in terms of the mean value resulted in higher values than the vowels produced by the placement of the tongue in the posterior position. As a matter of fact, this is one of the findings that can be another predictor of the reliability of EGG evaluations performed with front vowels. In this context, both our ICC results and the results obtained from the frequency periodicity parameter confirm each other in this direction.

Study Limitations

Additional predictive statistical measurements such as standard error measurement, minimum error and variation coefficient were not calculated in this study. Perceptual evaluation of healthy voice was carried out only by the researcher conducting the recording process, and in this context, additional statistical analyses such as interpersonal measurement reliability for perceptual voice evaluation parameters were not available. Criterion in the selection of participants; EGG periodicity parameter is less than 20.

CONCLUSION

As a result, in EGG measurements obtained by continuous phonation of /ɛ/ vowel for both genders and /i/ vowel for only males, moderate, good and excellent ICC values were obtained in all measurement parameters examined and between the paired measurement times.

This shows that the use of the /ɛ/ vowel for both genders, especially in the recordings taken with EGG, can give more consistent results in terms of test-retest, regardless of the recording time, compared to other vowels.

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Ethics Committee Approval: For the study, Ethics Committee approval was obtained from Üsküdar University Non-interventional Research Evaluation Board (decision no: 61351342-/2019-216, date: 25.04.2019).

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REFERENCES

1. Baken RJ. Electroglottography. J Voice 1992; 6: 98-110.
2. Herbst CT. Electroglottography - sn Update. J Voice 2020; 34: 503-26.
3. Maccallum JK, Zhang Y, Jiang JJ. Vowel selection and its effects on perturbation and nonlinear dynamic measures. Folia Phoniatr Logop 2011; 63: 88-97.
4. Higgins MB, Netsell R, Schulte L. Vowel-related differences in laryngeal articulatory and phonatory function. J Speech Lang Hear Res 1998; 41: 712-24.
5. Orlikoff RF. Vocal stability and vocal tract configuration: an acoustic and electroglottographic investigation. J Voice 1995; 9: 173-81.
6. Kent RD. Vocal tract acoustics. Journal of Voice 1993; 7: 97-117.
7. Honda K. Relationship between pitch control and vowel articulation. Haskins Laboratories Status Report on Speech Research 1983; 73: 269-82.
8. Lin E, Jiang J, Noon SD, Hanson DG. Effects of head extension and tongue protrusion on voice perturbation measures. J Voice 2000; 14: 8-16.
9. Howard DM. The real and the non-real in speech measurements. Med Eng Phys. 2002; 24: 493-500.
10. Leeper HA Jr, Graves DK. Consistency of laryngeal airway resistance in adult women. J Commun Disord 1984; 17: 153-63.
11. Wilson JV, Leeper HA. Changes in laryngeal airway resistance in young adult men and women as a function of vocal sound pressure level and syllable context. J Voice 1992; 6: 23545.
12. Lee L, Stemple JC, Kizer M. Consistency of acoustic and aerodynamic measures of voice production over 28 days under various testing conditions. J Voice 1999; 13: 477-8.
13. Garrison CR. Repeatability of aerodynamic measurements of voice (dissertation) Miami: Miami Univ. 2009.
14. Awan SN, Novaleski CK, Yingling JR. Test-retest reliability for aerodynamic measures of voice. J Voice 2013; 27: 674-84.
15. Higgins MB, Netsell R, Schulte L. Aerodynamic and electroglottographic measures of normal voice production: intrasubject variability within and across sessions. J Speech Hear Res 1994; 37: 38-45.
16. Winstanley S, Wright H. Vocal fold contact area patterns in normal speakers: an investigation using the electrolaryngograph interface system. Br J Disord Commun 1991; 26: 25-39.
17. Demirhan E, Unsal EM, Yilmaz C, Ertan E. Acoustic voice analysis of young Turkish speakers. J Voice 2016; 30: 378.e21-5.
18. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979; 86: 420-8.
19. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016; 15: 155-63.
20. Avelino H. Acoustic and electroglottographic analyses of nonpathological, nonmodal phonation. J Voice 2010; 24: 270-80.
21. Bier SD, Watson CI, McCann CM. Using the perturbation of the contact quotient of the EGG waveform to analyze age differences in adult speech. J Voice 2014; 28: 267-73.
22. Konstantopoulos K, Vikelis M, Seikel JA, Mitsikostas DD. The existence of phonatory instability in multiple sclerosis: an acoustic and electroglottographic study. Neurol Sci 2010; 31: 259-68.
23. Yamout B, Al-Zaghal Z, El-Dahouk I, Farhat S, Sibai A, Hamdan AL. Mean contact quotient using electroglottography in patients with multiple sclerosis. J Voice 2013; 27: 506-11.
24. Villafuerte-Gonzalez R, Valadez-Jimenez VM, Sierra-Ramirez JA, Ysunza PA, Chavarria-Villafuerte K, Hernandez-Lopez X. Acoustic analysis and electroglottography in elite vocal performers. J Voice 2017; 31: 391.e1-6.
25. Hosokawa K, Ogawa M, Hashimoto M, Inohara H. Statistical analysis of the reliability of acoustic and electroglottographic perturbation parameters for the detection of vocal roughness. J Voice 2014; 28: 263. e9-263.e16.
26. Higgins MB, Saxman JH. A comparison of selected phonatory behaviors of healthy aged and young adults. J Speech Hear Res 1991; 34: 1000-10.
27. Ma EP, Love AL. Electroglottographic evaluation of age and gender effects during sustained phonation and connected speech. J Voice 2010; 24: 146-52.
28. Awan SN, Awan JA. The effect of gender on measures of electroglottographic contact quotient. J Voice 2013; 27: 433-40.
29. Paul N, Kumar S, Chatterjee I, Mukherjee B. Electroglottographic parameterization of the effects of gender, ævowel and phonatory

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registers on vocal fold vibratory patterns: an Indian perspective. Indian J Otolaryngol Head Neck Surg 2011; 63: 27-31.

30. Orlikoff RF, Baken RJ, Kraus DH. Acoustic and physiologic characteristics of inspiratory phonation. J Acoust Soc Am 1997; 102: 1838-45.
31. Faria BS, Oliveira KV, Silva JP, Reis C, Ghio A, Gama AC. Electroglottography of speakers of Brazilian Portuguese through Objective Multiparameter Vocal Assessment (EVA). Braz J Otorhinolaryngol 2012; 78: 29-34.
32. Pentax K. (2013). Reel-Time EGG Analysis, model 6103. Software instruction Manual, Issue F. Lincoln Park, NJ, USA.
33. Yılmaz G. Farklı ünlü fonasyonlarına ilişkin akustik ve elektroglottografik ölçüm parametrelerinin karşılaştırılması ve bu parametrelere ait özgüllük ve duyarlılık değerlerinin belirlenmesi. Yüksek Lisans Tezi. Üsküdar Üniversitesi, 2020.

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Functional and Radiological Outcomes of Intra-articular Calcaneus Fractures: A Comparison Between Accompanying Skeletal Injuries and Isolated Fractures

Esra Çirci, Alican Barış

University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Turkey

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ABSTRACT

Objective: This study aimed to compare between accompanying skeletal injuries and isolated fractures in terms of the functional and radiological results of treating intra-articular displaced calcaneus fractures with calcaneal locking compression plate.

Methods: Thirty-three patients with displaced intra-articular fracture of the calcaneus were included in the study. All patients were operated on using the lateral extensile approach with open reduction and internal fixation technique with a follow-up of more than four years. Böhler angle and crucial angle of Gissane were documented on preoperative and post-operative radiographs. The American Orthopaedic Foot and Ankle Society (AOFAS) hindfoot scores were evaluated.

Results: There was no significant difference between patients with and without accompanying injuries in terms of the duration of follow-up (p=0.646), complication rate (p=0.797) and final outcome distribution (p=0.309). In patients with no additional injuries, AOFAS scores (p=0.036) and post-operative Böhler angle (p=0.007) were significantly higher. The post-operative Gissane angle did not significantly differ between the two groups (p=0.241).

Conclusion: In our study, we concluded that the accompanying injuries in the calcaneus will adversely affect the radiological results and functional outcomes. During the management of calcaneus fractures, the accompanying injuries and their negative effects on the healing process should be taken into consideration.

Keywords: Calcaneus fracture, bilaterally, accompanied injury, radiological evaluation, functional evaluation

INTRODUCTION

The calcaneus is the most commonly fractured tarsal bone, representing 60% of all tarsal fractures and nearly 2% of all fractures (1). The subtalar joint is often involved at a rate of approximately 75%. In the young adult population, most intra-articular calcaneus fractures caused by axial loading result from traffic accidents or falls from a height and often have associated damages. An axial load power affects the posterior facet of the calcaneus through the talus, and shear powers are focused through the posterior facet toward the medial wall of the calcaneus (2).

The computerised tomography scans describe comminution and displacement of the posterior facet. Sanders classification is used to assess intra-articular calcaneus fractures, owing to its precision regarding the location and number of fracture lines through the posterior facet (3).

ORCID IDs of the authors: E.Ç. 0000-0001-6515-4324; A.B. 0000-0001-6031-6777.

Corresponding Author: Esra Çirci,
E-mail: esracirci@hotmail.com

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Calcaneal fractures are a considerable challenge for orthopedists because the displays of the fracture are various, and complications commonly occur. Anatomical reduction with stable fixation is the treatment of choice for displaced intra-articular fractures (4). The lateral approach is commonly used for open reduction and internal fixation (ORIF) of complex calcaneus fractures. This exposure provides anatomical reduction of the subtalar joint, restoration of the calcaneal morphology and stable locking compression plate fixation; therefore, early range of motion is encouraged. Anatomical reduction and stable fixation to avoid complications improve the functional outcomes, decrease morbidity and shorten recovery time (5).

Calcaneus fractures are severe high-energy injuries with the potential for considerable morbidity. Accompanying injuries and bilateral calcaneal fractures should be considered in the diagnosis and treatment process. The socioeconomic burden of calcaneus fractures is significant.

This study aimed to compare between accompanying skeletal injuries and isolated fractures in terms of the functional and radiological results of the treatment of intra-articular displaced calcaneus fractures with calcaneal locking compression plate. Our hypothesis was that ORIF of displaced intra-articular calcaneal fractures in patients without additional injuries would result in better outcomes.

METHODS

This study was approved by the Clinical Research Ethics Committee of İstanbul Training and Research Hospital (decision no: 886, date: 25.11.2016), and informed consent was obtained from the patients.

All patients admitted from January 2011 to November 2015 with a diagnosis of unilateral or bilateral displaced intra-articular fractures of the calcaneus were considered for inclusion. A consecutive series of 33 patients with displaced intra-articular fractures were treated by open reduction through an extended lateral approach and internal fixation with a locking compression plate and followed for more than four years post-operatively.

The study included three (9.1%) females and 30 (90.9%) males. The average age of the patients at the time of surgery was 38.5±10.6 years (range: 20-56). Both calcanei were injured in eight male patients (three of them had accompanying injuries, and five of them had isolated bilateral calcaneus fractures).

The exclusion criteria were patients who were treated conservatively and the lack of surgical conditions. Patients with no intra-articular calcaneus fractures, those with open fractures, those who had a previous foot or ankle surgery, accompanying neural or vascular pathology, neuropathic foot, and pathologic fractures of the calcaneus, those younger than 18 years and those unable to come for follow-ups were excluded from this study.

For the precise assessment of intra-articular calcaneus fractures, preoperative conventional radiographs and computerised tomography with three-dimensional analysis were used. Sanders classification is used to assess intra-articular calcaneus fractures, owing to its precision regarding the location and number of fracture lines through the posterior facet. Fractures were categorised according to Sanders classification as follows. Type I fractures include all minimally displaced (≤2 mm) articular fractures, regardless of the number of fracture lines and fragments present. Type II fractures are displaced two-part fractures of the posterior facet with one primary fracture line that can be accompanied by one or more accessory fracture lines that do not involve the posterior articular facet. Type III fractures include three-part fractures of the posterior facet from two primary fracture lines commonly accompanied by a central area of depression. Type IV fractures involve three or more primary fracture lines, resulting in four or more articular fragments with severe comminution (3).

Surgery was carried out after the swelling diminished and skin wrinkles emerged. The average duration between the injury and surgery was five days (range: 2-11 days). Antibiotic prophylaxis was administered. The operations were performed under spinal anaesthesia with the patient in the lateral decubitus position, and a tourniquet was applied.

The surgery was performed using the lateral extensile approach (Figure 1). The full-thickness skin flap was retracted using one K-wire in the fibula and two in the talus. Anatomical reduction was achieved, and the Böhler and Gissane angles were restored. A calcaneal plate (TST® locking calcaneus plate) was used (Figure 2). To maintain the height of the posterior facet, calcium phosphate cement (NeoCement®) and allograft cancellous chips (Gencure®) were supplemented according to the surgeon's preference in the presence of bone defects. The skin was closed using Ethilon 3.0. A wound drainage was used. A pressure bandage was applied for a few days.

Sutures were removed three weeks after the operation. Motion exercises were avoided during that time to lessen the shear forces under the flap. Protection was supplied using a removable posterior splint. Then, active range of motion of the ankle and subtalar joint was started. No weight-bearing was approved for the initial six to eight weeks, and then, gradual weight-bearing was introduced. Full weight-bearing was allowed after 12 weeks.

Patients were divided into two groups according to the presence of accompanying skeletal injuries.

Patients were asked to complete a questionnaire to calculate the outcome score, the disease-specific American Orthopaedic Foot and Ankle Society (AOFAS) hindfoot score for patient satisfaction, at the last follow-up (6). Based on the AOFAS hindfoot score, a total score ranging from 90 to 100 points was considered 'excellent', a range from 75 to 89 points was considered 'good', a range from 50 to 74 points was considered 'fair' and a score below 49 points was considered 'poor'.

Böhler angle and crucial angle of Gissane were documented on preoperative and post-operative radiographs at the last follow-

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up. The comparison views were used for surgical guidance in restoring normal anatomy in the contralateral foot in the unilateral cases.

Statistical Analysis

For the descriptive statistics of the data, mean, standard deviation, frequency, median lowest and highest values and ratio values were used. The distribution of the variables was measured using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for the analysis of quantitative independent data. The Wilcoxon test was used for the analysis of the quantitative-dependent data. The chi-square test was used for the analysis of the qualitative independent data. Fisher's Exact test was used when the chi-square test conditions were not provided. The data were analysed using the Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc. Chicago, IL). A p value less than 0.05 was considered statistically significant.

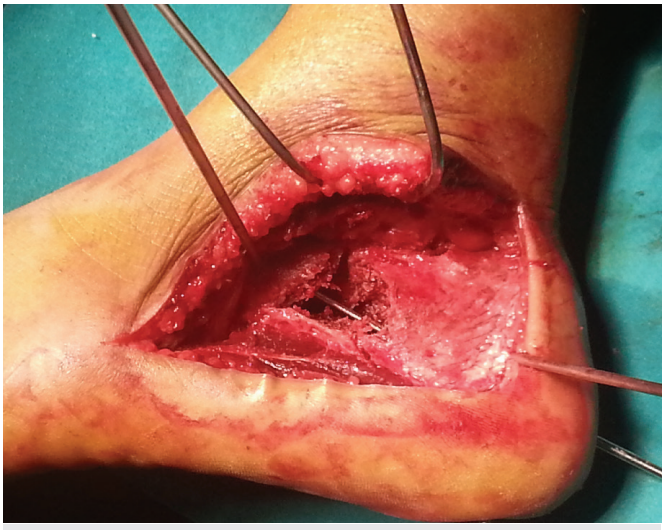

Figure 1. Lateral extensile approach

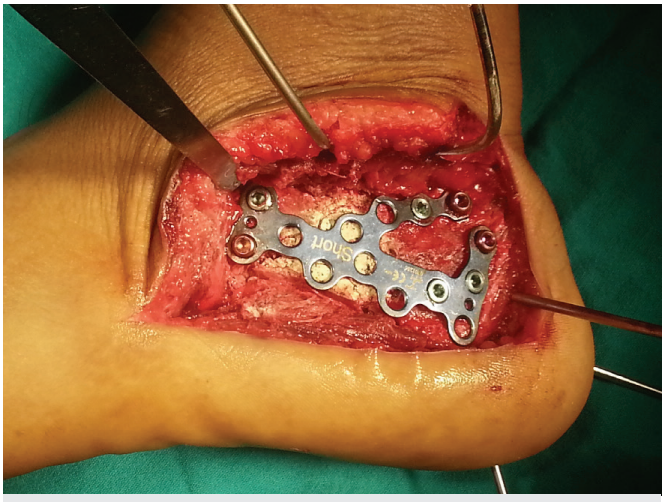

Figure 2. Placement of the low-profile locking anatomic plates with grafting

RESULTS

The mechanism of trauma is summarised in Table 1. The mean follow-up after surgery was 66.7±16.7 months (range: 48-96 months). According to Sanders classification, 17 fractures (41.5%) were Sanders II, 14 fractures (34.1%) were Sanders III and 10 fractures (24.4%) were Sanders IV.

Accompanying injuries were present in 14 patients (42.4%): Four patients had ipsilateral lower leg fracture; one patient, vertebra fracture (the patient with bilateral calcaneus fracture); three patients, vertebra and ipsilateral lower leg fracture (two of these patients with bilateral calcaneus fracture); one patient, upper extremity and lower leg fracture; five patients, isolated bilateral calcaneus fractures (without other injuries).

A total of 11 patients (33.3%) had complications in this study. Six patients (18.2%) had Sudeck's atrophy. Four patients (12.1%) had superficial wound infection and delayed healing. One patient (3.0%) had screw cut-out. The screw was removed, and acceptable functional improvement was achieved. The patient's complaints regressed.

Sudeck's atrophy developed six to fifteen weeks after the operation in six patients. Physical therapy exercises were increased. Hot and cold pack applications, nonsteroidal anti-inflammatory drugs, administration of calcium and vitamin D were initiated. After the treatment, all patients recovered fully.

Post-operative superficial wound infection and delayed healing were present in four patients. They were treated with local wound care, debridement, changing dressing daily with povidone iodine and administration of intravenous antibiotics (first generation cephalosporin) for two weeks according to the bacterial culture results. One patient developed skin flap necrosis at the corner of the lateral L-shaped incision. Debridement of the necrotic tissue yielded a good result.

Thirteen patients (39.4%) recovered normally; eleven patients (33.4%) recovered with subtalar arthrosis; nine (27.3%) patients recovered with mild subtalar arthrosis.

There were no significant differences between those who had accompanies injuries and those who did not in terms of age (p=0.345), sex (p=0.539), duration of follow-up (p=0.646), complication rate (p=0.797) and final outcome distribution (p=0.309).

The median AOFAS hindfoot score was 84.4±9.0 points (range: 68-97) at the last follow-up. According to this score, 13 patients (39.4%) had excellent scores, 11 patients (33.3%) had good results and nine patients (27.3%) had fair results.

Table 1. The mechanism of trauma

Motor vehicle injury	1 (3%)
Fall from height	28 (84.8)
Work accident	2 (6.1%)
Suicide (fall from height)	2 (6.1%)

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The AOFAS scores were significantly different between patients who had accompanying injuries and those who did not. In patients who did not have accompanying injuries, AOFAS scores were significantly higher (p=0.036). The demographic, functional and clinical detailed evaluations of the two groups are summarised in Table 2.

The mean preoperative and post-operative Böhler angles were 7.9±9.1 (range: -15-30) and 25.1±9, respectively. The mean preoperative and post-operative Gissane angles were 143.1±13.1 (range: 110-170) and 120±11.2 (range: 104-145), respectively.

The preoperative Böhler angle was not significantly different between the groups (p=0.772). In patients with no accompanying injuries, the post-operative Böhler angle was significantly higher than in those with accompanying injuries (p=0.007). In both groups, the post-operative Böhler angle increased significantly compared with the preoperative outcomes (p<0.000). The preoperative (p=0.630) and post-operative (p=0.241) Gissane angles did not differ significantly between the groups. The post-operative Gissane angle decreased significantly compared with the preoperative score in both groups (p<0.000). The radiological results of the patients are summarised in Table 3.

Table 2. Demographic features, functional scores and clinical results of the patients according to accompanying injury

		Mean ± standard deviation/(%)		
		Group without accompanying injury	Group with accompanying injury	p
Age (years)		39.6±9.9	36.0±12.2	0.345[m]
Sex	Female	3 (15.8%)	0 (0.0%)	0.539[x2]
	Male	16 (84.2)	14 (100.0%)	-
Follow-up (months)		66.4±17.6	68.2±21.0	0.646[m]
AOFAS		87.4±9.8	80.5±6.3	0.036[m]
Complication	No	13 (68.4%)	9 (64.3%)	0.797[x2]
	Yes	6 (31.6%)	5 (35.7%)	-
Sudeck atrophy		3 (15.8%)	3 (21.4%)	-
Screw pull-out		1 (5.3%)	0 (0.0%)	-
Delayed wound healing		2 (10.5%)	2 (14.3%)	-
Healing		-	-	-
Normal		9 (47.4%)	4 (28.6%)	0.309[x2]
Mild subtalar arthrosis		5 (26.3%)	4 (28.6%)	-
Subtalar arthrosis		5 (26.3%)	6 (42.9%)	-

[m]Mann-Whitney U test, [x2]chi-square test (Fisher's Exact test), AOFAS: The American Orthopaedic Foot & Ankle Society

DISCUSSION

Displaced intra-articular calcaneus fractures are common injuries. However, their surgical treatment remains challenging. Anatomical reduction is the crucial approach for successful management of calcaneal fractures (4). Surgical treatment with the anatomical reduction of the calcaneal facets and restoration of overall calcaneal anatomy offer better clinical and functional results (7). The main goal of managing these fractures is to restore the congruity of the posterior calcaneal facet. Calcaneus height and width, varus-valgus alignment and calcaneocuboid involvement should be evaluated at the same time. Precise reduction of the subtalar joint may permit earlier mobilisation of the ankle. Additionally, the restoration of the calcaneal structure preserves the Achilles tendon lever arm and midfoot biomechanics (4). In this study, stable fixation with complete anatomical reduction was preferred.

The extended lateral approach has been considered the standard approach for performing ORIF of displaced intra-articular calcaneus fractures (8). Long et al. (9) revealed that locking plate provides good stability for calcaneal fracture even in elderly patients with osteoporotic fractures, which allows weight-bearing at an early stage without exerting any adverse effect on stabilisation. Despite the advantages of the standard technique, a less invasive technique, sinus tarsi approach, was popularised in the last decade (10). Schepers et al. (10) revealed that the sinus tarsi approach reduces the rate of wound complication and has a shorter operative time. However, this approach cannot provide joint height and axial alignment. Additionally, percutaneous arthroscopic calcaneal osteosynthesis seems to be a good option for displaced intra-articular calcaneal fractures as it has a low complication rate. Long-term randomised controlled studies are needed to prove the effectiveness of this technique (11). We prefer lateral extensile approach and locking compressive plate to ensure anatomical calcaneus reduction and rigid fixation. Therefore, we provided early mobilisation, and we did not have

Table 3. Radiological evaluation of the patients with and without accompanying injury

	Group without accompanying injury	Group with accompanying injury	Group difference p value
Böhler angle (point)			
Preoperative	8.0±10.2	7.5±6.1	0.772[m]
Post-operative	26.9±9.4	21.0±7.1	0.007[m]
Preoperative/ post-operative difference p value	0.000[w]	0.000[w]	-
Gissane angle (point)			
Preoperative	141.6±14.5	146.5±8.9	0.63[m]
Post-operative	118.6±10.8	123.3±12.0	0.241[m]
Preoperative/ post-operative difference p value	0.000[w]	0.000[w]	-

[m]Mann-Whitney U test, [w]Wilcoxon test

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any wound healing problems, which could be a serious problem in the mid-term follow-up.

Intra-articular calcaneus fractures are severe, high-energy injuries with the potential for considerable morbidity, given the high rate of concomitant orthopaedic injuries. These high-energy fractures are accompanied by a significant disability and notable socioeconomic burden (12). In accordance with other series (13), most of our patients were males in their thirties with a history of falling from a height as the most common type of injury. Simultaneously, the presence of injuries accompanied by these high-energy injuries and bilateral fractures are among the important factors affecting the treatment and follow-up period. Agren et al. (14) stated that the patient's demographics should be considered when choosing the treatment option. Patients with disadvantageous prognostic factors should be presented, and realistic expectations were revealed. These fractures mostly affect young active male patients; for this reason, the socioeconomic importance should not be overlooked. The patient should return to the preinjury condition as soon as possible.

Mitchell et al. (15) discussed the mechanism of injury and associated injuries of calcaneus fractures. They found that more than 70% of fractures had resulted from falling from a height. Myerson and Quill (16) also discussed the injury mechanism, and they revealed that fractures resulted from a fall from a height in 33 (77%) patients and a motor vehicle accident in 6 (14%) patients. Similarly, in our study, falling from a height is the predominant cause. We think that open fractures are more common in motor vehicle injuries. Since we included closed fractures in this study, we think that falling from a height may be the reason why it is frequently included in the aetiology. We presented accompanying injuries in 14 patients (42.4%). In our study, more than 80% of the aetiology was falling from a height. We think that accompanying injuries are frequently encountered due to the aetiology of such a high-energy injury.

Böhler angle is the most important prognostic radiological parameter, which shows the compression and deformity after trauma. Restoration of Böhler angle is associated with better outcomes (17). Researchers have revealed that the restoration of Böhler angle and quality of the subtalar joint reduction predict the outcome for treating displaced intra-articular calcaneal fractures, regardless of the treatment modality (18,19). Gotha and Zide (7) revealed that restoration of Böhler angle at the operation, regardless of the angle at presentation, may be the better predictor of results over the time. When the radiological parameters were evaluated, in patients with isolated fractures, Böhler angle was higher than in patients with bilateral fractures and those with additional in the last follow-up in our study. This was thought to be due to axial loading during mobilisation. We recommend avoiding early axial loading and bone graft support in patients with bilateral fractures and those who have accompanying injuries.

In this study, of the 33 patients, 24 achieved good-to-excellent results according to AOFAS scores. The finding was comparable to the results of previous studies (20). In the group with no accompanying injuries, the AOFAS score was higher than in the group with accompanying injuries. This result is related to the rehabilitation process in the post-operative period. We concluded that, in the presence of accompanying injuries, the rehabilitation process is prolonged and this leads to negative effects on the functional outcomes.

Yu et al. (21) revealed that the timing of the surgery, preference of the surgical exposure, reduction of the fracture and perioperative management should be planned carefully, so that the complication rates could be reduced, which is in agreement with our results. The patients were operated on within five days on average, which is consistent with other series (13). In our study, complications were observed in 11 patients (33.3%), including Sudeck's atrophy, superficial wound infection and delayed healing and screw cut-out. Researchers revealed that wound healing problems occurred in 25-32% of the patients in whom lateral exposure was preferred (22,23). Therefore, a higher incidence of wound problems arises due to this technique. These wound problems do not affect the mild-term functional clinical outcomes.

Bone grafting is a common procedure in calcaneus fracture restoration (24). Bone graft or bone graft substitute can be placed in the defects to provide additional stability for elevating the articular segment and prevent late collapse. The choice of graft material can include autogenous bone graft, allograft cancellous chips, bone graft substitutes (Pro-Osteon, DBX bone matrix, Norian SRS) or injectable calcium phosphate cement (25). Bone graft substitutes have been popularised to prevent complications associated with autogenous bone harvest. Bone grafts provide structural support for calcaneus anatomic restoration and may allow earlier weight-bearing. Malreduction could be prevented by incorporating into the bone substitutive of the posterior calcaneal facet. We used bone graft substitutes in all of the bilateral calcaneus fractures. We also used bone graft substitutes in unilateral cases when it was necessary. Schildhauer et al. (26) treated 32 patients with ORIF supplemented by calcium phosphate cement. Patients showed no loss of reduction. In accordance with the literature, we did not experience a loss of reduction in our patients. Patients with bilateral calcaneus fractures could be supported with a graft to sustain anatomical reduction and additional stability.

Study Limitations

The study has a limited number of patients. Radiological parameters in early post-operative and final follow-up were not compared. The relatively short follow-up period and unavailability of quality-of-life assessment constitute the weak points of the study.

CONCLUSION

Accompanying injuries in the calcaneus will adversely affect the radiological results and functional outcomes. During the management of calcaneus fractures, the accompanying injuries and their negative effects on the healing process should be taken into consideration.

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REFERENCES

1. Cohen M: Calcaneal fractures. Foot Ankle Surg 2001; 2: 1819-63.
2. Dhillon MS, Bali K, Prabhakar S. Controversies in calcaneus fracture management: a systematic review of the literature. Musculoskelet Surg 2011; 95: 171-81.
3. Sanders R, Fortin P, DiPasquale T, Walling A. Operative treatment in 120 displaced intraarticular calcaneal fractures. Results using a prognostic computed tomography scan classification. Clin Orthop Relat Res 1993; 87-95.
4. Asik M, Sen C, Bilen FE, Hamzaoglu A. [Surgical management of intraarticular calcaneus fractures]. Acta Orthop Traumatol Turc 2002; 36: 35-41. (Turkish)
5. Sharr PJ, Mangupli MM, Winson IG, Buckley RE. Current management options for displaced intra-articular calcaneal fractures: non-operative, ORIF, minimally invasive reduction and fixation or primary ORIF and subtalar arthrodesis. A contemporary review. Foot Ankle Surg 2016; 22: 1-8.
6. Kitaoka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, Sanders M. Clinical rating systems for the ankle-hindfoot, midfoot, hallux, and lesser toes. Foot Ankle Int 1994; 15: 349-53.
7. Gotha HE, Zide JR. Current controversies in management of calcaneus fractures. Orthop Clin North Am 2017; 48: 91-103.
8. Gougoulias N, Khanna A, McBride DJ, Maffulli N. Management of calcaneal fractures: systematic review of randomized trials. Br Med Bull 2009; 92: 153-67.
9. Long C, Fang Y, Huang FG, Zhang H, Wang GL, Yang TF, et al. Sanders II-III calcaneal fractures fixed with locking plate in elderly patients. Chin J Traumatol 2016; 19: 164-7.
10. Schepers T, Backes M, Dingemans SA, de Jong VM, Luitse JSK. Similar anatomical reduction and lower complication rates with the sinus tarsi approach compared with the extended lateral approach in displaced intra-articular calcaneal fractures. J Orthop trauma 2017; 31: 293-8.
11. Pastides PS, Milnes L, Rosenfeld PF. Percutaneous arthroscopic calcaneal osteosynthesis: a minimally invasive technique for displaced intra-articular calcaneal fractures. J Foot Ankle Surg 2015; 54: 798-804.
12. Coughlin MJ. Calcaneal fractures in the industrial patient. Foot Ankle Int 2000; 21: 896-905.
13. Jain S, Jain AK, Kumar I. Outcome of open reduction and internal fixation of intraarticular calcaneal fracture fixed with locking calcaneal plate. Chin J Traumatol 2013; 16: 355-60.
14. Agren PH, Mukka S, Tullberg T, Wretenberg P, Sayed-Noor AS. Factors affecting long-term treatment results of displaced intraarticular calcaneal fractures: a post hoc analysis of a prospective, randomized, controlled multicenter trial. J Orthop Trauma 2014; 28: 564-8.
15. Mitchell MJ, McKinley JC, Robinson CM. The epidemiology of calcaneal fractures. Foot (Edinb) 2009; 19: 197-200.
16. Myerson M, Quill GE. Late complications of fractures of the calcaneus. J Bone Joint Surg Am 1993; 75: 331-41.
17. Basile A. Operative versus nonoperative treatment of displaced intra-articular calcaneal fractures in elderly patients. J Foot Ankle Surg 2010; 49: 25-32.
18. Buckley R, Tough S, McCormack R, Pate G, Leighton R, Petrie D, et al. Operative compared with nonoperative treatment of displaced intra-articular calcaneal fractures: a prospective, randomized, controlled multicenter trial. J Bone Joint Surg Am 2002; 84: 1733-44.
19. Loucks C, Buckley R. Bohler's angle: correlation with outcome in displaced intra-articular calcaneal fractures. J Orthop Trauma 1999; 13: 554-8.
20. Cao L, Weng W, Song S, Mao N, Li H, Cai Y, et al. Surgical treatment of calcaneal fractures of Sanders type II and III by a minimally invasive technique using a locking plate. J Foot Ankle Surg 2015; 54: 76-81.
21. Yu X, Pang QJ, Chen L, Yang CC, Chen XJ. Postoperative complications after closed calcaneus fracture treated by open reduction and internal fixation: a review. J Int Med Res 2014; 42: 17-25.
22. Folk JW, Starr AJ, Early JS. Early wound complications of operative treatment of calcaneus fractures: analysis of 190 fractures. J Orthop Trauma 1999; 13: 369-72.
23. De Groot R, Frima AJ, Schepers T, Roerdink WH. Complications following the extended lateral approach for calcaneal fractures do not influence mid- to long-term outcome. Injury 2013; 44: 1596-600.
24. Fitzgibbons TC, Hawks MA, McMullen ST, Inda DJ. Bone grafting in surgery about the foot and ankle: indications and techniques. J Am Acad Orthop Surg 2011; 19: 112-20.
25. Younger EM, Chapman MW. Morbidity at bone graft donor sites. J Orthop Trauma 1989; 3: 192-5.
26. Schildhauer TA, Bauer TW, Josten C, Muhr G. Open reduction and augmentation of internal fixation with an injectable skeletal cement for the treatment of complex calcaneal fractures. J Orthop Trauma 2000; 14: 309-17.

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Relationship Between the Levels of 25-hydroxyvitamin D at Presentation and the Clinical, Laboratory and Follow-up Data of Children and Adolescents with Type-1 Diabetes Mellitus

Gökçen Karamık[1], Aslıhan Araslı Yılmaz[2], Zehra Aycan[2], Şenay Savaş Erdeve[2], Semra Çetinkaya[2]

[1]University of Health Sciences Turkey, Dr. Sami Ulus Gynecology Obstetrics and Child Health and Diseases Training and Research Hospital, Clinic of Pediatrics, Ankara, Turkey
[2]University of Health Sciences Turkey, Dr. Sami Ulus Gynecology Obstetrics and Child Health and Diseases Training and Research Hospital, Clinic of Pediatric Endocrinology, Ankara, Turkey

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ABSTRACT

Objective: This study aimed to assess the relationship of 25-hydroxyvitamin D [25(OH)D] levels at presentation with the clinical, laboratory and follow-up data of children and adolescents with type-1 diabetes mellitus.

Methods: Patients who had available follow-up data and were diagnosed to have type-1 diabetes mellitus in our clinic between 2009 and 2015 were included. Patient files were screened for data regarding presentation, history/family history and clinical, laboratory and follow-up data. Data were also assessed in the context of threshold values for sufficiency, insufficiency or deficiency of 25(OH)D.

Results: The mean age was 8.62±14.19 years. Type-1 diabetes mellitus was diagnosed as diabetic ketoacidosis in 53.9% of the patients. The mean 25(OH)D level was 18.90±11.07 ng/mL at the time of diagnosis. The mean time to subcutaneous insulin therapy through the resolution of ketosis/diabetic ketoacidosis in the group with vitamin D deficiency was significantly longer than vitamin D insufficient and sufficient groups (p=0.020). The mean 25(OH)D levels were lower in patients diagnosed with moderate and severe diabetic ketoacidosis (p=0.020). Insulin doses at discharge were significantly lower in patients with a mean 25(OH)D level of 10-20 ng/mL (p=0.039). The relationship of vitamin D groups with HbA1c and insulin doses in the follow-up period was not significant.

Conclusion: This pilot study assessed the clinical, laboratory and follow-up data and the honeymoon status on month 2 (±1). We found that 25(OH)D levels affected clinical features at the time of diagnosis but not during follow-up.

Keywords: 25-hydroxyvitamin D, type-1 diabetes mellitus, children, adolescence, ketoacidosis

ORCID IDs of the authors: G.K. 0000-0002-8678-1666; A.A.Y. 0000-0003-4403-2381; Z.A. 0000-0003-4584-2976; Ş.S.E. 0000-0002-4164-5089; S.Ç. 0000-0003-3974-2872.

Corresponding Author: Gökçen Karamık,
E-mail: gkcn06@gmail.com

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INTRODUCTION

Type-1 diabetes mellitus (T1DM) is an autoimmune disorder whose incidence increases because of beta cell destruction. Its pathogenesis involves autoimmunity, genetics and environmental factors. Although the causes of T1DM have not been fully elucidated, genetic factors in human leucocyte–antigen complexes and environmental factors, such as diet or viral infections, are likely implicated in the T1DM pathogenesis (1). The incidence of autoimmune disorders, such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis and T1DM, is high in northern countries, and the frequency of vitamin D deficiency in people living in these countries is high; as such, vitamin D is highly related to the immune system and autoimmune disorders. The EURODIAB Work Group reported that the risk of T1DM development decreases by 33% in children who receive vitamin D supplementation compared with those who have no supplementation (2). Type-1 helper, type-2 helper and regulatory T-cells participate in the interaction between vitamin D and the immune system. Vitamin D may slow down the process of autoimmune insulitis in T1DM (3,4).

Our study aimed to assess the relationship of 25-hydroxyvitamin D [25(OH)D] levels at presentation with the clinical, laboratory and follow-up data of children and adolescents with T1DM. We also determined the effects of vitamin D on the T1DM pathogenesis.

METHODS

Study Population

Dr. Sami Ulus Gynecology Obstetrics and Child Health and Diseases Training and Research Hospital Ethics Committee ethical approval was obtained for the retrospective review of the cohort of patients diagnosed with T1DM (approval number: 2016/73799008). A total of 115 patients who had positive diabetes-associated autoantibodies and were diagnosed with T1DM in accordance with the 2014 American Diabetes Association Diabetes Mellitus Diagnosis and Classification criteria between 2009 and 2015 were included. Their 25(OH) D levels were measured at presentation, and their follow-up data were collected for at least 2 years. The following data were extracted from patient records: Age, gender, physical examination and laboratory findings at presentation, diagnosis at presentation (hyperglycaemia, ketosis and ketoacidosis), time to the resolution of ketoacidosis, insulin doses at discharge (U/kg/day), insulin doses and honeymoon status in the first control visit (on month 2±1), mean insulin doses per year during follow-up and HbA1c levels.

Acquisition and Definition of Data

Diabetic ketoacidosis (DKA) was diagnosed on the basis of the following criteria (5): Plasma glucose level ≥200 mg/dL, venous pH<7.3 or HCO_3<15 mEq/L and total ketone bodies >5 mmol/L. DKA was classified according to pH and HCO_3 as follows (6): Mild DKA, pH<7.3 and HCO_3<15 mmol/L; moderate DKA, pH<7.2 and HCO_3<10 mmol/L; and severe DKA, pH<7.1 and HCO_3<5 mmol/L.

Metabolic control was assessed in terms of mean insulin doses per year, which was the arithmetic mean of HbA1c levels measured at 3-month interval during follow-up: HbA1c <7.5%, good metabolic control; 7.6-9%, moderate metabolic control; and >9.1%, poor metabolic control (7). Honeymoon status was defined as an insulin requirement of <0.5 U/kg/day in the first control visit (on month 2±1) (8).

Serum 25(OH)D levels were measured and classified as follows: Deficient, <20 ng/mL; insufficient, 21-29 ng/mL; and sufficient, >30 ng/mL (9,10). All the patients were initially given 2000 IU/day vitamin D3 replacement therapy for 6 weeks at discharge. After the supplementation therapy, our patients were prescribed to have 1000 IU/day vitamin D. The relationship of 25(OH)D level with T1DM clinical features at the time of diagnosis and follow-up data was investigated.

Statistical Analysis

Data were analysed by using SPSS version 15.0 and expressed as n (%), mean ± standard deviation (SD) or median (minimum-maximum) as appropriate. SD scores (SDS) were calculated by subtracting the patient's value from the mean value of that age and dividing by the SD value determined for that age. A chi-square test was conducted to assess the relationship between two categorical variables. Clinical and laboratory values were given as descriptive statistics. Student's t and Mann-Whitney U tests were performed to compare parametric and non-parametric data. For quantitative data, One-Way ANOVA was carried out to compare categorical variables with three or more categories in case of normal distribution. Kruskal-Wallis test was used in case of skewed distribution. Results with $p<0.05$ were considered statistically significant.

RESULTS

A total of 115 children and adolescents with T1DM were included in this study. T1DM was diagnosed in the prepubertal period of 59.1% of the patients. The mean age was 8.62±4.19 years, whilst most patients (41.9%) were 10-14 years old. Of the patients, 53.9% were girls. The patients' demographics and laboratory data are summarised in Table 1. The mean body weight, height and body mass index-SDS values were found to be normal at the time of presentation, in the first control visit (on month 2±1) and in the final control visit. However, the lowest values were detected at the time of presentation. The mean 25(OH)D level was lower in girls than in boys ($p=0.020$) The phosphor and alkaline phosphatase (ALP) levels were lower in girls than in boys. However, age-adjusted ALP levels were within normal ranges in all cases.

A comorbid autoimmune disorder was detected in 23.4% of the patients (including Hashimoto thyroiditis in 18 cases and celiac disease in 8 cases). When autoantibodies were considered, positive anti-islet antibodies were found in 72.1% of the patients, positive anti-glutamic acid decarboxylase (anti-GAD) antibodies

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were detected in 69.5% of the patients, and positive anti-insulin antibodies were observed in 4.3% of the patients. The most common antibodies were anti-islet plus anti-GAD antibodies, which were found to be positive in 32.2% of the patients.

T1DM was diagnosed as DKA in 53.9% of the patients, hyperglycaemia in 25.2% of the patients and ketosis in 20.9% of the patients (Table 2). Of the patients presenting with DKA, 79% were 10-14 years old. Furthermore, 27.4% had mild DKA, 33.9% had moderate DKA, and 38.7% had severe DKA. The mean time to subcutaneous insulin therapy via the resolution of ketosis and DKA was 14.48 h. The mean insulin doses were 0.59 U/kg/day at discharge and 0.55±0.27 U/kg/day on month 2±1 after discharge. In addition, 52.2% of the patients were in the honeymoon phase in the first control visit (on month 2±1) after discharge.

No significant differences were observed between clinical presentation and vitamin D groups (p=0.774). DKA was detected in 55.1%, 50% and 56.2% of the patients in the deficient, insufficient and sufficient groups, respectively. Additionally, the rates of severe DKA in the deficient, insufficient and sufficient groups were 36.8%, 33.3% and 44.4%, respectively (p=0.314).

The following results of the mean time to subcutaneous insulin therapy via the resolution of ketosis/DKA were found: 16.89 h (range: 4-53 h) in the group with vitamin D deficiency, 9.70 h (range 1-20 h) in the group with vitamin D insufficiency and 13.21 h (range 3-36 h) in the group with sufficient vitamin D levels. This parameter was significantly longer in the group with vitamin D deficiency than vitamin D insufficient and sufficient groups (p=0.020). No significant relationship was observed between vitamin D groups and follow-up data (Table 3).

The mean 25(OH)D level was 17.68 ng/mL in patients in the honeymoon phase in the first control visit (on month 2±1). In cases without honeymoon status, the mean 25(OH)D level was 20.34 ng/mL, which was not significantly different from that of the patients in the honeymoon phase (p=0.213). Vitamin D replacement was given to the patients with a low 25(OH)D level. The assessment of the mean 25(OH)D levels in the metabolic control groups

Table 1. Patients' anthropometric measurements and laboratory data at presentation

	Total (n=115)	Girl (n=62)	Boy (n=53)	p value
Weight-SDS, mean, (min-max)	-0.49±1.18 [-3.50-(+2.88)]	-0.63±1.24 [-3.50-(+2.05)]	-0.32±1.08 [-2.92-(+2.88)]	0.154
Height-SDS, mean, (min-max)	-0.02±1.16 [-3.05-(+3.18)]	-0.07±1.15 [-3.05-(+3.18)]	0.14±1.17 [-2.95-(+2.26)]	0.328
BMI-SDS, mean, (min-max)	-0.75±1.41 [-6.20-(+3.16)]	-0.88±1.54 [-6.20-(+1.89)]	-0.60±1.24 [-3.83-(+3.16)]	0.287
Pre-puberty, n (%)	68 (59.1%)	41 (%66.1)	27 (%50.9)	0.102
Puberty, n, (%)	47 (40.9%)	21 (%33.9)	26 (%49.1)	
25(OH)D, ng/mL, mean, (min-max)	18.90±11.07 (3.00-61.00)	15.98±10.16 (3.00-60.00)	22.32±11.21 (6.90-61.00)	0.020*
Glucose, mg/dL, mean, (min-max)	412.96±162.88 (106-855)	404.69±160.37 (106-780)	422.62±166.77 (118-855)	0.560
C-peptide, ng/mL, mean, (min-max)	0.55±0.62 (0.03-3.60)	0.56±0.70 (0.03-3.60)	0.54±0.51 (0.07-2.44)	0.880
HbA1c, %, mean, (min-max)	12.11±2.36 (5.20-16.40)	12.32±2.41 (5.20-16.40)	11.87±2.30 (5.50-16.10)	0.310
pH, mean, (min-max)	7.23±0.16 (6.70-7.55)	7.21±0.16 (6.70-7.55)	7.26±0.14 (6.93-7.48)	0.106
HCO_3, mmol/lt, mean, (min-max)	12.83±7.54 (0.60-29.00)	11.90±7.67 (1.10-29.00)	13.92±7.30 (0.60-29.00)	0.152
Calcium, mg/dL, mean, (min-max)	9.65±0.46 (8.40-10.70)	9.59±0.49 (8.40-10.70)	9.71±0.43 (8.80-10.50)	0.200
Phosphor, mg/dL, mean, (min-max)	4.19±1.11 (1.40-8.80)	3.87±0.93 (2.20-6.20)	4.54±1.19 (1.40-8.80)	0.010*
Alkaline phosphatase, U/Lt, mean, (min-max)	262.74±113.39 (117-840)	241.42±81.79 (117-483)	288.94±139.55 (121-840)	0.040*
Albumin, g/dL, mean, (min-max)	4.31±0.42 (3.20-5.40)	4.27±0.43 (3.20-5.10)	4.35±0.40 (3.40-5.40)	0.306
TSH, µIU/mL, mean, (min-max)	2.35±2.36 (0.46-23.60)	2.31±1.47 (0.46-7.55)	2.39±3.11 (0.62-23.60)	0.865

25(OH)D: 25-hydroxyvitamin D, SDS: standard deviation score, TSH: thyroid stimulating hormone, BMI: body mass index, min: minimum, max: maximum
*Statistically significant

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stratified according to the mean HbA1c level in the 1st and 2nd years revealed no significant differences amongst the groups (p=0.784 and p=0.834).

After the patients with acidosis were stratified according to 25(OH)D levels, the mean 25(OH)D levels were lower in the patients diagnosed with moderate and severe DKA (p=0.020; Table 4).

In the patients stratified into two groups according to their 25(OH)D levels, the time to subcutaneous insulin therapy via the resolution of ketosis/ketoacidosis was 16.89 h in patients with a mean 25(OH)D level of <20 ng/mL. By comparison, this parameter was 11.03 h in patients with a mean 25(OH)D level of >20 ng/mL. The time to resolution of ketosis/ketoacidosis was significantly longer in patients with a mean 25(OH)D level of <20 ng/mL (p=0.020). Additionally, insulin doses at discharge were significantly lower in patients with a mean 25(OH)D level of 10-20 ng/mL (p=0.039).

DISCUSSION

Although sunlight is a major source of vitamin D, individual factors, genetic variation and environmental factors may alter vitamin D levels. Blood 25(OH)D level represents the stored vitamin D from cutaneous synthesis and dietary intake (11). However, no consensus has been obtained on deficient or sufficient vitamin D levels. Different studies have revealed varying threshold levels. For instance, the optimal vitamin D level in children is 20 ng/mL (3). Furthermore, regional and geographic variations have been found in studies evaluating vitamin D levels in patients with T1DM. In a study on 88 patients with newly diagnosed T1DM, Pozzilli et al. (12) found that the mean 1,25(OH)D level in diabetic patients is lower than that in the controls. They also observed that vitamin D level had no correlation with age, gender, season at diagnosis and HbA1c levels. In a diabetes incidence study in Sweden, Littorin et al. (13) observed that mean 25(OH)D levels at presentation and on year 8 are significantly lower in 459 patients with T1DM than in the controls. In our study, the majority of the patients with T1DM had deficient/insufficient mean 25(OH)D levels when the groups were compared on the basis of their vitamin D levels. The mean 25(OH)D levels were <30 and <20 ng/mL in 86% and 60% of the patients, respectively. In addition, the mean 25(OH)D levels were <20 and <10 ng/mL in 70.9% and 30.7% of the girls, respectively. The mean 25(OH)D level was lower in girls than in boys. Furthermore, vitamin D deficiency/insufficiency was more common in the former than in the latter. Consistent with previous findings, our results revealed that low vitamin D levels in this age group might be due to poor dietary habits in the adolescence period and the accelerated growth rate in puberty. Consequently, their vitamin D requirement increased.

Table 2. Clinical features at the time of diagnosis and follow-up

	Total (n=115)
Clinical presentation at diagnosis	
DKA, n, (%)	62 (53.9%)
Hyperglycaemia, n, (%)	29 (25.2%)
Ketosis, n, (%)	24 (20.9)
Time to resolution of ketosis/ketoacidosis, h, mean, (min-max)	14.48±10.59 (1-53)
Mean insulin doses at discharge, U/kg/day, mean, (min-max)	0.59±0.29 (0-1.80)
Mean insulin doses in the first control visit (on month 2±1), U/kg/day, mean, (min-max)	0.55±0.27 (0.07-1.80)
Honeymoon present, n, (%)	60 (52.2%)
First year control	
HbA1c, %, mean, (min-max)	10.26±2.51 (5.50-15.90)
Insulin dose, U/kg/day, mean, (min-max)	0.56±0.24 (0.00-1.44)
Second year control	
HbA1c, %, mean, (min-max)	7.03±1.17 (5.20-12.90)
Insulin dose, U/kg/day, mean, (min-max)	0.67±0.24 (0.00-1.33)

25(OH)D: 25-hydroxyvitamin D, DKA: diabetic ketoacidosis, min: minimum, max: maximum

Several studies on the relationship between acidosis and vitamin D have suggested that a sufficient vitamin D level protects against DKA, particularly in cases induced by infection (14). Studies have also demonstrated that chronic metabolic acidosis decreases 1-alpha-hydroxylase levels, thereby transforming 25(OH)D to 1,25(OH)D; by contrast, other studies have shown that chronic metabolic acidosis increases 1,25(OH)D levels (15,16). In an Italian study on 58 patients with T1DM, 25(OH)D level is lower in the patient group than in the controls; furthermore, vitamin D levels are lower in patients presenting with ketoacidosis than in patients without ketoacidosis (17). In our study, the mean 25(OH)D level was significantly higher in 17 cases with mild ketoacidosis than in cases with moderate or severe ketoacidosis. According to vitamin D deficiency/insufficiency/sufficiency, the time to subcutaneous insulin therapy through the resolution of ketosis/ketoacidosis was significantly longer in patients with a mean 25(OH)D level of <20 ng/mL. This finding suggested that 25(OH)D levels could be associated with ketoacidosis at presentation, and 25(OH)D levels might affect insulin synthesis and secretion mechanisms. Therefore, vitamin D levels likely influenced data at presentation, but they did not affect the subsequent process. However, further studies with a larger sample size should be conducted.

Aljabri et al. (18) investigated the effects of vitamin D replacement on patients with T1DM and vitamin D deficiency. They gave vitamin D and calcium supplement to patients with vitamin D deficiency and assessed the mean HbA1c and 25(OH)D levels after 12 weeks. They found that vitamin D positively affects the metabolic control of patients with diabetes. Similarly, Svoren et al. (19) and Giri et al. (20) observed that

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Table 3. Relationship of 25-hydroxyvitamin D levels with follow-up data

Total (n=115)	Deficient (n=69) <20 ng/mL	Insufficient (n=30) 20-30 ng/mL	Sufficient (n=16) >30 ng/mL	p value
25(OH)D, ng/mL, mean, (min-max)	11.97±4.04 (3.00-19.30)	23.85±2.89 (20.20-29.70)	39.52±10.90 (30.50-61.00)	0.001*
Time to the resolution of ketosis/ketoacidosis, h, mean, (min-max)	16.89±11.47 (4-53)	9.70±5.99 (1-20)	13.21±10.71 (3-36)	0.020*
Insulin doses at discharge, U/kg/day, mean, (min-max)	0.58±0.28 (0.05-1.40)	0.56±0.26 (0.31-1.29)	0.67±0.38 (0.00-1.80)	0.487
Insulin doses at first control visit (on month 2±1), U/kg/day, mean, (min-max)	0.52±0.26 (0.07-1.31)	0.54±0.23 (0.24-1.22)	0.68±0.37 (0.19-1.80)	0.104
Honeymoon present	37 (543.47%)	18 (60%)	5 (31.2%)	0.162
Honeymoon absence	312 (456.63%)	12 (40%)	11 (68.8%)	
HbA1c at year 1, n, (%)				
Good (<7.5%)	10 (14.5%)	4 (13.3%)	1 (6.3%)	0.693
Moderate (7.5-9%)	19 (27.5%)	5 (14.7%)	7 (43.8%)	
Poor (>9%)	40 (58%)	21 (70%)	8 (50%)	
HbA1c at year 2, n, (%)				
Good (<7.5%)	49 (721.10%)	24 (820.80%)	9 (6056.3%)	0.329
Moderate (7.5-9%)	167 (234.56%)	45 (136.86%)	56 (337.35%)	
Poor (>9%)	3 (4.4%)	1 (3.4%)	1 (6.72%)	
Insulin dose at year 1, U/kg/day, mean, (min-max)	0.53±0.24 (0.00-0.17)	0.48±0.66 (0.25-1.27)	0.53±0.82 (0.32-1.44)	0.118
Insulin dose at year 2, U/kg/day, mean, (min-max)	0.66±0.27 (0.00-1.24)	0.69±0.24 (0.27-1.33)	0.66±0.14 (0.47-0.97)	0.871

25(OH)D: 25-hydroxyvitamin D, min: minimum, max: maximum, *Statistically significant

Table 4. Relationship of 25-hydroxyvitamin D levels with ketoacidosis

Mean 25(OH)D level according to acidosis severity, ng/mL, (min-max)		p value
Mild acidosis (n=17)	24.45±11.58 (7.40-60.00)	0.020*
Moderate acidosis (n=21)	16.11±7.74 (3.00-39.20)	
Severe acidosis (n=24)	16.18±10.72 (4.90-51.00)	

25(OH)D: 25-hydroxyvitamin D, min: minimum, max: maximum, *Statistically significant

25(OH)D deficiency is associated with poor metabolic control. In our study, 60% of the patients had poor metabolic control, as indicated by their mean HbA1c level in the 1st year. Conversely, 71.3% of the patients had good metabolic control, as shown by their mean HbA1c level in the 2nd year. According to vitamin D deficiency, insufficiency and sufficiency, mean HbA1c levels and metabolic control were comparable in our study. Although glycaemic control following vitamin D replacement could not be addressed because of our retrospective study design, our data suggested that vitamin D could regulate glycaemic control because of its protective features and positive effects on beta cell function and insulin sensitivity.

Study Limitations

Our study had some limitations. Firstly, this study was retrospective and had relatively few patients. We could not assess the exact effect of vitamin D replacement therapy on clinical outcomes because vitamin D treatment could be affected by a number of factors, such as patient compliance, season, baseline vitamin D level and dietary intake. Secondly, the follow-up period might not be long enough. Lastly, a control group consisting of healthy children in the same age group was lacking.

CONCLUSION

This pilot study assessed the 25(OH)D levels at the time of diagnosis in the context of the clinical, laboratory and follow-up data of patients with T1DM. We found that vitamin D levels affected the severity of clinical presentation, time to the resolution of ketoacidosis and insulin doses at discharge, but these levels had no effect on follow-up data. However, the measurement of vitamin D levels at the time of diagnosis and replacement therapy might contribute to the honeymoon status of 52.2% of the patients in their control visit on month 2±1. As such, prospective studies on this topic should be further performed.

Ethics Committee Approval: Dr. Sami Ulus Gynecology Obstetrics and Child Health and Diseases Training and Research Hospital Ethics Committee ethical approval was obtained for the retrospective review

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of the cohort of patients diagnosed with T1DM (approval number: 2016/73799008).

Informed Consent: Retrospective study.

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REFERENCES

1. Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. N Engl J Med 1994; 331: 1428-36.
2. Dahlquist GG, Patterson C, Soltesz G. Perinatal risk factors for childhood type 1 diabetes in Europe. The EURODIAB Substudy 2 Study Group. Diabetes Care 1999; 22: 1698-702.
3. Zella JB, DeLuca HF. Vitamin D and autoimmune diabetes. J Cell Biochem 2003; 88: 216-22.
4. Gregori S, Giarratana N, Smiroldo S, Uskovic M, Adorini L. A 1alpha 25 dihydroxyvitamin D (3) analog enhances regulatory T-cells and arrests autoimmune diabetes in NOD mice. Diabetes 2002; 51: 1367-74.
5. Dunger DB, Sperling MA, Acerini CL, Bohn DJ, Daneman D, Danne TPA, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child 2004; 89: 188-94.
6. Chase HP, Garg SK, Jelley DH. Diabetic ketoacidosis in children and the role of outpatient management. Pediatr Rev 1990; 11: 297-304.
7. Rosenbauer J, Dost A, Karges B, Hungele A, Stahl A, Bächle C, et al. Improved metabolic control in children and adolescents with type 1 diabetes. Diabetes Care 2012; 35: 80-6.
8. Abacı A, Böber E, Büyükgebiz A. Type 1 diabetes. Current Pediatrics 2007; 5: 1-10.
9. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-30.
10. Holick MF. Vitamin D: extraskeletal health. Rheum Dis Clin North Am 2012; 38:141-60.
11. Zerwekh JE. The measurement of vitamin D: analytical aspects. Ann Clin Biochem 2004; 41: 272-81.
12. Pozzilli P, Manfrini S, Crinò A, Picardi A, Leomanni C, Cherubini V, et al. Low levels of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 in patients with newly diagnosed type 1 diabetes. Horm Metab Res 2005; 37: 680-3.
13. Littorin B, Blom P, Schölin A, Arnqvist HJ, Blohmé G, Bolinder J, et al. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). Diabetologia 2006; 49: 2847-52.
14. Grant WB. Hypothesis--ultraviolet-B irradiance and vitamin D reduce the risk of viral infections and thus their sequelae, including autoimmune diseases and some cancers. Photochem Photobiol 2008; 84: 356-65.
15. Kraut JA, Gordon EM, Ransom JC, Horst R, Slatopolsky E, Coburn JW et al. Effect of chronic metabolic acidosis on vitamin D metabolism in humans. Kidney Int 1983; 24: 644-8.
16. Kraph R, Vetsch R, Vetsch W, Hulter HN. Chronic metabolic acidosis increases the serum concentration of 1,25-dihydroxyvitamin D in humans by stimulating its production rate. Critical role of acidosis-induced renal hypophosphatemia. J Clin Invest 1992; 90: 2456-63.
17. Franchi B, Piazza M, Sandri M, Mazzei F, Maffeis C, Boner AL. Vitamin D at the onset of type 1diabetes in Italian children. Eur J Pediatr 2014; 173: 477-82.
18. Aljabri KS, Bokhari SA, Khan MJ. Glycemic changes after vitamin D supplementation in patients with type 1 diabetes mellitus and vitamin D deficiency. Ann Saudi Med 2010; 30:454-8.
19. Svoren BM, Volkening LK, Wood JR, Laffel LM. Significant vitamin D deficiency in youth with type 1 diabetes Mellitus. J Pediatr 2009; 154: 132-4.
20. Giri D, Pintus D, Burnside G, Ghatak A, Mehta F, Paul P, et al. Treating vitamin D deficiency in children with type I diabetes could improve their glycaemic control. BMC Res Notes 2017; 10: 46.

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A New Algorithm for Dynamic Vestibular System Analysis with Wearable Pressure and Motion Sensors

Eyyup Kara[1], Serhat İkizoğlu[2], Kaan Şahin[2], Tunay Çakar[2], Ahmet Ataş[3]

[1]İstanbul University-Cerrahpaşa, Faculty of Health Science, Department of Audiology, İstanbul, Turkey
[2]İstanbul Technical University Faculty of Engineering, Department of Control and Automation Engineering, İstanbul, Turkey
[3]İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Otorhinolaryngology, İstanbul, Turkey

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ABSTRACT

Objective: Balance is a complex state that requires integrating information from many systems into various levels of the nervous system and the actions of commands from the central nervous system and the musculoskeletal system. Postural control is the ability to maintain body position against forces that threaten the individual's orientation or balance. In our study, a mobile prototype system was used to create equilibrium data of subjects and generate a set of normal values, diseases and fuzzy decisions.

Methods: This study included 106 adults (55 females, 51 males) with no vestibular, neurologic, orthopaedic and eye problems to create the normalisation data. Also, 60 patients (37 females, 23 males) with different vestibular pathologies (23 benign paroxysmal positional vertigo, 12 Meniere's disease, 10 vestibular neuritis, 15 unilateral vestibular hypofunction) comprised the patient group.

Results: With the newly developed system, step length and symmetry, distance between feet, gait symmetry, ankle mobility and symmetry and phases of each step and step symmetry were collected. Significant differences were found between the normal and pathological groups in the data obtained from the dynamic balance and pressure sensors on the sole of the foot.

Conclusion: Dynamic balance and walking analysis by our system are considered important in audiology, orthopaedics and neurology. It can contribute clinically by collecting data from several patients with different pathologies.

Keywords: Balance, posture, mobile vestibular algorithm, motion and pressure sensors, motion/walking analysis

INTRODUCTION

Balance is a complex state that requires the integration of information from many systems into various levels of the nervous system and the actions of commands from the central nervous system and the musculoskeletal system (1). The regulation of sensory stimuli to provide vertical posture is complex and related to perception and movement planning (2). While vision, perception and the vestibular system (VS) provide detailed information about the environment, the coordinated motor response occurs through spinal stretch reflexes and long latency reflexes (3). Body posture and position "postural adjustments", which are static or dynamic, maintain balance (4).

Postural control is the ability to maintain body position against forces that threaten the individual's orientation or balance (5). The vestibular, visual and somatosensory systems are effective in normal postural control and stabilisation (6). All these systems are under the influence of varying environmental conditions of

ORCID IDs of the authors: E.K. 0000-0002-4015-4560; S.İ. 0000-0003-2394-7988; K.Ş. 0000-0003-3886-6187; T.Ç. 0000-0001-6440-5814; A.A. 0000-0002-8673-6793.

Corresponding Author: Eyyup Kara,
E-mail: eyup.kara@istanbul.edu.tr

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the neck, lower extremity and trunk muscles allow the body to maintain an upright position (7).

Current systems to evaluate balance usually use a fixed platform in the clinical setting and are based on data evaluated from plantar measures. Video nystagmography (VNG) and dynamic posturography are used in the clinical setting but are costly for clinics. The mobile systems used in recent years are aimed only to monitor body movements.

In today's world, systems are getting smarter every day. The system first learns about a particular issue and then decides how to react depending on the case and/or classifies the new data. This whole procedure is called machine learning (ML). The key point here is to develop the proper algorithm to teach the machine how to attain high overall accuracy. In this study, we took substantial steps to develop an algorithm to identify the reason behind the balance disorder of the patient and differentiated between VS dysfunction-based diseases. Finally, we aim to develop a dynamic VS analysis algorithm and produce a balance detector (BD) to determine the balance performance of the patient with high accuracy in the diagnosis and treatment of vestibular disorders by measuring postural control and static/dynamic balance parameters via wearable sensors.

The purpose of our study is to measure postural control, static and dynamic balance parameters with portable equipment on the patient. It aims to develop a dynamic VS analysis algorithm and produce a BD to determine the balance performance of the patient with high accuracy in the diagnosis and treatment of vestibular disorders. In clinical practice, especially in pathologies with difficult decision-making challenges, a ML model can make the correct diagnosis using the findings of gait and body swing limits to create an algorithm and hardware that efficiently process the different data obtained and make small changes that clinicians have difficulty seeing.

METHODS

This study included 106 adults (55 females, 51 males; ages ranging between 25 and 60 years; mean, 45.1 years) with no vestibular, neurologic, orthopaedic and eye problems from normalisation data and 60 patients (37 females, 23 males; ages ranging between 27 and 60, mean 47.3 years) with different vestibular pathologies [23 benign paroxysmal positional vertigo (BPPV), 12 Meniere's disease (MD), 10 vestibular neuritis (VN), 15 unilateral vestibular hypofunction (UVH)] comprised the patient group at İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, ENT/Audiology Unit. The study has been approved by the institutional review board with the approval number A-57/07.07.2015, and written consent was obtained from the participants before the study.

Middle ear systems and acoustic reflexes were tested with GSI Tympstar (Grason-Stadler, USA) immittance meter while hearing tests were performed with GN Otometrcis Aurical (GN Otometrics, Denmark) audiometry. Vestibulo-ocular and positional testing of the subjects were performed with GN Otometrics ICS Chartr 200 VNG (GN Otometrics, Denmark); vestibulo-spinal, dynamic balance assessments were carried out using Neurocom SMART Balance Master® (Natus Medical, USA) computerised dynamic posturography.

In general terms, the study involved the steps of 'data collection, data transmission, data processing and evaluation on the computer'. Technical equipment of the device was developed in İstanbul Technical University, Control & Automation Department. İstanbul University-Cerrahpaşa, Audiology Department facilities were utilised to create a data bank, determine the correlation between data from various sensors and evaluate these medically and test the device on patients.

With the equipment developed; force sensors embedded in the insole (heel, toe, metatarsal area) and motion sensors on the body; data was collected to characterise the following discriminative features: Walking speed, average step length, step speed, step symmetry in the distance walked, toes motion characteristics during feet's lifting from the floor, the distance between steps, anterior-posterior swing angle of the body and maximum limits for the movement, anterior swing of the body, the posterior swing of the body, body tilt angle during gait, lateral swing limits of the body, the maximum bending angle of each knee during gait, lateral swing limits of each knee. Also, from the pressure sensors on the sole usage percentage of right heel, right medial forefoot, right lateral forefoot, right toe, left heel, right medial forefoot, left lateral forefoot, left toe during steps were calculated.

Collecting Data Through a Newly Developed System

A mobile prototype system was used to create equilibrium data of subjects and a set of normal values, disease and fuzzy decisions. The hardware block diagram of the system is shown in Figure 1. Special insole with piezoresistive analogue pressure sensors embedded appropriately (4 sensors/insole) to be worn under the foot was designed to obtain plantar pressure distribution during walking (Figure 2). Signals from plantar sensors were transferred to a data acquisition unit (Figure 1-DAQ1) located on the subject's body. Signals were amplified and conditioned, then converted into digital data via an analogue/digital converter. Data concerning body movements and the changing distance between legs when walking was obtained with motion and position sensors (Five XSens MTI-G (Xsens North America Inc. USA) (Figure 3) placed on the body. Data collected from the pressure and motion sensors were transmitted simultaneously to a computer via a second data acquisition unit using wireless communication (Figure 1-DAQ2).

In our study, in distinguishing two classes (in our case: The classes 'Healthy & diseased', or two different diseases), correlation statistics can directly be used to speak of one-dimensional vectors. In our case, this corresponds to a single feature only. Thus, as an example, if we search for the separation ability of the

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feature 'stride length' between two diseases, we can apply the p value test. Nevertheless, in our study, we use several features; our vector is not one-dimensional but multi-dimensional.

In our work, the starting number of features was around 150. All these features were constituted by the data collected from eight pressure sensors (four under each foot) and five motion sensors (placed on the body). Examples for these features are: walking speed, average step length, use of forefoot (frequency and time-domain analysis of pressure data), correlations of all these features, others. Thus, on a mathematical basis, we cannot speak of a single point as the intersection of different classes but a spatial clustering in an n-dimensional space (n: number of features). We may not expect that every feature can distinguish between two classes (two diseases), but the whole set of features should perform the correct discrimination. This is exactly the point where ML helps.

We implemented a two-step classification algorithm. At the first step, the new subject was decided as belonging either to the healthy group or to the suffering. For this part of the procedure, we entered all data collected from normal and diseased subjects (106+60=166 subjects in total) to train the machine. The 5-fold cross-validation ML resulted in the best accuracy of 99.4%, achieved by applying the Support Vector Machines (SVM) method. This means that we reached 99.4% of success in distinguishing between healthy and vestibular disorders groups for new subjects.

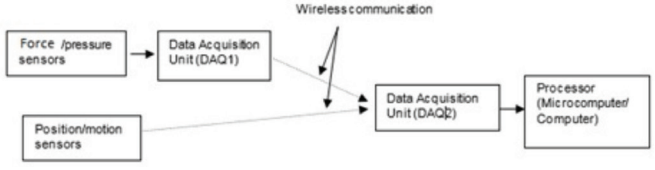

Figure 1. Block diagram of the mobile dynamic system

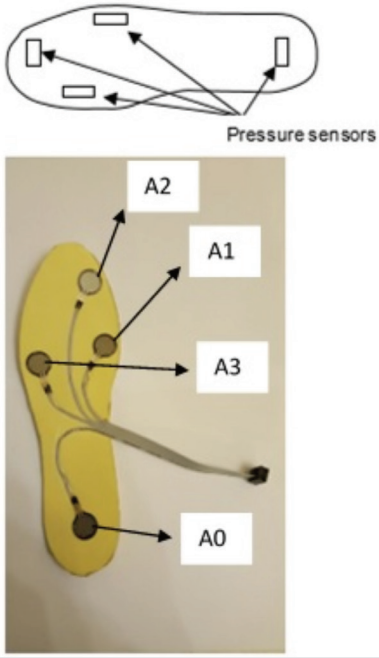

Figure 2. Positioning of insole pressure sensors and placement inside the insole

As the second step of the classification, we tried to classify between different diseases in case the first step ended up with the decision 'Belonging to vestibular disorders group'. This time we trained the machine with data collected from the diseased subjects (60 subjects) only.

Combining the two steps resulted in the overall accuracy in determining the specific disease related to vestibular disorders was 99.4%*94.4%=93.8%.

Calculations for both steps were performed in a Matlab environment using classification tools. For that, we used another two-step algorithm. We first selected the most significant features by applying the 'dimensionality reduction' step, where the principal component analysis method performed best. As the second step, the machine was trained using these selected features.

Collecting Vestibular/Walking Data

The motion of the lower body was analysed during walking in the proposed system. This system included five sensor units in total. One unit was placed on each of the feet and knees. One was positioned on the back of the waist (Figure 3). An inertial measurement unit with an accelerometer, gyroscope and magnetometer (MTw Development Kit of Xsens) was used (8).

ML was implemented in two stages: In the first stage, the values of normal subjects were obtained, loaded on the machine and learning of normality values was provided. Then, the data of individuals with pathology were obtained, loaded on the machine and the distinction between normal and pathological individuals was made. After this phase, by recognising the diseases within themselves, the classification was performed.

First Stage

Data from subjects were applied to the ML method. For this purpose, the data of 106 (normal subjects) and 60 patient subjects clusters were evaluated as education. The accuracy of the training models was determined with 5-fold "cross-validation" to prevent over-fitting.

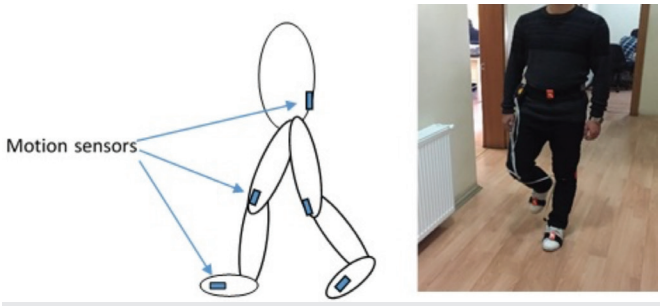

Figure 3. Several locations where motion/position sensors are placed on the body

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Second Stage (Determination of Disease)

Different algorithms were tried for this phase. As a patient set, data for 60 subjects belonging to BPPV, MD, VN and UVH sets were used. Measurements provided data to prefer SVM for ML. A two-step decision mechanism was operated for the diagnosis. In this framework, a double classification procedure was applied in the first stage only as patient-healthy. If the person was determined to be in the "patient" group, the disease was tried to be determined by moving to the second stage.

Gait parameters were processed with separate and integrated data, extracting the features that could affect balance. The data of normal subjects were compared with the data of the patient group, and the most significant values are presented. An analysis according to gender, weight and height was performed. Also, the side of the vestibular disorder according to different characteristics was calculated.

Statistical Analysis

The statistical analysis was performed using the SPSS 21 programme. The comparison of normal and patient groups was made by the Student's t-test, and correlations between normal and patients having BPPV, MD, VN and UVH were made by the Spearman correlation test.

RESULTS

The data relating to gait characteristics recorded from the body sensors of normal subjects and patients with various disorders are shown in Table 1, which demonstrates significant differences in these parameters. In Table 2, the data collected from sole pressure sensors from normal and patient subjects are presented. The comparison of average step length, step symmetry in the distance walked, step speed, back of the waist anterior-posterior, tilt angle during gait, back of the waist lateral swing maximum (max), max. left knee bending angle, max. left lateral swing, max. right knee bending angle, max. right lateral swing in normal subjects and patients with vestibular pathology were significantly different (Table 3).

Table 4 presents the correlation analysis of different gait characteristics recorded from body sensors. In this analysis, walking speed, average step length, step symmetry in the distance walked, step speed, back of the waist anterior swing, tilt angle during gait, max. left knee bending angle, max. left lateral swing, max. right knee bending angle, max. right lateral swing values of normal subjects and patients with BPPV were significantly correlated. Analysis of normal subjects and MD revealed a significant correlation with walking speed, average step length, step symmetry in the distance walked, average step width, back of the waist anterior-posterior, back of the waist anterior swing, back of the waist lateral swing right, back of the waist lateral swing max., max. left knee bending angle, max. left lateral swing, max. Right knee bending angle. The correlations between normal subjects and patients with VN revealed a significant difference in walking speed, average step length, step symmetry in the distance walked, step speed, average step width, back of the waist anterior-posterior, max. left knee bending angle, max. right knee bending angle. In UVH and normal subject analysis,

Table 1. Averages gait parameters in normal subjects and patients with different vestibular pathologies

Gait Parameters	Normal	BPPV	Meniere's disease	Vestibular neuritis	Unilateral vestibular hypofunction
Walking speed (m/s)	2.03	2.04	2.00	1.97	1.95
Average step length (m)	0.63	0.51	0.57	0.58	0.60
Step symmetry in the distance walked	1.02	1.61	2.69	2.19	2.85
Step speed (m/s)	1.36	1.03	1.13	1.13	1.18
Lifting height of the right foot (m)	0.11	0.09	0.11	0.09	0.10
Lifting height of the left foot (m)	0.12	0.09	0.12	0.11	0.13
Average step width (m)	0.19	0.11	0.26	0.16	0.14
Back of the waist anterior-posterior (Deg)	14.6	10.58	10.47	9.62	10.60
Back of the waist anterior swing (Deg)	4.6	5.09	5.25	4.71	5.63
Back of the waist posterior swing (Deg)	3.63	5.35	5.22	4.91	4.98
Tilt angle during gait (Deg)	6.72	2.70	2.59	3.26	2.95
Back of the waist lateral swing right (Deg)	6.09	4.87	6.28	6.27	4.85
Back of the waist lateral swing left (Deg)	5.62	3.80	5.12	5.37	5.15
Back of the waist lateral swing max. (Deg)	10.85	8.66	11.40	11.68	9.96
Max. left knee bending angle (Deg)	65.64	55.84	43.34	45.65	50.89
Max. left lateral swing (Deg)	13.44	19.21	15.68	16.69	16.62
Max. right knee bending angle (Deg)	62.9	54.64	43.36	44.47	51.21
Max right lateral swing (Deg)	12.9	20.18	16.95	18.52	17.48

m/s: meter/second, max.: maximum, m: meter, Deg: degree, BPPV: benign paroxysmal positional vertigo

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Table 2. Average plantar pressure parameters of normal subjects and patients with different vestibular pathologies

Plantar pressure parameters	Normal	BPPV	Meniere's disease	Vestibular neuritis	Unilateral vestibular hypofunction
Right heel (A0) %	60.75	67.6	66.4	77.2	70.8
Right medial forefoot (A1) %	60.5	65.2	67.8	71.5	69.8
Right lateral forefoot (A3) %	86.9	90.8	91.1	96.5	91.4
Right toe (A2) %	55.9	62.3	64.2	67.7	65.5
Left heel (A4) %	61.3	66.8	69.9	78.6	74.3
Right medial forefoot (A7) %	58.4	64.7	65.1	69.3	67.2
Left lateral forefoot (A5) %	86.5	92.3	94.6	98.4	93.7
Left toe (A6) %	58.8	65.5	64.8	70.1	67.6

BPPV: benign paroxysmal positional vertigo

Table 3. Parameters found significant between the patient group with peripheral vestibular pathology and normal subjects to differentiate normal from pathology

	Normal	Vestibular pathology	p values
Average step length (m)	0.64±0.06	0.56±0.09	0.0000*
Step symmetry in the distance walked	1.23±0.69	2.23±1.65	0.0000*
Step speed (m/s)	1.36±0.16	1.11±0.20	0.0000*
Back of the waist anterior-posterior (Deg)	8.08±1.32	10.40±3.94	0.0000*
Tilt angle during gait (Deg)	6.57±1.08	2.83±1.03	0.0000*
Back of the waist lateral swing max. (Deg)	11.37±2.01	10.04±2.96	0.0037*
Max. left knee bending angle (Deg)	63.57±9.38	50.40±2.08	0.0000*
Max. left lateral swing (Deg)	13.80±2.08	17.44±6.49	0.0000*
Max. right knee bending angle (Deg)	60.13±7.62	49.83±12.76	0.0000*
Max. right lateral swing (Deg)	13.61±2.60	18.58±6.56	0.0000*

*p≤0.005; m: meter, m/s: meter/second, Deg: degree, max.: maximum

Table 4. Correlation analysis of walking parameters between normal subjects and individual vestibular pathologies

Normal subjects	BPPV (p and r values)	Meniere's disease (p and r values)	Vestibular neuritis (p and r values)	Unilateral vestibular hypofunction (p and r values)
Walking speed (m/s)	0.003/0.597	0.020	0.036/0.664	0.001/0.779
Average step length (m)	0.047/0.782	0.037/0.669	0.041/0.652	0.001/0.780
Step symmetry in the distance walked	0.041/0.419	0.001/0.512	0.001/0.469	0.001/0.686
Step speed (m/s)	0/0.791	-	0.041/0.652	0.001/0.750
Average step width (m)	-	0.037/-0.606	0.022/0.709	-
Back of the waist anterior-posterior (Deg)	-	0.003/0.781	0.016/0.731	-
Back of the waist anterior swing (Deg)	0.04/0.431	0.043/-0.592	-	-
Back of the waist posterior swing (Deg)	-	-	-	-
Tilt angle during gait (Deg)	0.033/0.446	-	-	-
Back of the waist lateral swing right (Deg)	-	0.01/0.708	-	-
Back of the waist lateral swing max. (Deg)	-	-	-	0.009/0.645
Max. left knee bending angle (Deg)	0.031/0.451	0.002/0.798	0.009/-0.773	-
Max. left lateral swing (Deg)	0/0.558	0.028/0.612	-	0.048/-0.518
Max. right knee bending angle (Deg)	0.005/0.887	0.034/0.614	0.041/-0.651	-
Max. right lateral swing (Deg)	0.006/0.467	-	-	0.023/-0.583

(r: Spearman coefficient, blank lines are non-significant relations)
max.: maximum, m/s: meter/second, m: meter, Deg: degree, BPPV: benign paroxysmal positional vertigo

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a significant correlation was detected in walking speed, average step length, step symmetry in the distance walked, step speed, back of the waist lateral swing max., max. left lateral swing, max. right lateral swing (Table 4). Apart from walking speed and step speed, none of the features displayed significant difference. For the differentiation of the pathologic side in different disorders, the most significant features were left and right step symmetry in the distance walked, left and right back of the waist lateral swing. The dissociation rate of normal and pathological subjects was found to be 99.4%. The rate of separation of pathologies within themselves was 94.4%.

DISCUSSION

Walking is the most important factor in human dynamic balance. Several spatial position and mobilisation parameters exist in gait data, such as anterior-posterior and lateral swing angle, gait speed and symmetry (9). Extracting and processing data related to gait provide critical clues to understand dynamic balance and reveal underlying pathologies (10). In this study, we evaluated the features of balance and walking. We detected that anterior-posterior body swing angle values of male and female subjects were similar to those in the literature (11). Also, the results of our study were aligned with those in the literature regarding lateral swing limit values for both genders. Jarchi et al. (12) recorded body mobility with accelerometers and extracted walking parameters. In our study, the significant correlation between body swing limits and ankle mobility was consistent with the findings of Jarchi et al. (12). In our patients, we detected a significant difference in left/right step symmetry in the distance walked and maximum waist lateral sway according to the pathologic side. In patients with left/right vestibular pathology, the left/right sway was prominent. When the walking characteristics of the patients with different vestibular pathology were evaluated individually, in the BPPV and MD groups waist lateral sway right/left measurements, again in MD average step length and step speed, and in the VN group step symmetry in the distance walked, and step speed measurements were significantly different from normal subjects. However, in the patients with UVH, none of the walking parameters was significantly different (Table 3).

Ankle mobility is important for choosing the falling strategy and vestibular data to be used in the regulation of walking (10). In our study, this data was processed with motion sensors placed on the toe and, the usage level of the ankle in the walking cycle was established. The significant correlation found between ankle mobility and the knee bending angle in our study will contribute greatly to identifying walking problems that can emerge, especially with lower extremity and balance problems (Table 4). In previous studies, only the effect of the ankle was determined; the knee joint was not considered (13-15).

Examination of the step lengths and widths of the subjects produced results similar to previous studies. The stepping width and step speed were established as important clues for walking and some pathologies (16). Similarly, our study found a significant relationship between step width-stepping speed and body anterior swing angle, body lateral swing limit angles and ankle mobility. Angunsri et al. (17) studied subjects with various vestibular pathologies and exhibited differences regarding step speed, symmetry and width. Data from our study revealed that the relations between walking pattern and body stability are consistent with the previous studies. Our study revealed that the average step length in BPPV, MD, VN, UVH and normal subjects were significantly different (Table 4). The BPPV group's average step length was lower and knee bending angle was higher than those of the MD, VN and UVH groups. It was emphasised that Borel in MD, Kubo in VN, Horak in patients with unilateral vestibular involvement had a significant deterioration in walking parameters such as step length and step speed, especially in the acute period (18-20). Demian found that patients with acute vestibular disorders generally kept balance by sustaining their step length short and extending the arms (21). In our study, similar findings were obtained, and it was seen that patients in the acute period felt safer by keeping their step length short, similar to the acute phase patients in Demian et al. (19) study. Also, the relationship between the parameters of the groups with peripheral vestibular pathology was examined, which demonstrated that in patients with BPPV, the increase in the average step length resulted in the distortion of the step symmetry, increase in the knee bending angle and waist anterior sway. Similar findings were also found in UVH group patients (Table 4).

Data from ankle sensors allows predicting symmetrical walking pattern, the motion of feet with relation to earth's axis, feet symmetry and height and the relation between toes up and falling and balance loss (11). Our equipment collected data simultaneously, such as duration, pattern, lifting off the floor, the symmetry between feet, angular direction, whereas computerised dynamic posturography cannot generate. In unilateral vestibular pathologies, locomotor activity deviates toward the pathology direction (17). The level of impairment in walking speed and symmetry (foot sensors 1&2), the percentage increase in the use of the foot sensor on the side of the pathology gives information on the pathology's degree (Table 2). Ankle sensors detect differences in the distance between feet, regularity, deviation towards a certain direction and obtain information about the degree and side of the pathology (Table 4).

In peripheral vestibular lesions, knee dorsiflexion is impaired, lateral vestibulo-spinal and relevant tracts are affected (22). Data from knee sensors, such as maximum movement angle and lateral swing degree of the knee, enables the detection of problems in motor tracts. With anterior-posterior angle data obtained from knee sensors (sensors 3-4), the knee bending angle of the individual during dynamic walking was calculated. Calculation of the lateral movement angle of the knee can help detect the impact of problems arising from the knee joint on walking and dynamic balance (Table 4).

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The sensor on the back of the waist (sensor 5) provides information on the change of the centre of gravity (COG) and leaving the centre during active walking. The impaired ability to walk in a straight line, often seen in unilateral vestibular weaknesses, can easily be observed. This data helps diagnose unilateral and bilateral vestibular weakness. The anterior-posterior and lateral swing degrees obtained from the sensor on the back of the waist enable access to COG. The z- and y-axis information provides COG data and allows for comment on the sensory organisation (23). Body lateral sway angles provide detailed and instant information on rhythmic load transfer strategy, which is one of the most challenging activities for individuals with vestibular problems. The data obtained in our study demonstrated that the amount of anterior-posterior sway was higher in the pathological group; however, waist lateral sway values were lower. O'Sullivan et al. (24) found that anterior-posterior sway was higher in patients with vestibular pathology, which was higher than lateral sway. In addition, if the patient's anteroposterior stability limit was reduced, walking with short steps and if the mediolateral stability limit was decreased, a broad-based walking pattern was detected. Our study was in accordance with the current literature and provided information about the body sway amount and limits in the normal and pathological group (Table 4).

Sensors in the insole recorded data related to changes in the plantar load distribution during gait, plantar load transfer between feet, symmetric distribution of load, calculation of load per foot during gait, forming even pressure area on plantar surface and distribution during gait, feet involvement in dynamic balance and can be compared with gyroscope data from ankle sensors to establish gait symmetry, walking speed, moving away from the centre and plantar pressure. Crea analysed walking patterns of healthy individuals with plantar sensors to determine the body stability and distribution of plantar pressure. The data collected from plantar sensors in our study support this, revealing a correlation between toe sensors and lateral swing angle values (25). Also, we showed a high correlation between data obtained from toe sensors and step length data obtained from motion sensors. Moreover, we demonstrated a correlation between rhythmic weight transfer symmetry and the load on foot. Motion sensor data on gait asymmetry towards a direction and plantar usage percentage differences were also highly correlated. Foot sensors can also provide information on walking stability, pressure differentiation, impairment in pressure distribution on static standing, impaired continuity in dynamic walking, plantar pressure distribution and pressure centre. Maximum usage values for dynamic walking were examined for each sensor, and the general gait line and the loaded line were determined. The most crucial gait parameters in the literature are distance, speed, gait pattern and independence (26). In our study, data related to these and additional parameters were successfully determined. Walking, regularity and speed data were established on a subject basis by examining the duration of the pressure applied on each sensor. Therefore, walking symmetry was calculated for both feet via pressure sensors (Tables 2, 4).

The comparison of subjects with/without pathologies can yield detailed information on the location and characteristic of the pathology. Several studies that obtained data on decrease in step speed, the decline in the general speed of walking, narrow-angle at the ankle on heel's contact with the floor, changes in ankle angle and heel pressure with increasing pathology severity provided findings supportive of our study (9,17,22,27-29). In our study, patterns related to walking speed and the body's sway limits were examined, in subgroups with peripheral pathology, walking pattern and body stability parameters were significantly different. In the literature, examination of the variables in the posture and swing phase among normal subjects and patients with peripheral vestibular pathology revealed that walking pattern played an effective role in diagnosing vestibular pathology (Table 4) (16,17).

The success of the system in the binary (healthy-pathologic) classification was 99.4%, and the success in the disease classification was 94.4%. Thus, the total performance is evaluated as 93.8%. On the other hand, it was observed that there were three self-attributes among the correlations of force, motion and force-motion sensor data, which contribute to our predictions about the original aspect of the project (Table 3). According to our study results, our algorithm has three main determinants of step length/speed, step symmetry/pressure distribution and angular values of body swing in recognising/classifying vestibular pathologies.

Study Limitations

Normalisation data in our study will provide critical clues for distinguishing between individuals with and without disorders. Dynamic balance and walking analysis by our system are considered important in audiology, orthopaedics and neurology. It can contribute clinically by collecting data from several patients with different pathologies. The most important limitations of our study were the absence of normal individuals in different age groups, normalisation and classification in large subject groups with different pathologies (bilateral vestibular weakness, neurological diseases, stroke, orthopaedic disabilities, cerebral palsy, different gait disorders, others).

CONCLUSION

In this study, normal and pathological conditions could easily be distinguished by our algorithm (healthy-pathological classification reliability: 99.4%). In the pathological group, although working in a small sample size various disorders have been differentiated with 94.4% accuracy. Our system could reliably measure even minor differences that could not be detected by other conventional equipment.

Ethics Committee Approval: The study has been approved by the İstanbul University Cerrahpaşa Faculty of Medicine with the approval number A-57 (date: 07.07.2015).

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REFERENCES

1. Ferrè ER, Bottini G, Iannetti GD, Haggard P. The balance of feelings: vestibular modulation of bodily sensations. Cortex 2013; 49: 748-58.
2. Palm HG, Lang P, Strobel J, Riesner HJ, Friemert B. Computerized dynamic posturography. Am J Phys Med Rehabil [Internet] 2014; 93: 49-55.
3. Nesti A, Barnett-Cowan M, Macneilage PR, Bülthoff HH. Human sensitivity to vertical self-motion. Exp Brain Res 2014; 232: 303-14.
4. Şimşek D, Ertan H. Control and sport : muscular fatıgue and postural control relationship. Spormetre Beden Eğitimi ve Spor Bilim Derg 2011; 9: 119-24.
5. Bertolini G, Straumann D. Moving in a Moving World: A Review on Vestibular Motion Sickness. Front Neurol 2016; 15; 7:14.
6. Mast FW, Preuss N, Hartmann M, Grabherr L. Spatial cognition, body representation and affective processes: the role of vestibular information beyond ocular reflexes and control of posture. Front Integr Neurosci 2014; 8: 44. doi: 10.3389/fneur.2016.00014.
7. Hegde N, Bries M, Sazonov E. A Comparative Review of Footwear-Based Wearable Systems. Electronics. 2016; 5. https://doi.org/10.3390/electronics5030048 [E-pub online ahead]
8. Roetenberg D, Luinge H, Slycke P. Xsens MVN : Full 6DOF Human Motion Tracking Using Miniature Inertial Sensors. Technical report. 2013. Available from: http://en.souvr.com/product/pdf/MVN_white_paper.pdf
9. Dye DC, Eakman AM, Bolton KM. Assessing the validity of the dynamic gait index in a balance disorders clinic: an application of Rasch analysis. Phys Ther 2013; 93: 809-18.
10. Bent LR, Inglis JT, McFadyen BJ. When is vestibular information important during walking? J Neurophysiol 2004; 92: 1269-75.
11. Shull PB, Jirattigalachote W, Hunt MA, Cutkosky MR, Delp SL. Quantified self and human movement: a review on the clinical impact of wearable sensing and feedback for gait analysis and intervention. Gait Posture 2014; 40: 11-9.
12. Jarchi D, Wong C, Kwasnicki RM, Heller B, Tew GA, Yang GZ. Gait parameter estimation from a miniaturized ear-worn sensor using singular spectrum analysis and longest common subsequence. IEEE Trans Biomed Eng 2014; 61: 1261-73.
13. Howell AM, Kobayashi T, Hayes HA, Foreman KB, Bamberg SJ. Kinetic gait analysis using a low-cost ınsole. IEEE Trans Biomed Eng 2013; 60: 3284-90.
14. Mariani B, Rouhani H, Crevoisier X, Aminian K. Quantitative estimation of foot-flat and stance phase of gait using foot-worn inertial sensors. Gait Posture 2013; 37: 229-34.
15. Riaz Q, Tao G, Krüger B, Weber A. Motion reconstruction using very few accelerometers and ground contacts. Graphical Models 2015; 79: 23-38.
16. Khandelwal S, Wickstrom N. Gait event detection in real-world environment for long-term applications: ıncorporating domain knowledge ınto time-frequency analysis. IEEE Trans Neural Syst Rehabil Eng 2016; 24: 1363-72.
17. Angunsri N, Ishikawa K, Yin M, Omi E, Shibata Y, Saito T, et al. Gait instability caused by vestibular disorders - analysis by tactile sensor. Auris Nasus Larynx 2011; 38: 462-8.
18. Borel L, Harlay F, Lopez C, Magnan J, Chays A, Lacour M. Walking performance of vestibular-defective patients before and after unilateral vestibular neurotomy. Behav Brain Res 2004; 150: 191-200.
19. Demain A, Westby GW, Fernandez-Vidal S, Karachi C, Bonneville F, Do MC, et al. High-level gait and balance disorders in the elderly: a midbrain disease? J Neurol 2014; 261: 196-206.
20. Kubo T, Kumakura H, Hirokawa Y, Yamamoto K, Imai T, Hirasaki E. 3D analysis of human locomotion before and after caloric stimulation. Acta Otolaryngol. 1997; 117: 143-8.
21. Horak FB, Dozza M, Peterka R, Chiari L, Wall C 3rd. Vibrotactile biofeedback improves tandem gait in patients with unilateral vestibular loss. Ann N Y Acad Sci 2009; 1164: 279-81.
22. Barker SP. Changes in gait, balance, and function with vestibular rehabilitation [Internet]. Vol. 3126514, ProQuest Dissertations and Theses. 2004. Available from: http://search.proquest.com/docview/305179306?accountid=14701%5Cnhttp://sfx.scholarsportal.info/ottawa?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:dissertation&genre=dissertations+%26+theses&sid=ProQ:ProQuest+Dissertat ions+%26+Theses+Global& atitle
23. Alberts JL, Hirsch JR, Koop MM, Schindler DD, Kana DE, Linder SM, et al. Using Accelerometer and Gyroscopic Measures to Quantify Postural Stability. J Athl Train 2015; 50: 578-88.
24. O'Sullivan M, Blake C, Cunningham C, Boyle G, Finucane C. Correlation of accelerometry with clinical balance tests in older fallers and non-fallers. Age Ageing 2009; 38: 308-13.
25. Crea S, Donati M, De Rossi SM, Oddo CM, Vitiello N. A wireless flexible sensorized insole for gait analysis. Sensors (Basel) 2014; 14: 1073-93.
26. Bohannon RW, Horton MG, Wikholm JB. Importance of four variables of walking to patients with stroke. Int J Rehabil Res 1991; 14: 246-50.
27. Lang J, Ishikawa K, Hatakeyama K, Wong WH, Yin M, Saito T, et al. 3D body segment oscillation and gait analysis for vestibular disorders. Auris Nasus Larynx 2013; 40: 18-24.
28. Liu T, Inoue Y, Shibata K. Development of a wearable sensor system for quantitative gait analysis. Meas J Int Meas Confed 2009; 42: 978-88.
29. Hung TN, Suh YS. Inertial sensor-based two feet motion tracking for gait analysis. Sensors (Basel) 2013; 13: 5614-29.

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Investigation of the Effectiveness of Laser Therapy in Myofascial Pain Syndrome

Nuran Öz[1], Nil Sayıner Çağlar[2], Nezihe Akar[3], Abdullah Akar[3], Ebru Aytekin[2]

[1]Marmara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Division of Rheumatology, İstanbul, Turkey
[2]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Turkey
[3]Yalova State Hospital, Clinic of Physical Medicine and Rehabilitation, Yalova, Turkey

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ABSTRACT

Objective: Myofascial pain syndrome (MPS) is a common chronic pain condition affecting the musculoskeletal system and there are various treatment options. In this study, we investigated the efficacy of laser therapy in MPS.

Methods: Sixty patients (35 female, 25 male) diagnosed with MPS due to trigger points in the upper trapezius muscle were included in our study. The patient files were evaluated in two groups of 30 people, each waiting in line with the diagnosis of MPS (n=30) and those who were not yet treated with the same diagnosis (n=30). LED gallium-aluminium-arsenide 1.6 W, 808 nm wavelength diode laser therapy and exercise therapy were applied to the treatment group for 12 minutes once a day for 10 days, while the control group received only exercise therapy. The level of pain at rest and during activity was measured by visual analog scale (VAS); pain intensity and sensitivity was measured by algometric measurement and 0-5 Likert scale; the functional status of the patients was evaluated using the Neck Pain and Disability scale (NPADS) and the quality of life of the patients using the Short Form-36 (SF-36). All these tests were recorded before the treatment, after the treatment and at the 1st month after the treatment in both groups, and the effectiveness of the treatment was examined.

Results: The mean age of the cases was 33.4±10.5 in the treatment group and 36.1±10.6 in the control group. There was no significant difference between the demographic data of the patients in the control group and laser group. The 15th and 30th day VAS resting scores, VAS activity scores, 0-5 Likert scale and NPADS scores were found to be significantly lower in the treatment group compared to the control group. Algometric measurement score and SF-36 score on the 15th and 30th days were found to be significantly higher in the treatment group than in the control group.

Conclusion: In this study, it is seen that conventional laser therapy application in the treatment of MPS is effective on pain complaints at rest and during activity, besides, it decreases the trigger point sensitivity and increases the pressure pain threshold on the trigger point.

Keywords: Exercise, laser therapy, myofascial pain syndrome

ORCID IDs of the authors: N.Ö. 0000-0002-1002-962X; N.S.Ç. 0000-0002-6882-8686; N.A. 0000-0002-3838-5167; A.A. 0000-0001-6094-4431; E.A. 0000-0002-9619-3374.

Sorumlu Yazar/Corresponding Author: Nuran Öz,
E-mail: nrnkvrgcz@gmail.com

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INTRODUCTION

Myofascial pain syndrome (MPS), which is a regional pain syndrome, occurs with pain and pain originating from foci in the muscles and/or fascia, called trigger points, as well as referred pain, muscle spasm, tenderness, regional twitching, sensory changes, and sometimes autonomic dysfunctions. MPS is the most common cause of regional pain such as shoulder pain, back pain, tension-type headache and facial pain (1,2). Although it has been suggested that mechanical, nociceptive and genetic pathologies and primary muscle dysfunctions play a role in the pathogenesis of MPS, the exact mechanisms have not been clarified yet (3). There are many treatment methods such as modification of relevant factors, medication, stretching exercises, acupuncture, injections, manual therapy, ultrasound (US), laser therapy, electrical stimulation, transcutaneous electrical nerve stimulation (TENS), acupuncture (4), stretching exercise (5), mesotherapy, massage therapy (6) and biofeedback. These methods are effective in breaking the vicious circle at the trigger point with thermal and/or mechanical effects (7). Recently, some studies have shown that low-level laser therapy may have a therapeutic effect in the treatment of MPS (8,9). The analgesic effect of laser has been shown to stimulate endogenous endorphin synthesis (β-endorphin), reduce the activity of C fibers and bradykinin, and change the pain threshold (4). The aim of this study was to evaluate the effects of low-level 830-nm gallium-aluminium-arsenide (Ga-Al-As) laser therapy on the treatment of MPS.

METHODS

This study was planned retrospectively to examine the efficacy of laser therapy in patients diagnosed with MPS based on the diagnostic criteria of Simons et al. (10) in İstanbul Training and Research Hospital Physical Therapy and Rehabilitation Outpatient Clinic. In the study; chronic pain (>6 months), limitation of neck movements, and at least one active trigger point in the trapezius muscle were determined as inclusion criteria, while the presence of neck and/or back pain due to other causes (disc herniation, brachial plexus lesion, degenerative diseases, psychological etc.), previous surgery in the painful area, detection of infection/inflammation, fibromyalgia syndrome (FMS), pregnancy and malignancy history, and abnormal detection of infection parameters were defined as exclusion criteria from the study. Demographic characteristics of the patients, laboratory parameters (biochemistry, erythrocyte sedimentation rate, whole blood analysis, C-reactive protein) and cervical X-rays were examined. All patients were shown a 15-day exercise program and home practice was suggested with posture, active joint range of motion and muscle strengthening (resistance exercises) and stretching exercises for the upper trapezius, levator scapula, scalene, sternocleidomastoid, suboccipital and rhomboid muscles twice a day and 10 repetitions of each exercise. The patients who received laser therapy in addition to exercise therapy constituted the laser group (n=30), and the patients who were recommended exercise therapy but were in the queue for laser therapy constituted the control group (n=30).

Laser treatment with LED Ga-Al-As 808 nm wavelength and 1.6 Watt power diode laser device (Elettronica Pagani class 1 type BF Italy) for a total of 10 sessions for 12 minutes, 3 joules/cm², pulse in 20 sec periods was applied to the painful muscle area at 3,500 Hz with full contact technique and at a right angle (Figure 1).

The patient files were reviewed retrospectively and the efficacy results of the treatment were compared by analyzing the recorded data. Along with the symptoms and signs recorded in the efficacy evaluation files: Visual analog scale (VAS) was used for myofascial pain assessment at rest and activity; algometric measurement and a 0-5 Likert scale to assess pain severity and sensitivity; Neck Pain and Disability scale (NPADS) to assess functional status; Short Form-36 (SF-36) records were used to evaluate quality of life. Pre-treatment, second week and first month post-treatment data, which were used to evaluate the efficacy of treatment in all patients in the treatment and control groups, were collected retrospectively from the recorded files.

Assessment of Pain

VAS: The meaning of the numbers placed from zero to ten on a 10 cm line as points: zero as no pain, ten as unbearable pain, and five as moderate pain. After this explanation, the patients were asked to show their pain at rest and during movement on a 10 cm line (11).

0-5 Likert scale: It is used to determine the severity of pain felt during palpation of the trigger point and is scored between zero and five. 0: Absence of pain, 1: Pain on deep palpation, 2: Pain on superficial palpation, 3: Painful facial expression upon palpation, 4: Jumping with palpation, 5: Avoidance movement with palpation (12).

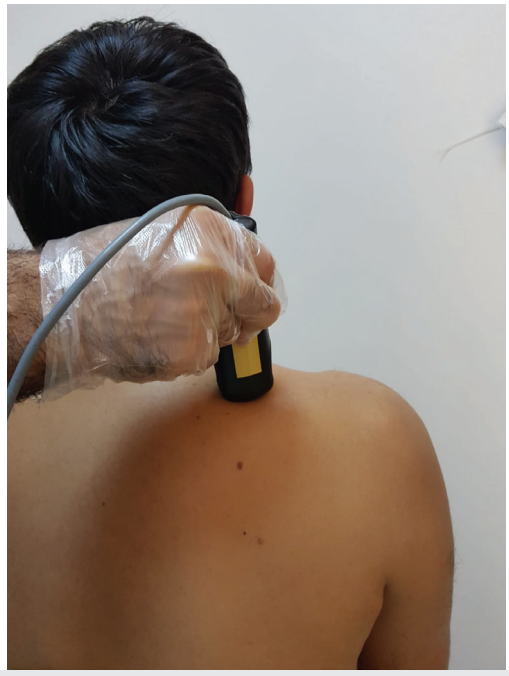

Figure 1. Low-intensity laser application to a patient with myofascial pain syndrome in the upper trapezius muscle

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Algometer (Dolorimeter): Algometer is used to objectively evaluate pain tolerance and pain threshold. Once the trigger point is located, the applied pressure is increased by 1 kg per second. As soon as the patient first feels the pain, the device is removed from the body surface, while the constant value on the needle is read and the pressure at which the patient feels the pain is recorded as a value of kg/cm^2. The application is repeated three times with an interval of 1 minute and the mean value is recorded as the pressure pain threshold (13).

Functional Status Assessment

NPADS: NPADS was used to evaluate the disability that occurs in daily life due to neck pain. It consists of 10 items, 4 of which are related to subjective symptoms (pain intensity, concentration, headache, sleep), and 6 of them are related to activities of daily living (personal care, driving, lifting, work life, leisure activities, reading). In NPADS, 0-4 points means no disability, 5-14 points mild disability, 15-24 points moderate disability, 25-34 points severe disability and above 35 points total disability (14).

Quality of Life Assessment

SF-36 quality of life scale: Consisting of 36 items, it is a criterion used in the evaluation of patients with musculoskeletal complaints. It consists of eight separate parameters. Ten items are used in the assessment of physical function, two items in the assessment of social function, four items in the assessment of role limitations due to physical problems, three items in the assessment of role limitations due to emotional problems, five items in the assessment of mental health, four items in the assessment of vitality, two items in the assessment of pain, five items in the assessment of general health and one item in the assessment of change in health. Both positive and negative aspects of health are questioned. The scores of the items for each parameter are coded and then converted into a scored scale form from zero (worst health condition) to 100 (best health condition) (15).

Statistical Analysis

Mean, standard deviation, median, frequency and ratio values were used in the statistical evaluation of descriptive data. The distribution of variables was evaluated using the Kolmogorov-Smirnov test. Independent sample t-test and Mann-Whitney U test were used in the evaluation of quantitative independent data. The chi-square test was used in the evaluation of qualitative independent data. SPSS 22.0 program was used to evaluate the analyzes. The effect size (Cohen's d) and power value (1-β) of the study were calculated using G*Power software (V.3.1.9.2). The effect size and power value were determined as 2.06 and 0.95, respectively. A $p<0.05$ level was accepted as statistical alpha significance. Informed consent was obtained from all patients before starting the treatment. Ethics approval was obtained from the İstanbul Training and Research Hospital Clinical Research Ethics Evaluation Committee (decision no: 1001, date: 26.05.2017).

RESULTS

There was no statistically significant difference between the groups in the age, gender distribution, height, weight and body mass index (BMI) values of the patients in the control group and laser group (Table 1). VAS resting score before treatment, VAS activity score, algometric measurement, 0-5 Likert scale, NPADS, SF-36 mental and physical component score did not differ significantly ($p>0.05$) in the control group and laser group. In the laser group, VAS resting and activity score, algometric measurement, 0-5 Likert scale, NPADS, SF-36 mental and physical component scores were found to be significantly lower than the control group in the second week and first month after treatment (Table 2). In the laser group, the algometric measurement, SF-36 mental and physical component score at the second week and the first month after treatment were found to be significantly higher than the control group (Table 2).

DISCUSSION

In this study, pain (VAS, 0-5 Likert scale and algometric measurement), functional status (NPADS) and quality of life (SF-36 scale) were evaluated before and after treatment in patients who received laser therapy in addition to exercise therapy for MPS and who did not. There was no statistical difference between laser treatment and control groups in terms of age, gender and BMI values. There was no difference in pain, functional status and quality of life assessments between the pre-treatment groups, but significant improvements were observed in pain, functional status and quality of life in the 2nd week and 1st month after treatment in the laser treatment group.

Table 1. Demographic characteristics

		Control group		Laser group		
		Mean ± SD	Median	Mean ± SD	Median	p value
Age (year)		36.1±10.6	35.5	33.4±10.5	30.5	0.320^t
Gender	Female	18 (%60)	-	17 (%56.7)	-	0.793$^{X^2}$
	Male	12 (%40)	-	13 (%43.3)	-	-
Height, m		1.70±0.10	1.7	1.69±0.09	1.7	0.463^m
Weight, kg		69.5±10.8	70	71.1±13.5	75.5	0.678^m
BMI, kg/m^2		24.0±2.4	23.7	25.0±4.2	25	0.140^m

^{t}t-test, ^{m}Mann-Whitney U test, $^{X^2}$chi-square test. BMI: body mass index, SD: standard deviation

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MPS is a disease characterized by sensitivity and pain in regional muscles and is the most common cause of local pain such as shoulder pain, back pain, tension-type headache and facial pain. Studies have reported that MPS is detected in approximately 30-50% of patients who apply to a health institution due to musculoskeletal symptoms (5,16). In two separate studies conducted on patients who applied to the pain outpatient clinic, it was revealed that myofascial pain was the most common cause of pain accompanying 54.6% of patients with chronic head and neck pain and 85% of those with back pain (17).

The main focus in the treatment of MPS is the elimination of the trigger point and breaking the loop in the muscles where the "spasm-pain spasm" vicious circle is present. For this reason, various physical therapy methods such as injections applied to the trigger point, low-intensity laser, stretch-spray technique or US, hot pack and TENS can be used. The common effect of these methods disrupts the trigger point with its thermal or mechanical effects and ultimately inactivates it (18). In addition, the effectiveness of exercise on pain is revealed by breaking the vicious circles by reducing facial constraints and muscle tensions, bringing the sarcomere to the optimal length (5). In this study, we aimed to investigate the effectiveness of low-intensity laser therapy in the treatment of MPS, which is very common in the community.

Although myofascial pain and trigger points are predominantly seen in women, they are seen in both sexes. It has been shown in previous studies that it can develop at any age, especially the prevalence of 30-49 years (5,6). In our study, the female sex ratio was found to be 58% similar to the studies in the literature. The possible reasons for this were thought to be the fact that the majority of patients who applied to our outpatient clinic were women and that female patients remained sedentary in their daily lives. The mean age was 33. The possible reason for this was thought to be the higher prevalence of MPS at these ages and may be related to the inclusion criteria of the study.

Pain is the most important complaint in patients with MPS. For this reason, various scales related to pain are used to evaluate the effectiveness of treatment, and we used VAS, 0-5 Likert scale and algometric measurement parameters in our study. The most commonly used pain assessment scale is VAS (11,18). In a study comparing the efficacy of low-energy laser therapy (LLLT) and pharmacotherapy in patients with temporomandibular disease, it was shown that while a decrease in VAS was observed in the LLLT group, it was not observed in the medical treatment group (19). In a randomized clinical study comparing LLLT with anesthetic lidocaine in patients with orofacial pain diagnosed with FMS, it was found that there was a significant decrease in pain assessed by VAS in both groups, but there was no significant difference

Table 2. Comparison of the VAS, algometric, 0-5 likert scale, NPADS and SF-36 scores

		Control group		Laser group		
		Mean ± SD	**Median**	**Mean ± SD**	**Median**	**p value**
VAS rest	Before treatment	6.4±1.5	6.5	6.1±1.8	7	0.541
	2nd week	4.7±1.3	5	1.6±1.4	1.5	<0.001
	1st month	4.9±1.5	5	1.9±1.4	2	<0.001
VAS activity	Before treatment	6.8±1.5	7	6.5±2.1	6.5	0.488
	2nd week	4.9±1.1	5	2.0±1.4	2	<0.001
	1st month	5.3±1.5	6	2.2±1.6	2	<0.001
Algometric measurement	Before treatment	7.2±1.1	7	9.5±12.4	7.5	0.693
	2nd week	8.1±1.1	8	11.4±1.1	11.5	<0.001
	1st month	7.9±1.2	7.8	11.4±1.4	11.5	<0.001
0-5 Likert scale	Before treatment	3.6±0.7	4	3.6±0.6	3.5	0.570
	2nd week	2.8±0.7	3	0.8±0.6	1	<0.001
	1st month	3.1±0.7	3	0.8±0.8	1	<0.001
NPADS	Before treatment	17.5±6.7	16	18.0±6.6	17	0.716
	2nd week	14.6±5.8	14	6.9±4.5	6	<0.001
	1st month	16.4±5.9	15	7.7±5.7	5.5	<0.001
SF-36 mental component	Before treatment	53.1±17.2	52.5	56.6±18.6	55.9	0.487
	2nd week	54.0±16.1	51	70.9±11.4	70.9	<0.001
	1st month	52.4±18.6	51	71.4±11.2	71.4	<0.001
SF-36 physical component	Before treatment	59.1±16.9	61.5	61.5±18.4	59.5	0.657
	2nd week	60.5±17.3	60.2	77.1±12.1	78	<0.001
	1st month	60.1±17.4	60	77.8±11.3	78	<0.001

VAS: visual analog scale, NPADS: Neck Pain and Disability scale, SF-36: Short Form-36, SD: standard deviation

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between the groups (20). In our study, activity and resting VAS values were found to be statistically significantly lower in the treatment group for the 2nd week and 1st month. It was observed that these values decreased compared to the baseline values in both groups, but the rate of this decrease was higher in the treatment group than in the control group.

Detection of the trigger point is one of the most important findings with diagnostic value in MPS. Studies have shown that focal tenderness and trigger point of pain are the most reliable physical examination findings (21,22). They are the methods used to determine the trigger point sensitivity via a 0-5 Likert scale and the pressure pain threshold via an algometer (23,24). Pressure pain threshold measurements are frequently used in the evaluation of pain in MPS, cervical region diseases and FMS. The efficacy of the treatment is evaluated with the pressure pain threshold measured using the algometer, from which more reliable numerical and quantitative data are obtained. In a study evaluating the results of VAS, 0-5 Likert scale and algometric measurement parameters, pain and sensitivity at the trigger point decreased statistically in both groups after treatment and 1 month after treatment compared to pre-treatment status, while pressure pain threshold value increased significantly. However, in the mutual evaluation of both groups, improvement was found to be statistically significantly higher in the treated group (18). In a study conducted by Esenyel et al. (25), a statistically significant decrease was found in the 0-5 Likert scale scale and a statistically significant increase in algometer measurements in the groups treated with US and injected compared to the control group. In our study, results similar to previous studies were obtained in the treatment group with a 0-5 Likert scale and an algometer value. Thus, it was possible to evaluate the pain quantitatively. In a study conducted by Delaney and McKee (26), in which the reliability of algometry was investigated in the measurement of trigger point sensitivity, reliable results were found between the measurements of the same and different patients with the algometer in assessing trigger point sensitivity, and it was concluded that it was a convenient method in their follow-up. In our study, it was shown that algometry is a reliable and effective method in the evaluation of response to treatment.

NPADS has been used effectively and safely in many studies in the literature in the clinical follow-up of treatment responses of patients with neck pain and MPS (27,28). It has been shown that the patients in the treatment group were relieved in their functional activities in daily life and this state of well-being continued in the 1-month period after the treatment.

Chronic pain can negatively affect family relationships, work life and social performance of patients with myofascial pain by causing significant difficulties in their daily living activities. Post-treatment SF-36 mental component score and physical component score were found to be significantly higher in the laser group than in the control group. This showed that laser therapy is effective in improving physical and mental functions.

Various studies have shown the effectiveness of low-dose laser therapy in the inactivation of myofascial trigger points and in the treatment of neck pain when applied correctly (7,19,20,29). The aim is to mediate the inflammatory process, regulate physiological cell functions, accelerate the tissue repair process, and provide analgesia in acute or chronic painful conditions (30). When laser therapy is applied to the myofascial trigger point area, it increases local microcirculation, provides oxygen support to hypoxic cells, helps to remove cell metabolic waste products, and breaks the vicious circle between muscle spasm and pain (31). In animal studies, it has been shown that laser therapy decreases intramuscular COX-2 and TNF-alpha levels, and increases beta-endorphin levels in serum, muscle and spinal dorsal root ganglia. In addition, it is thought that laser has a reducing effect on hyperalgesia by decreasing COX-2 mRNA expression in the central nervous system (32). Simunovic (31) showed that HeNe laser therapy was applied to trigger points in different areas and was beneficial, with pain relief, improvement of mobility and reduction of stiffness in myofascial pain. In another study comparing the short-term administration of placebo and LLLT in patients with MPS, laser was found to be effective in reducing pain, improving functional ability and improving quality of life (33). In addition, Altan et al. (34) showed no superiority in a study comparing exercise alone and GaAs laser therapy in the treatment of myofascial pain; however, improvement was observed in both groups. According to the results of another review by Gross et al. (35), including 17 studies published in the literature, 11 of which were chronic myofascial pain; for low-dose laser therapy in trigger point inactivation, treatment parameters with a treatment time of 30-196 seconds, 2-7 days a week, a total of 10 days to 7 weeks have been suggested. In our study, treatment with LED Ga-Al-As laser device was given in accordance with the doses and frequencies recommended in the treatment of chronic myofascial pain in the literature, and we found significant improvements in pain intensity in patients with MPS in one month after the treatment. The features of our study that distinguish it from other laser studies are that no drug treatment is applied, the scope of the exercise program given, the type of laser applied and the application area are different.

Study Limitations

Our study had the following limitations. First, the limited number of cases included in the study and the fact that it was performed in a single center were the main limitations. Therefore, multicenter studies with large subject groups are needed to confirm our study results. Second, our study was not a placebo-controlled study. Finally, the mean follow-up time of the MPS cases included in the study was relatively short. Longer follow-up studies are required as this period is not sufficient to demonstrate the long-term effects of laser therapy.

CONCLUSION

We think that the following mechanisms are effective in the inactivation of trigger points in laser therapy: 1) By regulating microcirculation, increasing tissue oxygenation, and normalizing

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the metabolic effects of tissues, 2) by increasing the levels of endogenous opioids and endorphins, affecting the gate control mechanism of pain. To maintain the therapeutic efficacy for a long time, the elimination of the continuation factors present in the patients, provision of posture training, the stretching of the tense and short muscles and the strengthening of the weak muscles are of great importance. On the other hand, there are various studies conducted to determine the optimal dose, duration and frequency of laser therapy to be used in patients with MPS. Further studies with larger patient groups and longer follow-up are needed to determine the optimal dose and duration of treatment, especially since there are no standard guidelines for laser application in terms of duration, frequency, and optimal effective treatment dosages.

Ethics Committee Approval: Ethics approval was obtained from the İstanbul Training and Research Hospital Clinical Research Ethics Evaluation Committee (decision no: 1001, date: 26.05.2017).

Informed Consent: Informed consent was obtained from all patients before starting the treatment.

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REFERENCES

1. Vázquez-Delgado E, Cascos-Romero J, Gay-Escoda C. Myofascial pain syndrome associated with trigger points: a literature review. (I): epidemiology, clinical treatment and etiopathogeny. Med Oral Patol Oral Cir Bucal 2009; 14: e494-8.
2. Hong CZ, Simons DG. Pathophysiologic and electrophysiologic mechanisms of myofascial trigger points. Arch Phys Med Rehabil 1998; 79: 863-72.
3. Grayston R, Czanner G, Elhadd K, Goebel A, Frank B, Üçeyler N, et al. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis. Semin Arthritis Rheum 2019; 48: 933-40.
4. Alexander J, Black A. Pain mechanisms and the management of neuropathic pain. Curr Opin Neurol Neurosurg 1992; 5: 228-34.
5. Bron C, de Gast A, Dommerholt J, Stegenga B, Wensing M, Oostendorp RA. Treatment of myofascial trigger points in patients with chronic shoulder pain: a randomized, controlled trial. BMC Med 2011; 9: 8.
6. Moraska AF, Schmiege SJ, Mann JD, Butryn N, Krutsch JP. Responsiveness of Myofascial Trigger Points to Single and Multiple Trigger Point Release Massages: A Randomized, Placebo Controlled Trial. Am J Phys Med Rehabil 2017; 96: 639-45.
7. Hakgüder A, Birtane M, Gürcan S, Kokino S, Turan FN. Efficacy of low level laser therapy in myofascial pain syndrome: an algometric and thermographic evaluation. Lasers Surg Med 2003; 33: 339-43.
8. Munguia FM, Jang J, Salem M, Clark GT, Enciso R. Efficacy of low-level laser therapy in the treatment of temporomandibular myofascial pain: a systematic review and meta-analysis. J Oral Facial Pain Headache 2018; 32: 287-97.
9. Mansourian A, Pourshahidi S, Sadrzadeh-Afshar MS, Ebrahimi H. A comparative study of low-level laser therapy and transcutaneous electrical nerve stimulation as an adjunct to pharmaceutical therapy for myofascial pain dysfunction syndrome: a randomized clinical trial. Front Dent 2019; 16: 256-64.
10. Simons DG, Travell JG, Simons LS. General Overview. In: Johnson EP, editor. Myofascial Pain and Dysfunction: The Trigger Point Manual. 2nd ed. Baltimore: Williams & Wilkins, 1999: 11-89.
11. Dixon JS, Bird HA. Reproducibility along a 10 cm vertical visual analogue scale. Ann Rheum Dis 1981; 40: 87-9.
12. Treaster D, Marras WS, Burr D, Sheedy JE, Hart D. Myofascial trigger point development from visual and postural stressors during computer work. J Electromyogr Kinesiol 2006; 16: 115-24.
13. Fischer AA. Documentation of myofascial trigger points. Arch Phys Med Rehabil 1988; 69: 286-91.
14. De Meulemeester KE, Castelein B, Coppieters I, Barbe T, Cools A, Cagnie B. Comparing trigger point dry needling and manual pressure technique for the management of myofascial neck/shoulder pain: a randomized clinical trial. J Manipulative Physiol Ther 2017; 40: 11-20.
15. Çelik D, Çoban Ö. Short Form Health Survey version-2.0 Turkish (SF-36v2) is an efficient outcome parameter in musculoskeletal research. Acta Orthop Traumatol Turc 2016; 50: 558-61.
16. Borg-Stein J, Simons DG. Focused review: myofascial pain. Arch Phys Med Rehabil. 2002; 83(3 Suppl 1): S40-7, S48-9.
17. Yunus MB. Research in fibromyalgia and myofascial pain syndromes. Current status, problems and future directions. J. Musculoskeletal Pain 1993; 1: 23-41.
18. Kavadar G, Çağlar N, Özen Ş, Tütün Ş, Demircioğlu D. Efficacy of conventional ultrasound therapy on myofascial pain syndrome: a placebo controlled study. Agri 2015; 27: 190-6.
19. Khalighi HR, Mortazavi H, Mojahedi SM, Azari-Marhabi S, Moradi Abbasabadi F. Low level laser therapy versus pharmacotherapy in improving myofascial pain disorder syndrome. J Lasers Med Sci 2016; 7: 45-50.
20. de Souza RC, de Sousa ET, Scudine KG, Meira UM, de Oliveira E Silva EM, Gomes AC, et al. Low-level laser therapy and anesthetic infiltration for orofacial pain in patients with fibromyalgia: a randomized clinical trial. Med Oral Patol Oral Cir Bucal 2018; 23: e65-71.
21. Nice DA, Riddle DL, Lamb RL, Mayhew TP, Rucker K. Intertester reliability of judgments of the presence of trigger points in patients with low back pain. Arch Phys Med Rehabil 1992; 73: 893-8.
22. Hua NK, Van der Does E. The occurrence and inter-rater reliability of myofascial trigger points in the quadratus lumborum and gluteus medius: a prospective study in non-specific low back pain patients and controls in general practice. Pain 1994; 58: 317-23.
23. Jaeger B, Reeves JL. Quantification of changes in myofascial trigger point sensitivity with the pressure algometer following passive stretch. Pain 1986; 27: 203-10.
24. Abu Taleb W, Rehan Youssef A, Saleh A. The effectiveness of manual versus algometer pressure release techniques for treating active myofascial trigger points of the upper trapezius. J Bodyw Mov Ther 2016; 20: 863-9.
25. Esenyel M, Caglar N, Aldemir T. Treatment of myofascial pain. Am J Phys Med Rehabil 2000; 79: 48-52.
26. Delaney GA, McKee AC. Inter- and intra-rater reliability of the pressure threshold meter in measurement of myofascial trigger point sensitivity. Am J Phys Med Rehabil 1993; 72: 136-9.
27. Bicer A, Yazici A, Camdeviren H, Erdogan C. Assessment of pain and disability in patients with chronic neck pain: reliability and construct validity of the Turkish version of the neck pain and disability scale. Disabil Rehabil 2004; 26: 959-62.
28. Ilter L, Dilek B, Batmaz I, Ulu MA, Sariyildiz MA, Nas K, et al. Efficacy of pulsed and continuous therapeutic ultrasound in myofascial pain syndrome: a randomized controlled study. Am J Phys Med Rehabil 2015; 94: 547-5.
29. Kuan TS. Current studies on myofascial pain syndrome. Curr Pain Headache Rep 2009; 13: 365-9.
30. Uemoto L, Nascimento de Azevedo R, Almeida Alfaya T, Nunes Jardim Reis R, Depes de Gouvêa CV, Cavalcanti Garcia MA. Myofascial trigger point therapy: laser therapy and dry needling. Curr Pain Headache Rep 2013; 17: 357.
31. Simunovic Z. Low level laser therapy with trigger points technique: a clinical study on 243 patients. J Clin Laser Med Surg 1996; 14: 163-7.
32. Király M, Bender T, Hodosi K. Comparative study of shockwave therapy and low-level laser therapy effects in patients with myofascial pain syndrome of the trapezius. Rheumatol Int 2018; 38: 2045-52.

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33. Gur A, Sarac AJ, Cevik R, Altindag O, Sarac S. Efficacy of 904 nm gallium arsenide low level laser therapy in the management of chronic myofascial pain in the neck: a double-blind and randomize-controlled trial. Lasers Surg Med 2004; 35: 229-35.
34. Altan L, Bingöl U, Aykaç M, Yurtkuran M. Investigation of the effect of GaAs laser therapy on cervical myofascial pain syndrome. Rheumatol Int 2005; 25: 23-7.
35. Gross AR, Dziengo S, Boers O, Goldsmith CH, Graham N, Lilge L, et al. Low Level Laser Therapy (LLLT) for Neck Pain: A Systematic Review and Meta-Regression. Open Orthop J 2013; 7: 396-419.

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Surgical Treatment of Peyronie's Disease: Single-centre Experiments

Mehmet Eflatun Deniz, Umut Ünal

University of Health Sciences Turkey, Adana City Training and Research Hospital, Clinic of Urology, Adana, Turkey

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ABSTRACT

Objective: We aimed to share the data of the surgeries that we performed in our clinic and to compare this with other findings in the literature.

Methods: The files of 24 Peyronie's disease (PD) patients operated in our clinic between August 2015 and July 2018 were retrospectively reviewed. Eight of these patients had mild curvature (<60°), while the other 16 patients had severe curvature (>60°). The penile curvatures below 60° were corrected by the Nesbit method, and curvatures above 60° were operated by venous grafting. Erectile dysfunction (ED), International Index of Erectile Function (IIEF)-5 score and PD questionnaire (PDQ) were evaluated preoperatively and post-operatively. Moreover, anatomical and functional success was evaluated.

Results: The curvature of six patients operated using Nesbit method was 44.16°± 2°. No residual curvature was observed during the post-operative follow-up. The mean preoperative penile length derived from all the patients was 12.57±3.1 cm and the post-operative penile shortening was 15±9.2 mm. The curvature of 18 patients who underwent venous grafting was 77.5°±9.5°. Also, post-operative residual curvature was calculated to be 15.41°± 9.8°. A total of 12 of patients who underwent surgery using this technique had ED; however, only two of these patients did not benefit from the medical treatment. Therefore, these two patients underwent penile prosthesis implantation in the same session. IIEF-5 and PDQ scores improved significantly in both groups ($p<0.05$).

Conclusion: Surgical treatment is the gold standard for PD. An appropriate surgical procedure should be selected based on the degree of penile curvature and ED of the patient. Anatomic and functional success is quite satisfactory for patients.

Keywords: Peyronie's disease, erectile dysfunction, penile curvature, IIEF, PDQ, corporoplasty

INTRODUCTION

Peyronie's disease (PD) is a disease that affects the tunica albuginea of the penis. Elastic fibres in this tissue replaces fibrous scar, which causes deformity during penile erection. PD occurs in 0.7%-11% of adult males and is generally diagnosed by painful erections, sometimes with erectile dysfunction (ED) and palpable plaques (1). In general, this disease is observed in patients with diabetes mellitus (DM), hypertension (HT), lipid abnormalities, ischaemic cardiomyopathy, ED, smoking, alcohol consumption. Penile curvature is expected to worsen in 30% to 50% of the population and stabilise in 47% to 67% of patients. Approximately, 3%-13% of patients are spontaneously healed (2). The main goal of surgery is to correct the curvature and allow coitus. However, surgery is accompanied with certain risks, such as penile shortening, ED, penile numbness, recurrent curvature and palpable knots and stitches (3). There are two types of surgery defined for this purpose: Penile shortening and penile lengthening procedures.

ORCID IDs of the authors: M.E.D. 0000-0003-2570-3784; U.Ü. 0000-0003-4040-0044.

Corresponding Author: Mehmet Eflatun Deniz,
E-mail: eflatun7@gmail.com

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In cases of ED, the key determinant factors that influence the choice of surgery suitable for the patient include penile length assessment, curvature severity, erectile function status and response to pharmacotherapy. Penile shortening is applicable for degrees of curvature below 60°, and the Nesbit or plication procedures are generally suitable choices. Grafting procedure is a suitable method when the degree of curvature is above 60° or complex. The implantation of an inflatable penile prosthesis is considered the best option in cases where ED does not respond to pharmacological treatment.

METHODS

We retrospectively analysed the files of a total of 24 PD patients who underwent surgery in our clinic between August 2015 and July 2018. All patients were informed in detail before the surgery and their consents were obtained. First, the patients were evaluated using lateral, dorsal and ventral images while their penises were erect. An intracavernosal artificial erection was successful in patients without self-erection. Before the surgery, penile length, curvature degree and curvature localisation of the patients were recorded and compared with post-operative values in follow-up. Physical examination was performed to carefully observe any Dupuytren contracture or Ledderhose disease. In this study, patients without erectile pain, but having curvature for more than six months, were included.

In addition, degloving from the circumference line was performed for all patients. Also, patients with dorsal intervention were dissected and preserved on both sides with a neurovascular bundle. Nesbit method was applied for the penile curvature between 30° and 60°. Allis clamp was used to firmly grasp from the maximum curvature point after artificial erection was achieved. Tunica albuginea was superficially excised with a scalpel and scissors. The remaining layers were sutured with 2/0 polydioxanone sutures (PDS) and penile erection was examined. Lengthening surgery was performed on patients with severe curvature (>60°). The defects of the tunica albuginea were closed with autograft taken from the saphenous vein. The grafts were folded on their own and placed in the defect zone using 5/0 PDS. Patients who underwent penile prostheses were placed with a penoscrotal incision and, in this procedure, a two-piece inflatable penile prosthesis was used. On the first post-operative day, urethral catheters were withdrawn and patients were discharged. In the 3rd and 12th post-operative month, penile length and residual curvature were recorded. All patients were evaluated using Peyronie's disease questionnaire (PDQ) and International Index of Erectile Function (IIEF)-5 score preoperatively and post-operatively. At the end of one-year follow-up, the physical straightening achieved (including residual curvature of ≤30°) was accepted as anatomical success. The satisfaction in sexual intercourse (increase in IIEF-5 score) was accepted as functional success.

Statistical Analysis

Categorical measurements were summarised as numbers and percentages, while numerical measurements were summarised as mean and standard deviation. Chi-square test was used to compare categorical measurements between groups. In addition, Shapiro-Wilk test was used to determine whether the numerical measurements met the normal distribution assumption. For comparison of the numerical measurements between the groups, the Student's t-test was used in the independent groups, and the Mann-Whitney U test was used if the assumptions were not met. Paired t-test was used for the preoperative-post-operative comparisons. Preoperative-post-operative comparisons in the amounts exchange were analysed by Mann-Whitney U test. IBM SPSS Statistics, Version 20.0 for Windows (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. The statistical level of significance was set as 0.05 in all tests.

RESULTS

In this study, the mean age of the 24 patients was 60.87±6 years. There was no significant contracture in the other part of the body. Two patients had dorsal curvature, one patient had dorsolateral curvature and the remaining 21 patients had ventral curvature. The average curvature was 69.16°±16.9° and the mean penile length of the patients was 12.25±2.2 cm. After the lengthening surgery, the residual curvature level was 15.41°±9.8°; however, there was no residual curvature found in any of the patients who were treated by the Nesbit method. In addition, for patients who were treated by the Nesbit method, the mean penile length was 12.57±3.1 cm, while the mean shortening was 15±9.2 mm.

Furthermore, five patients had DM, four patients had HT and eight patients had both DM and HT. Also, two of the eight patients with both DM and HT had coronary artery disease. No additional morbidity was observed in seven patients.

Moreover, 12 out of 18 patients who had lengthening surgery had preoperative ED (Table 1). Penile prosthesis was performed on two patients, since they did not benefit from drug treatment. These two patients had curvatures of 75° and 90° preoperatively. In the surgery, Wilson manoeuvre was employed concurrently to straighten the penis. In the 3rd month of post-operative follow-up, only five patients were disturbed by suture line (palpable knots); however, they adapted to the situation and no irritating symptoms recurred. There was no complaint of penile numbness, wound infection, hematoma, penile skin necrosis or urethral injury.

Anatomical success was achieved in all patients, since the residual curvature was below 30° after the surgery. Functional success was accepted as an improvement in IIEF-5 and PDQ scores. Also, IIEF-5 scores increased significantly in both groups (p=0.001) (Table 2) (Figure 1). The increase in the lengthening group (12.4±2.9 mm) was statistically different from that in

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the shortening group (8.2±2.8 mm) (p=0.007) (Figure 2). PDQ scores decreased significantly in both groups (p<0.001) (Table 3) (Figure 3). When the amount of change was examined in PDQ scores, the decrease in the lengthening group (38.7±18.2 mm) was more than that in the shortening group (14.8±2.8 mm) (p=0.003) (Figure 4).

DISCUSSION

Surgical intervention is the gold standard treatment method for PD. Plication/Nesbit surgery should be prescribed for the patients with adequate erectile function (with or without pharmacotherapy), adequate penile length and mild curvature, but without the presence of hourglass deformity causing hinging. From two large case series investigating penile corporoplasty surgery, penile shortening with an interval of 1.5-3.0 cm was detected in 13% of the patients. Also, sexual disability due to shortness of the penis was reported in 1.6%-1.8% of the patients (4,5). The shortening measures employed in our series were similar to those series and our patients were satisfied with the penile shortening. They reported that performance of sexual functions and appearance for self-confidence was of utmost importance. Moreover, they did not realise the shortening in penile length. However, further

Table 1. Characteristics of patients with Peyronie's disease

	Shortening/Nesbit	Lengthening	p values
Patients number	6	18	-
Age (years)	61.16±7.4	60.77±5.7	0.894
Ventral	5	16	0.999
Dorsal	1	2	
Diabetes mellitus	3	10	0.999
Hypertension	3	9	0.999
Coronary artery disease	0	2	0.999
Curvature degree	44.16°±2°	77.5°±9.5°	<0.001
Penile length (cm)	12.57±3.1	12.06±2.4	0.679
Residual curvature	0	15.41°±9.8°	NA
Penile shortening (mm)	15±9.2	-	NA
Preoperative ED	0	12	0.014

ED: erectile dysfunction, NA: not applicable

Table 2. Changes in IIEF-5 scores

	Preoperative IIEF	Post-operative IIEF	p values
Shortening/Nesbit	11.0±3.7	19.2±1.5	0.001
Lengthening	8.2±1.9	20.7±2.0	<0.001

IIEF: International Index of Erectile Function

Table 3. Changes in PDQ score

	Preoperative PDQ	Post-operative PDQ	p values
Shortening/Nesbit	35.0±13.7	20.2±11.5	<0.001
Lengthening	45.3±18.9	6.6±1.5	<0.001

PDQ: Peyronie's disease questionnaire

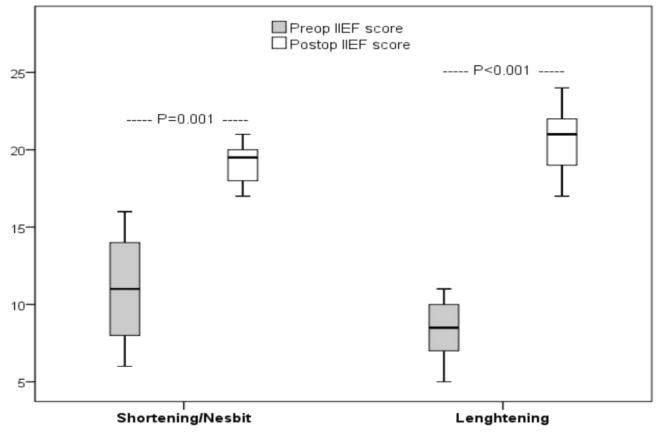

Figure 1. IIEF score changes in both methods
IIEF: International Index of Erectile Function

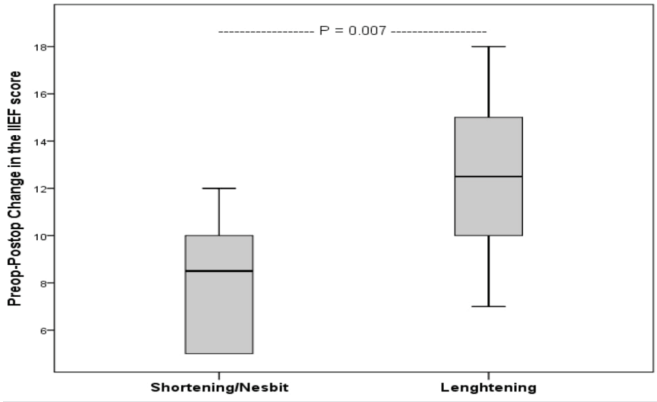

Figure 2. Comparing IIEF scores in both methods
IIEF: International Index of Erectile Function

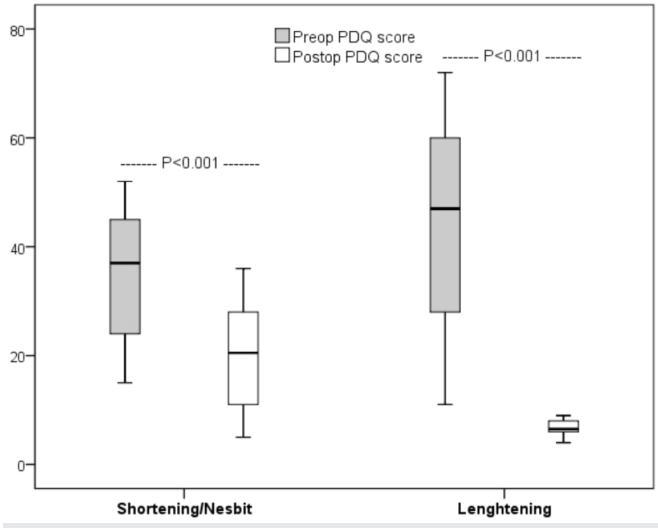

Figure 3. PDQ score changes in both methods
PDQ: Peyronie's disease questionnaire

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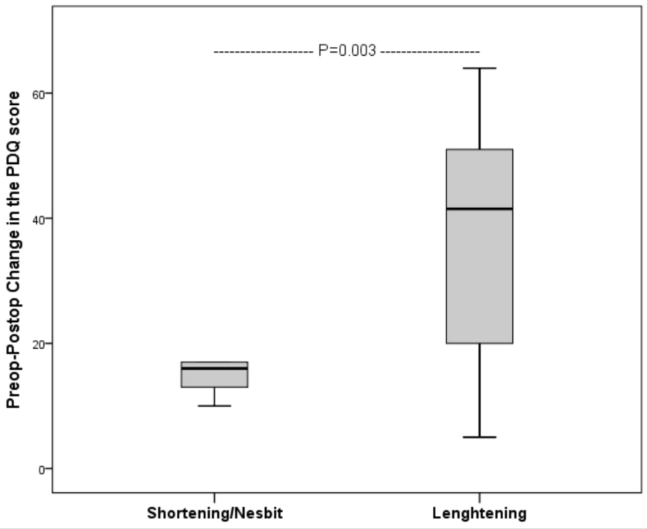

Figure 4. Comparing PDQ scores in both methods
PDQ: Peyronie's disease questionnaire

shortening of the penile length would probably be less tolerable by patients. The lengthening method was used in those with higher degrees of curvature.

Paulis et al. (6), in their series, detected 7.4% DM and 20.7% HT disease in a total of 309 PD patients. There was no significant difference in PD between ED and non-ED patients. In this study, patients with ED had these comorbidities; however, these diseases were not encountered in half of the non-ED group. Although these diseases were seen more frequently in patients with ED, they support our data. However, much larger series of studies are needed to find a more accurate relationship.

In the past, ED and temporary loss of penile sensation were reported in very high ratios. Presently, these ratios have significantly decreased. Çayan et al. (7) reported that 4.7% patients with post-operative ED experienced difficulty in sexual intercourse due to penile sensory loss. In contrast, ED was not observed in any of our patients after surgery. We were very careful during the dissection with neurovascular bundle in order to prevent both post-operative ED and loss of penile sensation. Correction of the physical deformity is very important for patients, but post-operative loss of penile sensation and even ED can be quite dissatisfying for patients. This affects their IIEF-5 and PDQ scores, resulting in decreased functional and anatomical success. IIEF-5 and PDQ scores are the most basic scales for erection power, duration and sexual satisfaction in patients. They are very useful in comparing subjective values to show the situation before and after surgery. Thus, they provide important information regarding whether the patients benefit from the surgical intervention or not. In literature, there are many studies investigating preoperative and post-operative IIEF score in PD (8,9). Also, PDQ is generally used for results of collagenase *Clostridium histolyticum* injection treatment successfully (10). According to our data, there is an improvement in these scores in both surgical methods. Post-operative values of the patients were quite satisfactory compared to their preoperative values. In fact, the lengthening surgery was found to be more successful in both scales than the shortening/Nesbit surgery. The reason for this is that the degree of curvature is higher, making the patients more desperate.

Study Limitations

This study has some potential limitations. First, the charts of the patients were gathered retrospectively. Second, in order to generate more accurate data, it is necessary to include a larger population of the patients, since the power analysis of our study was low. Lastly, the follow-up period of the patients is short. If the patients were followed for a longer period, we may have additional data to compare the preoperative and post-operative situations.

CONCLUSION

Surgery is the gold standard method of treatment for PD. The results are quite satisfactory when the appropriate surgical method is chosen. Post-operative successful results were obtained both anatomically and functionally after the surgery.

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Ethics Committee Approval: Ethics committee approval was not obtained as it is a retrospective study.

Informed Consent: All patients were informed in detail before the surgery and their consents were obtained.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - M.E.D., U.Ü.; Concept - M.E.D., U.Ü.; Design - M.E.D., U.Ü.; Data Collection and/or Processing - M.E.D.; Analysis and/or Interpretation - U.Ü.; Literature Search - M.E.D., U.Ü.; Writing - M.E.D.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Stuntz M, Perlaky A, des Vignes F, Kyriakides T, Glass D. The prevalence of peyronie's disease in the United States: a population-based study. PLoS One 2016; 11: e0150157.
2. Berookhim BM, Choi J, Alex B, Mulhall JP. Deformity stabilization and improvement in men with untreated Peyronie's disease. BJU Int 2014; 113: 133-6.
3. Chung E, Ralph D, Kagioglu A, Garaffa G, Shamsodini A, Bivalacqua T, et al. Evidence-based management guidelines on Peyronie's disease. J Sex Med 2016; 13: 905-23.
4. Savoca G, Scieri F, Pietropaolo F, Garaffa G, Belgrano E. Straightening corporoplasty for Peyronie's disease: a review of 218 patients with median follow-up of 89 months. Eur Urol 2004; 46: 610-4; discussion 613-4.
5. Ralph DJ, al-Akraa M, Pryor JP. The Nesbit operation for Peyronie's disease: 16-year experience. J Urol 1995; 4: 1362-3.
6. Paulis G, Romano G, Paulis A. Prevalence, psychological impact, and risk factors of erectile dysfunction in patients with Peyronie's disease: a retrospective analysis of 309 cases. Res Rep Urol 2016; 8: 95-103.
7. Çayan S, Aşcı R, Efesoy O, Kocamanoğlu F, Akbay E, Yaman Ö. Comparison of patient's satisfaction and long-term results of 2 penile

J Acad Res Med 2021;11(2):164-8

plication techniques: lessons learned from 387 patients with penile curvature. Urology 2019; 129: 106-12.

8. Gamidov S, Shatylko T, Gasanov N, Scherbakov D, Li K, Sukhikh G. Long-term outcomes of surgery for Peyronie's disease: focus on patient satisfaction. Int J Impot Res 2021; 33: 332-8.
9. Gamidov SI, Popkov VM, Shatylko TV, Ovchinnikov RI, Korolev AY, Popova AY, et al. [Erectile function after corporoplasty in patients with peyronies disease]. Urologiia 2019; 80-4.
10. Jensen CFS, Jacobsen FM, Quallich S, Fode M, Sønksen J, Malaeb BS, et al. CopMich Collaborative. Patient-reported outcomes from a single-centre prospective post-marketing study on Collagenase Clostridium Histolyticum injections for Peyronie's disease. Andrologia 2020; 52: e13733.

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Comparison of ESWL and RIRS for 2 Cm Lower Pole Renal Pelvis and Kidney Stones in Preschool Children

Mehmet Eflatun Deniz[1], Ali Çift[2]

[1]Adıyaman Kahta State Hospital, Clinic of Urology, Adıyaman, Turkey
[2]Adıyaman Training and Research Hospital, Clinic of Urology, Adıyaman, Turkey

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ABSTRACT

Objective: Surgically treating urinary tract stones in paediatric patient groups, especially in the preschool period, is more difficult than that in adult patient groups. For paediatric patients, non-invasive methods have many advantages and disadvantages. In this study, we compared the success rates of extracorporeal shock wave lithotripsy (ESWL) and retrograde intrarenal surgery (RIRS) for the treatment of lower pole renal pelvis and kidney stones.

Methods: Patients who had lower pole renal pelvis and kidney stones and were subjected to RIRS and ESWL in our clinic between March 2016 and October 2019 were retrospectively reviewed. The success rates and duration of anaesthesia were compared in terms of the size, localisation and hardness of the stones.

Results: Surgical success was achieved in 17 (80.9%) of 21 patients who underwent RIRS in the study and in 14 (73.6%) of 19 patients who had ESWL. No relationship was found amongst the size, location, Hounsfield degree and stone-free (SF) rate in either of the methods. RIRS and ESWL had 50% and 60% SF in the lower pole of the kidney, respectively. Conversely, the SF rate in the renal pelvis was around 80%. The anaesthesia duration for RIRS was longer in the successful cases than in the unsuccessful ones, whereas it was just the opposite in ESWL group so anaesthesia duration was longer in the unsuccessful cases.

Conclusion: ESWL and RIRS can be successfully applied to preschool children. They have similar success rates in terms of stone treatment. Therefore, the optimal technique should be used individually in each patient.

Keywords: Preschool age, paediatrics, urinary stones, RIRS, ESWL, stone location

INTRODUCTION

Managing urinary tract stones is crucial in paediatric patients. In this group, recurrences are common, but an underlying metabolic factor may be present. Although children cannot localise pain, they can visit a hospital and complain of abdominal pain. Typically, they may present with haematuria and symptoms such as dysuria and fever. In some cases, only urinary tract infection can be detected (1). Although this condition can be most accurately diagnosed with non-contrast abdominal tomography, urinary ultrasound should be performed primarily because of radiation exposure (2,3). Treatment methods are planned according to the location and size of stones. However, treatment for children is more difficult than that for adults because thin-walled instruments are needed for their anatomical structures, and anaesthesia is required for extracorporeal shock wave lithotripsy (ESWL). Furthermore, children may be exposed to radiation. As such, preschool children are the most difficult patient group. In this

ORCID IDs of the authors: M.E.D. 0000-0003-2570-3784; A.Ç. 0000-0002-2329-0149.

Corresponding Author: Mehmet Eflatun Deniz,
E-mail: eflatun7@gmail.com

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study, we aimed to compare ESWL and retrograde intrarenal surgery (RIRS) in paediatric patients with lower pole renal pelvis and kidney stones of less than 2 cm.

METHODS

Patients who underwent ESWL and RIRS in our clinic between March 2016 and October 2019 were retrospectively reviewed. We picked radiopaque, under 20 mm renal pelvis and lower pole stones, aged ≤6 years patients and excluded the ones who has a ureteral stent history in their past. Patients aged >6 years and having stones in different localisations were excluded. ESWL was performed by a urologist and a technician. Patients' stone size, location, degree of hardness [Hounsfield unit (HU)], duration of fluoroscopy and anaesthesia, stone-free (SF) and success rates were recorded and statistically compared. Their urine cultures were sterilised before the procedures. The patients were evaluated by anaesthesiologists to check any disease or drug use. None of them had a history of undergoing previous surgical procedures.

All surgeries were performed using 7.95 Fr urf-p6 digital ureteroscopes, 8.5 Fr digital ureteroscopes and Flex-X^c flexible ureteroscopes. A 9.5-11.5 Fr 20 cm ureteral access sheet was used as an accessory sheet for children. A holmium YAG laser with 30 Watts, 16 mAmps and 50/60 Hz was used. Cystoscopy was conducted in a lithotomy position, and a hydrophilic tipped guide wire was moved forward into the ureter. Control ureteroscopy with the help of semirigid ureterorenoscopy (7.5 Fr) was carried out over this guidewire to exclude ureteral pathologies and stone and perform dilatation. Afterwards, the access sheath was advanced over the guidewire until the proximal ureter was reached. The renal pelvis was reached with a flexible ureterorenoscope over the guidewire, and the stones were fragmented with the holmium YAG laser. When the kidney could not be accessed because of stenosis, a double J stent (DJ) was placed in the ureter, and the procedure was repeated 4 weeks later. The stones were fragmented until they reached a size that could fall spontaneously. At the end of the procedure, a 3 Fr double J ureteral stent was placed in the patients if necessary.

All the patients in the ESWL group were intubated under anaesthesia. ESWL was performed using a ModularisVario, which is a mobile, fully integrated, next-generation lithotripter with an electromagnetic shock wave source and a fully integrated fluoroscopic guided device. Energy levels were initially set at E0.1 and gradually increased to a maximum of E8.0 in 38 steps. Average energy level, maximum energy level and total energy delivered were displayed automatically at the end of each session. The patients were treated in a supine position. Fluoroscopy was performed to localise the stones. A lubricating gel was applied on the area to be subjected to ESWL. In each ESWL session, shocks between 1,500 and 2,000 at a frequency of 60 Hz were given. Shock wave number, shock wave intensity and shock wave energy were recorded.

Before the procedure, detailed information was given to all the patients, and their consents were obtained. All the cases were outpatients. Oral paracetamol was prescribed to alleviate pain. On the 10th day after ESWL, the patients were called for control visit. Residual stones were checked via plain abdominal radiography. Another session was planned for those with residues. The total duration of anaesthesia and fluoroscopy of the patients who had a maximum of three ESWL sessions was recorded. Patients without residual stones (0 mm, i.e. SF) were considered to be successfully treated. This study was approved by the Adıyaman University Non-Invasive Clinical Research Ethics Committee (decision no: 2020/11-21, date: 22.12.2020).

Statistical Analysis

Categorical measurements were summarised as numbers and percentages, and numerical measurements were presented as mean and standard deviation. Chi-square test (Pearson chi-square or Fisher's Exact test) was conducted to compare categorical measurements between groups. Shapiro-Wilk test was performed to determine whether numerical measurements provided the assumption of normal distribution. In the comparison of numerical measurements between the groups, a t-test was used in independent groups if the assumptions were met. Otherwise, Mann-Whitney U test was applied. Kruskal-Wallis test was utilised for the general comparison of numerical measurements of more than two groups. Mann-Whitney U test with Bonferroni correction was conducted for pairwise group comparisons. Data were statistically analysed with SPSS version 20.0 (IBM) and considered significant at a 0.05 level in all the tests.

RESULTS

The average age of the patients who underwent RIRS was 4.5±1.1 years. Amongst these patients, 13 were boys, and 8 were girls. Furthermore, 12 had stones in the right kidney, and 9 had stones in the left kidney. In addition, 4 had stones in the lower pole, and 17 had stones in the renal pelvis. The mean stone diameter was 13.6±1.5 mm.

The average age of the patients who underwent ESWL was 4.7±1.4 years. Amongst them, 12 were boys, and 7 were girls. Furthermore, 9 had stones in the right kidney, and 10 had stones in the left kidney. Moreover, 5 had stones in the lower pole of the kidney, and 14 had stones in the renal pelvis. The mean stone diameter was 10.1±3.2 mm.

Surgical success was achieved in 17 (80.9%) of 21 patients who were subjected to RIRS. In 13 of the patients (61.9%) who had RIRS, a DJ stent was placed initially (preop DJ +), and RIRS was then performed due to ureteral stricture. No statistical difference was found after the success was evaluated in patients who had preop DJ (-; Table 1).

The size and location of the stones were not related to the degree of HU and SF in either method (Table 2). No significant relationship was found between the number of times of ESWL and HU (Table 3). In RIRS and ESWL, 50% and 60% SF were detected in the lower pole of the kidney, respectively. By comparison, the SF rate in the renal pelvis was around 80%. Even when the stone size

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was divided into two groups (10 mm below and 10 mm above), the success rates of the methods had no difference (Table 4).

The duration of anaesthesia was examined in terms of success rate. The results revealed that the average duration of anaesthesia in the ESWL was almost one-third of successful RIRS. Conversely in unsuccessful cases, anaesthesia duration was longer in ESWL when it was compared to RIRS. The average duration of anaesthesia in ESWL is almost three times more than that in RIRS (Table 5; Figure 1).

DISCUSSION

Endourology plays an increasingly vital role in urological surgery. As the number of non-invasive procedures performed on patients increase, their hospitalisation time, post-operative pain and recovery time gradually decrease. Surgical experience increases success rates and lead to good results. In addition to the successful rates of ESWL in preschool children, the results of RIRS are excellent in terms of patient satisfaction. Our data on the surgical procedures performed revealed that the success rate of RIRS was 80.9%, which was similar to that reported in other studies. For instance, Mokhless et al. (4) performed a randomised prospective study and obtained 86.6% success rate. Wang et al. (5) and Berrettini et al. (6) achieved 86.7% and 81.2% success rates, respectively. Baş et al. (7) found 86.2% SF rate. However, studies have yet to present a consensus on the acceptable length (in millimetres) of residues to indicate the success of a procedure. In some studies, residual stones with a length of up to 3 mm can be acceptable and indicative of surgical success. Although the diameter of a ureter is smaller in children, stones can be dropped more easily in clinical practice than those in adults. Mokhless et al. (4) could not find a statistically significant difference in the success rate between RIRS and ESWL. In our study, the success rates of the two groups did not also differ in terms of location, size and HU.

The diameter of the ureteral lumen is an important factor in RIRS. An insufficient width causes an increase in intrarenal pressure during the procedure and consequently exacerbates complications. As such, the ureter should have an appropriate width, and a sheath must be placed before stones are fragmented. A short ureteral diameter, especially in the age group of 0-6 years, is one of the reasons that can determine the difficulty level of surgery. In our study, the success rate was 100% in patients with preop DJ (-), but the number of patients was insufficient to show the lower success

Table 1. DJ-SF rate relationship

	SF+ n=4	SF- n=17	p
Preop DJ-	0 (0%)	8 (100%)	0.131
Preop DJ+	4 (31%)	9 (69%)	

SF: stone-free, DJ: double J stent

Table 2. Patients who underwent RIRS and ESWL

	No success n=4	Success n=17	p
Stone size	13.3±2.8	13.8±1.3	0.737
Stone location			
Lower pole	2 (50%)	2 (50%)	0.148
Pelvis	2 (12%)	15 (88%)	
HU	725.0±188.2	865.1±191.2	0.202
	n=5	**n=14**	
Stone size	11.6±5.4	9.7±2.1	0.476
Stone location			
Lower pole	2 (40%)	3 (60%)	0.570
Pelvis	3 (21%)	11 (79%)	
HU	674.8±389.5	627.0±222.9	0.754

HU: Hountsfied unit %, RIRS: retrograde intrarenal surgery, ESWL: extracorporeal shock wave lithotripsy

Table 3. ESWL-HU relationship

	Number of ESWL sessions			
	1 n=9	2 n=4	3 n=6	p
HU	616.8±215.2	645.5±301.5	669.8±348.6	0.900

HU: Hountsfied unit %, ESWL: extracorporeal shock wave lithotripsy

Table 4. ESWL versus RIRS

Stone location		No success	Success	p
Lower pole	ESWL	2 (40%)	3 (60%)	0.999
	RIRS	2 (50%)	2 (50%)	
Pelvis	ESWL	3 (21%)	11 (79%)	0.636
	RIRS	2 (12%)	15 (88%)	
Stone size				
≤10 mm	ESWL	3 (25%)	9 (75%)	0.308
	RIRS	1 (100%)	0 (0%)	
>10 mm	ESWL	2 (29%)	5 (71%)	0.580
	RIRS	3 (15%)	17 (85%)	

RIRS: retrograde intrarenal surgery, ESWL: extracorporeal shock wave lithotripsy

Table 5. Durations of both methods

	ESWL n=19	RIRS n=21	p
Duration of anaesthesia (minute %)	92.3±96.3	95.7±35.5	0.054
Successful sessions	**ESWL n=14**	**RIRS n=17**	
Duration of anaesthesia (minute %)	38.4±19.2	95.3±39.3	<0.001
Unsuccessful sessions	**ESWL n=5**	**RIRS n=4**	
Duration of anaesthesia (minute %)	243.0±44.1	97.5±12.6	0.016

RIRS: retrograde intrarenal surgery, ESWL: extracorporeal shock wave lithotripsy

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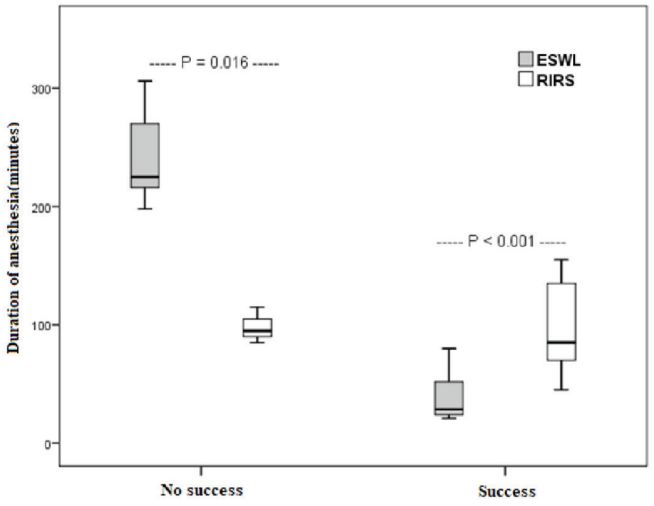

Figure 1. Relationship of RIRS and ESWL with anaesthesia
RIRS: retrograde intrarenal surgery, ESWL: extracorporeal shock wave lithotripsy

rate of patients with preop DJ (+). However, these findings could not support the assumption that preop DJ (+) decreased the success. Twenty-one patients were required per group to obtain a strong test result, but this result would be significant if the number of patients was three to four times higher. In some studies, a DJ catheter is placed in each patient for a while before RIRS. Therefore, this procedure should be performed depending on patients' preference. If necessary, a DJ should be used, and the procedure should be delayed until the next session.

A successful RIRS was completed in 95.3 min, but unsuccessful ones lasted 97.5 min. The total time of ESWL was 92.3 min. Berrettini et al. (6) found that successful and unsuccessful RIRS are completed in 95.8 and 108.3 min, respectively. Freton et al. (8) compared RIRS and ESWL and observed that the RIRS operation time is statistically longer, i.e. 28.9 min versus 105 min. This difference is attributed to lower pole stones. Mokhless et al. (4) revealed that the duration of anaesthesia is significantly longer in RIRS (40 and 27.9 min.). Wang et al. (5) observed that the duration of RIRS is 48 min. In our study, the duration of ESWL was long because more stone-breaking sessions were performed in many patients (52.6%). The specified time referred to the total session duration. When the successful and unsuccessful results were examined separately, the situation changed slightly. Our analysis of the successful results showed that the duration of ESWL was significantly shorter than that of RIRS. Conversely, in the unsuccessful group, the duration of the former was significantly longer than that of the latter. Therefore, when the stones were not fragmented in the first session, the possibility of being fragmented in the following sessions was low. After one session of ESWL, patients should be re-evaluated, and surgeons should consider if they need to continue the sessions or to change the procedure to RIRS. Interestingly, no relationship was found between the hardness of stones and the success of ESWL. If the number of patients was higher than that included in our study, then a different result would have been obtained.

Berrettini et al. (6) found SF in 2 of 3 stones in the renal pelvis and 7 of 9 stones in the lower kidney during RIRS. They could not find a significant difference between the location of stones and the success of the operation. However, when the stones were divided into two groups (16 mm and <16 mm), the success of the operation decreased significantly as the size of the stone increased. Our analysis showed no difference in the success between ESWL and RIRS in neither the lower pole of the kidney nor the renal pelvis even when the stone sizes were divided into two groups (≥10 mm and <10 mm). The success between these two methods was not significantly different. Therefore, both methods were equally efficient. In patients undergoing ESWL, lower pole renal pelvis stones could not easily fall spontaneously after the procedure, thereby reducing the SF rate. The disadvantage of RIRS is that the flexion capacity of the URS is limited, especially in the presence of a laser fibre. These disadvantages of lower pole stones in the two procedures might be the main factor contributing to the same success rate. Although the chances of successfully removing renal pelvis stones were the same for ESWL and RIRS, ESWL could be recommended to patients as the first treatment option because it is a non-invasive procedure.

Study Limitations

This study has some potential limitations. Firstly the charts of the patients were gathered retrospectively. Secondly in order to make more accurate datas, it is necessary to study on a population with a larger number of patients.

CONCLUSION

ESWL and RIRS could be successfully used to treat preschool children. They have similar success rates in terms of the treatment of lower pole renal pelvis stones. As such, the best option should be selected on the basis of patients' preference.

Ethics Committee Approval: This study was approved by the Adıyaman University Non-Invasive Clinical Research Ethics Committee (decision no: 2020/11-21, date: 22.12.2020).

Informed Consent: Before the procedure, detailed information was given to all the patients, and their consents were obtained.

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Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Sternberg K, Greenfield SP, Williot P, Wan J. Pediatric stone disease: an evolving experience. J Urol 2005; 174: 1711-4; discussion 1714.
2. Memarsadeghi M, Heinz-Peer G, Helbich TH, Schaefer-Prokop C, Kramer G, Scharitzer M, et al. Unenhanced multi-detector row CT in patients

J Acad Res Med 2021;11(2):169-73

suspected of having urinary stone disease: effect of section width on diagnosis. Radiology 2005; 235: 530-6.

3. Kwon JK, Chang IH, Moon YT, Lee JB, Park HJ, Park SB. Usefulness of low-dose nonenhanced computed tomography with iterative reconstruction for evaluation of urolithiasis: diagnostic performance and agreement between the urologist and the radiologist. Urology 2015; 85: 531-8.
4. Mokhless IA, Abdeldaeim HM, Saad A, Zahran AR. Retrograde intrarenal surgery monotherapy versus shock wave lithotripsy for stones 10 to 20 mm in preschool children: a prospective, randomized study. J Urol 2014; 191(Suppl 5): 1496-9.
5. Wang W, Ge Y, Wang Z, Wang L, Li J, Tian Y. Comparing micropercutaneous nephrolithotomy and retrograde intrarenal surgery in treating 1-2 cm solitary renal stones in pediatric patients younger than 3 years. J Pediatr Urol 2019; 15: 517.e1-6.
6. Berrettini A, Boeri L, Montanari E, Mogiatti M, Acquati P, De Lorenzis E, et al. Retrograde intrarenal surgery using ureteral access sheaths is a safe and effective treatment for renal stones in children weighing <20 kg. J Pediatr Urol 2018; 14: 59.e1-6.
7. Baş O, Dede O, Aydogmus Y, Utangaç M, Yikilmaz TN, Damar E. et al. Comparison of Retrograde Intrarenal Surgery and Micro-Percutaneous Nephrolithotomy in Moderately Sized Pediatric Kidney Stones. J Endourol 2016; 30: 765-70.
8. Freton L, Peyronnet B, Arnaud A, Tondut L, Hascoet J, Pradère B, et al. Extracorporeal Shockwave Lithotripsy Versus Flexible Ureteroscopy for the Management of Upper Tract Urinary Stones in Children. J Endourol 2017; 31: 1-6.

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Management of Women with Vaginismus-related Infertility Through Assisted Reproductive Techniques

Arzu Yurci[1], Şaban Karayağız[2]

[1]Memorial Kayseri In Vitro Fertilization Center, Department of Obstetrics and Gynecology, Kayseri, Turkey
[2]Nuh Naci Yazgan University Faculty of Science, Department of Psychology, Kayseri, Turkey

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ABSTRACT

Objective: To investigate reproductive outcomes of patients with infertility due to severe vaginismus undergoing in vitro fertilisation and embryo transfer (IVF-ET).

Methods: Twenty-nine patients were selected among patients who presented with complaints of vaginismus-related infertility. The diagnosis and severity of vaginismus were assessed according to the Lamont-Pacik system. Five women with milder forms of vaginismus were treated with other options. Of the remaining 24 patients with severe vaginismus, 20 had Lamont grade 3 and four with Lamont grade 4. Likewise, 24 patients who were diagnosed with unexplained infertility were selected as the control group.

Results: Of the 24 patients, 15 had first attempt, 8 had second and 1 had fourth attempt. Folliculometry was performed with abdominal ultrasonography in 21 women with normal body mass index. Folliculometry and endometrial evaluation were performed in three overweight cases with transvaginal ultrasonography under sedation. Single ET was performed in 27 cycles, and two ETs were performed in the others. Beta human chorionic gonadotropin positivity was detected in 20 of the 39 cycles. Similarly, in 20 patients, while clinical pregnancy was detected (20 of 39 cycles, 51.2%), the number of cycles with term and live births were 16 (16 of 39 cycles, 41.0%). While clinical pregnancy was detected in 25 of 35 cycles in the control group (71.4%), live birth was achieved in 22 cycles (62.8%). Compared with the vaginismus group, clinical pregnancy rate (20 vs 25, $p<0.09$) and live birth rate (LBR) (16 vs 22, $p<0.06$) were comparable.

Conclusion: Both clinical pregnancy and LBRs of women with infertility due to severe vaginismus undergoing IVF-ET are similar to women with unexplained infertility.

Keywords: Vaginismus, Lamont-Pacik scale, IVF-ET, fertility outcome

INTRODUCTION

Vaginismus is the recurrent and involuntary contraction of the paravaginal muscles, which interferes with sexual intercourse and may cause sexual penetration even impossible (1,2). It has both psychological and physical components and meets the fourth edition of Diagnostic and Statistical Manual of Mental Disorders Text Revision criteria (1,3). The definition of vaginismus was recently modified, and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders defined vaginismus as a subset of 'genito-pelvic pain and penetration disorder' (4). The diagnosis of vaginismus is made by detailed history and physical examination. The prevalence of vaginismus varies between 5% and 7%, and it is one of the more prevalent female sexual dysfunctions (5). It is divided into primary and secondary vaginismus. Primary vaginismus occurs when the woman has never been able to have penetrative intercourse. Secondary vaginismus occurs when a

ORCID IDs of the authors: A.Y. 0000-0003-4808-9019; Ş.K. 0000-0002-6914-4630.

Corresponding Author: Arzu Yurci,
E-mail: arzuyurci@yahoo.com

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woman has previously been able to have intercourse but cannot be penetrated anymore. Vaginismus can be mild, in which different treatments and sexual intercourse are possible; or severe, making treatment or sexual intercourse impossible (6). Since these patients cannot have sexual intercourse, it is not possible to have a natural pregnancy.

As with other sexual dysfunctions, vaginismus can lead to marital problems (7) and likely to result in infertility. To achieve pregnancy in women with vaginismus, it is necessary to either perform intra-uterine insemination (IUI) under sedation or to direct the patient to assisted reproductive techniques (ART). However, in cases where both IUI and in vitro fertilisation and embryo transfer (IVF-ET) are planned, performing folliculometry appears to be an important problem. In severe vaginismus, the vaginal muscles respond to any stimulus with increased contraction, and these patients cannot be evaluated by gynaecological examination or transvaginal ultrasonography (USG) without sedation (6). Abdominal USG may allow folliculometry and endometrial evaluation in cases with normal body mass index (BMI), but folliculometry with abdominal USG may not provide very clear information in obese cases. Women with vaginismus who cannot tolerate a transvaginal examination might have an examination under anaesthesia during which any vaginal spasm disappears. For all these reasons, patients with vaginismus who take ovulation stimulation drugs for IUI or IVF-ET may need to undergo a sedation anaesthesia two or three times during folliculometry.

Classifying patients with vaginismus according to the severity of the disease before taking IUI or IVF-ET treatment may make it possible to help patients further during the treatment. For this reason, we classified all vaginismus cases according to Lamont-Pacik system and then introduced them into their corresponding treatment (6,8). This scale classifies patients according to their response to the pelvic examination and penetration history. In this study, IVF-ET results of women diagnosed with severe vaginismus are presented in detail. To the best of our knowledge, this is the largest series on ART protocols and fertility outcomes of women with infertility due to severe vaginismus.

METHODS

In this retrospective case-control study, study participants were selected among patients who presented to our clinic with complaints of infertility due to vaginismus. Medical data were collected from our patient database. A total of 29 patients (3 had secondary infertility, 26 had primary infertility) who were admitted to the Memorial Kayseri Hospital IVF Centre between December 2012 and June 2020 were included in the study. Patients with other underlying infertility problems such as decreased ovarian reserve, male factor, endometriosis/endometrioma and polycystic ovary syndrome were excluded from the study. Moreover, 24 patients who were diagnosed with unexplained infertility and for whom IVF-ET decision was made were selected as the control group.

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Nuh Naci Yazgan University (decision no: 2020/2, date: 20.08.2020), and written informed consent was obtained from all participants at the time of enrolment. While some of the patients already presented with vaginismus, some were diagnosed with vaginismus following examination. In patients who presented with vaginismus, initial pelvic examination was performed without sedation, and a diagnosis of vaginismus was confirmed. The severity of vaginismus was assessed according to the Lamont scale. This scale was based on the patient's history, their behaviour during a routine gynaecologic examination, and physical demonstration of perineal muscular spasm (6,8). While three cases were Lamont grade 1 (first-degree vaginismus), two cases were Lamont grade 2 (second-degree vaginismus). These five women with milder forms of vaginismus cooperated with different treatment suggestions such as vaginal dilators, biofeedback therapy, psychotherapy, hypnotherapy and lubricant treatments. A total of 20 patients with Lamont grade 3 (third-degree vaginismus) and four with Lamont grade 4 (fourth-degree vaginismus) were diagnosed with serious vaginismus and were included in the study (Table 1). Of the 24 patients, three were previously pregnant with IUI, but they were included in the study as having secondary infertility because they could not conceive again. The remaining 21 patients were accepted as having primary infertility, who were terrified of any attempted vaginal penetration and declined treatment suggestions. As a result of the interviews with the patients, eight patients proceeded with IUI, while 13 patients who declined the IUI recommendation were taken directly to the IVF programme. Failure of two IUIs was declared as IUI failure. Pregnancy could not be obtained in any of the eight patients with at least two IUIs, and they were directed to IVF-ET. As a result, all 24 female patients (21 with primary infertility and three with secondary infertility) diagnosed with severe vaginismus were included in the IVF-ET programme. Antral follicle count and endometrial evaluation were performed with abdominal USG carried out on day 3 of the menstrual cycle. Likewise, on day 3 of the spontaneous cycle, basal hormonal levels of patients in the vaginismus and control groups were measured. A hysterosalpingogram was performed under sedation in all cases, and information was obtained about the fallopian tubes and endometrial cavity. Propofol (2 mg/kg, Polifarma, Tekirdağ, Turkey) was administered intravenously during sedation anaesthesia.

Patients were asked for psychiatric consultation before initiating controlled ovarian stimulation, and then detailed information about the treatment process was given. They were informed about follicle follow-up with abdominal USG, but folliculometry could be performed with USG under sedation if necessary, and their consent was obtained. All women with severe vaginismus were treated according to a standard antagonist protocol with individually dosed recombinant follicle-stimulating hormone starting on days 2-3 of the menstrual cycle. Gonadotrophin-releasing hormone antagonist was started on day 5 or 6 of

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stimulation. When at least three follicles reached 16-17 mm in diameter, maturation of follicles was induced with recombinant human chorionic gonadotropin (hCG) (Ovitrelle, Merck-Serono, 250 mg, Modugno, BA, Italy). In 21 of 24 cases, abdominal USG provided sufficient images of both follicle sizes and endometrial thickness, and no sedation was required. In the remaining three patients who were obese, folliculometry was performed under sedation each time, since follicle sizes were not clearly evaluated in abdominal USG. In all cases, serum oestradiol levels were measured at least three times during follow-up to minimise follicle measurement errors due to abdominal USG. Owing to the high-resolution quality of the USG used for folliculometry (GE Voluson 730), it was possible to follow the follicles in a healthy way, and the hCG application day was determined correctly. Oocyte collection was performed 36 h after hCG application. Ovarian follicles were aspirated using a single-lumen, 17-gauge needle (Cook Medical, Bloomington, IN, USA) guided by transvaginal USG.

Statistical Analysis

Statistical analyses were performed with the SPSS 20.0 software. Data were shown as mean ± standard deviation values or percentage. Percentages of demographic findings were compared using the paired t-test. A $p<0.05$ was considered significant.

RESULTS

Demographic characteristics of the vaginismus and control groups are shown in Table 2. This study included 24 patients with severe vaginismus, and the total number of IVF attempt performed on these patients was 35. Likewise, 35 cycles were performed on 24 patients in the control group. While 15 of 24 patients had their first attempt, eight patients had their second, and one patient had their fourth. Of the 35 cycles, 28 were fresh cycles and seven were freeze-thaw cycles. These three patients with infertility achieved their first pregnancy with IUI. However, they were directed to IVF because they could not get results from their IUI (transfer of washed sperm into the endometrium) trials for the second pregnancy. Of the 21 patients with primary infertility, eight tried IUI, but they were directed to IVF because pregnancy could not be obtained. The remaining 13 patients proceeded directly with IVF because they declined IUI. Folliculometry (measurement of follicle count and size) and endometrial evaluation was performed in three patients with BMI >30 with transvaginal scanning and under sedation. BMI of these patients were recorded as 34, 32 and 37, respectively. By contrast, in 21 patients with BMI within

Table 1. Classification of 24 women with vaginismus according to the Lamont-Pacik scale

Lamont grade	Severity	The number of patients (%)	IVF-ET
Lamont grade 1	First-degree vaginismus	3 (10.3%)	3 (follow-up)
Lamont grade 2	Second-degree vaginismus	2 (6.8%)	2 (follow-up)
Lamont grade 3	Third-degree vaginismus*	20 (68.9%)	20 (IVF-ET)
Lamont grade 4	Fourth-degree vaginismus*	4 (13.7%)	4 (IVF-ET)

*It is not possible to perform gynaecological examination and transvaginal ultrasonography without sedation in patients with Lamont grade 3 and 4 vaginismus.
IVF-ET: in vitro fertilisation and embryo transfer

Table 2. Demographic characteristics of participants with infertility due to vaginismus and control participants

Characteristics	Vaginismus (n=24)	Control (n=24)	p
Age (years)	29.3±4.4	29.0±3.7	0.678
Infertility duration (years)	4.9±2.9	6.0±3.3	0.129
IVF attempt, n	1.5±0.9	1.6±0.8	0.611
Day 2 E2 (pg/mL)	26.1±8.0	27.3±7.3	0.475
E2 on hCG day (pg/mL)	1338.6±453	1148.3±486	0.127
Day 2 P4 (ng/mL)	0.28±0.1	0.25±0.1	0.183
P4 on hCG day (ng/mL)	0.79±0.3	0.81±0.3	0.781
Total oocyte, n (per cycle)	11.2±4.9	9.94±3.8	0.277
MII oocyte, n	8.71±3.5	7.58±3.1	0.192
2 PN, n (per cycle)	6.61±3.0	6.00±2.7	0.413
Fresh or thaw cycle, n	31 fresh/8 thaw	28 fresh/7 thaw	1.0
Endometrial thickness (mm)	9.4±1.1	9.7±1.4	0.401
CPR*, n	20 of 39 cycles (51.2%)	25 of 35 cycles (71.4%)	0.097
LBR*, n	16 of 39 cycles (41.0%)	22 of 35 cycles (62.8%)	0.068

ET: embryo transfer, CPR: clinical pregnancy rate, LBR: live birth rate, PN: pronucleus, MII oocyte: metaphane II oocyte, IVF: in vitro fertilisation, hCG: human chorionic gonadotropin
*Data are given as mean ± standard deviation

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normal limits, folliculometry was performed with abdominal USG without sedation. Follicle measurements made with abdominal USG coincided with the measurements taken during the ovum pick-up (method for egg collection) in terms of both follicle size and number. ET (transfer of fertilised egg to the endometrial cavity via catheter) was performed on day 3 in 23 of the 35 cycles and day 5 in the remaining 12 cycles. Single ET was performed in a total of 27 cycles. In seven patients aged >35 years or were having their third or fourth attempt, two ETs were performed. Regardless of the infertility status, ET was performed under sedation in all cases.

Beta hCG positivity was detected in 20 of the 39 cycles. Similarly, in 20 cases, while clinical pregnancy was detected (20 of 39 cycles, 51.2%), the number of cycles with live births were 16 (16 of 39 cycles, 41.0%). While clinical pregnancy was detected in 25 of 35 cycles in the control group (71.4%), live birth was achieved in 22 cycles (62.8%). Compared with the vaginismus group, clinical pregnancy rate [clinical pregnancy rate (CPR); 20 vs 25, $p<0.09$] and live birth rate (LBR) were comparable (16 vs. 22, $p<0.06$). Although there was an increasing trend in CPR and LBR in the control group, the difference was not significant. No significant difference was found between the control group and vaginismus group in terms of other measured parameters (Table 2).

DISCUSSION

Vaginismus is a psychological and physical disorder manifested by fear and anxiety to penetration of the penis to vagina, and it is thought to be one of the most common female psychosexual dysfunctions (6). In the literature reviewed, no study was related to the management of infertile cases diagnosed with severe vaginismus, except case reports and small case series. Since it is not unusual to conduct a detailed research on women with vaginismus, it is not possible to describe clearly the fertility status of the patient and to determine the treatment method accordingly. In fact, it is incorrect to mention cases diagnosed as vaginismus as infertility. In mild vaginismus cases, different treatment approaches can be effective, whereas in severe cases, treatment is very difficult. For this reason, there is no option other than ART in patients who have been diagnosed with severe vaginismus and who desired pregnancy (9).

At present, many authors have regarded severe cases of vaginismus as the cause of infertility. Indeed, involuntary contractions in the paravaginal muscles sometimes lead to painful intercourse, sometimes making sexual intercourse impossible. By contrast, underlying psychosexual causes lead to loss of libido over time, contributing to the isolation of couples and thus to infertility (9,10). To our knowledge, there is no comprehensive research on the management of patients with vaginismus having infertility complaints. Most studies have been in the form of case reports and have focused on the diagnosis and treatment of vaginismus. In these studies, since patients were not classified according to the severity of vaginismus, all cases with mild, moderate, and severe vaginismus were placed in the same pool and treated as having a single form of disease. However, vaginismus has various subforms, with both psychological and physical components. Lamont and Pacik classified vaginismus according to their severity and offered treatment accordingly (6,8). Although a study suggested that patients with vaginismus can become pregnant with ejaculation exterior to the vagina, most patients require one of the ART techniques. Recently, Achour et al. (10) reported that 13 of 20 patients with vaginismus became pregnant with incomplete sexual intercourse without penetration. However, the authors did not specify the classification of vaginismus diagnosis and severity. This is a serious limitation, and data on vaginismus cases with spontaneous pregnancy are insufficient.

In the present study, we first confirmed the diagnosis of patients who presented with vaginismus complaints and who wanted to become pregnant. Then, we divided the patients into groups according to the Lamont scale (6,8). After classification, five patients with mild and moderate vaginismus (Lamont grade 1 and 2) were directed to personalised vaginismus treatment. Of these five patients, three had sexual intercourse after the treatments. The remaining two patients did not benefit from treatments for vaginismus. Classification of the severity of vaginismus is important as it assists in determining whether the patient will be directed to natural cycle or IVF-ET. Mild vaginismus may respond to sexual intercourse or IUI, whereas severe vaginismus requires IVF-ET. In patients with infertility due to vaginismus, disease severity should be evaluated according to the Lamont or Pacik scale and a treatment plan should be drawn accordingly. In patients with severe vaginismus (third or fourth degree), these cases should be directed to IUI or IVF as it is impossible to perform pelvic examination or transvaginal USG. Approximately 69% of our patients who presented with infertility complaint had third-degree vaginismus and 13% had fourth-degree vaginismus. None of the eight patients who had IUI from both groups could conceive, so they were referred to IVF-ET. As a result, clinical pregnancy was detected in 20 of the patients who underwent IVF-ET because of third- or fourth-degree vaginismus (57%), while term and live births were obtained in 16 cases (45.7%). In the light of these data, we can argue that in severe vaginismus, IUI is also futile similar to vaginal dilators, physical therapy with or without biofeedback, sex and relationship counselling, psychotherapy, cognitive behavioural therapy, hypnotherapy and lubricant treatments. For this reason, patients with severe vaginismus should be directed to IVF-ET immediately, and the loss of ovarian reserve should be prevented by averting delay due to palliative treatments.

Stratifying the severity of vaginismus in infertile cases helps the clinician choose among numerous infertility treatment options to better understand the disease form and patient's capability. Compared with other infertility disorders such as tubal factor or male factor infertility, treatment of vaginismus has potential for a high success rate following IVF-ET. In this study, approximately half of the patients achieved term pregnancy with IVF-ET. However, in severe cases, IUI failed. However, explaining the reason for IUI failure was the most challenging point. Three patients with severe

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vaginismus had previously achieved pregnancy with IUI. However, they could not conceive in their subsequent IUI. We believe that failure of subsequent IUI trials, despite successful pregnancy in the first IUI, was related to the individual characteristics of the patients rather than the severity of vaginismus. During our study, women with severe vaginismus had greater fear and anxiety to pelvic examination and had more difficulty with infertility treatment recommendations than women with milder forms of vaginismus. By contrast, many cases demonstrated palpitations, hyperventilation, trembling, uncontrollable shaking, screaming, hysteria, wanting to jump off the table, nausea and vomiting, both before and during sedation. In addition to fear and anxiety, all these visceral reactions encountered during IUI or ET may cause undesirable contractions in the sub-endometrial area, leading to decreased pregnancy rates. However, this idea should be clarified with further studies.

Study Limitations

Although this study presents original data, it has some limitations. Despite the low number of cases, this is the most comprehensive study addressing the management of vaginismus with ART. The fact that vaginismus is not considered a major problem in Western societies and this disease appears to be more of a problem in Middle East and Middle Asian societies does not weaken the power of this study. Despite all these limitations, this study provides comprehensive tips on management of infertile vaginismus cases.

CONCLUSION

This study is the most comprehensive series of management of infertility due to severe vaginismus, despite the small number of cases. In this study, patients with vaginismus more often presented to infertility clinics. Rather than providing patients with vaginismus directly with infertility treatment, classifying them according to the disease severity and treating them accordingly made the results more successful. In addition, classifying cases helps in the selection of treatable cases and individualisation of treatment. In severe vaginismus, couples may be directed to IUI and then IVF-ET. The CPR and LBR of women with infertility due to severe vaginismus receiving IVF-ET treatment are close to the infertile population without vaginismus. For this reason, IVF-ET may be one of the possible treatment options in the management of patients with infertility presenting with severe vaginismus.

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of the Nuh Naci Yazgan University (decision no: 2020/2, date: 20.08.2020).

Informed Consent: Written informed consent was obtained from all participants at the time of enrolment.

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REFERENCES

1. Basson R, Althof S, Davis S, Fugl-Meyer K, Goldstein I, Leiblum S, et al. Summary of the recommendations on sexual dysfunctions in women. J Sex Med 2004; 1: 24-34.
2. Amidu N, Owiredu W, Woo E, Addai Mensah O, Quaye L, Alhassan A, et al. Incidence of sexual dysfunction: a prospective survey in Ghanaian females. Reprod Biol Endocrinol 2010; 8: 106-11.
3. Bravo CS, Melendez JC, Ramirez SM, Lopez ME. Feminine and masculine sexual dysfunctions: gender comparison in a Mexico City sample [Disfunciones sexuales femininas y masculinas: Comparacion de genero en una muestra de la Ciudad de Mexico]. Salud Mental 2005; 28: 74-80.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders DSM-V, 5th ed. Washington, DC: American Psychiatric Association; 2013.
5. Spector IP, Carey MP. Incidence and prevalence of the sexual dysfunctions: a critical review of the empirical literature. Arch Sex Behav 1990; 19: 389-408.
6. Pacik PT. Understanding and treating vaginismus: a multimodal approach. Int Urogynecol J 2014; 25: 1613-20.
7. Catalan J, Bradley M, Gallwey J, Hawton K. Sexual dysfunction and psychiatric morbidity in patients attending a clinic for sexually transmitted diseases. Br J Psychiatry 1981; 138: 292-6.
8. Lamont JA. Vaginismus. Am J Obstet Gynecol 1978; 131: 633-66.
9. Souza MDCB, Gusmão MCG, Antunes RA, Souza MM, Rito ALS, Lira P, et al. Vaginismus in Assisted Reproductive Technology Centers: an invisible population in need of care. JBRA Assist Reprod 2018; 22: 35-41.
10. Achour R, Koch M, Zgueb Y, Ouali U, Ben Hmid R. Vaginismus and pregnancy: epidemiological profile and management difficulties. Psychol Res Behav Manag 2019; 12: 137-43.

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The Role of Procalcitonin and Other Markers of Inflammation in Predicting Spontaneous Passage of Ureteral Stones

Nusret Can Çilesiz[1], Burak Arslan[2], Mustafa Bahadır Can Balcı[2], Öykü Arslan[3], Barış Nuhoğlu[1]

[1]Biruni University Faculty of Medicine, Department of Urology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Urology, İstanbul, Turkey
[3]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Hematology, İstanbul, Turkey

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ABSTRACT

Objective: Ureteral stones are monitored for spontaneous passage in cases where there is no indication of interventional treatment. In this prospective study, we aimed to investigate the role of biochemical inflammation factors in predicting spontaneous passage.

Methods: Our study was conducted in patients who presented with ureteral stones between August and November 2016, following ethics committee approval and patient consent. The inflammatory markers [white blood cell (WBC), C-reactive protein, sedimentation, mean platelet volume, neutrophil/lymphocyte ratio, procalcitonin in serum; WBC and bacteria in urine] were recorded in 54 patients with 5-10 mm single ureteral stones and no indication for interventional treatment, and a control group of 33 volunteers with the same socio-demographic conditions. Medical expulsive therapy was applied to the case group and followed for 4 weeks. At the end of the follow-up, the case group was divided into two groups as passage (+) and passage (-). The groups' data were compared statistically.

Results: Distal localization (70% vs 37.5%; $p<0.05$) was significantly higher in the passage (+) group than in the passage (-). Procalcitonin (207±145.1 pg/mL) was significantly higher ($p<0.05$) in the passage (-) group than in the passage (+) group (132.7±28.1 pg/mL). In the passage (-) group, the rate of leukocyturia (58.3% vs 20%; $p<0.05$) was higher than in the passage (+) group. A significant activity of procalcitonin value [0.805 (0.687-0.923) under the curve] was observed in the separation of patients with and without passages. A significant activity of procalcitonin 160 pg/mL cut-off value [0.788 (0.658-0.917) under the curve] was observed in the separation of patients with and without passages. Sensitivity was 86.7%, specificity was 70.8%, positive estimate was 78.8%, negative estimate was 81.0%.

Conclusion: Spontaneous passage in ureteral stones can be estimated by looking at serum procalcitonin levels. The receiver operating characteristic curve showed that for serum procalcitonin, the cut-off value of 160 pg/mL may have significant effectiveness. In addition, leukocyturia is also one of the factors that negatively affect spontaneous passage.

Keywords: Ureteral stone, medical expulsive therapy, follow-up

ORCID IDs of the authors: N.C.Ç. 0000-0003-2115-698X; B.A. 0000-0001-6629-5153; M.B.C.B. 0000-0003-0395-1154; Ö.A. 0000-0003-0135-2967; B.N. 0000-0001-8104-0853.

Sorumlu Yazar/Corresponding Author: Nusret Can Çilesiz,
E-mail: nusretcancilesiz@gmail.com

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INTRODUCTION

Urinary tract stone disease is the third most common urinary tract disease after urinary tract infection and benign prostatic hyperplasia. The lifetime rate of urinary tract stone disease is 13% for men and 7% for women. It most affects the population aged 30-60 years. The likelihood of recurrence increases over the years and reaches 50% within 5 years (1). In recent years, the spread of sedentary life and poor eating habits has increased the likelihood of urinary tract stone disease.

Urinary tract stones are most commonly detected in the kidney, while 20% are detected in ureteral localization (2). The most common cause of renal colic, one of the common problems in the emergency department, is ureteral stones with a ratio of 60-95% (3). Renal colic, characterized by nausea-vomiting that accompanies sudden flank pain and lower urinary tract symptoms that may accompany it, significantly affects the quality of life.

A significant portion of ureteral stones can fall spontaneously. Follow-up with medical treatment of newly diagnosed ureteral stones less than 10 mm is a recommended treatment alternative. In recent years, spontaneous passage anticipation and medical expulsive therapy (MET) have been added to the European Urological Association urolithiasis and the American Urological Association (AUA) ureteral stone guidelines. In these guidelines, MET is recommended as an initial treatment for ureteral stones smaller than 10 mm (4).

Treatment options in ureteral stones are 3 main groups: MET, ureteroscopy (URS) and shock wave lithotripsy (SWL). MET is a lower-cost active observation option that can save administered patients from interventional therapies (URS, SWL) and the complications that these interventions can create. In the MET protocol, patients are followed up to 4-6 weeks by administration of hydration, analgesic (non-steroidal anti-inflammatory drug) and alpha-blocker drugs (mostly tamsulosin). In case of acute renal failure, sepsis, progressive hydronephrosis and uncontrollable pain that develops despite treatment in follow-up of patients, or if spontaneous passage does not occur after 4-6 weeks, the interventional treatment stage is switched (4).

Spontaneous passage cannot be achieved in all patients given MET. The most important predictive parameters in this regard are the size of the stone (<5 mm, >5 mm) and its localization (proximal, mid, distal). According to AUA, 68% of <5 mm stones; 47% of >5 mm stones observed spontaneous passages (5). In recent years, studies have been published showing that biochemical inflammation factors can predict spontaneous passage (6-8). In this study, we aimed to present the role of biochemical inflammation factors [serum white blood cell (WBC), C-reactive protein (CRP), sedimentation, mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), procalcitonin and urine WBC, bacteria] in predicting spontaneous passage in ureteral stones between 5-10 mm in size in line with statistical analysis.

METHODS

This prospective observational case-control study was conducted in patients who presented to our outpatient clinic between August 2016 and November 2016 and were diagnosed with ureteral stones, after ethics committee approval (decision no: 05/2016, date: 27.01.2021) and patient consent. The case group included 54 patients aged 20-60 years with an attack of renal colic and with a single ureteral stone of 5-10 mm in non-contrast computed tomography (CT) imaging.

Multiple stones, stone tract after SWL or URS, bilateral ureteral stones, solitary kidney, contralateral atrophic kidney, severe hydronephrosis, symptomatic urinary tract infection, signs of acute renal failure, congenital ureteral anomaly, history of ureteral stricture or reconstructive ureter surgery history, patients who were started on anti-inflammatory and/or antibiotic therapy for existing ureteral stones were not included. Exclusion criteria were active infectious disease, chronic inflammatory disease (ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, etc.), active neoplasia, cardiovascular disease, obesity, diabetes mellitus, thyroid disease or previous thyroid surgery, immunosuppression or immunosuppressive therapy.

In the control group, 33 healthy volunteers between the ages of 20-60, who had no history of stone disease, no chronic or active disease, whose socio-demographic characteristics were similar to the case group were included. Age, gender, body mass index (BMI), smoking habits, chronic diseases, drug allergies, history of stones (stone reduction, stone surgery or SWL treatment) were questioned and recorded during the first examination of the patients. The degree of pain was noted using the visual analog scale (VAS) score. A patient registration form containing patient socio-demographic information, laboratory results, procalcitonin results, imaging data and control records created during follow-up was completed for all cases. All forms were then registered using Microsoft® Excel®.

Case and control groups (n=87) were evaluated with complete blood stripping, CRP, sedimentation, serum procalcitonin, complete urinalysis and ICAB (urine culture antibiogram). WBC, NLR, MPV, red cell distribution width (RDW) values were noted in the complete blood count.

Leukocyturia and bacteriuria were recorded in the complete urinalysis. Presence and degree of hyphronephrosis of the case group were evaluated ultrasonographically. The serum obtained centrifuging the 5 mL blood sample taken during the first examination was kept until the day the procalcitonin kit will be used. It was stored -20 °C. Biovendor® (Czech Republic), Human Procalcitonin ELISA (RD191006200R) measurement kit was used for procalcitonin measurement. The serums studied by the Biotek Elx-800 microplate reader device were measured using the Biotek brand Gen5 software program. CT scans (n=54) taken at University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital were performed using Infiniti® software over the hospital Picture-Archiving and Communication

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System; in the axial and coronal sections, 1.5 and 5 mm sections were measured and recorded by a single physician. The side of the stone (right/left), location (proximal, mid, distal), size (measurement of the longest segment), area (width x height) and degree of hydronephrosis were noted using a spiral CT of the entire abdomen without contrast, in which patients received a diagnosis of ureteral stones. In determining the localization of the stone, the section up to the upper border of the sacroiliac joint was determined as the proximal urethra, the section extending along the sacroiliac joint was determined as the mid urethra, and the section from the lower border of the sacroiliac joint to the bladder was determined as the distal urethra. When calculating the size of the stone, coronal and axial images in cross-sectional imaging were also used. Patients who did not have indications for interventional treatment received monitoring by starting MET. For MET, patients were prescribed one diclofenac sodium 75 mg/day (if necessary) and one tamsulosin 0.4 mg/day. In addition, an average daily fluid intake of 2-3 liters was recommended. Patients who were started on MET were called to outpatient controls every two weeks, except for emergencies. During the control of the outpatient clinic, it was questioned whether the patients had passed the stone or not, whether they applied to the emergency department due to renal colic during this treatment period, and their VAS score. In addition, the presence of progressive hydronephrosis was checked with ultrasonography (USG). Among those who stated that they could not pass the stone, the presence of the stone was confirmed by Doppler USG in the second and fourth weeks in those with opaque stones, and in the fourth week of non-opaque non-contrast abdominal CT. At the end of the study, those who could not drop the stone passage (-); those who dropped the stone were grouped as passage (+).

Statistical Analysis

Mean, standard deviation, median, lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, Fisher's Exact test was used when chi-square test conditions were not met. Effect level and cut-off values were investigated using the receiver operating characteristic curve. SPSS 22.0 program was used in the analyses and $p<0.05$ was considered statistically significant.

RESULTS

At the end of the study, 30 patients (55.5%) were able to pass ureteral stones, it was found that 24 patients (45%) could not reduce it. During the follow-up period, none of the patients had findings that required interventional treatment such as fever, persistent and uncontrollable renal colic attacks, progressive hydronephrosis and renal failure. When the patients in the case and control groups were compared in terms of age, gender distribution, BMI value, smoking rate and stone surgery history, no significant difference was found. Considering the rate of extracorporeal SWL and stone-passing history, there was a significant increase in the case group compared to the control group ($p<0.05$) (Table 1).

Laboratory values were not significantly different between both groups in terms of WBC value, bacteriuria rate and CRP value, while RDW value, NLR value, leukocyturia rate, sedimentation value and procalcitonin value were significantly higher in the case group than in the control group ($p<0.05$) (Table 2).

Mean age was calculated (35.8±9.3) in the group with passage (-); and (38±10.9) in the group with passage (+). BMI was calculated (26.4±4.7) in the group with passage (-); and (26.5±3.6) in the group with passage (+). Compared statistically, no significant differences were found between the age, gender distribution, BMI, and smoking rates of patients in the group with and without a passage (Table 3).

Patients in the group with and without passages did not have statistically significant differences in terms of kidney stone reduction (36.7%/37.5%), SWL history (12.5%/16.7%) and stone surgery history (8.3%/6.7%). There were no statistically significant differences in stone size (6.5±1.4 mm vs 7±1.2 mm), stone area (36.4±12.9 mm^2 vs 37.5±10.3 mm^2), primary/secondary distribution and laterality in patients in the group with and without passages. However, compared to the non-passage group, the localization rate of the stone to the distal urethra in the passage group was statistically significant (70% vs 37.5%) ($p<0.05$) (Table 3).

No statistically significant difference was found between the two groups with and without a passage; in terms of WBC value (9.1±2.4 vs 8.4±2.3), RDW value (15.4±1.5 vs 15.5±2.4), NLR value (2.9±1.7 vs 2.8±1.7), MPV value (8.5±1.3 vs 8.7±0.6), CRP value (11.5±15.4 vs 9.8±8.2), sedimentation rate (14.7±11.7 vs 11.8±7.0), bacteriuria rate (6.7% vs 0%), and hydronephrosis grade. However, procalcitonin level (207±145.1 pg/mL vs 132.7±28.1 pg/mL) and leukocyturia rate (58.3% vs 20%) were significantly higher in the non-passage group ($p<0.05$) (Table 4).

In the differentiation of patients with and without passage, the procalcitonin value [area under the curve 0.805 (0.687-0.923)] and the procalcitonin 160 pg/mL cut-off value [area under the curve 0.788 (0.658-0.917)] was found to be significant. Sensitivity was 86.7%, specificity was 70.8%, positive prediction was 78.8%, and negative prediction was 81.0% (Table 5) (Figure 1).

When the initial VAS pain score was compared, there was no significant difference between the two groups, while the 2nd week VAS pain score of the non-passage group was significantly higher than the passage group (3.7±2.4 vs 2.7±1.8) ($p<0.05$). Similarly, the 4th week VAS pain score of the group without passage was significantly higher than the group with passage (3.0±1.8 vs 0.8±1.0) ($p<0.05$) (Table 6).

DISCUSSION

In recent studies, the probability of spontaneous passage of ureteral stones is 71-100% in <5 mm stones; it has been reported that it is 25-46% in stones between 5-10 mm, and the probability of spontaneous passage within 40 days of ureteral stones with a

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diameter of <4 mm is 95% (5,9,10). Demehri et al. (11) reported that spontaneous passage was seen in 89.9% of stones <5 mm, 63.4% of stones with a size of 5-10 mm, and only 9.1% of stones with a size >10 mm. Chau et al. (12) reported that spontaneous passage of ureteral stones between 5-10 mm was 50% and 81.8% in the control group given medical expulsive therapy. In our study, the spontaneous passage rate after 4 weeks of follow-up in patients with a stone size of 5-10 mm and undergoing medical expulsive therapy was calculated as 55.5%.

Factors that increase the likelihood of spontaneous passage in ureteral stones are generally known as the size of the stone <5 mm, distal placement, lack of hydronephrosis, while many studies have recently been published on these factors. In a study conducted by Ahmed et al. (13), factors that increase the likelihood of spontaneous passage in ureteral stones <10 mm were listed as less than <5 mm in size, distal placement, serum WBC height, perinephric fat thickening. Aldaqadossi (14) reported that those with CRP height in distal ureteral stones were less likely to have spontaneous passage.

In another study, Hwang et al. (15) reported URS findings of impacted distal ureteral stones <5 mm. In this study, luminal stenosis caused by severe mucosal edema was reported in 30% of the patients, and it was emphasized that mucosal inflammation, which is generally seen in impacted stones, can also be revealed by the tissue rim-sign finding on imaging. Sarica et al. (16) reported that the ureteral wall thickness had a very high effect

Table 1. Comparison of the socio-demographic characteristics of the case and control groups

		Control			Case			p
		Mean ± SD/n-%		Med	Mean ± SD/n-%		Med	
Age		33.9±8.3		32.0	37.1±10.2		36.0	0.159[m]
Gender	Female	6	18.2%	-	16	29.6%	-	0.233[X²]
	Male	27	81.8%		38	70.4%		
BMI		24.8±5.1		25.4	26.5±4.1		26.2	0.245[m]
Smoking	No	21	63.6%	-	26	48.1%	-	0.293[X²]
	Yes	12	36.4%		28	51.9%		
P/S	Primary	33	100.0%	-	32	59.3%	-	0.000[X²]
	Secondary	0	0.0%		22	40.7%		
ESWL history	No	33	100.0%	-	46	85.2%	-	0.020[X²]
	Yes	0	0.0%		8	14.8%		
Stone dropping history	No	33	100.0%	-	36	66.7%	-	0.000[X²]
	Yes	0	0.0%		18	33.3%		
Stone surgery history	No	33	100.0%	-	50	92.6%	-	0.293[X²]
	Yes	0	0.0%		4	7.4%		

[m]Mann-whitney U test, [X²]chi-square test. BMI: body mass index, ESWL: extracorporeal shock wave lithotripsy, SD: standard deviation, Med: median, P/S: primary/secondary

Table 2. Comparison of serum and urinary inflammation markers of case and control groups

		Control group		Case group		p
		Mean ± SD/n-%	Med	Mean ± SD/n-%	Med	
WBC		8.0±1.9	7.5	8.8±2.3	8.3	0.053[m]
RDW		12.8±0.9	12.5	15.5±1.9	15.2	0.000[m]
NLR		2.0±0.3	2.2	2.8±1.7	2.3	0.009[m]
MPV		8.5±0.7	8.4	8.6±1.0	8.6	0.451[m]
Bacteriuria	No	33/100%	-	52/96.3%	-	0.524[X²]
	Yes	0/0.0%	-	2/3.7%	-	
Leukocyturia	No	33/100%	-	34/63.0%	-	0.000[X²]
	Yes	0/0.0%	-	20/37.0%	-	
CRP		4.0+1.1	3.4	10.4±12.6	4.7	0.088[m]
Sedimentation		4.2+1.3	4.0	13.4±9.9	11.0	0.000[m]
Procalcitonin		128.2+36.6	124.6	165.7±104.7	145.8	0.004[m]

[m]Mann-Whitney U test, [X²]chi-square test. WBC: white blood cell, RDW: red cell distribution width, NLR: neutrophil/lymphocyte ratio, MPV: mean platelet volume, CRP: C-reactive protein, SD: standard deviation, Med: median

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on the stone-free rates in impacted proximal ureteral stones that underwent SWL. In this study, the sensitivity of the cut-off value of 3.55 mm for ureteral wall thickness was reported as 91.7%, the specificity as 77%. In light of this information, we investigated the predictability of spontaneous passage with serum inflammation markers based on the association of impacted ureteral stone-mucosal inflammation. As a result of our study, serum WBC, RDW, NLR, MPV, CRP, sedimentation values did not have a role in determining spontaneous passage in patients we followed up with medical expulsive therapy, however, leukocyturia rate and high serum procalcitonin values were statistically significant (p=0.004, p<0.001). We concluded that it reduces the possibility of spontaneous passage. As a result of statistical analysis, we concluded that those whose serum procalcitonin value is less than 160 pg/mL are more likely to have spontaneous passage. In addition, in parallel with other studies, we found that distal ureteral stones are significantly more likely to be spontaneous passage (p<0.05). We believe that it is important to demonstrate the ability of procalcitonin and leukocyturia to predict passage, unlike other markers.

Procalcitonin is a polypeptide consisting of 116 amino acids with a molecular weight of about 13 kilodaltons. This hormone was first described by Ghillani et al. (17) in 1989 as a precursor of calcitonin, which is produced in the thyroid gland and contains 32 amino acids. Activated calcitonin is produced by proteolytic enzymes in the C-cells of the thyroid. Production of procalcitonin and calcitonin begins with the transcription of the preprocalcitonin precursor containing 141 amino acids. It has been shown that endotoxins increase in sepsis and inflammation, and procalcitonin levels increase in the body shortly after the release of immune mediators (18). Studies have shown that procalcitonin causes significant inhibition of prostaglandin and thromboxane synthesis in lymphocytes *in vitro*. Inhibition of cyclooxygenase activity has been held responsible for this inhibition (19).

Procalcitonin increases 4-6 hours after endotoxin administration, peaks at 6-8 hours, and plateaus from 12-48 hours due to a half-life of 25-30 hours (20). The value of procalcitonin in the normal population is known as <0.05 ng/mL. In systemic infections, it can reach levels of 2 ng/mL; in sepsis, it can reach levels of 10 ng/mL (21,22).

Table 3. Comparison of socio-demographic and stone history characteristics of the group with and without passage

		Passage (-)		Passage (+)		p
		Mean ± SD/n (%)	Med	Mean ± SD/n (%)	Med	
Age		35.8±9.3	35.0	38.0±10.9	38.0	0.381[m]
Gender	Female	10 (41.7%)	-	6 (20.0%)	-	0.083[X²]
	Male	14 (58.3%)		24 (80.0%)		
BMI		26.4±4.7	26.2	26.5±3.6	26.2	0.781
Smoking	No	12 (50.0)	-	14 (46.7%)	-	0.808[X²]
	Yes	12 (50.0)		16 (53.3%)		
2nd week passage		-	-	8 (26.7%)	-	-
4th week passage				26 (86.7%)		
Stone dropping history	No	15 (62.5%)	-	19 (63.3%)	-	0.950[X²]
	Yes	9 (37.5%)	-	11 (36.7%)	-	
	Right	6 (25.0%)	-	6 (20.0%)	-	
	Left	3 (12.5%)	-	5 (16.7%)	-	
ESWL history	No	21 (87.5%)	-	25 (83.3%)	-	0.668[X²]
	Yes	3 (12.5%)	-	5 (16.7%)	-	
Stone surgery history	No	22 (91.7%)	-	28 (93.3%)	-	0.816[X²]
	Yes	2 (8.3%)	-	2 (6.7%)	-	
Stone size (mm)		7.0±1.2	7.0	6.5±1.4	6.4	0.200[m]
Stone area (mm²)		37.5±10.3	34.2	36.4±12.9	30.0	0.310[m]
P/S	Primary	15 (62.5%)	-	17 (56.7%)	-	0.665[X²]
	Secondary	9 (37.5%)	-	13 (43.3%)	-	
Side	Right	10 (41.7%)	-	12 (40.0%)	-	0.901[X²]
	Left	14 (58.3%)	-	18 (60.0%)	-	
Localization	Proximal	7 (29.2%)	-	2 (6.7%)	-	0.029[X²]
	Mid	8 (33.3%)	-	7 (23.3%)	-	
	Distal	9 (37.5%)	-	21 (70.0%)	-	

[m]Mann-Whitney U test, [X²]chi-square test, SD: standard deviation, BMI: body mass index, ESWL: extracorporeal shock wave lithotripsy, Med: median, P/S: primary/secondary

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Table 4. Statistical comparison of stone size, area, side and localization of the case group in the group with and without passage

		Passage (-)	Pasaj (+)	p
		Mean ± SD (Med)/n (%)	Mean ± SD (Med)/n (%)	
WBC		8.4±2.3 (8.0)	9.1±2.4 (8.7)	0.261[m]
RDW		15.5±2.4 (15.1)	15.4±1.5 (15.4)	0.657[m]
NLR		2.8±1.7 (2.3)	2.9±1.7 (2.6)	0.821[m]
MPV		8.7±0.6 (8.7)	8.5±1.3 (8.5)	0.721[m]
CRP		9.0±8.2 (5.4)	11.5±15.4 (14.2)	0.875[m]
Sedimentation		11.8±7.0 (11.0)	14.7±11.7 (12.0)	0.558[m]
Procalcitonin		207.0±45.1 (173.1)	132.7±28.1 (134.6)	0.000[m]
Bacteriuria	Yok	24 (100%)	28 (93.3%)	0.497[X²]
	Var	0 (0.0%)	2 (6.7%)	
Leukocyturia	Yok	10 (41.7%)	24 (80.0%)	0.004[X²]
	Var	14 (58.3%)	6 (20.0%)	
Hydronephrosis	I	12 (50.0%)	19 (63.3%)	0.325[X²]
	II	11 (45.8%)	10 (33.3%)	
	III	1 (4.2%)	1 (3.3%)	

[m]Mann-Whitney U test, [X²]chi-square test. SD: standard deviation, WBC: white blood cell, RDW: red cell distribution width, NLR: neutrophil/lymphocyte ratio, MPV: mean platelet volume, CRP: C-reactive protein, Med: median

Table 5. Sensitivity and specificity of procalcitonin 160 pg/mL cut-off value in predicting spontaneous passage of ureteral calculi according to ROC

	Area under the curve	95% Confidence interval	p
Procalcitonin	0.805	0.687-0.923	0.000
Cut-off 160 pg/mL	0.788	0.658-0.917	0.000
ROC		Sensitivity	86.7%
		Positive prediction	78.8%
		Specificity	70.8%
		Negative prediction	81.0%

ROC: receiver operating characteristic curve

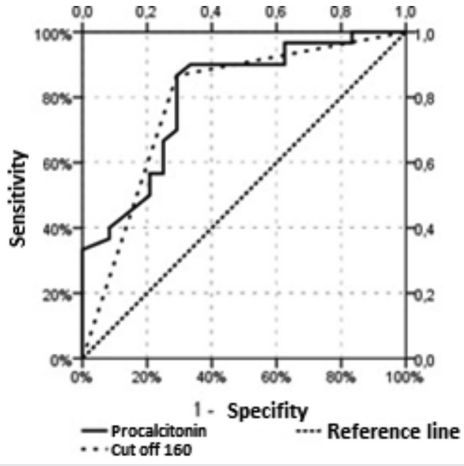

Figure 1. ROC for procalcitonin 160 pg/mL cut-off value in predicting spontaneous passage
ROC: receiver operating characteristic curve

In our study, the cut-off value of procalcitonin in estimating the passage was calculated as 160 pg/mL (=0.16 ng/mL). The average value of the non-passage group was 207+145.1 pg/mL and the non-passage group was 132.7+28.1 pg/mL. We think that the elevation of procalcitonin in the non-passage group is associated with the excess of mucosal inflammation. The excess of this mucosal inflammation may have increased the impaction of the stones in the future and made their passage difficult. Between the two groups; The statistically significant difference in the second week (3.7/2.7) and fourth week (3.0/0.8) VAS scores may also explain the difference in mucosal inflammation and edema.

Procalcitonin is used in the early and reliable diagnosis of sepsis, in determining the severity of sepsis, in the differential diagnosis of acute pancreatitis infection and sterile necrosis, in autoimmune diseases, in differentiating acute organ rejection from bacterial infection, as an early indicator of post-operative bacterial or septic infectious complications, and in the follow-up of neutropenic patients after chemotherapy (18,23). In addition, studies have been published in recent years indicating that procalcitonin can detect relapses in patients with chronic prostatitis, that the infection rate in obstructed ureteral stones and the elevation of procalcitonin are correlated, that it can detect the severity of inflammation in patients with cholecystitis, and its importance in the diagnosis of bacterial arthritis (24-27). In our study, it was investigated whether procalcitonin values were effective in the decision to follow-up of patients diagnosed with ureteral stones.

When the study groups were compared, it was revealed by statistical analysis that the patients were homogeneous in terms of socio-demographic characteristics (age, gender distribution, BMI, smoking) and features that may cause anatomical stenosis (history of stone loss, open ureterolithotomy, URS, SWL). Procalcitonin elevation and the presence of leukocyturia were

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Table 6. Comparison of the group with and without passage according to baseline, 2nd and 4th week control VAS scores

	Passage (-)		Passage (+)		p
	Ortalama ± SD	Med	Ortalama ± SD	Med	
VAS pain score					
Start	9.1±1.0	9.5	8.6±1.2	8.0	0.089[m]
2nd week	3.7±2.4	4.0	2.7±1.8	3.0	0.049[m]
4th week	3.0±1.8	3.0	0.8±1.0	0.0	0.000[m]

[m]Mann-Whitney U test, SD: standard deviation, VAS: visual analog scale, Med: median

found to be statistically significantly higher in the two groups, which were homogeneous with all their features except localization distribution. We think that finding a statistically significant cut-off value of 160 pg/mL for procalcitonin in our study is promising. We believe that procalcitonin can be effective in the decision of follow-up or interventional treatment of patients, especially in ureteral stones with a size of 5-10 mm, which are less likely to have spontaneous passage compared to stones <5 mm.

In a study conducted by Ahmed et al. (13), it was reported that the number of leukocytes in urine microscopy did not differ statistically significantly in the group with and without passages. In one study, it was noted that treatment with Rowatinex® after SWL is an effective treatment for getting rid of residual fragments, and leukocyturia is significantly reduced after Rowatinex® use (28). In our study, leukocyturia was observed in 20% of the group with passage and in 58.3% of the group without passage, and a statistically significant difference was found between them (p=0.004). We think that the higher rate of sterile leukocyturia seen in urine analysis in the non-passage group indicates excess mucosal inflammation.

Study Limitations

We think that the small number of our cohort and the lack of repeated measurements are limitations. We think that the large number of case groups may enable analysis by dividing them into subgroups (proximal, mid and distal), especially according to the localization of ureteral stones at the initial diagnosis stage, and the analysis of these homogeneous groups may increase the value of the study.

CONCLUSION

In recent years, studies have been conducted that predict that biochemical inflammation factors may be one of the predictive factors in predicting spontaneous passage. In our study, procalcitonin levels were used for the first time to predict the passage of ureteral stones between 5-10 mm, and it was found that the height of the level may be a factor that complicates the passage. Our findings suggest that procalcitonin level measurement may be possible to take place in daily urology practice after studies with higher series. In addition, our findings suggest that the presence of leukocyturia in patients with ureteral stones may be a factor that complicates spontaneous passage.

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Gaziosmanpaşa Training and Research Hospital (decision no: 05/2016, date: 27.01.2021).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Jungers P, Joly D, Barbey F, Choukroun G, Daudon M. ESRD caused by nephrolithiasis: prevalence, mechanisms, and prevention. Am J Kidney Dis 2004; 44: 799-805.
2. Pak CY. Kidney stones. Lancet 1998; 351: 1797-801.
3. Tamm EP, Silverman PM, Shuman WP. Evaluation of the patient with flank pain and possible ureteral calculus. Radiology 2003; 228: 319-29.
4. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU guidelines on diagnosis and conservative management of urolithiasis. Eur Urol 2016; 69: 468-74.
5. Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck AC, Gallucci M, et al; American Urological Association Education and Research, Inc.; European Association of Urology. 2007 Guideline for the management of ureteral calculi. Eur Urol 2007; 52: 1610-31. 6.Sfoungaristos S, Kavouras A, Katafigiotis I, Perimenis P. Role of white blood cell and neutrophil counts in predicting spontaneous stone passage in patients with renal colic. BJU Int 2012; 110: E339-45. doi: 10.1111/j.1464-410X.2012.11014.x.
7. Kim BH. the authors reply: relationship between spontaneous passage rates of ureteral stones less than 8 mm and serum C-reactive protein levels and neutrophil percentages. Korean J Urol 2013; 54: 889-90.
8. Angulo JC, Gaspar MJ, Rodríguez N, García-Tello A, Torres G, Núñez C. The value of C- reactive protein determination in patients with renal colic to decide urgent urinary diversion. Urology 2010; 76: 301-6.
9. Skolarikos A, Laguna MP, Alivizatos G, Kural AR, de la Rosette JJ. The role for active monitoring in urinary stones: a systematic review. J Endourol 2010; 24: 923-30.
10. Miller OF, Kane CJ. Time to stone passage for observed ureteral calculi: a guide for patient education. J Urol 1999; 162: 688-90; discussion 690-1.
11. Demehri S, Steigner ML, Sodickson AD, Houseman EA, Rybicki FJ, Silverman SG. CT- based determination of maximum ureteral stone area: a predictor of spontaneous passage. AJR Am J Roentgenol 2012; 198: 603-8.
12. Chau LH, Tai DC, Fung BT, Li JC, Fan CW, Li MK. Medical expulsive therapy using alfuzosin for patient presenting with ureteral stone less than 10mm: a prospective randomized controlled trial. Int J Urol 2011; 18: 510-4.
13. Ahmed AF, Gabr AH, Emara AA, Ali M, Abdel-Aziz AS, Alshahrani S. Factors predicting the spontaneous passage of a ureteric calculus of ≤10 mm. Arab J Urol 2015; 13: 84-90.
14. Aldaqadossi HA. Stone expulsion rate of small distal ureteric calculi could be predicted with plasma C-reactive protein. Urolithiasis 2013; 41: 235-9.

J Acad Res Med 2021;11(2):179-86

15. Hwang E, Kim YH, Yuk SM, Sul CK, Lim JS. Factors that predict spontaneous passage of a small distal ureteral stone <5 mm. J Endourol 2010; 24: 1681-5.
16. Sarica K, Kafkasli A, Yazici Ö, Çetinel AC, Demirkol MK, Tuncer M, et al. Ureteral wall thickness at the impacted ureteral stone site: a critical predictor for success rates after SWL. Urolithiasis 2015; 43: 83-8.
17. Ghillani PP, Motte P, Troalen F, Jullienne A, Gardet P, Le Chevalier T, et al. Identification and measurement of calcitonin precursors in serum of patients with malignant diseases. Cancer Res 1989; 49: 6845-51.
18. Meisner M. Procalcitonin: a new innovative infection parameter. In: Meisner M, editor. Biochemistry. Stuttgart: Brahms Diagnostica; 2000. p.15
19. Oczenski W, Fitzgerald RD, Schwarz S. Procalcitonin: a new parameter for the diagnosis of bacterial infection in the peri-operative period. Eur J Anaesthesiol 1998; 15: 202-9.
20. Demirdağ K, Özden M, Gödekmerdan A, Cihangiroğlu M, Kalkan A. Sepsis olgularında prokalsitonin, TNF- ve C-reaktif protein düzeylerinin değerlendirilmesi. Klimik Derg 2003; 16: 21-4.
21. Braithwaite SS. Procalcitonin: new insights on regulation and origin. Crit Care Med 2000; 28: 586-88.
22. Claeys R, Vinken S, Spapen H, ver Elst K, Decochez K, Huyghens L, et al. Plasma procalcitonin and C-reactive protein in acute septic shock: Clinical and biological correlates. Crit Care Med 2002; 30: 757-62.
23. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation,infection, and sepsis: clinical utility and limitations. Crit Care Med 2008; 36: 941-52.
24. Çakıroğlu B, Eyyüpoğlu E, Balcı MBC, Hazar Aİ, Uyanık BS, Doğan AN. The evaluation of the procalcitonin levels in chronic prostatitis patients. Nobel Med 2016; 12: 60-5.
25. Yuzbasioglu Y, Duymaz H, Tanrikulu CS, Halhalli HC, Koc MO, Tandoğan M, et al. Role of procalcitonin in evaluation of the severity of acute cholecystitis. Eurasian J Med 2016; 48: 1621-6.
26. Martinot M, Sordet C, Soubrier M, Puéchal X, Saraux A, Lioté F, et al. Diagnostic value of serum and synovial procalcitonin in acute arthritis: a prospective study of 42 patients. Clin Exp Rheumatol 2005; 23: 303-10.
27. Papagiannopoulos D, Whelan P, Ahmad W, Rybak J, Hota B, Deane L, et al. Procalcitonin is a strong predictor of urine culture results in patients with obstructing ureteral stones: A prospective, pilot study. Urol Ann 2016; 8: 277-80.
28. Alyaev YG, Rudenko VI, Perekalina AN, Kraev IG, Inoyatov ZS. Plant-derived terpenes in treating patients with urolithiasis. Urologiia. 2016; (Suppl 2): 103-10. (Russian)

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Hematological Parameters and Leukocyte Formulas in Predicting Celiac Disease in Children with Iron Deficiency Anemia

Zeynep Canan Özdemir[1], Yeter Düzenli Kar[1], Polat Cengiz Bektaş[2], Makbule Eren[3], Muzaffer Bilgin[4], Özcan Bör[1]

[1]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology and Oncology, Eskişehir, Turkey
[2]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Eskişehir, Turkey
[3]İstinye University Faculty of Medicine; Liv Hospital, Department of Pediatrics, Divison of Pediatric Gastroenterology Hepatology and Nutrition, İstanbul, Turkey
[4]Eskişehir Osmangazi University Faculty of Medicine, Department of Biostatistics, Eskişehir, Turkey

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ABSTRACT

Objective: Celiac disease (CD) is a systemic inflammatory disease associated with a number of hematological findings. The most common symptom other than the intestinal system is iron deficiency anemia (IDA). It is difficult to distinguish IDA that occurs in CD from nutritional IDA. In this study, the use of hematological parameters and leukocyte formulas, which are reported to be of diagnostic importance in inflammatory diseases, as a screening test in predicting CD in children with IDA was investigated.

Methods: Forty-six children with CD and IDA, 46 children with nutritional IDA and 46 healthy children as a control group were included in the study. The patient files were examined retrospectively. The blood count parameters [Hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte, leukocyte, neutrophil, lymphocyte, platelet count] of the patients before starting iron therapy were recorded. Leukocyte formulas [neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), RDW/lymphocyte ratio (RLR)] were calculated.

Results: There was no difference between the patient and control groups in terms of age and gender distribution ($p>0.05$). Hb, MCV, MCH, MCHC values of CD+IDA and IDA groups were lower than the values of the control group ($p<0.001$, for all), RDW, RLR, PLR values, and platelet count were higher than the values of the control group ($p<0.001$ and $p<0.001$; $p<0.05$ and $p<0.01$; $p<0.05$ and $p<0.05$; $p<0.001$ and $p<0.05$, respectively). Leukocyte, neutrophil, lymphocyte, erythrocyte counts, MPV, PDW, NLR were found to be similar in the patient and control groups ($p>0.05$ for all). There was no difference between the patient groups in terms of NLR, PLR, and RLR ($p>0.05$ for all).

Conclusion: Our study showed that hematological parameters and leukocyte formulas are not useful in predicting CD in children with IDA.

Keywords: Child, celiac disease, iron deficiency anemia, hematological parameters, leukocyte formulas

ORCID IDs of the authors: Z.C.Ö. 0000-0002-9172-9627; Y.D.K. 0000-0003-2917-7750; P.C.B. 0000-0001-9757-5692; M.E. 0000-0002-7105-7165; M.B. 0000-0002-6072-6466; Ö.B. 0000-0002-1662-3259.

Sorumlu Yazar/Corresponding Author: Zeynep Canan Özdemir,
E-mail: efecanan@yahoo.com

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INTRODUCTION

Celiac disease (CD) is an autoimmune disease of the small intestines triggered by a protein called gluten, found in dietary wheat, barley and rye in genetically susceptible individuals. It is an irreversible but treatable multifactorial disease (1). It is a common disease worldwide and its prevalence varies between 0.3-3% (1). In pathogenesis; the conversion of glutamine-forming gliadin proteins to deamide peptides by the tissue transglutaminase enzyme in the intestinal submucosa plays a role in presenting these peptides, which are resistant to proteolysis, to CD4+ T-cells, which trigger an inflammatory reaction by binding to HLA-DQ2 and/or DQ8 molecules on the surface of antigen presenting cells in the lamina propria (2). Activation of these cells causes epithelial cell destruction and villous atrophy, probably mediated by non-gluten-specific intraepithelial cytotoxic T-lymphocytes (3). Villous atrophy reduces the functional capacity of the intestine, resulting in malabsorption (4).

Iron deficiency anemia (IDA) is a well-known clinical form of CD. Evaluating patients with IDA without gastrointestinal symptoms as nutritional iron deficiency and trying to treat them with different iron preparations many times causes the diagnosis of celiac to be missed or delayed. Delay in diagnosis leads to increased treatment costs and causes patients to apply to the hospital unnecessarily many times. Red cell distribution width (RDW), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), RDW/lymphocyte ratio (RLR) were used as laboratory tests to help evaluate the diagnosis of CD, adherence to a gluten-free diet, and the severity of histopathological findings (5-8). Screening suspected celiac patients with the use of these frequently used laboratory indices and biomarkers before proceeding to the diagnostic steps in children with IDA may be an advantage.

In this study, the usability of hematological parameters, NLR, PLR and RLR formulas as a screening test in predicting CD in children with IDA was investigated.

METHODS

In this single-centered, cross-sectional, retrospective study, 57 children (IDA+CD group) who were followed up in the pediatric hematology and oncology outpatient clinic with IDA unresponsive to iron treatment and diagnosed with celiac by the pediatric gastroenterology department, 46 children diagnosed with nutritional IDA (IDA group) and 46 healthy children (control group) were included in this study. The diagnosis of CD was made by clinical, serological, histopathological and genetic correlations.

The file records of all children included in the study were reviewed retrospectively. Hemoglobin (Hb) at diagnosis, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RDW, mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte, leukocyte, neutrophil, lymphocyte, platelet count, ferritin level, transferrin saturation were recorded. Leukocyte formulas (NLR, PLR, RLR) were calculated. Laboratory parameters of the three groups were compared.

Anemia is defined as a Hb level below 11 g/dL at the age of 6 months-5 years, 11.5 g/dL at the age of 5-11 years, and below 12 g/dL at the age of 12-18 years (9); iron deficiency was defined as a transferrin saturation of <16% and a ferritin level of <12 µg/L for children under the age of five, and <15 µg/L for children over the age of five (10). The study was conducted in accordance with the principles of the Declaration of Helsinki and approval was obtained from the Eskişehir Osmangazi University Non-Invasive Clinical Research Ethics Committee on 06.11.2018 (decision no: 26).

Exclusion Criteria

In the CD and IDA group, a total of 11 patients, including 6 patients who had received iron therapy in the last three months before admission, and 5 patients with acute inflammation at the time of admission, were excluded from the study.

Laboratory Analyzes

All blood samples were collected after 8 hours of fasting. Complete blood count was performed freshly on an automated blood count analyzer (Beckman Coulter LH750, Kraemer Blud. Brea, CA, US). Blood samples taken into flat tubes for biochemical analysis were centrifuged at 1,500 g for 10 minutes, then their serum was separated and studied within the same day. Serum iron level was analyzed by photometric method (Cobas c502, Roche Diagnostics, Germany), ferritin level was analyzed by electrochemiluminescent method (Cobas E-602, Roche Diagnostics, Germany). Transferrin saturation was calculated with the formula serum ironx100/total iron binding capacity.

Statistical Analysis

SPSS 21 (IBM SPSS Corp.; Armonk, NY, USA) package program was used for statistical analysis of the data. Categorical data were expressed as frequency (n) and percentage (%). Shapiro-Wilk test was used to evaluate the normality distributions of the data. In the comparisons between groups, descriptive statistics were given as mean ± standard deviation for data showing conformity with normal distribution, and median (25-75%) for non-conforming data. One-Way ANOVA test was used for data conforming to normal distribution, and Kruskal-Wallis H test was used for variables not conforming to normal distribution. $P<0.05$ was considered statistically significant.

RESULTS

A total of 138 children were included in the study. The patient group consisted of 92 (CD+IDA group: 46, IDA group: 46) and the control group consisted of 46 children. Number of girls/boys in CD+DA group, IDA group, and control group were 25/21, 30/16, 24/22; median ages were 7 (3.7-10), 5.5 (2.8-13.2), 6 (4.8-10.2) years, respectively. There was no difference in age and gender distribution between the three groups ($p>0.05$ for all). There was no difference between the three groups in terms

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of erythrocyte, leukocyte, neutrophil, lymphocyte count, MPV, PDW, NLR values (p>0.05, for all). Hb, MCV, MCH, MCHC values of CD+IDA group are lower than control group (p<0.001, for all); RDW, PLR, RLR values and platelet count were higher than control group (p<0.001, p<0.05, p<0.05, p<0.001, respectively). Hb, MCV, MCH values of the CD+IDA group were higher than the IDA group (p<0.05, p<0.001, p<0.001, respectively) and lower than the control group (p<0.001, for all). There was no difference between CD+IDA and IDA group in terms of NLR, PLR, and RLR (p>0.05, for all). Transferrin saturation of CD+IDA group was higher than that of IDA group (p<0.001) and ferritin level was similar (p>0.05). The characteristics and laboratory parameters of the study groups are shown in Table 1.

DISCUSSION

IDA is the most common sign of CD other than the intestinal system at the time of diagnosis (11,12). It has been found that the frequency of IDA is between 6-82% (13-17) and anemia is associated with greater disease severity and slower histological recovery in response to a gluten-free diet (18-20). For this reason, it is important to diagnose CD and start treatment in a short time in patients with CD accompanied by IDA.

It is known that RDW is an early indicator of iron deficiency and altered erythropoiesis in celiac patients (5). In two studies conducted in large patient series, it was reported that elevated RDW is a sensitive marker for the diagnosis of celiac in patients with strong clinical suspicion (21,22). Our study showed that the RDW values of the CD+IDA group and the IDA group were similar, therefore, RDW could not be an indicator for the diagnosis of celiac in the presence of IDA.

The MPV is a marker of platelet function and activation and is affected by inflammation. The relationship between changes in MPV and celiac was first reported by O'Grady et al. (23). O'Grady et al. (23) and Purnak et al. (24) found that MPV in celiac patients was higher than the values in the control group, Demirezer Bolat et al. (25) reported that the MPV value was similar in the patient and control groups. In two studies, it has been reported that MPV is a useful biomarker to monitor adherence to the diet in the three-month period after starting a gluten-free diet (24,26). Demirezer Bolat et al. (25), on the other hand, reported that MPV is not useful either in the diagnosis of celiac or in monitoring adherence to diet (in a 1-year follow-up). In our study, we found that the MPV value in the CD+IDA group was similar to that of the IDA and control groups. Our results supported that MPV could not be used in the diagnosis of CD.

Apart from anemia in celiac patients, leukopenia, thrombocytopenia (27) and lymphopenia (5,28) are other hematological abnormalities reported. It has been reported that low lymphocyte counts are

Table 1. Characteristics and laboratory parameters of the patient and control groups

	CD+IDA group (n=46)	IDA group (n=46)	Control group (n=46)	p
Age (years)	7 (3.7-10)	5.5 (2.8-13.2)	6 (4.8-10.2)	>0.05
Gender (female/male)	25/21	30/16	24/22	>0.05
Hb (g/dL)	10 (8.5-10.4)	9.5 (8.3-10.6)	12.7 (12.0-13.1)	$<0.05^{a}$ $<0.001^{b.c}$
RBC ($x10^6/mm^3$)	4.8 (4.5-5.1)	4.7 (4.4-5.0)	4.8 (4.6-4.9)	>0.05
MCV (fL)	66.8±5.1	63.2±5.6	79.0±3.1	<0.001
MCH (pg)	21.5±2.2	19.9±2.5	26.3±3.4	<0.001
MCHC (%)	32 (31-33.2)	31.6 (30.2-32.5)	33.3 (32.9-33.7)	$<0.001^{b.c}$
RDW (%)	17.9 (15.8-19.7)	19.5 (12.8-14.7)	13.3 (12.8-14.7)	$<0.001^{b.c}$
Leukocyte count ($x10^9/L$)	7.8 (6.2-9.1)	7.9 (6.1-9.5)	7.7 (6.1-9.2)	>0.05
Neutrophil count ($x10^9/L$)	3.3 (2.4-4.4)	3.5 (2.3-5.2)	3.2 (2.6-4.4)	>0.05
Lymphocyte count ($x10^9/L$)	3 (2.4-5)	2.9 (2.2-4.7)	2.9 (2.3-4.2)	>0.05
Platelet count ($x10^9/L$)	356 (283.5-405)	339 (267.2-397)	270 (245.7-319)	$<0.001^{b}$ $<0.05^{c}$
MPV (fL)	8.4 (7.8-9.1)	8 (7.6-8.9)	8 (7.6-8.6)	>0.05
PDW (%)	16.6 (16.3-17.4)	16.6 (16.4-17.1)	16.4 (16.2-16.7)	>0.05
NLR	1.1 (0.7-1.5)	1.1 (0.7-2.2)	1.1 (0.7-1.6)	>0.05
PLR	111.3 (82.1-154.4)	117 (71.6-158.8)	85.9 (70.7-112.9)	$<0.05^{b.c}$
RLR	5.7 (4.2-7.4)	6.6 (3.8-8.7)	4.5 (3.4-5.5)	$<0.05^{b}$ $<0.01^{c}$
Saturation (%)	8 (4-8.9)	5.1 (3.9-7.1)	-	<0.001
Ferritin (ng/mL)	6 (4-8.9)	6.9 (4.2-8.7)	-	>0.05

Hb: hemoglobin, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, MPV: mean platelet volume, PDW: platelet distribution width, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, RLR: RDW/lymphocyte ratio [a]comparison of CD+IDA group and IDA group, [b]Comparison of CD+IDA group and control group, [c]comparison of IDA group and control group, IDA: iron deficiency anemia, CD: celiac disease, RBC: red blood cell

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associated with celiac (5,28,29). Studies have shown that the diagnostic power of NLR and PLR indices for celiac is high (6,7), and the diagnostic power of RLR is better than NLR and PLR (5). Uslu ve ark. (8) have shown that the number of neutrophils in celiac patients compared to the control group at the time of diagnosis is high, the number of lymphocytes is low, NLR is high, the number of neutrophils and NLR values in patients who do not follow the diet after a year of gluten-free diet remain high, and the neutrophil number and NLR values in those who follow the diet are at the same level as the control group and they have also shown that NLR is useful for predicting patients who are not compliant with the gluten-free diet. It is thought that changes in the leukocyte formula in active CD may be related to lymphocytic infiltration in the gastrointestinal tract and inflammation and cytokines that play a role in the pathogenesis of the disease (7). In our study, we showed that there was no difference between the patient groups and the control group in terms of leukocyte, neutrophil and lymphocyte count NLR values, RLR and PLR values were higher than the control group, and there was no difference between the CD+IDA group and IDA group in terms of the same parameters. The reason for the difference in RLR and PLR values was probably that the RDW and platelet values of the patient groups were significantly higher than the control group. High RDW and platelet values were also a finding that could be explained by iron deficiency. Therefore, we thought that this difference was not specific to CD.

CD, similar to many other autoimmune diseases, includes innate and acquired immune responses (30). Both experimental and clinical studies emphasize the importance of iron's effects on innate immunity (decreased bactericidal activity, respiratory burst in neutrophils) and cellular immunity (decreased lymphocyte proliferation and delayed hypersensitivity responses) (31,32). Iron has important effects on the immune system due to its growth and differentiation stimulating properties, especially in lymphocytes (33). Iron is also important for monocyte/macrophage differentiation (34). Iron is also critical for enzymes involved in deoxyribonucleic acid synthesis and is an essential element for the proliferative phase of lymphocyte activation, and this phase can be weakened when iron is deficient (35). This may result in altered expression of cell surface markers and decreased T-cell proliferation (36). The fact that we did not find any change in hematological indices such as NLR and PLR in many inflammatory diseases in the CD+IDA group can be explained by the fact that iron deficiency affects the immune response and the response of the developing immune system to inflammatory events is different in children.

Study Limitations

The small number of patients and the retrospective nature of the study.

CONCLUSION

It was determined that the inflammatory response was different in children with CD accompanied by IDA, and that the NLR, RLR and PLR formulas did not have diagnostic power for the diagnosis of CD. There is a need for studies showing how humoral and cellular immunity are affected when these two conditions are combined, which cause changes in the immune system.

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and approval was obtained from the Eskişehir Osmangazi University Non-Invasive Clinical Research Ethics Committee on 06.11.2018 (decision no: 26).

Informed Consent: Retrospective study.

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REFERENCES

1. Guandalini S. The approach to Celiac Disease in children. Int J Pediatr Adolesc Med 2017; 43: 124-7.
2. Abadie V, Sollid LM, Barreiro LB, Jabri B. Integration of genetic and immunological insights into a model of celiac disease pathogenesis. Annu Rev Immunol 2011; 29: 493-525.
3. Setty M, Discepolo V, Abadie V, Kamhawi S, Mayassi T, Kent A, et al. Distinct and synergistic contributions of epithelial stress and adaptive immunity to functions of intraepithelial killer cells and active celiac disease. Gastroenterology 2015; 149: 681-91.e10.
4. Green PH, Cellier C. Celiac disease. N Engl J Med 200; 357: 1731-43.
5. Balaban DV, Popp A, Beata A, Vasilescu F, Jinga M. Diagnostic accuracy of red blood cell distribution width-to-lymphocyte ratio for celiac disease. Rev Română de Medicină de Lab 2018; 26; 45-50. (Romanian)
6. Sarikaya M, Dogan Z, Ergul B, Filik L. Neutrophil- to-lymphocyte ratio as a sensitive marker in diagnosis of celiac disease. Ann Gastroenterol 2014; 27: 431-2.
7. Sarikaya M, Dogan Z, Ergul B, Filik L. Platelet-to-lymphocyte ratio for early diagnosis of celiac disease. Indian J Gastroenterol 2015; 34: 182-3.
8. Uslu AU, Korkmaz S, Yonem O, Aydın B, Uncu T, Sekerci A, et al. Is there a link between neutrophil-lymphocyte ratio and patient compliance with gluten free diet in celiac disease? Gulhane Med J 2016; 58: 353-6.
9. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organization; 2011. Available from: http://www.who.int/vmnis/indicators/haemoglobin.pdf
10. WHO, UNU, UNICEF. Iron deficiency anaemia: assessment, prevention and control, a guide for programme managers. Geneva, World Health Organization; 2001. Available from: https://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf
11. Sansotta N, Amirikian K, Guandalini S, Jericho H. Celiac disease symptom resolution:effectiveness of the gluten-free diet. J Pediatric Gastroenterol Nutr 2018; 66; 48-52.
12. Ferrara M, Coppola L, Coppola A, Capozzi L. Iron deficiency in childhood and adolescence: retrospective review. Hematology 2006; 11; 183-6.
13. Berry N, Basha J, Varma N, Prasad KK, Vaiphei K, Dhaka N, et al. Anemia in celiac disease is multifactorial in etiology: A prospective study from India. JGH Open 2018; 2: 196-200.
14. Haapalahti M, Kulmala P, Karttunen TJ, Paajanen L, Laurila K, Mäki M, et al. Nutritional status in adolescents and young adults with screen-detected celiac disease. J Pediatric Gastroenterol Nutr 2005; 40: 566-70.
15. Kuloglu Z, Kirsaclioglu CT, Kansu A, Ensari A, Girgin N. Celiac disease: presentation of 109 children. Yonsei Med J 2009; 50: 617-23.
16. Wessels MM, van Veen II, Vriezinga SL, Putter H, Rings EH, Mearin ML. Complementary serologic investigations in children with celiac disease is unnecessary during follow-up. J Pediatrics 2016; 169: 55-60.
17. Deora V, Aylward N, Sokoro A, El-Matary W. Serum Vitamins and Minerals at Diagnosis and Follow-up in Children with Celiac Disease. J Pediatric Gastroenterol Nutr 2017; 65; 185-9.

J Acad Res Med 2021;11(2):187-91

18. Saukkonen J, Kaukinen K, Koivisto AM, Mäki M, Laurila K, Sievänen H, et al. Clinical characteristics and the dietary response in celiac disease patients presenting with or without anemia. J Clin Gastroenterol 2017; 51: 412-6.
19. Rajalahti T, Repo M, Kivelä L, Huhtala H, Mäki M, Kaukinen K, et al. Anemia in Pediatric Celiac Disease: Association with Clinical and Histological Features and response to gluten-free diet. J Pediatr Gastroenterol Nutr 2017; 64: e1-6. doi: 10.1097/MPG.0000000000001221.
20. Singh P, Arora S, Makharia GK. Presence of anemia in patients with celiac disease suggests more severe disease. Indian J Gastroenterol 2014; 33: 161-4.
21. Brusco G, Stefani MD, Corazza GR. Increased red cell distribution width and coeliac disease. Digest Liver Dis 2000; 32: 128-30.
22. Sategna Guidetti CS, Scaglione N, Martini S. Red cell distribution width as a marker of celiac disease: a prospective study. Eur J Gastroenterol Hepatol 2002; 14: 177-81.
23. O'Grady JG, Harding B, Stevens FM, Egan EL, McCarthy CF. Influence of splenectomy and the functional hyposplenism of coeliac disease on platelet count and volume. Scand J Haematol 1985; 34: 425-8.
24. Purnak T, Efe C, Yuksel O, Beyazit Y, Ozaslan E, Altiparmak E. Mean platelet volume could be a promising biomarker to monitor dietary compliance in celiac disease. Ups J Med Sci 2011; 116: 208-11.
25. Demirezer Bolat A, Köseoğlu H, Akın FE, Yürekli ÖT, Tahtacı M, Başaran M, et al. Can serum mean platelet volume be used as an inflammatory marker in patients with celiac disease? The Turkish Journal of Academic Gastroenterology 2018; 17: 62-5.
26. Ramachandran M, Agarwal A, Ravi M, Rajeshwari K, Lomash A, S. Mean platelet volume as short-term follow-up biomarker in children with celiac disease. Indian J Child Health 2017; 4: 515-7.
27. Fisgin T, Yarali N, Duru F, Usta B, Kara A. Hematologic manifestation of childhood celiac disease. Acta Haematol 2004; 111: 211-4.
28. Di Sabatino A, Bertrandi E, Casadei Maldini M, Pennese F, Proietti F, Corazza GR. Phenotyping of peripheral blood lymphocytes in adult coeliac disease. Immunology 1998; 95: 572-6.
29. Di Sabatino A, D'Alò S, Millimaggi D, Ciccocioppo R, Parroni R, Sciarra G, et al. Apoptosis and peripheral blood lymphocyte depletion in coeliac disease. Immunology 2001; 103: 435-40.
30. Stepniak D, Koning F. Celiac disease-sandwiched between innate and adaptive immunity. Hum Immunol 2006; 67: 460-8.
31. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr 2001; 131: 568S-79S.
32. Ekiz C, Agaoglu L, Karakas Z, Gurel N, Yalcin I. The effect of iron deficiency anemia on the function of the immune system. Hematol J 2005; 5: 579-83.
33. Weiss G. Iron, infection and anemia a classical triad. Wein Klin Wochenschr 2000; 114: 357-67.
34. Collins HL. The role of iron in infections with intracellular bacteria. Immunol Lett 2003; 133: 336S-40S.
35. Brock JH, Mulero V. Cellular and molecular aspects of iron and immune function. Proc Nutr Soc 2000; 59: 537-40.
36. Kuvibidila SR, Porretta C. Iron deficiency and in vitro iron chelation reduce the expression of cluster of differentiation molecule CD28 but not CD3 receptors on murine thymocytes and spleen cells. Br J Nutr 2003; 90: 179-89.

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Surgeries Performed Within 3 Months in the Neurosurgery Clinic of a Coronavirus Disease-2019 Hospital and Its Effects on Coronavirus Disease-2019 Transmission

Mert Şahinoğlu, Derya Karaoğlu Gündoğdu, Murat Ertaş, Fırat Yıldız, Ender Köktekir, Hakan Karabağlı

Selçuk University Faculty of Medicine, Department of Neurosurgery, Konya, Turkey

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ABSTRACT

Objective: Health workers are on the frontlines in the fight against coronavirus disease-2019 (COVID-19) and are unfortunately the occupational group with the highest risk of infection. For this reason, as in all surgical branches, neurosurgery organisations have recommended postponing or limiting surgeries during the pandemic to reduce the risk of transmission. In our literature review, no study reported the number of neurosurgeons infected with COVID-19 following surgeries performed during the first 3 months of the pandemic. This study examined surgeries performed during the first 3 months of the pandemic in Turkey and COVID-19 transmission to neurosurgeons involved in these cases.

Methods: Records of 188 patients who underwent surgery in our neurosurgery clinic during the first wave of the pandemic in Turkey (March 11-31 May 2020) were examined retrospectively. Characteristics of the operations performed, COVID-19 tests performed and results, intraoperative measures taken and frequency of COVID-19 symptoms among neurosurgeons after the surgery were determined.

Results: Of the 188 patients included in the study, none had a definitive diagnosis of COVID-19 at the time of surgery. However, 25 patients (13.29%) had a history of unsafe contact or symptoms suggestive of COVID-19. Moreover, 9 (36%) patients had a positive result from the COVID-19 polymerase chain reaction test. A total of nine neurosurgeons who participated in surgeries were included in the study and none of them exhibited COVID-19 symptoms during the 3-month pandemic period.

Conclusion: Although many surgeries were performed during the first wave of the pandemic in Turkey, with some simple precautions, none of the neurosurgeons developed COVID-19. We think that this is a pioneering study since this quantitatively demonstrates the extent of COVID-19 transmission to neurosurgeons during surgery.

Keywords: COVID-19, neurosurgeon, pandemic, surgery, transmission

INTRODUCTION

The novel coronavirus disease-2019 (COVID-19) pandemic has been the most significant global event of 2020. This highly contagious and life-threatening viral disease was first officially reported in Turkey on 11 March 2020 (1). As in the rest of the world, it has adversely affected all aspects of life in Turkey, with the health sector receiving the greatest impact. The decision was to suspend elective surgeries and only perform emergency and urgent procedures in surgical departments of all hospitals, including neurosurgery.

Under the circumstances of this pandemic, which is new to the global health sector, neurosurgeons in Turkey have also taken

ORCID IDs of the authors: M.Ş. 0000-0003-0633-8304; D.K.G. 0000-0003-2345-8818; M.E. 0000-0001-5722-9832; F.Y. 0000-0003-0921-8658; E.K. 0000-0002-6442-6663; H.K. 0000-0002-1184-3965.

Corresponding Author: Mert Şahinoğlu,
E-mail: msahinoglu09@gmail.com

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preventive measures along with the rest of the world (1,2). However, owing to the many unknown aspects of the disease, neurosurgeons were still concerned about contracting COVID-19 despite all of the preventive measures (1). This is because initial publications reported distressingly high rates of transmission to health workers (2,3). Although the Turkish Neurosurgical Society (TNS) has issued risk-based recommendations of surgeries that can be performed during the pandemic to guide neurosurgeons, concerns still exist for emergency neurosurgeries (4). In fact, the initial 3-month pandemic period affected later elective cases, indirectly leading to disruption of neurosurgical health care services.

In our literature review, no find study has reported the number of neurosurgeons infected with COVID-19 following surgeries performed during the first 3 months of the pandemic. Therefore, this study aimed to evaluate the types of surgeries performed in our centre, precautions taken during surgery and rates of COVID-19 transmission among neurosurgeons following surgeries performed during the first 3 months of the COVID-19 pandemic in Turkey.

METHODS

Records of 188 patients who underwent surgery in our department during the first wave of the COVID-19 pandemic in Turkey (March 11-31 May 2020) were examined retrospectively. Patients' sex, mean age, diagnosis, surgery type, department from which the patient was referred for surgery and department to which the patient was admitted after surgery were noted. Patients who had a history of suspected COVID-19 and underwent polymerase chain reaction (PCR) analysis and/or rapid antibody test (RAT) were identified. If available, results of blood tests and thoracic computed tomography (CT) were also examined. Information on whether the tests were performed before or after surgery was noted. Patients with test results and findings supporting a diagnosis of COVID-19 were recorded. Which neurosurgeons had participated in each operation was also determined. Emergence of COVID-19 symptoms, positive test results and/or thoracic CT findings in patients within 14 days after surgery were recorded. For patients who were followed in a ward or intensive care unit for 14 days post-operatively, these data were obtained by reviewing their follow-up charts. Patients who were discharged before the end of 14 days were contacted by phone. Appearance of COVID-19 symptoms in the operating neurosurgeons and results of their COVID-19 tests were evaluated.

The study was approved by the Medical Faculty of Selçuk University, Local Ethics Committee (decision no: 2020/452, date: 14.10.2020).

Statistical Analysis

Statistical analysis was performed using SPSS 18.0 programme. Compliance with normal distribution was tested with Shapiro-Wilk test. Statistical analysis between two percentages was tested with Pearson chi-square and likelihood ratio test due to the lack of normal distribution. Multi-group median values were also analysed with Kruskal-Wallis test. A value of $p<0.05$ was considered significant.

RESULTS

This study included 188 patients who underwent emergency or urgent surgeries, all of which were performed under general anaesthesia. The patient group was composed of 103 male (54.78%) and 85 female (45.22%) patients. The mean age was 42.08 (range, 1 day-83) years. Moreover, 88 patients were referred to surgery from the emergency department, 39 from other wards and 61 from the neurosurgery outpatient clinic.

Thirty-six patients underwent surgery due to lumbar disc herniation. These patients developed cauda equina syndrome or had severe pain that severely impaired their quality of life despite analgesic treatment. Ten patients with cervical disc herniation and one patient with lumbosacral listhesis underwent surgery due to uncontrolled pain. In addition, six patients with spinal mass, two with spinal infection, two with cervical stenosis and three with lumbar stenosis underwent surgical treatment due to newly emerging or worsening neurodeficits. Thirty-five patients underwent surgery because of intracranial mass, and four of these patients had pituitary macroadenoma that caused apoplexy and/or increased vision loss. Other intracranial masses were malignant glial mass in 12 patients, intracerebral metastasis in seven, meningioma in four and pilocytic astrocytoma in two. These patients underwent early surgical treatment due to clinical signs of herniation, diffuse cerebral oedema or progressive deterioration in neurological examinations. Another four patients (one with ependymoma, two with medulloblastoma and one with colloid cyst) underwent surgery because of acute hydrocephalus caused by the mass. Surgery was performed due to cranial nerve palsy in one patient with an epidermoid tumour in the posterior fossa and due to uncontrolled pain in one patient with trigeminal neuralgia. During this period, the third most common surgery was surgical treatment of hydrocephalus, which was performed in 31 patients. Six of these patients underwent endoscopic third ventriculostomy, seven underwent shunt removal and 16 patients underwent shunt insertion. Emergency surgery was performed in 12 patients with unstable vertebral fracture, nine with epidural haemorrhage, eight with subdural haemorrhage, four with intracerebral haemorrhage, three with calvarial collapse fracture, four with myelomeningocele, six with intracerebral abscess and two with ruptured cerebral aneurysm. In addition, nine patients who developed malignant oedema due to cerebrovascular disease underwent decompressive

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craniectomy, one patient with Chiari malformation and symptoms of cranial nerve compression underwent decompression surgery and two patients with iatrogenic or traumatic cerebrospinal fluid leak underwent duraplasty. One patient with tethered cord syndrome underwent surgery for urinary incontinence (Table 1).

None of the patients had a definitive diagnosis of COVID-19 at the time of surgery. However, 25 (13.29%) patients had history of unsafe contact or symptoms suggestive of COVID-19. No significance was found between the diagnosis of the patients who underwent surgery and suspicion of COVID-19 (likelihood ratio test, p=0.811) (Table 2). No significance was found between patients diagnosed with COVID-19 and the operation diagnosis (likelihood ratio test, p=0.973) (Table 3). At the same time, no significance was found between the department where the patient was hospitalised and the suspicion of COVID-19 (Pearson chi-square test, p=0.179) (Table 4). All patients underwent RAT, PCR analysis and thoracic CT. Nine (36%) patients had a positive result from the COVID-19 PCR test. Three of these patients had a lumbar degenerative disease, two had hydrocephalus, one had intracranial tumour, one had epidural haematoma, one had lumbar vertebral fracture and one had cervical degenerative disease (Table 2). PCR analysis was repeated for only five of these patients during post-operative follow-up; all results were positive. Forty patients who were discharged before completing 14 days of follow-up could not be contacted. Therefore, it was not possible to ascertain whether they had tested positive for COVID-19 after discharge. Moreover, 3 (1.59%) patients died in the early post-operative period. Autopsy reports indicated that no signs of COVID-19 were detected in these patients.

No significance was found between the department (emergency, outpatient and other wards) and COVID-19 diagnosis (likelihood ratio test, p=0.115) (Table 5).

A total of nine neurosurgeons who participated in surgeries were included in the study. The average number of surgeries performed by these neurosurgeons was 39 (23-58). The average number of surgeries received from the emergency clinic was 15.8 (3-36), the number of operations received from the outpatient clinic was 15.3 (9-30) and the number of operations received from the other ward clinic was 7.7 (2-13) (Table 6). No significant difference was found between the number of patients who underwent surgery performed by the nine neurosurgeons and the median of the number of patients they received from clinics (Kruskal-Wallis test, p=0.433) (Table 7).

Table 1. Distribution of patients in terms of diagnosis

Disease	Number of patients who underwent surgery (%)
Lumbar degenerative disease	40 (21.27%)
Cervical degenerative disease	12 (6.38%)
Spinal infection	2 (1.06%)
Intracranial infection	6 (3.19%)
Spinal tumours	6 (3.19%)
Intracranial tumours	35 (18.61%)
Cranial trauma	24 (12.76%)
Spinal trauma	12 (6.38%)
Hydrocephalus	31 (16.48%)
CSF fistula	2 (1.06%)
Malign cerebral oedema (associated with CVD)	9 (4.78%)
Ruptured cerebral aneurysm	2 (1.06%)
Trigeminal neuralgia	1 (0.53%)
Myelomeningocele	4 (2.12%)
Chiari malformation	1 (0.53%)
Tethered cord syndrome	1 (0.53%)

CSF: cerebrospinal fluid, CVD: cerebrovascular disease

Table 2. Distribution of patients suspected with coronavirus disease-2019 according to the diagnosis during surgery

		Not suspected	Suspected	Total
Cerebrospinal fluid fistula	n	1	1	2
	%	50.0%	50.0%	100.0%
Cervical degenerative disease	n	11	2	13
	%	84.6%	15.4%	100.0%
Cranial trauma	n	19	3	22
	%	86.4%	13.6%	100.0%
Hydrocephalus	n	27	4	31
	%	87.1%	12.9%	100.0%
Intracranial tumour	n	32	3	35
	%	91.4%	8.6%	100.0%
Lumbar degenerative disease	n	33	7	40
	%	82.5%	17.5%	100.0%
Malign cerebral oedema	n	7	2	9
	%	77.8%	22.2%	100.0%
Others	n	18	1	19
	%	94.7%	5.3%	100.0%
Spinal trauma	n	11	1	12
	%	91.7%	8.3%	100.0%
Spinal tumour	n	4	1	5
	%	80.0%	20.0%	100.0%
Total	n	163	25	188
	%	86.7%	13.3%	100.0%

*Analysed by likelihood ratio test, p=0.811

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During this period, RAT was performed by six neurosurgeons who participated in the surgery of patients who became positive of COVID-19 post-operatively. The results of the tests were negative. During the 3-month study period, none of the nine neurosurgeons experienced COVID-19 symptoms. Therefore, except for the six neurosurgeons mentioned, blood test (haemogram, C-reactive protein, D-dimer), thoracic CT scan, RAT and PCR analysis were not needed.

Table 3. Distribution of patients diagnosed with coronavirus disease-2019 according to the diagnosis for the operation

		Diagnosed	No diagnosis	Total
Cerebrospinal fluid fistula	n	0	2	2
	%	0.0%	100.0%	100.0%
Cervical degenerative disease	n	1	12	13
	%	7.7%	92.3%	100.0%
Cranial trauma	n	1	21	22
	%	4.5%	95.5%	100.0%
Hydrocephalus	n	2	29	31
	%	6.5%	93.5%	100.0%
Intracranial tumour	n	1	34	35
	%	2.9%	97.1%	100.0%
Lumbar degenerative disease	n	3	37	40
	%	7.5%	92.5%	100.0%
Malign cerebral oedema	n	0	9	9
	%	0.0%	100.0%	100.0%
Others	n	0	9	9
	%	0.0%	100.0%	100.0%
Spinal trauma	n	1	11	12
	%	8.3%	91.7%	100.0%
Spinal tumour	n	0	5	5
	%	0.0%	100.0%	100.0%
Total	n	9	169	178
	%	5.1%	94.9%	100.0%

*Analysed by likelihood ratio test, p=0.973

Table 4. Number and percentage of coronavirus disease-2019 suspicion in the clinic where the patient was admitted

		Not suspected	Suspected	Total
Emergency	n	72	15	87
	%	82.8%	17.2%	100.0%
Other ward	n	37	2	39
	%	94.9%	5.1%	100.0%
Outpatient	n	54	8	62
	%	87.1%	12.9%	100.0%
Total	n	163	25	188
	%	86.7%	13.3%	100.0%

*Analysed by Pearson chi-square test, p=0.179

DISCUSSION

There were several reasons for limiting or halting elective surgeries during the COVID-19 pandemic. The first reason was to increase bed capacity by decreasing patient density and to assign health workers to COVID-19 cases. The second reason was to reduce the risk of COVID transmission to patients who presented to hospitals due to diseases other than COVID-19. The implementation of curfews also caused a decrease or halt in elective procedures. Another important aim was to protect health workers, who are the frontline fighters against the pandemic, to reduce workforce loss (3,5).

Because this study was performed during the first 3 months of the pandemic, the virus transmission rate was high and the number of tests was inadequate. For this reason, the COVID-19 status of patients scheduled for elective surgery was unknown, which placed all surgical teams at great risk. Therefore, in our centre and unit, surgeries were only performed in emergency and urgent cases. Under normal pre-pandemic circumstances, approximately 450 surgeries were performed in our clinic during a 3-month period, including elective and emergency cases. However, within this 3-month period during the pandemic, a total of 188 surgeries were performed, all of which were emergency or urgent cases. In accordance with the recommendations of the TNS, other than emergency neurosurgery cases, patients with progressive neurological deficit or those with cranial and spinal conditions with very low survival potential were regarded as urgent cases (e.g., intracranial masses without neurodeficit but with brain oedema that does not regress substantially with medical treatment or spinal degenerative diseases with severe, medically refractory pain) (4).

The TNS, Society of British Neurosurgical Surgeons and many other organisations specifically advised against performing endonasal surgery (3,6). Owing to the presence of the virus in the mucus of the respiratory

Table 5. Number and percentage of coronavirus disease-2019 diagnosis in the clinic where the patient was admitted

		With diagnosis	Without diagnosis	Total
Emergency	n	5	82	87
	%	5.7%	94.3%	100.0%
Other ward	n	0	39	39
	%	0.0%	100.0%	100.0%
Outpatient	n	4	58	62
	%	6.5%	93.5%	100.0%
Total	n	9	179	188
	%	4.8%	95.2%	100.0%

*Analysed by likelihood ratio test, p=0.115

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Table 6. Total number of surgeries in which neurosurgeons were involved and the total number of surgeries performed according to the department the patients were admitted to

Number of neurosurgeons	Number of surgeries	Outpatient surgeries	Emergency surgeries	Other ward surgeries
1	39 (11.1%)	24 (17.3%)	8 (5.6%)	7 (10%)
2	42 (12%)	30 (21.7%)	3(2.1%)	9 (12.9%)
3	44 (12.5%)	17 (12.3%)	14 (9.8%)	13 (18.5%)
4	35 (10%)	12 (8.7%)	16 (11.2%)	7 (10%)
5	44 (12.5%)	12 (8.7%)	26 (18.2%)	6 (8.6%)
6	53 (15.1%)	10 (7.2%)	36 (25.1%)	7 (10%)
7	29 (8.3%)	11 (8%)	16 (11.2%)	2 (2.8%)
8	37 (10.5%)	13 (9.5%)	14 (98%)	10 (14.3%)
9	28 (8%)	9 (6.6%)	10 (7%)	9 (12.9%)

Table 7. Median, minimum and maximum number of surgeries performed by neurosurgeons according to the clinics where their patients were hospitalised

Neurosurgeon	1	2	3	4	5	6	7	8	9	p value
Number of operations	8 (7-24)	9 (3-30)	14 (13-17)	12 (7-16)	12 (6-26)	10 (7-36)	11 (2-16)	13 (10-14)	9 (9-10)	0.433*

*Analysed by Kruskal-Wallis test

tract and paranasal sinuses, procedures in these areas were determined to be high risk. Therefore, performing COVID-19 tests for each patient before the operation was recommended (7). During the study period, four endoscopic pituitary surgeries were performed in our clinic. Three were performed by a microscopic endonasal transsphenoidal approach and one via an endonasal transsphenoidal approach. These patients were not suspected of having COVID-19 and were not tested pre- or post-operatively. As tests were performed for only 25 patients with suspected COVID-19, the incubation time of the virus was 5 days while symptoms could appear up to 14 days after infection, test reliability was not above 90% and the COVID-19 status of patients was unknown. Since the transmission rate was high in the initial 3-month period, it is also highly likely that some asymptomatic or untested patients were carrying COVID-19. In our study, only 25 patients who were found suspicious were analysed for PCR and 36% of them were COVID-19 positive. Considering this high percentage, it is likely that other patients were not tested because there was no suspicion, so the number of people carrying COVID-19 will not be low. Thus, although different procedures were performed in our clinic, many of which were high risk of COVID-19 transmission; thus, it is important that none of the neurosurgeons who participated in these operations developed COVID-19 symptoms.

We attribute this to the protective measures we took in the clinic. We would like to underline that these precautions were not complex and did not include various categorisations described in the literature (3,5). Considering the incubation time of the virus and the time required for symptoms to emerge, it is impossible to determine which patient may be carrying COVID-19; therefore, personal protective measures should always be kept in mind (3,8). Other than endonasal procedures and patients with suspected or confirmed COVID-19, we did not use N95 masks [filtering face piece-2 (FFP2)] or protective shields. We continued to use standard surgical masks, disposable gloves, hair restraints, reusable scrubs and personal surgical clogs as in the pre-pandemic period, and there was no limitation on the number of surgeons involved in surgeries. For endonasal cases and patients with suspected or confirmed COVID-19, we used N95 masks (FFP2), protective shields, disposable gloves and hair restraints, reusable scrubs and personal surgical clogs (Figure 1). Unless absolutely necessary, a maximum of two neurosurgeons were involved in these surgeries. During intubation, a single neurosurgeon waited in the operating room.

In our clinic, RAT, PCR analysis and thoracic CT were not performed routinely before and after each operation. Consistent with other studies, thoracic CT, RAT and/or PCR analysis were performed only if the patient had a history suggestive of COVID-19, suspicious blood test results, or suspicious chest X-ray findings. Patients who required emergency surgery were assessed by RAT preoperatively and PCR analysis post-operatively. For patients who did not require emergency surgery, PCR analysis was performed preoperatively instead of RAT. However, thoracic CT, RAT and PCR analysis were not performed for patients who had no history suggesting COVID-19 and no suspicious blood test or chest X-ray findings. Another important matter was the

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evaluation of thoracic CT in patients with trauma. COVID-19 involvement was particularly difficult to distinguish in patients with lung contusion. If the radiologist had any suspicion, the same algorithm was used.

Neurosurgeons involved in the operations included in our study only underwent blood tests, thoracic CT, RAT and PCR analysis in case of risky contact or if the surgeon exhibited typical COVID-19 symptoms (Figure 2).

Study Limitations

We were not able to show the rates of COVID-19 transmission in asymptomatic cases, because the study was carried out during the first wave of the pandemic and thoracic CT, RAT and PCR analysis could not be performed routinely or periodically on asymptomatic neurosurgeons or each patient. Moreover, these evaluation tools will be performed with more cases in a longer time. Prospective studies are needed to examine this topic in the future.

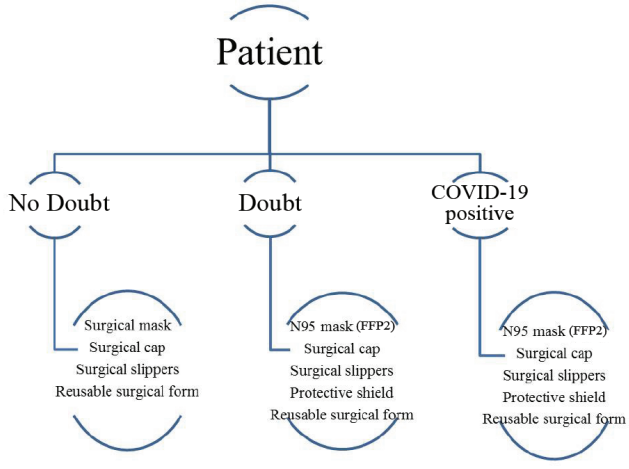

Figure 1. Our personal protection measures in surgery according to patients suspected with COVID-19 or with COVID-19 diagnosis
COVID-19: coronavirus disease-2019, FFP2: filtering face piece-2

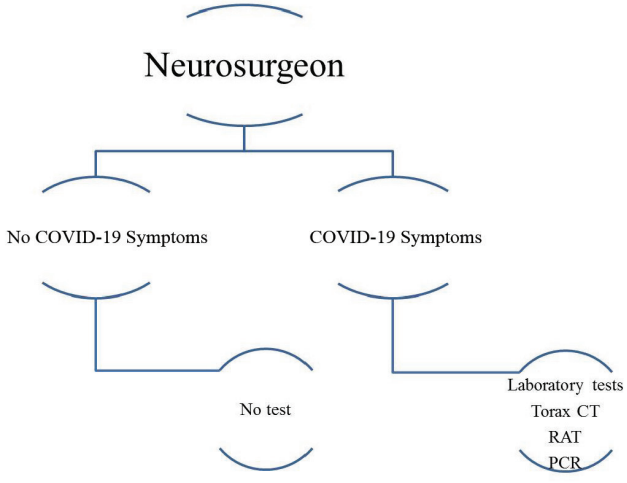

Figure 2. Our approach for the diagnosis of COVID-19 according to the presence of symptoms in the neurosurgeon
COVID-19: coronavirus disease-2019, RAT: rapid antibody test, CT: computed tomography, PCR: polymerase chain reaction

CONCLUSION

To the best of our knowledge, this is a pioneering study that quantitatively demonstrates the extent of COVID-19 transmission to neurosurgeons who performed surgeries to patients with COVID-19. Although different procedures were performed during the first wave of the pandemic in Turkey, none of the neurosurgeons participating in procedures developed COVID-19 despite following only simple precautions implemented in our clinic. Our knowledge and experience during the first wave of the pandemic was practically low; however, recently, we have gained more information and experience to wield in future waves. These results should serve as a guide for performing all operations, including neurosurgical elective procedures and endonasal surgeries in particular, with minimal concern. The ability to minimise transmission with uncomplicated diagnostic algorithms and simple but necessary precautions is important in terms of assuaging concerns of neurosurgeons.

Ethics Committee Approval: The study was approved by the Medical Faculty of Selçuk University, Local Ethics Committee (decision no: 2020/452, date: 14.10.2020).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - M.Ş., D.K.G., M.E., F.Y., E.K., H.K.; Concept - M.Ş., E.K., H.K.; Design - H.K.; Data Collection and/or Processing - M.E., F.Y.; Analysis and/or Interpretation - M.Ş.; Literature Search - D.K.G.; Writing - H.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Yilmaz A, Karakoyun DO, Isik HS, Bostan S. The effect of the COVID-19 pandemic on functioning of neurosurgery clinics and the anxiety levels of neurosurgeons in Turkey. Turk Neurosurg 2020; 30: 944-51.
2. Sheng L, Chen Y, Li H, Wang Z, Bie B, You H, et al. Experience in Neurosurgery During the Prevalence of COVID-19. J Craniofac Surg 2020; 31: e622-4.
3. Ozoner B, Gungor A, Hasanov T, Toktas ZO, Kilic T. Neurosurgical practice during coronavirus disease 2019 (COVID-19) Pandemic. World Neurosurg 2020; 140: 198-207.
4. Turkish Neurosurgery Society. Egitim gruplarımızın acil önerileri. Available from: https://www.turknorosirurji.org.tr/1/haberler/894/duyuru-egitim-gruplarimizin-acil-onerileri; 2020.
5. Iorio-Morin C, Hodaie M, Sarica C, Dea N, Westwick HJ, Christie SD, et al. Letter: The risk of COVID-19 ınfection during neurosurgical procedures: a review of Severe Acute Respiratory Distress Syndrome Coronavirus 2 (SARS-CoV-2) modes of transmission and proposed neurosurgery-specific measures for mitigation. Neurosurgery 2020; 87: E178-85.
6. Jenkins A. Letter: Transmission of COVID-19 during neurosurgical procedures-some thoughts from the United Kingdom. Neurosurgery 2020; 87: E68.

J Acad Res Med 2021;11(2):192-8

7. Ahluwalia R, Rocque BG, Shannon CN, Blount JP. The impact of imposed delay in elective pediatric neurosurgery: an informed hierarchy of need in the time of mass casualty crisis. Childs Nerv Syst 2020; 36: 1347-55.

8. Manusubroto W, Wicaksono AS, Tamba DA, Sudiharto P, Pramusinto H, Hartanto RA, et al. Neurosurgery services in Dr. Sardjito General Hospital, Yogyakarta, Indonesia, During the COVID-19 pandemic: experience from a developing country. World Neurosurg 2020; 140: e360-6.

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Evaluation of the Appearance Characteristics of Suspicious Microcalcifications Detected by Ultrasonography

Yasemin Kayadibi[1], Deniz Esin Tekcan Şanlı[2], Neşe Uçar[3], Emine Yıldırım[4], Ahmet Necati Şanlı[5]

[1]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Radiology, İstanbul, Turkey
[2]İstanbul Rumeli University, Vocational School of Health Services, Department of Medical Imaging Techniques, İstanbul, Turkey
[3]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Radiology, İstanbul, Turkey
[4]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
[5]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

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ABSTRACT

Objective: To investigate the imaging properties of mammographically suspicious microcalcifications (MC) that can be detected by ultrasonography (USG).

Methods: Cases with suspected MC in categories 4 and 5 according to the Breast Imaging-Reporting and Data System (BI-RADS) in screening mammography between June 2019 and January 2021 were included in the study. The patients were scanned with USG. USG guided core needle biopsy was performed for those whose MC area could be detected by USG and evaluated histopathologically. Mammographic features of MCs [morphological type (fine pleomorphic, amorphic, coarse heterogeneous, fine linear pleomorphic branching)], distribution (clustered, regional, segmental, diffuse, linear) and BI-RADS (4A, 4B, 4C, 5) category was determined. Other findings accompanying MC areas on mammography and USG were recorded.

Results: The mean age of 43 patients included in the study was 45.27±8.58 (30-84). 48.8% (n=21) of the calcifications were fine pleomorphic, 30% (n=13) amorphous, 16% (n=7) coarse heterogeneous, 4.6% (n=2) fine pleomorphic branching type. While 70% (n=30) of the patients had asymmetrical density accompanying MCs on mammography, parenchymal distortion was found in 12% (n=5); on USG, hypoechoic area was found in 58% (n=25) of the patients, irregular ductal ectasia in 19% (n=8), parenchymal distortion in 9% (n=4), and 10% (n=4) microcyst cluster were accompanying pathologies. As a result of the histopathological evaluation, 42% of the patients had benign histopathology (n=18), 16% had ductal carcinoma *in situ* (n=7), and 42% (n=18) had invasive ductal cancer.

Conclusion: In our study, the distinctive features of BI-RADS 4 and 5 MCs that can be followed by USG were evaluated. Although MCs that can be detected on USG are more likely to be malignant than benign ones, fine pleomorphic MC areas can be observed most frequently. Knowing the features of mammographic suspected MCs on USG will be helpful in daily radiology practice and biopsy planning.

Keywords: Microcalcification, mammography, ultrasonography, ultrasound guided biopsy

ORCID IDs of the authors: Y.K. 0000-0003-1590-5382; D.E.T.Ş. 0000-0002-6545-5757; N.U. 0000-0003-2233-4338; E.Y. 0000-0003-2733-402X; A.N.Ş. 0000-0002-1483-8176.

Sorumlu Yazar/Corresponding Author: Yasemin Kayadibi, E-mail: ysmnkayadibi@gmail.com

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INTRODUCTION

Mammography is the gold standard imaging method for detecting and characterizing microcalcifications (MC) (1). Ductal carcinoma *in situ* (DCIS) constitutes 25% of suspected MC on mammography (2,3). 90% of DCIS cases are detected through mammography, which is classified as category 4 or 5 according to the Breast Imaging-Reporting and Data System (BI-RADS) and through mammograms recommended histopathological evaluation (4-7). Ultrasonography (USG) has an important role in the characterization of breast lesions detected by mammography (8). However, the diagnostic power of USG is limited in the detection of MCs that may not be accompanied by a mass, which may be a sign of malignancy (9,10). The detection of MCs with USG becomes easier thanks to the new technological algorithms such as use of high-frequency probes, the development of artifact removal software, tissue harmonic and compound imaging and MicroPure imaging (9,11,12). This situation has raised the question of whether USG guided biopsy can be applied in the histopathological diagnosis of MCs. Although stereotaxic biopsy is the most reliable method for sampling MCs, it has some disadvantages such as prolonged compression, radiation exposure and expensive equipment requirement. In addition, it is difficult to access the pathological area in cases where it is not available in all health centers, the breast volume is very small, and close to the chest wall or axilla (5-7,13). Compared to stereotaxic biopsy, USG guided biopsy is a less painful, faster, more comfortable, cheaper, radiation-free, real-time method that allows manipulation (6,12). The disadvantage of USG-guided biopsy is that it is difficult to detect MCs without a mass, and this rate varies between 24% and 93% according to publications in the literature (9,11,12,14,15). Our aim in this study was to investigate the sonographic features of MCs that can be detected by USG, are not accompanied by a mammographic mass, and classified as category BI-RADS 4 or 5.

METHODS

Patient Group

After the approval of the local hospital ethics committee (approval number 252 dated 14/04/2021), patients with BIRADS 4 or 5 microcalcifications were screened between 2019-2021. Patients whose non-mass microcalcifications could be observed under USG and who underwent USG-guided core needle biopsy were included in the study. Patients who had undergone previous breast surgery, treated for breast cancer, and were in the ongoing pregnancy or breastfeeding period were excluded from the study. In addition, a signed informed consent form was obtained from all patients.

Imaging Method and Image Analysis

Images of all patients were taken in standardized mediolateral oblique and craniocaudal positions with our hospital mammography device (Giotto Image MC, IMS, Italy). Mammography images of the patients were reviewed retrospectively from the hospital Picture Archiving and Communication System (PACS). According to BI-RADS 5th edition (2013), patients were evaluated for mammographic breast density (type A-B-C-D), type of MC (amorphous, fine pleomorphic, coarse heterogeneous, fine linear and fine pleomorphic branching), distribution pattern (clustered, regional, segmental, diffuse, linear) and the BI-RADS category (4A, 4B, 4C, 5) was determined (4). Other accompanying findings (asymmetrical density increase, parenchymal distortion) on mammography were recorded. Then, USG examination was performed on these patients. All sonographic examinations were performed with the Toshiba Aplio 500 machine (software version 6.0, Toshiba Medical Systems, Tokyo, Japan). First, routine breast USG was performed on both breasts. Then, the region containing the MC was tried to be localized according to the clock dial, its depth from the skin, its distance from the nipple, chest wall and intramammary lymph nodes. Sonographic findings (hypoechoic area, irregularly dilated ducts, microcyst cluster, parenchymal distortion) accompanying MC areas that could be detected as echogenic focus on USG were evaluated. The USG images of the patients were retrieved retrospectively from the PACS system and evaluated by a consensus of two radiologists (YK and NU) experienced in breast radiology.

Biopsy Technique

Sampling of mammographic MCs that could be detected by USG was performed under local anesthesia with a 14-gauge fully automatic core needle (Geotek, Ankara, Turkey). At least 5 samples were taken from each lesion. Whether the samples taken contained MC was evaluated with the X-ray of the specimen, and if it did not contain MC, the biopsy procedure was repeated. All biopsy procedures were performed under sterile conditions and the samples were sent to the pathology laboratory in sterile boxes.

Histopathological Evaluation

The histological type and grade of the samples (according to the Scarff-Bloom-Richardson grading system), estrogen receptor, progesterone receptor status and human epidermal growth factor receptor (HER)-2 positivity were examined.

Statistical Analysis

Data were evaluated numerically and as a percentage. Since the overall number of cases was relatively small, inferential statistical analysis was not performed.

RESULTS

Between June 2019 and January 2021, BI-RADS 4-5 MC were detected without accompanying mass in 50 of 9468 cases (0.7%) who underwent mammography in our hospital, and MCs could be detected by USG in 43 (83%) of these cases and core needle biopsy was performed under USG guidance. Seven patients with suspected MCs that were seen with mammography but could not be detected by USG were sent for excisional biopsy by mammography-guided wire marking (Figure 1). The mean

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age of the patients participating in the study was 45.27±8.58 (30-84). While 39 patients were detected by normal routine breast screening, 4 patients under the age of 40 with a family history applied with palpable stiffness. While mammographic breast density was type C in 63% (n=27) of the patients, type D in 23% (n=10) and type B in 14% (n=6), no patients were found in type A category. 48.8% (n=21) of the calcifications were fine pleomorphic, 30% (n=13) amorphous, 16% (7) coarse heterogeneous, 4.6% (2) fine pleomorphic branching type. The mean mammographic MC area was 35.60±19.24 mm (7-90). While 70% (n=30) of the patients had asymmetrical density accompanying MCs on mammography, parenchymal distortion was found in 12% (n=5); on USG, hypoechoic area was found in 56% (n=24) of the patients, irregular ductal ectasia in 19% (n=8), parenchymal distortion in 9% (n=4) and microcyst cluster was the accompanying pathology in 10% (n=4).

As a result of histopathological evaluation, benign pathology was found in 42% of patients (n=18). In the benign group, 10 patients had non-proliferative fibrocystic change (NPFC) [fibrosis (n=3), apocrine change (n=1), mild ductal hyperplasia (n=2), and NPFC (n=4)]; 8 patients were diagnosed with PFC [usual ductal hyperplasia without atypia (n=3), fluoride type hyperplasia without atypia (n=1), columnar cell hyperplasia without atypia (n=1), sclerosing adenosis (n=2), and complex sclerosing lesion (n=1)]. An accompanying invasive component in the absolute pathology was detected in 10 patients who were diagnosed and marked with DCIS by core needle biopsy and referred for surgical operation. In total, 16% (n=7) of patients had DCIS [cribriform (n=5), comedo (n=2)] and 42% of patients (n=18) had malignant [invasive ductal carcinoma with *in situ* component (IDC+DCIS) (n=10); pure IDC (n=7); invasive lobular carcinoma (n=1)] diagnosis. According to nuclear grading, 6 of DCIS were low grade (grade 1) and luminal A subtype, 1 was high grade (grade 2) and HER-2 (+). Rest of the malignant lesions were high grade grade 2-3) [8 luminal A, 3 luminal B, 7 HER-2 (+)] except one.

While the most common type of MC was fine pleomorphic in the benign group, the most common type of MC was amorphous MC in the PFC group and fine pleomorphic MC in the NPFC group. While the most common accompanying USG finding was a hypoechoic background in the malignant group (n=17) and NPFC group (n=6), the most common accompanying finding in the PFC group (n=3) was ductal ectasia. In the malignant group, while ductal ectasia was observed in the DCIS group (pure DCIS and DCIS with IDC), it was a finding that was not observed in pure invasive cancers. While microcyst clusters were observed in the PFC group (n=2) and DCIS group (n=2), no microcyst clusters were found in the NPFC group and invasive ductal carcinoma group. The findings are summarized in Table 1. Case examples are shared in Figure 2-6.

DISCUSSION

Mammography is the most reliable imaging method used to detect and characterize MCs (13). BI-RADS was developed by the American College of Radiology in order to use a common language by making a standardized assessment (16). As stated in the BI-RADS mammography edition; skin and vascular calcifications, coarse or popcorn type, round, rim, dystrophic, tea-cut, suture calcifications are ate typically benign calcifications; amorphous, coarsely heterogeneous, fine pleomorphic and fine pleomorphic branching MCs are considered suspicious (17). In addition, the distribution of MCs is also important in terms of predicting malignancy; MCs with linear and segmental distribution are the riskiest distribution pattern in terms of malignancy (13,16,18). Those with bilateral diffuse distribution are MCs that generally develop on the basis of fibrocystic disease (4,16). The estimated value of BI-RADS for malignant MCs (BI-RADS 4-5) varies between 13% and 70% (16). Although stereotaxic biopsy is the most reliable method in the evaluation of suspicious patients, USG-guided biopsy is more advantageous compared to stereotaxic biopsy due to the above-mentioned features (12,19). The disadvantage is that not all MCs without an accompanied mass can be detected by USG. While MCs in the 50-100 micron range can be observed on mammography, those in the 200-500 micron range can be observed on USG (20). Benign MCs that do not accompany the mass can usually be overlooked due to mottling artifact in the echogenic breast tissue, while malignant MC areas can be observed more easily with USG due to the hypoechoic pathological background (10,12). In our study, we were able to detect 83% of suspicious and non-mass MCs with USG, and this rate is within the limits of the literature (6,9,11,15,18,21). The malignancy risk of suspected MCs that can be detected by USG is higher than those detected only by mammography (12,22,23). In our study, the majority of MCs detected by USG were malignant. In our study, the most common accompanying finding on USG in the malignant group was hypoechoic background, while in the benign group, the MC area was mostly observed on an isoechoic background. This finding is consistent with the literature (10). In USG, MCs can be seen as an echogenic focus alone, or they can be associated with irregular ductal ectasia with thickened walls, microcyst clusters, parenchymal distortion areas, heterogeneous hypoechoic areas or mass formation (10-12). These findings can be observed in both benign fibrocystic diseases and malignancy (12,14). In our study, ductal ectasia and microcyst clusters are observed in PFCs, in DCIS with accompanying pure DCIS and invasive component, and they were not observed in the group with pure invasive cancer. The MCs that we could detect with USG were the MCs that clustered most frequently, followed by segmental and regional distribution. When the MC area was evaluated, except for two of the cases (7 mm and 8 mm, both were invasive ductal carcinoma), the largest diameter of all was more than 1 cm. While 62% of breasts with MC that can be observed by USG were category BI-RADS type "C", no type "A" breasts were observed.

Fine pleomorphic type was the most commonly detected among MCs that could be observed by USG in both the malignant and benign groups, and the least common was the fine pleomorphic branching type. There are literature studies showing that the fine pleomorphic type is observed more frequently with USG

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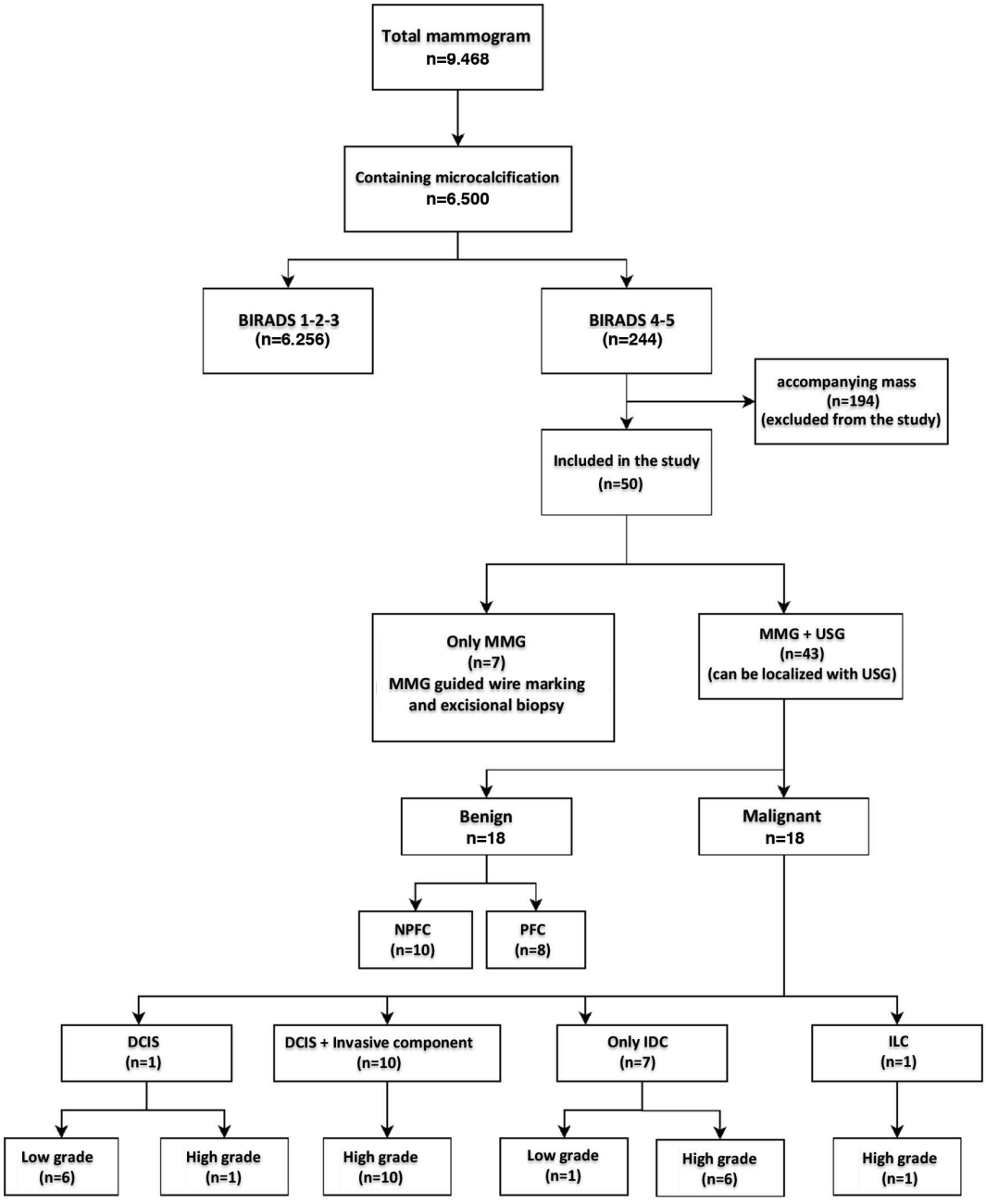

Figure 1. Algorithm for inclusion in the study
MMG: mammography, DCIS: ductal carcinoma in situ, NPFC: non-proliferative fibrocystic change, ILC: invasive lobular carcinoma, IDC: invasive ductal carcinoma, USG: ultrasonography, PFC: proliferative fibrocystic change, BI-RADS: Breast Imaging-Reporting and Data System

(15,21,24). The low number of thin pleomorphic branching type can be explained by the exclusion of lesions accompanying the mass from the study. In the benign group, 8 had a cystic component and 6 had ductal ectasia. 6 of these patients had amorphous MC on mammography, 1 had coarse heterogeneous MC and 2 had fine pleomorphic MC. The majority of benign MCs without an accompanying cysts or dilated ducts were observed as echogenic spots on an isoechoic background, and the mammographic MC shape was amorphous and fine pleomorphic type.

The gold standard imaging method in the evaluation of MCs is mammography (5). The reason for investigating this area with USG is that the mass component, which is the marker of the possible invasive area, can be determined by USG and it allows biopsy to be performed from this solid area. Our study showed that USG is a useful method in the evaluation and biopsy of MCs without a mass. According to our results, we observed that hypoechoic background is a helpful finding in malign lesions and microcystic structures in lesions containing more *in situ* components, but it is not typical and can be observed in benign lesions as well.

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Table 1. Mammographic and sonographic findings by histopathological types

		MMG breast density BI-RADS	n	MMG MC type	n	MMG distribution	n	MMG associated findings	n	MMG category BI-RADS	n	Accompanying findings on USG	n
Benign (18)	PFC (8)	Type B	2	P	3	R	5	AD	5	4B	5	DE	3
		Type C	5	A	4	C	2	D	2	4A	3	Hypo	2
		Type D	1	CH	1	S	1	-	1	-	-	CM	2
		-	-		-	-	-	-	-	-	-	Dis	1
	NPFC (10)	Type B	1	P	5	C	7	AD	5	4B	5	DE	2
		Type C	6	A	4	R	3	D	1	4A	5	Dis	2
		Type D	3	CH	1	-	-	-	2	-	-	Hypo	6
DCIS (7)	Cribriform type (5)	Type B	1	FP	3	C	3	AD	4	4C	3	Hypo	3
		Type C	3	A	2	S	1	D	1	4B	2	CM	1
		Type D	1	FP	1	R	1	-	-	-	-	DE	1
	Comedo type (2)	Type C	2	FP	1	S	2	AD	2	5	2	Hypo	1
		-	-	FPB	1	-	-	-	-	-	-	CM	1
Invasive (18)	IDC+DCIS (10)	Type B	1	FP	6	R	5	AD	7	4B	4	DE	2
		Type C	6	A	1	C	3	-	3	4C	3	Hypo	5
		Type D	3	CH	2	S	2	-	-	5	3	Dis	1
		-	-	FPB	1	-	-	-	-	-	-	-	-
	IDC (7)	Type B	1	FP	3	C	4	AD	5	4B	3	Hypo	7
		Type C	5	CH	3	S	2	D	1	5	2	-	-
		Type D	1	A	1	R	1	AD	1	-	-	-	-
	ILC (1)	Type D	1	FP	1	R	1	AD	1	5	1	Hypo	1

A: amorphous, AD: asymmetric density, C: clustering, CH: coarse heterogeneous, CM: clustered microcysts, Dis: distortion, DCIS: ductal carcinoma *in situ*, DE: ductal ectasia, FP: fine pleomorphic, FPB: fine pleomorphic branching, Hypo: hypoechogenicity, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, MC: microcalcification, MMG: mammography, NPFC: non-proliferative fibrocystic change, P: pleomorphic, PFC: proliferative fibrocystic change, R: regional, S: segmental, USG: ultrasonography

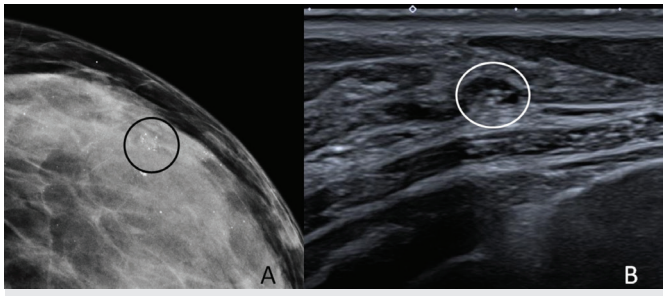

Figure 2. Example of mild epithelial hyperplasia: Asymptomatic 43-year-old woman, clustered amorphous microcalcifications in the outer part of the left breast were observed on screening mammography (A), and echogenic foci on a microcystic background were observed on ultrasonography (B)

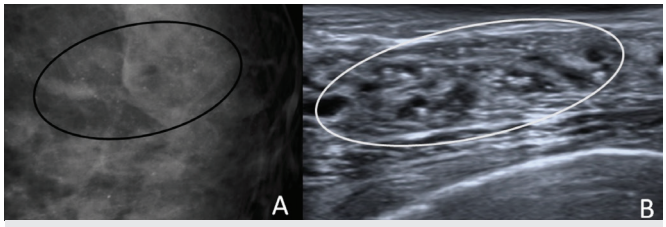

Figure 3. Example of proliferative type fibrocystic change: A 42-year-old asymptomatic woman, regional amorphous microcalcifications in the retroareolar area were observed on screening mammography (A), and echogenic foci and accompanying dilated ductal enlargements on a microcystic background were observed on ultrasonography (B)

Prospective studies with larger number of patients are needed to reveal the importance of these accompanying findings in the prediction of malignancy and invasiveness.

Study Limitations

The most important limitation of our study is the small number of patients. Another limitation of ours is the lack of long-term follow-up of patients who had benign results with core biopsy. In our study, MCs occupying less than 0.7 cm could not be evaluated because they could not be observed by USG. In addition, another limitation of our study is that USG is operator dependent and researchers may have dissensus.

CONCLUSION

Although USG is a limited imaging method in the evaluation of MCs, it is a technique that can help radiologists to increase the specificity of mammography especially in the evaluation

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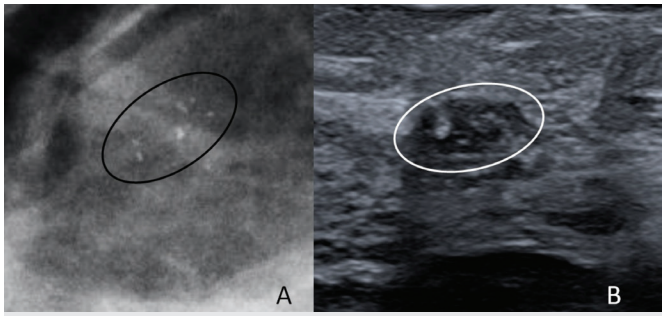

Figure 4. Example of high-grade ductal carcinoma *in situ*: A 38-year-old female patient, previously diagnosed with invasive ductal carcinoma of the left breast, had clustered fine pleomorphic microcalcifications in her right breast (A), and echogenic spots on a hypoechoic background on ultrasonography (B)

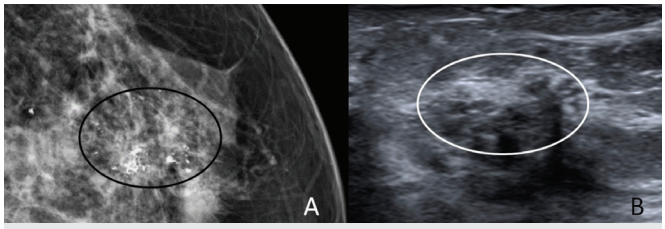

Figure 5. Example of invasive carcinoma accompanying ductal carcinoma *in situ*: In the mammography of a 45-year-old woman for screening, finely branching microcalcifications showing a regional distribution in the upper part of the right breast was observed (A); accompanying microcystic structures on a hypoechoic background and slightly dilated ducts were observed on ultrasonography (B)

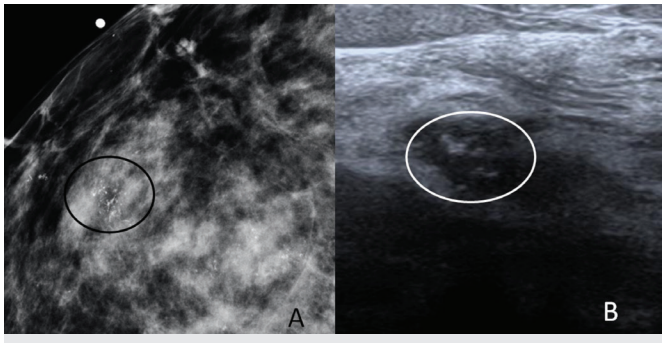

Figure 6. Example of invasive ductal carcinoma: In the mammography of a 43-year-old female patient taken before breast reduction surgery, thin pleomorphic branching type microcalcifications with focal distribution in the upper part of the right breast were observed (A) and echogenic foci on a hypoechoic background were observed on ultrasonography (B)

of MC clusters larger than 1 cm, determine the indication and priority of biopsy, and guide the biopsy procedure.

Ethics Committee Approval: This retrospective study was conducted following Gaziosmanpaşa Training and Research Hospital Ethics Committee approval (approval number: 252, approval date: 14/04/2021).

Informed Consent: Informed consents was obtained in order to use the recorded data of the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - E.Y., A.N.Ş.; Concept - Y.K., N.U.; Design - Y.K.; Data Collection and/or Processing - Y.K., N.U.; Analysis and/or Interpretation - Y.K., D.E.T.Ş.; Literature Search - D.E.T.Ş.; Writing - Y.K., D.E.T.Ş.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Dershaw DD, Abramson A, Kinne DW. Ductal carcinoma in situ: mammographic findings and clinical implications. Radiology 1989; 170: 411-5.
2. Schnitt SJ, Silen W, Sadowsky NL, Connolly JL, Harris JR. Ductal carcinoma in situ (intraductal carcinoma) of the breast. N Engl J Med 1988; 318: 898-903.
3. Stomper PC, Connolly JL, Meyer JE, Harris JR. Clinically occult ductal carcinoma in situ detected with mammography: analysis of 100 cases with radiologic-pathologic correlation. Radiology 1989; 172: 235-41.
4. Bent CK, Bassett LW, D'Orsi CJ, Sayre JW. The Positive predictive value of bı-rads microcalcification descriptors and final assessment categories. Am J Roentgenol 2010; 194: 1378-83.
5. Craft M, Bicknell AM, Hazan GJ, Flegg KM. Microcalcifications detected as an abnormality on screening mammography: outcomes and followup over a five-year period. Int J Breast Cancer 2013; 2013: 458540.
6. Liu J, Huang L. Image-guided vacuum-assisted breast biopsy in the diagnosis of breast microcalcifications. J Int Med Res 2018; 46: 2743-53.
7. Peng Y, Luo Z, Ni J, Cui H, Lu B, Xiang A, et al. Precision biopsy of breast microcalcifications: An improvement in surgical excision. Oncol Lett 2018 May 22 [cited 2020 Dec 21]; doi: 10.3892/ol.2018.8787
8. Gokhale S. Ultrasound characterization of breast masses. Indian J Radiol Imaging 2009; 19: 242-7.
9. Machado P, Eisenbrey JR, Stanczak M, Cavanaugh BC, Zorn LM, Forsberg F. Characterization of breast microcalcifications using a new ultrasound ımage-processing technique. J Ultrasound Med 2019; 38: 1733-8.
10. Moon WK, Im JG, Koh YH, Noh DY, Park IA. US of Mammographically Detected Clustered Microcalcifications. Radiology. 2000; 217: 849-54.
11. Relea A, Alonso JA, González M, Zornoza C, Bahamonde S, Viñuela BE, et al. Usefulness of the twinkling artifact on Doppler ultrasound for the detection of breast microcalcifications. Radiologia (Engl Ed) 2018; 60: 413-23.
12. Soo MS, Baker JA, Rosen EL. Sonographic detection and sonographically guided biopsy of breast microcalcifications. Am J Roentgenol 2003; 180: 941-8.
13. Wilkinson L, Thomas V, Sharma N. Microcalcification on mammography: approaches to interpretation and biopsy. Br J Radiol. 2016; 90: 20160594.
14. Soo MS, Baker JA, Rosen EL, Vo TT. Sonographically guided biopsy of suspicious microcalcifications of the breast: a pilot study. Am J Roentgenol2002; 178: 1007-15.
15. Yang WT, Suen M, Ahuja A, Metreweli C. In vivo demonstration of microcalcification in breast cancer using high resolution ultrasound. Br J Radiol 1997; 70: 685-90.
16. Sickles EA, D'Orsi CJ, Bassett LW, Appleton CM, Berg WA, Burnside ES. ACR BI-RADS® Atlas, Breast imaging reporting and data system. Reston, VA: American College of Radiology. 2013; 39-48.
17. Nalawade YV. Evaluation of breast calcifications. Indian J Radiol Imaging 2009; 19: 282-6.
18. Hadi Q, Masroor I, Hussain Z. Mammographic criteria for determining the diagnostic accuracy of microcalcifications in the detection of malignant breast lesions. Cureus 2019; 11: e5919.
19. Liberman L. Percutaneous imaging-guided core breast biopsy: state of the art at the millennium. Am J Roentgenol 2000; 174: 1191-9.
20. Wang LC, Sullivan M, Du H, Feldman MI, Mendelson EB. US Appearance of Ductal Carcinoma in Situ. Radiographics 2013; 33: 213-28.
21. Duran Özel B, Özel D, Özkan F, Halefoğlu AM, Özer Ö, Başak M. Can we determine biopsy indication by using BI-RADS ultrasonography findings for solid breast masses. Ş.E.E.A.H. Tıp Bülteni 2015; 49: 284-8.

J Acad Res Med 2021;11(2):199-205

22. Bitencourt AGV, Graziano L, Guatelli CS, Albuquerque MLL, Marques EF. Ultrasound-guided biopsy of breast calcifications using a new image processing technique: initial experience. Radiol Bras 2018; 51: 106-8.
23. Teh WL, Wilson ARM, Evans AJ, Burrell H, Pinder SE, Ellis IO. Ultrasound guided core biopsy of suspicious mammographic calcifications using high frequency and power Doppler ultrasound. Clin Radiol 2000; 55: 390-4.
24. Pan S, Liu W, Jin K, Liu Y, Zhou Y. Ultrasound-guided vacuum-assisted breast biopsy using Mammotome biopsy system for detection of breast cancer: results from two high volume hospitals. Int J Clin Exp Med 2014; 7: 239-46.

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Comparison of Two Different Photorefractors with Skiascopy Measurements in Healthy Children

Gülay Yalçınkaya, Osman Bulut Ocak, İhsan Çakır, Aslı İnal, Birsen Gökyiğit

University of Health Sciences Turkey, İstanbul Beyoğlu Eye Research and Training Hospital, Clinic of Ophthalmology, İstanbul, Turkey

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ABSTRACT

Objective: Comparing refractive values determined by two photorefractory devices (Plusoptix® A09, GmbH, Nuremberg, Germany and SureSight®, Welch Allyn Co, New York, USA) with refractive values obtained by skiascope after cycloplegia with 1% cyclopentolate hydrochloride in healthy children.

Methods: Cases aged between 48 and 132 months were evaluated for this cross-sectional study. Cases with no ophthalmic pathology in both eyes and uncorrected visual acuity of 1.0 were included in the study. In all cases, refractive measurements were performed first with Plusoptix® and then with SureSight®. After providing cycloplegia with 1% cyclopentolate hydrochloride, skiascopy was performed. The correlation between the measurements obtained was evaluated with the Pearson correlation coefficient, and the compatibility was evaluated with the Bland-Altman analysis.

Results: The mean spherical values of 52 subjects measured by cycloplegic skiascopy, Plusoptix® and SureSight® were 0.88±2.07 dioptry (D), 0.69±1.78D and 1.64±1.06D, respectively; mean of cylindrical measurements are -0.73±0.68D, -0.92±0.67D and -0.83±0.70D, respectively. Comparing Plusoptix® with skiascopy, SureSight® with skiascopy, Plusoptix® with SureSight® measurements, a high positive correlation was found between spherical values (r=0.861, r=0.736, r=0.721, respectively); a positive correlation was also found between cylindrical values (r=0.602, r=0.675, r=0.901, respectively). Skiascopic spherical and cylindrical measurements with Plusoptix®, and skiascopic spherical and cylindrical measurements with SureSight® were found to be compatible with each other (within 95% confidence interval, lower limit: -2.65, upper limit: 1.89; lower limit: -1.35, upper limit: 0.95; lower limit: -3.56, upper limit: 2.06; lower limit: -1.20, upper limit: 0.98). Spherical and cylindrical measurements obtained with Plusoptix® and SureSight® were found to be consistent with each other (within 95% confidence interval, lower limit: -3.39, upper limit: 1.49; lower limit: -0.67, upper limit: 0.51).

Conclusion: It was concluded that the results of these three measurements in childhood were compatible with each other.

Keywords: Photorefractometer, Plusoptix®, retinoscopy, cycloplegic skiascopy, SureSight®

INTRODUCTION

Ophthalmological examination begins with the detection of the refractive error (1). In the early detection of anisometropia, which is a cause that may lead to vision loss, especially amblyopia, the detection of refractive error is necessary (2-5).

The gold standard for the detection of refractive error is skiascopic measurement after cycloplegia with 1% atropine sulfate (6-8). It has been shown that skiascopic measurements after 1% cyclopentolate hydrochloride drop give similar results with measurements after cycloplegia with atropine (9). In recent studies, it has been shown that photorefractors, which are used as scanning programs, are also reliable and effective in detecting refractive errors (10,11).

Our aim in this study is to compare the refractive error measurement values determined by two separate photorefractors (Plusoptix®

ORCID IDs of the authors: G.Y. 0000-0001-6248-5902; O.B.O. 0000-0002-8154-6771; İ.Ç. 0000-0003-3784-1607; A.İ. 0000-0003-1944-5731; B.G. 0000-0002-4154-4106.

Sorumlu Yazar/Corresponding Author: Gülay Yalçınkaya, E-mail: ykgulay@gmail.com

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A09, GmbH, Nuremberg, Germany and SureSight®, Welch Allyn Co, New York, USA) and the refractive error measurement values obtained by skiascopy after cycloplegia with 1% cyclopentolate hydrochloride in healthy children without amblyopia. There has been no previous study comparing these two devices with each other and with the skiascopic measurement after a drop of 1% cyclopentolate hydrochloride.

METHODS

The cases aged between 48 and 132 months, who applied to our hospital's general polyclinic unit for routine control between May 2019 and August 2019, were evaluated for this cross-sectional study. The cases with no ophthalmic pathology in both eyes and a corrected visual acuity of 1.0 with Snellen or E chart were included in the study. The ones with corrected visual acuity of 1.0 in one or both eyes, and with corrected visual acuity of 1.0 in both eyes but with ophthalmic pathology (acute bacterial conjunctivitis, previous keratitis, etc.) and cases with no vision data in Snellen or E chart were excluded from the study.

Approval for our study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital with the decision number 1975 dated 13.09.2019, and our study was carried out in accordance with the terms of the Declaration of Helsinki. Informed written consent was obtained from the parents of each child included in the study.

Plusoptix® A09

It is a non-invasive, binocular photorefractometer that can be used in children aged 6 months and older, with symbols and sounds that will attract the attention of the child (12). It consists of a portable infrared camera (13). It is aimed to minimize the effect of accommodation by taking measurements from a distance of 1 meter. The measuring range starts from -7.00 dioptry (D) for spherical and cylindrical values and continues by increasing 0.25D until +5.00D (12). There is no need for cycloplegia when measuring (14).

SureSight®

SureSight® is an easily portable, noninvasive, monocular photorefractometer. The measured distance is 35 centimeters (14). The central red light enables the child to fixate while the measurement is taken (15). The measuring range starts from -5.00D for spherical and cylindrical values and continues by increasing 0.25D until +5.00D (14). It shows the reliability of the obtained values by grading from 1 to 9 (16). In this study, the measurement was repeated when the confidence value was less than 6. Like Plusoptix®, this photorefractometer does not require cycloplegia for measurement (14).

Cycloplegic Skiascopy

Skiascopy (retinoscopy) is the detection of the refractive error by subtracting +1.50D from the measurements made at an arm distance (67 cm) from the patient through the retinoscope. In order to detect the refractive error of the patient's right eye, the person performing the test holds the retinoscope with his/her right hand and evaluates with his/her right eye. The same situation is opposite for the left eye (17). Heine Beta® 200 retinoscope (HEINE Ophthotecnic, Herrsching, Germany) was used for skiascopy in this study.

Refractive Error Measurements

The refractive error measurements of all cases were first recorded by the technician in the dark room from a distance of 1 m using Plusoptix®. Refractive values were then measured by the clinician from a 35 cm distance with SureSight® device. The visual acuities of the cases were evaluated by the same clinician using Snellen or E charts, each eye separately, and complete ophthalmological examinations were performed. At the end of the examination, one drop of 1% cyclopentolate hydrochloride was administered to all patients for cycloplegia 3 times at five-minute intervals. Forty minutes later, skiascopic examination was performed by the other clinician, who was unaware of the refractive values gathered with Plusoptix® and SureSight®, and the measurement values were recorded.

Statistical Analysis

The refractive error measurement values for both eyes were statistically analyzed with the SPSS 20.0® for Windows program. In order not to affect the reliability of the study statistically, the right eye of all cases was evaluated. The relationship between the measurements taken from the devices was examined with the Pearson correlation coefficient, and the compatibility with the Bland-Altman analysis.

RESULTS

Fifty-two right eyes of 52 cases were included in the study. 18 of the cases were female and 34 were male. The mean age was 91.50±25.96 (range 53-141) months. The averages of the refractive measurement values are shown in Table 1, and the lower and upper limits are shown in Table 2.

Comparing Plusoptix® with skiascopy, SureSight® with skiascopy and Plusoptix® with SureSight® measurements, a high positive correlation was found between spherical values (r=0.861, r=0.736, r=0.721, respectively). The cylindrical values obtained with Plusoptix® and SureSight® were highly positively correlated (r=0.901), while Plusoptix® and skiascopy and SureSight® and skiascopy cylindrical measurements were moderately positively correlated (r=0.602, r=0.675, respectively). A high positive correlation was found between spherical equivalents from Plusoptix® and skiascopic measurement (r=0.863). Spherical equivalents obtained from Plusoptix® and SureSight® and SureSight® and skiascopic measurements were moderately positively correlated (r=0.683, r=0.685, respectively). A moderate positive correlation was found between the axis values obtained with Plusoptix® and skiascopy, SureSight® with skiascopy,

and Plusoptix® with SureSight® devices (r=0.550, r=0.363, r=0.482, respectively).

According to the Bland-Altman analysis, it was determined that both photorefractometers were compatible with the skiascopic measurement and with each other (Figures 1, 2 and 3). The results of the Bland-Altman analysis, in which the compatibility of spherical measurements obtained from two different photorefractometers with the spherical measurements obtained by skiascope are evaluated, are shown in Figures 1 and 2, and the results of the Bland-Altman analysis in which the compatibility with each other is evaluated are shown in Figure 3. When Plusoptix® and skiascopic cylindrical measurements were evaluated, only 1 case was found outside the confidence interval (within 95% confidence interval, lower limit: -1.35, upper limit: 0.95, mean: -0.20, standard deviation: 0.58). Considering SureSight® and skiascopic cylindrical measurements, 2 cases were outside the confidence interval (within 95% confidence interval, lower limit: -1.20, upper limit: 0.98, mean: -0.11, standard deviation: 0.55). When the cylindrical measurements obtained with Plusoptix® and SureSight® were evaluated, it was observed that 2 subjects were outside the confidence interval (within 95% confidence interval, lower limit: -0.67, upper limit: 0.51, mean: -0.08, standard deviation: 0.30).

DISCUSSION

Detection of refractive error in the pediatric age group is one of the most important factors in the detection of amblyopia, which can be treated in this age (18). Screening tests to be performed with photorefractometry in the early period for the determination of amblyopia have been used frequently, especially in school-age children (19-21). Our aim in this study is to evaluate the compatibility of measurements obtained with two separate photorefractometer devices with skiascopic measurements performed after cycloplegia with 1% cyclopentolate hydrochloride.

Table 1. Refractive error measurement values determined by 3 different methods in cases

	Plusoptix A09®	SureSight®	Skiascopy after cycloplegia
Spherical (D)	0.69±1.78	1.64±1.06	0.88±2.07
Cylindrical (D)	-0.92±0.67	-0.83±0.70	-0.73±0.68
Spherical equivalent (D)	0.23±1.68	1.23±0.99	0.52±2.01
Axis (°)	69.77±70.64	76.15±72.41	91.67±77.19

Means of refractive measurements ± standard deviation, D: dioptry

Table 2. Lower and upper limits of refractive error measurements determined by 3 different methods in cases

	Plusoptix A09®	SureSight®	Skiascopy after cycloplegia
Spherical (D)	-5.25 to +4.25	-1.00 to +4.00	-3.75 to +5.00
Cylindrical (D)	-2.75 to 0	-3.00 to 0	-3.00 to 0
Spherical equivalent (D)	-5.50 to +3.75	-1.13 to +3.63	-4.00 to +5.00

D: dioptry

The gold standard for the determination of refractive error is skiascopy performed after cycloplegia obtained with 1% atropine sulfate drop (6-8). In recent studies in the literature, it has been shown that photorefractometers also give results compatible with skiascopy (10-13). Photorefractometers are devices that enable the determination of refractive error as a result of the reflection of the red reflex of the retina through the non-dilated pupil and its detection with infrared cameras and evaluation with various software (22). Photorefractometers are easy to use and provides non-contact, fast and comfortable measurements to be taken (22,23).

The advantages of taking measurements with Plusoptix® are that cycloplegia is not required and the device is portable and easy to

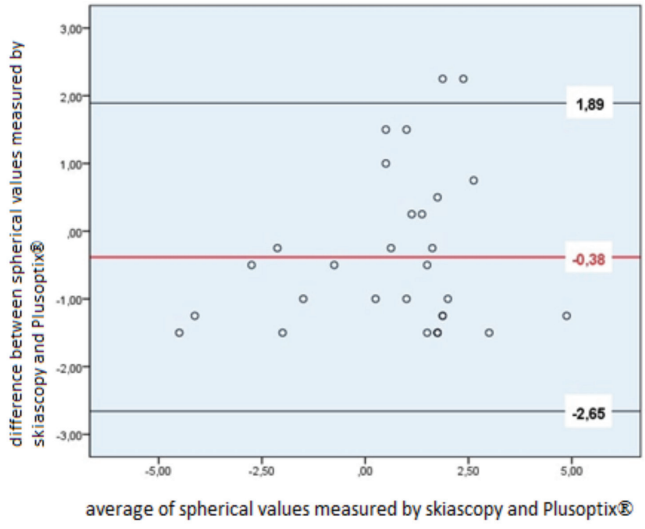

Figure 1. Bland-Altman compatibility analysis of spherical refractive values in Plusoptix® and skiascopic measurements

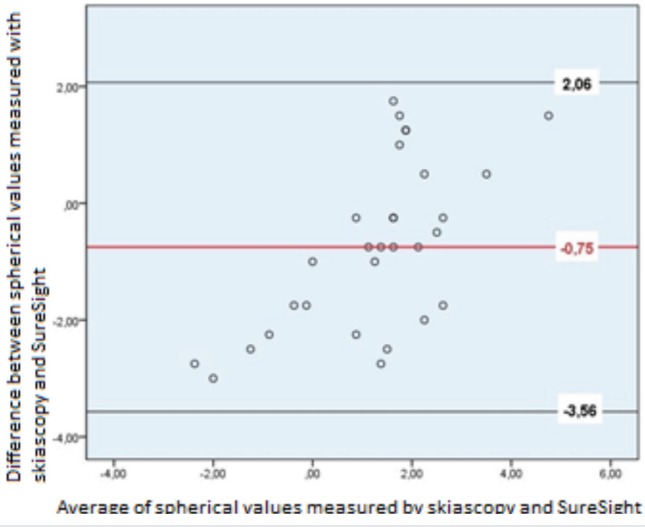

Figure 2. Bland-Altman compatibility analysis of spherical refractive values in SureSight® and skiascopic measurements

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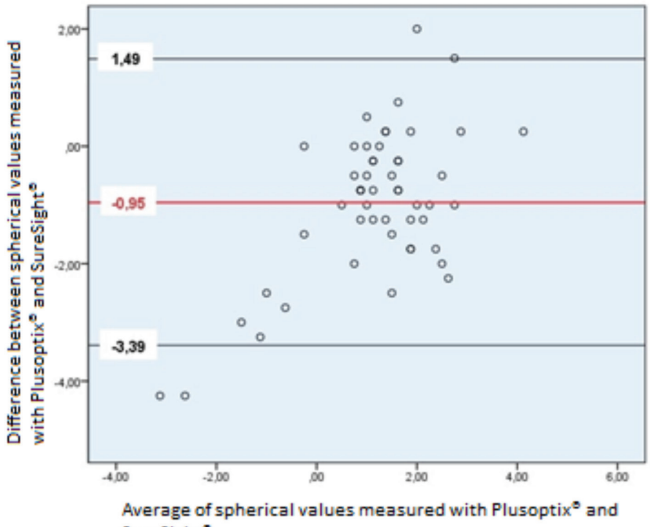

Figure 3. Bland-Altman compatibility analysis of spherical refractive values in Plusoptix® and SureSight® measurements

use. The disadvantage of Plusoptix® is that it cannot numerically detect refractive errors outside the range of -7.00D to +5.00D. In addition, it requires a dark environment for measurement, which makes the examination of the pediatric group more difficult, where it is not easy to cooperate during the examination. Yılmaz et al. (12) compared Retinomax®, retinoscopy and Plusoptix® A09 measurements in 200 cases aged 4-12 years, and found no significant difference between spherical and cylindrical values between the three measurement methods, and stated that all three methods could be used in screening. Erdurmus et al. (24) compared Plusoptix® and cycloplegic skiascopy measurements with Pearson correlation analysis in 204 eyes and found positive correlations between spherical, cylindrical and spherical equivalents (r=0.63, r=0.70, r=0.63, respectively). In our study, there was a positive correlation between the refractive values obtained by skiascopy by providing cycloplegia and the values obtained by Plusoptix®. Our measurements with cycloplegic skiascopy and Plusoptix® were consistent with each other (Figure 1). On the other hand, in a study conducted by Yan et al. (4), Plusoptix® and cycloplegic retinoscopy measurements of 178 cases were compared, and they found a significant difference between spherical values ($p<0.001$) and found no significant difference between cylindrical values ($p=0.14$). Based on these results, they stated that Plusoptix® measurements were not compatible with cycloplegic skiascopy and their use in screening was doubtful (4). The fact that there were 86 amblyopian cases in the study, that 63 cases with strabismus were not excluded from the study, and that the corrected visual acuity of the cases were in a wide range from 0.1 to 1.0 may have played a role in the lack of agreement between the two measurement methods.

When evaluating refractive errors with SureSight®, the fact that cycloplegia is not required, the device is portable, measurement can be taken in any dark or bright environment provides comfort in clinical practice; however, a distance of 35 cm is required during the measurement, which can frighten children and make the examination difficult. In a study conducted by Silverstein et al. (25) with 15,749 cases, they stated that SureSight® photorefractometer could be used in screening programs. In a study conducted by Ying et al. (11) with 4,040 preschool children aged 3-5 years, they compared cycloplegia-free retinoscopy, Retinomax® and SureSight® measurements, and found no significant difference in scans between the three measurements, and suggested that any one of them could be used for refractive error screening in the pediatric group. In our study, there was a positive correlation between the refractive values obtained by skiascopy by providing cycloplegia and the values obtained by the SureSight® photorefractometer, and the values obtained by both methods were compatible with each other (Figure 2).

Silbert et al. (14) retrospectively measured the refractive values with SureSight® and Plusoptix® A09 in 90 children aged 1-17 years and found no significant difference between the devices in the refractive values they obtained. Silbert et al. (16) reported that Plusoptix® and SureSight® photorefractometers could be used in screening programs in their study with 216 cases with a mean age of 9 years. We also found that the measurements we made with both photorefractometers were compatible with each other (Figure 3). There is no study in the literature comparing cycloplegic skiascopy, Plusoptix® and SureSight® photorefractometers with each other.

Study Limitations

Although the age group was appropriate in our study, the number of cases was a limiting factor. Since eyes with uncorrected visual acuity of 1.0 were included, eyes with extreme refractive error were excluded from the study, which is one of the limitations of our study.

CONCLUSION

As a result, it was seen that the results of these three measurements in childhood were compatible with each other.

Ethics Committee Approval: Approval for our study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital with the decision number 1975 dated 13.09.2019.

Informed Consent: Informed written consent was obtained from the parents of each child included in the study.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Bennett AG. An historical review of optometric principles and techniques. Ophthalmic Physiol Opt 1986; 6: 3-21.

2. Gupta M, Rana SK, Mittal SK, Sinha RNP. Profile of amblyopia in school going (5-15 years) children at state level referral hospital in Uttarakhand. J Clin Diagn Res 2016; 10: SC09-11. doi: 10.7860/JCDR/2016/16026.8866.
3. Kurt A, Kılıç R, Polat OA. Refraksiyon kusuru ve şaşılığı olan hastalarda ambliyopi sıklığı. MN Ophthalmology 2016; 23: 174-8.
4. Yan XR, Jiao WZ, Li ZW, Xu WW, Li FJ, Wang LH. Performance of the Plusoptix A09 photoscreener in detecting amblyopia risk factors in Chinese children attending an eye clinic. PLoS One 2015; 10: e0126052. doi: 10.1371/journal.pone.0126052.
5. Duman R, Atilla H, Çatak E. Characteristics of anisometropic patients with and without strabismus. Turk J Ophthalmol 2018; 48: 23-6.
6. Su T, Min X, Liu S, Li F, Tan X, Zhong Y, et al. Accuracy of three common optometry methods in examination of refraction in juveniles. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2016; 41: 174-81.
7. Hernandez-Moreno L, Vallelado-Alvarez A, Martin R. Repeatability of ARK-30 in a pediatric population. Indian J Ophthalmol 2018; 66: 1262-7.
8. Schimitzek T, Haase W. Efficiency of a video-autorefractometer used as a screening device for amblyogenic factors. Graefes Arch Clin Exp Ophthalmol. 2002; 240: 710-6.
9. Sanchez RN, Choudhury F, Tarczy-Hornoch K, Borchert M, Cotter SA, Azen S, et al. Effect of cyclopentolate versus atropine on cycloplegic refraction: The multi-ethnic pediatric eye disease study. Invest Ophthalmol Vis Sci 2008; 49: 1454.
10. Kinori M, Molina I, Hernandez EO, Robbins SL, Granet DB, Coleman AL, et al. The plusoptix photoscreener and the retinomax autorefractor as community-based screening devices for preschool children. Curr Eye Res 2018; 43: 654-8.
11. Ying G, Maguire M, Quinn G, Kulp MT, Cyert L, Vision In Preschoolers (VIP) Study Group. ROC analysis of the accuracy of non cycloplegic retinoscopy, retinomax autorefractor, and suresight vision screener for preschool vision screening. Invest Ophthalmol Vis Sci 2011; 52: 9658-64.
12. Yılmaz İ, Özkaya A, Alkın Z, Özbengi Ş, Yazıcı AT, Demirok A. Comparasion of the plusoptix A09 and retinomax k-plus 3 with retinoscopy in children. J Pediatr Ophthalmol Strabismus 2015; 52: 37-42.
13. Yalcın E, Sultan P, Yılmaz S, Pallikaris IG. A comparison of refraction defects in childhood measured using plusoptix S09, 2WIN photorefractometer, benchtop autorefractometer, and cycloplegic retinoscopy. Semin Ophthalmol 2017; 32: 422-7.
14. Silbert D, Matta N, Tian J, Singman E. Comparing the suresight autorefractor and the plusoptix photoscreener for pediatric vision screening. Strabismus 2014; 22: 64-7.
15. Vision in Preschoolers (VIP) Study Group. Impact of confidence number on accuracy of the suresight vision screener. Optom Vis Sci 2010; 87: 96-103.
16. Silbert DI, Matta NS, Ely AL. Comparison of SureSight autorefractor and plusoptiX A09 photoscreener for vision screening in rural Honduras. J AAPOS 2014; 18: 42-4.
17. Doherty SE, Doyle LA, McCullough SJ, Saunders KJ. Comparison of retinoscopy results with and without 1% cyclopentolate in school-aged children. Ophthalmic Physiol Opt 2019; 39: 272-81.
18. Mitchell DE, Freeman RD, Millodot M, Haegerstrom G. Meridional amblyopia: evidence for modification of the human visual system by early visual experience. Vision Res 1973; 13: 535-58.
19. Teberik K, Eski MT, Kaya M, Ankaralı H. A comparison of three different photoscreeners in children. J Pediatr Ophthalmol Strabismus 2018; 55: 306-11.
20. Williams T, Morgan LA, High R, Suh WD. Critical assessment of an ocular photoscreener. J Pediatr Ophthalmol Strabismus 2018; 55: 194-9.
21. Peterseim MM, Papa CE, Wilson ME, Davidson JD, Shtessel M, Husain M, et al. The effectiveness of the Spot Vision Screener in detecting amblyopia risk factors. J AAPOS 2014; 18: 539-42.
22. Miller JM, Lessin HR. Instrument-based pediatric vision screening policy statement. Pediatrics 2012; 130: 983-6.
23. Kılavuzoğlu AEB, Coşar CB, Üçbaşaran E. Plusoptix CR03 fotorefraktometre cihazı ile rutin göz muayenesi yapılan bir yaşındaki bebeklerin refraksiyon değerleri. MN Ophthalmology 2014; 21: 52-5.
24. Erdurmus M, Yagci R, Karadag R, Durmus M. A comparison of photorefraction and retinoscopy in children. J AAPOS 2007;11: 606-11.
25. Silverstein E, Lorenz S, Emmons K, Donahue SP. Limits on improving the positive predictive value of the Welch Allyn SureSight for preschool vision screening. J AAPOS 2009; 13: 45-50.

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Comparison of Enteropathogens in Hospitalized Children with Acute Gastroenteritis

Merve Arslan[1], Melike Mercan Başpınar[1], Seda Geylani Güleç[2], Okcan Basat[1]

[1]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey
[2]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Pediatrics, İstanbul, Turkey

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ABSTRACT

Objective: This study aimed to compare enteropathogens in children with acute gastroenteritis (AGE) and evaluate their rotavirus (RV) immunization, length of hospitalization, and clinical severity by Ruuska-Vesikari clinical scoring system.

Methods: A retrospective data-based study including 642 hospitalized children with AGE aged between 1 month and 18 years who were admitted to the pediatrics department of a tertiary care hospital from 2014 to 2018.

Results: RV vaccination was not reported in any of the patients. Of the 642 patients hospitalized for AGE, cases included 179 RV enteritis (27.9%), 22 adenovirus enteritis (3.4%), 14 Entamoeba histolytica enteritis (2.2%), 11 Giardia enteritis (1.7%), and 413 unidentified pathogens (64%). The Ruuska-Vesikari score was not correlated to the length of hospitalization (p=0.31; r=0.04). RV enteritis was higher in the winter season (26.8%) and in April (16.8%) than at other times. Most common age range of the RV cases (36.9%) were between 12 and 24 months. The clinical severity of children with AGE was classified as a mild, moderate, and severe (14.5%, 35.5%, and 50%), respectively. About 73.2% of RV cases had severe disease (Ruuska-Vesikari score ≥11) and had a higher score than other pathogens (p<0.001).

Conclusion: In this study, RV was the most identified AGE pathogen among hospitalized children without RV vaccination. Future studies comparing AGE cases with or without RV immunization would be helpful for health policies.

Keywords: Diarrhea, gastroenteritis, pediatrics, rotavirus, Ruuska-Vesikari score

INTRODUCTION

In Turkey, among 117,741 children with diarrhea, there were 26,566 children with rotavirus (RV) gastroenteritis (31.8%) based on the 98 studies published from 1987-2016 (available at https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease). In 2013, the World Health Organization recommended all countries to introduce RV vaccines into their national immunization program, after which there were dramatic reductions in clinical visits, hospitalization, and RV-associated deaths in most of the countries (available at: https://apps.who.int/iris/handle/10665/331323). Changes in acute gastroenteritis (AGE) hospitalization during RV seasons before and after the universal mass vaccination at Estonia (2014) showed a reduction in overall AGE accompanied by a decrease in the infection severity among the hospitalized children (1). Although the expanded immunization program against the 13 diseases in childhood is done free of charge, mainly by the family physicians in Turkey, the RV vaccine was not introduced into the national free immunization program (2). Changes in sociodemographic factors (immigration, wars, etc.), sanitation problems, and inadequate immunization rates may affect future health policies.

ORCID IDs of the authors: M.A. 0000-0001-8452-6381; M.M.B. 0000-0003-3183-3438; S.G.G. 0000-0002-6402-2175; O.B 0000-0002-5222-9136.

Corresponding Author: Melike Mercan Başpınar,
E-mail: drmelikemercan@gmail.com

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This retrospective study aimed to describe enteropathogens among hospitalized children with AGE, the prevalence of RV vaccination, the length of the hospital stay, and the clinical severity by the Ruuska-Vesikari score.

METHODS

We retrospectively analyzed hospitalization data of 4 years which were associated with AGE in the pediatrics department of a training and research hospital from January 1, 2014 to January 1, 2018. The demographic and clinical data of 642 hospitalized children with AGE aged between 1 month and 18 years old were analyzed. Informed consent of the patients was obtained from the parents. Taksim Training and Research Hospital's Clinical Research Ethics Committee approved this study on March 21, 2018 (approval no: 34).

This study assumed that the patients who were hospitalized with AGE or diarrhea had the occurrence of three or more loose or liquid stools per day. We excluded children from this study if i) children had chronic diarrhea or have another disease that might have caused chronic diarrhea ii) children had a factor that might have negatively affected the length of hospitalization, such as immunodeficiency, malnutrition, or multiple malformations iii) patients who did not have a stool test result iv) newborn babies (<1 month of age). Laboratory markers were measured in patients' peripheral blood on the first day of hospitalization. Stool samples were collected from each child for enteropathogen analysis, stool culture, measurement of occult blood, and leukocytes.

Seven scoring parameters in Ruuska-Vesikari clinical severity scoring system consider each of the symptoms identified: diarrhea, vomiting, fever, dehydration, the duration of diarrhea, and vomiting. Treatment status is considered as an additional parameter. Each of the seven parameters is broken into thirds according to an equally divided severity distribution as identified by Ruuska and Vesikari (3) in 1990. The scores for each parameter within the clinical severity scoring system are added, allowing for a severity score between 0 and 20 points. Severity scores ≥11 are considered severe, scores between 7 and 10 are considered moderate, and scores <7 are considered mild (3).

Statistical Analysis

Data were analyzed by the IBM SPSS Statistics 22 program (SPSS IBM, Turkey). Normality control of the data distribution was performed by the Shapiro-Wilk test and the Kolmogorov-Smirnov test. Results were calculated as the mean, median, frequency, and percentage. Kruskal-Wallis test was used to compare enteropathogenic groups and numeric variables, chi-square test was used to compare enteropathogenic groups and categorical variables, and Spearman's rho correlation test was used to analyze the relationship between the length of hospitalization and Ruuska-Vesikari score.

RESULTS

Out of 642 patients, 380 (59%) were male, and and 262 (41%) were female. The mean age was 2.4 years. Enteropathogens were identified in 229 (46.7%) of 642 patients. Agents were RV in 179 (27.9%) patients, adenovirus in 22 (3.4%) patients, Entamoeba histolytica in 14 (2.2%) patients, Giardia in 11 of 642 (1.7%) patients, mix type (RV plus adenovirus) in 3 (0.5%) patients and unidentified pathogens in 413 (64.3%) patients. RV was present in in 78% (179/229) of all the identified AGE cases, and nearly 40% (71/179) occurred in patients <12 months of age. Table 1 shows the comparison of pathogens based on hospital stay, Ruuska-Vesikari score, age, gender, seasonality, and hospitalization period. The RV group (36.9%) had a higher presence than other pathogens with a longer hospital stay than the adenovirus and unidentified groups (p=0.00 and p=0.002, respectively). The Ruuska-Vesikari score was 10.4±3.2, which was significantly different among the pathogen types (p<0.001). The RV group had a higher Vesikari score than others (p<0.001).

A total of 149 cases in 2017, 222 cases in 2016, 170 cases in 2015, and 101 cases in 2014 were hospitalized for gastroenteritis. Regarding the seasonal and monthly distribution of the AGE cases, the highest AGE approval number was in the summer season (29.6%, 190 cases), especially in the month of May (12.3%, 79 cases).

Although it was not significant (p=0.837), as seen in Figure 1, boys had a higher AGE rate than that of girls, except for E. histolytica in summer (100% female) and adenovirus in autumn (66.7% female).

The highest RV cases were observed in spring, especially in April and May, but the statistical difference was observed in the winter (p<0.001). The seasonal rate of RV (26.8%) in the winter was higher than that of adenovirus (13.6%), unidentified types (17.9%), E. histolytica (7.1%), and Giardia (18.2%) with p=0.010, p<0.001, p<0.001, and p=0.003 values, respectively.

As seen in Figure 2, the AGE rate of RV was highest in April (16.8%) and significantly higher than that of other pathogens.

Dehydration was mild in 62.9%, moderate in 36.1%, and heavy in 0.9% of all patients. Table 2 shows the comparison of pathogens based on fever, dehydration, and clinical severity. In the comparison of fever (body temperature, 38-38.4°) between pathogens, the E. histolytica group (42.9%) had significantly higher rates than RV (10.1%), adenovirus (4.5%), giardia (%9.1) and unidentified type (10.7%) groups (p=0.001, p=0.002, p<0.001 and p<0.001, respectively.

In the comparison of RV positive (20.4%) and negative (15.7%) AGE, we found a significant difference in moderate dehydration for RV (p<0.001). There was no difference for mild or severe dehydration. As seen in Table 2, 87.2% of RV cases were of high clinical severity. Table 3 shows the evaluation of diarrhea and vomiting in AGE based on enteropathogen types. The duration of diarrhea among 76% of cases was 1-4 days long, while the

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most common diarrhea frequency was detected (36.4%) as 1-3 times a day. The rate of short diarrhea duration (1-4 days) in the unidentified group (81.8%) was significantly higher than that in the RV (65.9%) and adenovirus (54.5%) groups (p<0.000 and p<0.000). The frequency of diarrhea between 1-3 times was significantly higher in the unidentified group (52.5%) than in the RV (8.9%), adenovirus (0%), Giardia (18.2%) and E. histolytica (14.3%) groups (p<0.001, p<0.001, p=0.019 and p=0.017, respectively).

There was a difference among the pathogen groups regarding vomiting frequency and duration (p<0.001). The duration of vomiting 2 days long was significantly lower in the unidentified type group (12.3%), than in the RV (31.3%), adenovirus (31.8%), E. histolytica group (14.3%) and Giardia (45.5%) groups (p<0.001, p<0.001, p<0.001 and p=0.009, respectively). Vomiting frequency >3 times a day was significantly higher in the E. histolytica group (28.6%) than in the RV (46.9%) and adenovirus (50%) groups (p<0.001, p=0.037). Vomiting frequency 5 times a day was

Table 1. Comparison of pathogens based on hospital stay (day), Ruuska-Vesikari score, age, gender, seasonality, and hospitalization periods (month/year)

		Enteropathogens					
		Rotavirus (+)	Adenovirus (+)	Unidentified enteropathogen	E. histolytica (+)	Giardia (+)	
Variables		Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	p-value
Hospital stay (days)		5.3±2.9 (5)	3.5±2.0 (3)	4.6±2.8 (4)	4.1±1.6 (4)	5.5±1.6 (6)	[1]0.001*
Ruuska-Vesikari score		13.01±2.2 (13)	13±1.9 (13)	9.1±2.8 (9)	11.7±2.8 (12)	11.73±1.95 (12)	[1]0.000*
		n (%)	n (%)	n (%)	n (%)	n (%)	p-value
Age	1-12 months	71 (39.7%)	5 (22.7%)	198 (47.9%)	3 (21.4%)	3 (27.3%)	[2]0.000*
	12-24 months	66 (36.9%)	8 (36.4%)	99 (24%)	1 (7.1%)	3 (27.3%)	
	24-48 months	24 (13.4%)	4 (18.2%)	40 (9.7%)	2 (14.3%)	1 (9.1%)	
	48-60 months	11 (6.1%)	1 (4.5%)	17 (4.1%)	2 (14.3%)	0	
	5-12 years	7 (3.9%)	4 (18.2%)	55 (13.3%)	4 (28.6%)	2 (18.2%)	
	>12 years	0	0	4 (1%)	2 (14.3%)	2 (18.2%)	
Gender	Male	109 (60.9%)	12 (54.5%)	243 (58.8%)	9 (64.3%)	7 (63.6%)	[2]0.957
	Female	70 (39.1%)	10 (45.5%)	170 (41.2%)	5 (35.7%)	4 (36.4%)	
Season	1st quarter	48 (26.8%)	3 (13.6%)	74 (17.9%)	1 (7.1%)	2 (18.2%)	[2]0.000*
	2nd quarter	74 (41.3%)	5 (22.7%)	90 (21.8%)	3 (21.4%)	0	
	3rd quarter	35 (19.6%)	6 (27.3%)	143 (34.6%)	1 (7.1%)	4 (36.4%)	
	4th quarter	22 (12.3%)	8 (36.4%)	106 (25.7%)	9 (64.3%)	5 (45.5%)	
Month	January	21 (11.7%)	0	19 (4.6%)	0	1 (9.1%)	[2]0.000*
	February	20 (11.2%)	1 (4.5%)	30 (7.3%)	0	0	
	March	15 (8.4%)	1 (4.5%)	19 (4.6%)	2 (14.3%)	0	
	April	30 (16.8%)	1 (4.5%)	25 (6.1%)	1 (7.1%)	0	
	May	29 (16.2%)	3 (13.6%)	46 (11.1%)	0	0	
	June	25 (14%)	1 (4.5%)	44 (10.7%)	0	1 (9.1%)	
	July	2 (1.1%)	3 (13.6%)	45 (10.9%)	1 (7.1%)	3 (27.3%)	
	August	8 (4.5%)	2 (9.1%)	54 (13.1%)	0	0	
	September	3 (1.7%)	3 (1.6%)	32 (7.7%)	5 (35.7%)	0	
	October	11 (6.1%)	0	45 (10.9%)	3 (21.4%)	3 (27.3%)	
	November	8 (4.5%)	5 (2.7%)	29 (7%)	1 (7.1%)	2 (18.2%)	
	December	7 (3.9%)	2 (9.1%)	25 (6.1%)	1 (7.1%)	1 (9.1%)	
Year	2017-2018	41 (22.9%)	5 (22.7%)	94 (22.8%)	8 (57.1%)	0	[2]0.000*
	2016-2017	78 (43.6%)	5 (22.7%)	133 (32.2%)	2 (14.3%)	3 (27.3%)	
	2015-2016	37 (20.7%)	7 (31.8%)	113 (27.4%)	4 (28.6%)	8 (72.7%)	
	2014-2015	23 (12.8%)	5 (22.7%)	73 (17.7%)	0	0	

[1]Kruskal-Wallis test, [2]chi-square test, *p<0.05. SD: standard deviation

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significantly higher in the E. histolytica group (42.9%) than in the RV (36.3%), adenovirus (36.4%), and Giardia (27.3%) groups (p<0.00, p=0.003, and p=0.020, respectively).

Additional symptoms were reported (13.4% RV, 15.7% unidentified, 28.6% E. histolytica, and 18.2% Giardia). Hepatic transaminases [alanine transaminase (ALT), aspartate transaminase (AST)] were higher in the RV group (10.6%) than with the other enteropathogens (9.1% Giardia, 7.3% unidentified, 4% adenovirus). The rate of rashes in the E. histolytica group was 21.4% (1.1% RV, 2.9% unidentified), which was significantly higher than that with other pathogens (p<0.001; p<0.001). At the same time, one appendicitis case in patients with giardia enteritis, two invagination cases in RV group, one invagination case in E. histolytica group, 13 convulsion cases in unidentified group were detected.

Enteropathogens and hospital stay were evaluated based on the season and Ruuska-Vesikari score (Figure 3). RV and unidentified enteropathogens were the most common reasons for hospital stay. The mean hospital stay was 4.7 (2.8) days, and the RV positive group had a longer stay than that of the RV negative cases (p=0.01). RV had a higher Ruuska-Vesikari score and hospitalization time both in winter and spring at a high rate. There was no relationship between Ruuska-Vesikari score and hospital stay in the AGE cases (p=0.312, r=0.04).

DISCUSSION

The most striking part of this retrospective analysis was that no children with AGE had RV immunization before, and RV enteritis had a longer length of hospital stay and clinical severity than other enteropathogens.

The presence of RV was reported to be 7.8-41% in Turkey (4,5). High presence of RV has been reported in the literature in Canada (71.7%), China (68.7%), South Korea (66.7%), and Saudi Arabia (50%) (6-9). The presence of RV in our study was 27.9%, similar to that reported in Turkey.

In a study from Saudi Arabia, 69.6% of cases were <12 months of age, and there was a dramatic decline in the incidence of RV positive diarrhea after the age of 1 year (9). Similarly, 96% of children with RV enteritis and 88% of all AGE cases were <5 years of age in our study. Around 40% of all RV cases were <12 months of age, and the RV phrequency (36.9%) was significantly higher than other AGE groups aged between 12-24 months.

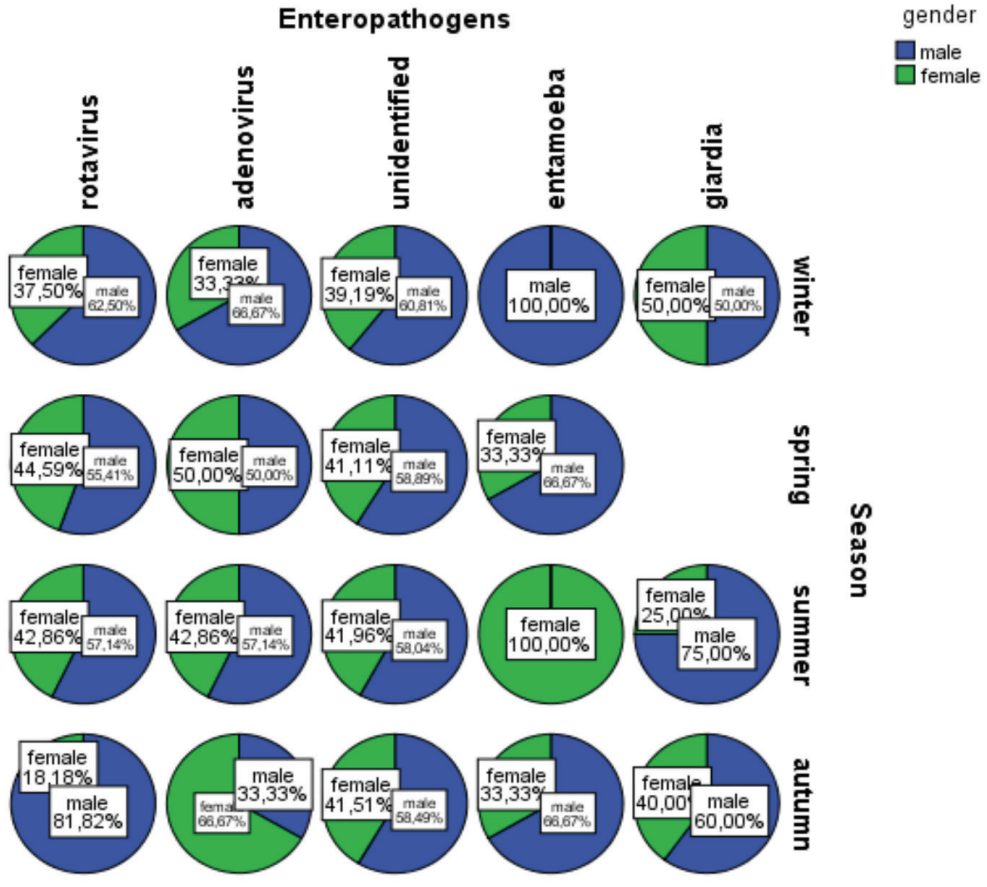

Figure 1. Evaluation of enteropathogens and seasonal rates based on gender

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In a study by Salami et al. (10), E. histolytica was the leading enteropathogen in 27.8% of cases, followed by RV, adenovirus, and mixed group (two or more identified enteropathogens) with 13.6%, 6.1%, and 6.1%, respectively. Around 96% of cases were classified as unidentified enteropathogens. This might have been caused by the absence of advanced bacterial diagnosis and the lack of detection of some viruses (astrovirus and norovirus), as in our study. In our study, the unidentified enteropathogen had the highest ratio. We thought that this might have been due to factors that cause diarrhea, such as additional food. More frequent diarrhea in children <48-60 months may be associated with additional foods beginning in the sixth month. Because of the humoral and cellular anti-infective properties of human milk, breast milk protects babies against diarrhea (11).

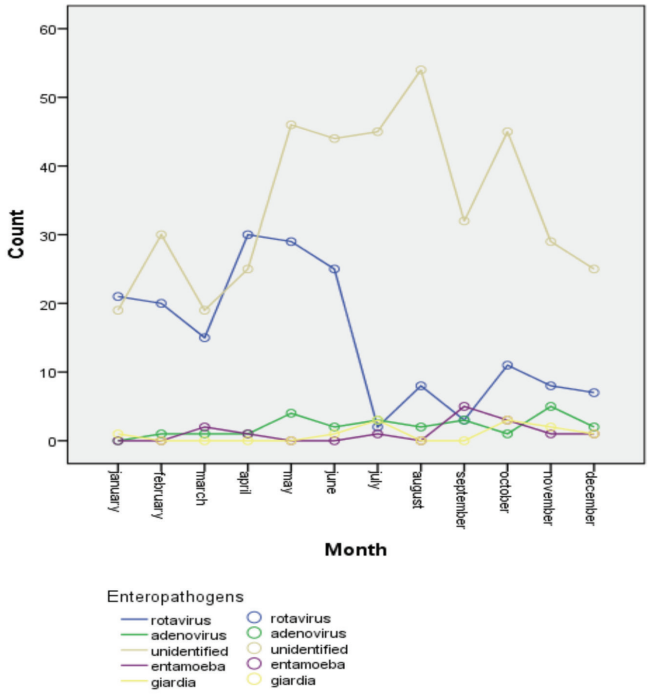

Figure 2. Evaluation of enteropathogens and monthly rates

In France, RV infections mostly occur during the winter and spring seasons, with a peak between January and April (12). Before vaccine introduction (2002-2006), RV-coded hospitalizations in New York City were elevated during each winter, with epidemics typically beginning in January, peaking in March, and declining by May (13). In our study, the seasonal rate of RV was higher in winter, peaked in April, and declined by July. We thought the difference in comparison of months might have originated from the the climate zone of our country. For example, more RV cases were observed during the spring and summer in a Saudi Arabian study (9).

Diarrhea in children living in Turkey is observed most commonly in the eastern region. A study showed that the prevalence of diarrhea is 1,581-fold higher in rural, rural-to-urban, and urban-to-rural children compared to urban children and that internal migration was observed to increase the frequency of diarrhea (14). In our study, the RV rate in 2016 was significantly higher than that of other years.

Simultaneously, the hospital's location might have been another reason, because it receives high internal immigration from low socio-economic regions. We thought that increased AGE cases in our hospital during 2016 would depend on

Table 2. Comparison of enteropathogens based on body fever, dehydration, and clinical severity of gastroenteritis

	Enteropathogens					
	Rotavirus (+)	Adenovirus (+)	Unidentified enteropathogen	E. histolytica (+)	Giardia (+)	
Variables	n (%)	n (%)	n (%)	n (%)	n (%)	p-value
Body fever (°C)						
<36.6 °C	60 (33.5%)	11 (50%)	218 (52.8%)	1 (7.1%)	4 (36.4%)	[1]0.000*
36.6-37.9 °C	92 (51.4%)	10 (45.5%)	122 (29.5%)	5 (35.7%)	6 (54.5%)	
38-38.4 °C	18 (10.1%)	1 (4.5%)	44 (10.7%)	6 (42.9%)	1 (9.1%)	
≥38.5 °C	9 (5%)	0	29 (7%)	2 (14.3%)	0	
Dehydration						
Mild (<1%)	47 (26.3%)	5 (22.7%)	342 (82.8%)	7 (50%)	3 (27.35%)	[1]0.000*
Moderate (1-5%)	131 (73.2%)	17 (77.3%)	66 (16%)	7 (50%)	8 (72.7%)	
Severe (≥6%)	1 (0.6%)	0	5 (1.2%)	0	0	
Clinical severity						
Mild	0	0	93 (22.5%)	0	0	[1]0.000*
Moderate	23 (12.8%)	1 (4.5%)	198 (47.9%)	4 (28.6%)	2 (18.2%)	
High	156 (87.2%)	21 (95.5%)	122 (29.5%)	10 (71.4%)	9 (81.8%)	

[1]chi-square test, *p<0.05

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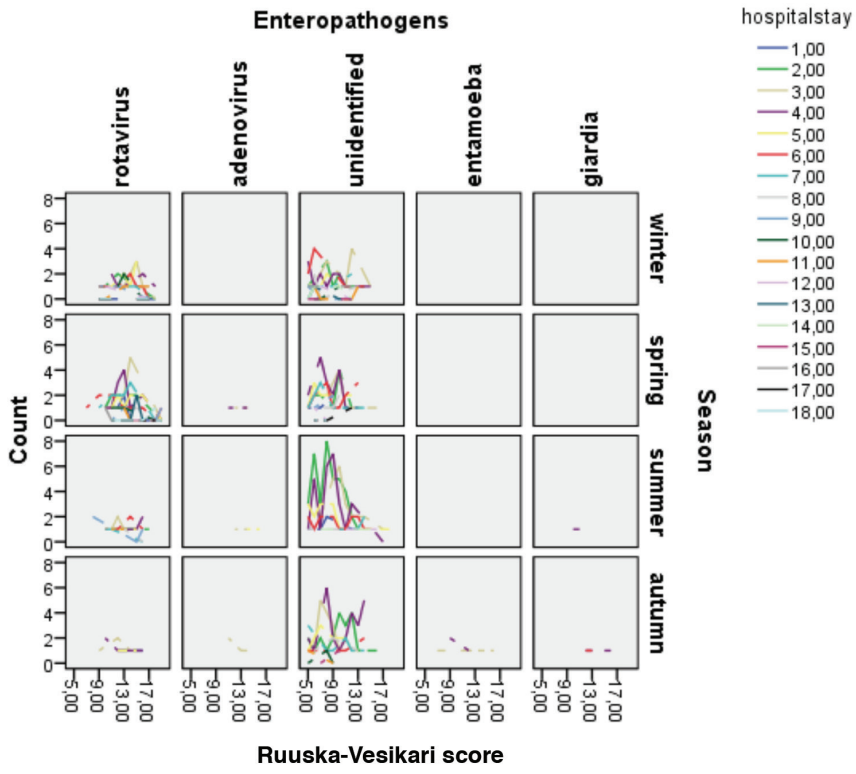

Figure 3. Evaluation of enteropathogens and hospital stay based on season and Ruuska-Vesikari score

Table 3. Evaluation of diarrhea and vomiting according to enteropathogen type

Variables	Enteropathogens					
	Rotavirus (+)	Adenovirus (+)	Unidentified enteropathogen	E. histolytica (+)	Giardia (+)	
	n (%)	n (%)	n (%)	n (%)	n (%)	p-value
Duration of diarrhea						
1-4 days	118 (65.9%)	12 (54.5%)	338 (81.8%)	11 (78.6%)	9 (81.8%)	[1]0.000*
5 days	25 (14%)	5 (22.7%)	15 (3.6%)	1 (7.1%)	0	
≥6 days	36 (20.1%)	5 (22.7%)	60 (14.5%)	2 (14.3%)	2 (18.2%)	
Episodes of diarrhea						
1-3 times	16 (8.9%)	0	217 (52.5%)	2 (14.3%)	2 (18.2%)	[1]0.000*
4-5 times	78 (43.6%)	12 (54.5%)	115 (27.8%)	5 (35.7%)	6 (54.5%)	
≥6 times	85 (47.5%)	10 (45.5%)	81 (19.6%)	7 (50%)	3 (27.3%)	
Duration of vomiting						
No vomiting	4 (2.2%)	1 (4.5%)	166 (40.2%)	6 (42.9%)	1 (9.1%)	[1]0.000*
1 days	35 (19.6%)	3 (13.6%)	114 (27.6%)	2 (14.3%)	3 (27.3%)	
2 days	56 (31.3%)	7 (31.8%)	51 (12.3%)	2 (14.3%)	5 (45.5%)	
≥3 days	84 (46.9%)	11 (50%)	82 (19.9%)	4 (28.6%)	2 (18.2%)	
Episodes of vomiting (maximum number/day)						
No times	4 (2.2%)	1 (4.5%)	166 (40.2%)	6 (42.9%)	1 (9.1%)	[1]0.000*
1 time	9 (5%)	0	71 (17.2%)	1 (7.1%)	0	
2-4 times	101 (56.4%)	13 (59.1%)	144 (34.9%)	1 (7.1%)	7 (63.6%)	
≥5 times	65 (36.3%)	8 (36.4%)	32 (7.7%)	6 (42.9%)	3 (27.3%)	

[1]chi-square test, *p<0.05

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increased applies based on Syrian refugees living near the hospital location.

RV has been reported to be associated with encephalopathy, myositis, and elevated hepatic transaminases, and even simultaneous presentation of all these conditions was published in a case report of a 17-month-old girl (hypernatremia, encephalopathy, myositis, transaminitis, and hypoalbuminemia) (15). In a study by Teitelbaum and Daghistani (16), 20% of children had elevated ALT and AST (16). In our study, the rate of elevated hepatic transaminase was 10.6% in cases of RV, 9.1% in cases of Giardia, and 7.3% in cases of of unidentified gastroenteritis.

A study by Ogawa et al. (17) reported that RV infection is a risk factor for splenic lesions in patients with benign convulsions having mild gastroenteritis, suggesting that RV causes edema in the corpus callosum. We found 14 cases (2.2%) with convulsion symptoms who already had a febrile convulsion history in 4 patients, but magnetic resonance of patients had no specific results.

Concerning viral pathogens in a study on appendicitis etiology by Richardsen et al. (18), adenovirus was the most common with an incidence of 5.4%, followed by RV (4.7%). In our study, appendicitis developed in one case, caused by Giardia.

The rate of rashes in the E. histolytica group was 21.4% (1.1% RV, 2.9% unidentified), which was significantly higher than other pathogens. We thought that the high rash rate in E. histolytica might have resulted from the fever reaction, because the E. histolytica group's fever rate was significantly higher than that of other pathogens.

Study Limitations

Firstly, as we started this study, our goal was to descriptively analyze children with AGE and compare groups with or without the RV vaccine. However, we found that no child was vaccinated in our study sample. We thought that this might have been due to the vaccine fee, insufficient level of knowledge about vaccination,or socio-economic factors. Secondly, the retrospective study design did not permit us to ask parents about some demographic variables (such as using the hand for oral feeding, living in a large family, socio-economic level, maternal education level, disposal methods of children's feces, source of water, etc.) that would negatively affect sanitation and hygiene. Thirdly, the norovirus detection kit was absent in our hospital laboratory, which might have been responsible for the high presence of unidentified pathogens.

CONCLUSION

This retrospective study demonstrated that the highest ratio of identified enteropathogens of AGE in hospitalized children belonged to RV, of which all cases had not received RV vaccination. We described that RV may cause severe complications with severe gastroenteritis and highlighted the importance of RV vaccination in the national immunization program, which may prevent long hospital stays.

Ethics Committee Approval: Taksim Training and Research Hospital's Clinical Research Ethics Committee approved this study on March 21, 2018 (approval no: 34).

Informed Consent: Informed consent of the patients was obtained from the parents.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept - M.A., M.M.B., S.G.G., O.B.; Design - M.A., M.M.B., S.G.G., O.B.; Data Collection and/or Processing - M.A., M.M.B.; Analysis and/or Interpretation - M.A., M.M.B., S.G.G., O.B.; Literature Search - M.A., M.M.B., S.G.G., O.B.; Writing - M.A., M.M.B., S.G.G., O.B.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Kõivumägi K, Toompere K, Soeorg H, Kallas E, Jõgeda E-L, Huik K, et al. Acute gastroenteritis hospitalizations after implementation of universal mass vaccination against rotavirus. Vaccine 2020; 38: 2879-86.
2. TC Sağlık Bakanlığı Sağlık İstatistikleri Yıllığı, Sağlık Araştırmaları Genel Müdürlüğü Ankara. 2016: 181-209. Available from: https://www.saglik.gov.tr/TR,31249/saglik-istatistikleri-yilligi-2016-yayinlanmistir.html
3. Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis 1990; 22: 259-67.
4. Ulukanlıgil M, Bakır M, Arslan G, Soran M, Seyrek A. Şanlıurfa'da 0-5 yaş arası çocuklarda ishal etkenlerinin araştırılması. Mikrobiyoloji Bülteni 2001; 35: 307-12.
5. Gültepe B, Yaman G, Çıkman A, Güdücüoğlu H. Çocukluk yaş grubu gastroenteritlerde rotavirus ve adenovirus sıklığı. Türk Mikrobiyol Cem Derg 2012; 42: 16-20.
6. Rivest P, Proulx M, Lonergan G, Lebel MH, Bédard L. Hospitalisations for gastroenteritis: the role of rotavirus. Vaccine 2004; 22: 2013-7.
7. Huh J-W, Kim W-H, Moon S-G, Lee J-B, Lim Y-H. Viral etiology and incidence associated with acute gastroenteritis in a 5-year survey in Gyeonggi province, South Korea. J Clin Virol 2009; 44: 152-6.
8. Zhang S, Chen TH, Wang J, Dong C, Pan J, Moe C, et al. Symptomatic and asymptomatic infections of rotavirus, norovirus, and adenovirus among hospitalized children in Xi'an, China. J Med Virol 2011; 83: 1476-84.
9. Nahari A, AlGhamdi SM, Alawfi A, Faqeehi H, Alzahrani S, Abu-Shaheen A, et al. The clinical burden of rotavirus gastroenteritis: a prospective study. Cureus 2017; 9: e1903. doi: 10.7759/cureus.1903.
10. Salami A, Fakih H, Chakkour M, Salloum L, Bahmad HF, Ghssein G. Prevalence, risk factors and seasonal variations of different Enteropathogens in Lebanese hospitalized children with acute gastroenteritis. BMC Pediatr 2019; 19: 137.
11. Popkin BM, Adair L, Akin JS, Black R, Briscoe J, Flieger W. Breast-feeding and diarrheal morbidity. Pediatrics 1990; 86: 874-82.
12. De Rougemont A, Kaplon J, Fremy C, Legrand-Guillien M-C, Minoui-Tran A, Payan C, et al. Clinical severity and molecular characteristics of circulating and emerging rotaviruses in young children attending hospital emergency departments in France. Clin Microbiol Infect 2016; 22: 737. e9-15. doi: 10.1016/j.cmi.2016.05.025
13. Olson DR, Lopman BA, Konty KJ, Mathes RW, Papadouka V, Ternier A, et al. Surveillance data confirm multiyear predictions of rotavirus dynamics in New York City. Sci Adv 2020; 6 :eaax0586. doi: 10.1126/sciadv.aax0586.
14. Şantaş G. Türkiye'de iç göçün beş yaş altı çocuklarda ölümlülük ve ishal üzerindeki etkisine ilişkin bir araştırma. Celal Bayar Üniversitesi Sağlık Bilimleri Enstitüsü Dergisi 2018; 5: 199-208.
15. Trivedi M, Jain A, Shah D, Gupta P. Rotavirus Gastroenteritis associated with encephalopathy, myositis, transaminitis and hypoalbuminemia. Indian J Pediatr 2019; 86: 642-4.

16. Teitelbaum JE, Daghistani R. Rotavirus causes hepatic transaminase elevation. Dig Dis Sci 2007; 52: 3396-8.
17. Ogawa C, Kidokoro H, Ishihara N, Tsuji T, Kurahashi H, Hattori A, et al. Splenial lesions in benign convulsions with gastroenteritis associated with rotavirus infection. Pediatr Neurol 2020; 109: 79-84.
18. Richardsen I, Schöb D, Ulmer T, Steinau G, Neumann U, Klink C, et al. Etiology of appendicitis in children: the role of bacterial and viral pathogens. Journal of Investigative Surgery 2016; 29: 74-9.

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Evaluation of the Causes for Repeated Endoscopic Retrograde Cholangiopancreatography in the Early Period

Murat Akaydın[1], Okan Demiray[2]

[1]Academic Hospital, Clinic of General Surgery, İstanbul, Turkey
[2]University of Health Sciences Turkey, Taksim Research and Training Hospital, Clinic of General Surgery, İstanbul, Turkey

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ABSTRACT

Objective: Endoscopic retrograde cholangiopancreatography (ERCP) is the most important invasive endoscopic procedure for the clearance of bile duct stones. Several factors may interfere with a positive outcome in the first attempt. It is important for the endoscopist and the patient to predict under which circumstances repeated intervention may be required. The aim of this study was to determine the conditions in which the need for repeated ERCP increases in patients who have undergone ERCP for bile duct stones.

Methods: Data collected from the procedures performed by a single endoscopist between 2005 and 2020 were analyzed retrospectively. The findings obtained from 100 cases whose bile duct stones were cleared in a single procedure were compared with those of 100 cases who required repeated ERCP in the early period. The demographic findings of the patients, laboratory examinations, difficulty of common bile duct (CBD) stones, clinical manifestation of cholangitis, anatomical and pathological conditions of the patients, factors that complicated the ERCP procedure, and consequently the effect of these factors on post-ERCP complications were investigated in both groups.

Results: According to the results of this study, the diameter of the CBD and the number of stones increased in elderly patients. On the other hand, the presence of stenosis, enclaved stones in the CBD, and accompanying pancreatitis increased the need for repeated ERCP in young patients. In the prediction of single and repeated ERCP using the univariate model, a significant association ($p<0.05$) was observed between post-ERCP complications and age, white blood cell count, aspartate aminotransferase (AST), alanine aminotransferase, total bilirubin, direct bilirubin, width, angulation, and shape of the CBD, fever and chills, biliary pancreatitis, cholangitis, and difficult stones. In the prediction of single and repeated ERCP using the multivariate model, a significant association ($p<0.05$) was observed between post-ERCP complications and AST, fever and chills, biliary pancreatitis, and difficult stones.

Conclusion: The need for stenting was higher in both age groups when cholangitis was present. The success rate of ERCP was not affected by a single factor, but by all clinical and pathological factors that increase the difficulty of the procedure.

Keywords: Bile duct angulation, cholangitis, choledocholithiasis, common bile duct stones, difficult common bile duct stones, ERCP, pancreatitis, pre-cut sphincterotomy, repeated ERCP, suppurative cholangitis

ORCID IDs of the authors: M.A. 0000-0002-1828-7068; O.D. 0000-0001-6920-7585.

Corresponding Author: Okan Demiray,
E-mail: drokandemiray@gmail.com

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INTRODUCTION

Despite it being the gold standard for the treatment of choledochal stones, clearance of the common bile duct (CBD) stones with endoscopic retrograde cholangiopancreatography (ERCP) may not be successful in the first attempt in some patients. Although gallstones are prevalent in 15-20% of the general population, the prevalence of the choledochal stones observed concomitantly with gallstones is reported to be 3-10% in the literature (1-7). In addition to clinical evaluation, advanced imaging methods, such as ultrasonography (USG), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasonography (EUS) are diagnostic modalities used to diagnose bile duct stones. With a success rate of 90%, MRCP is the most accurate imaging method (6,8). The invasive ERCP procedure is widely replaced by MRCP and EUS as a diagnostic tool and is predominantly used for treatment purposes in current practice (9). The failure rate of selective CBD cannulation in ERCP varies between 5 and 15% (5,10,11). Advanced endoscopic, surgical, and percutaneous techniques may be indicated in the presence of CBD stones which cannot be removed with a standard ERCP intervention and in cases with altered biliary anatomy (6,9).

The incidence rate of CBD stones is currently increasing with advanced age due to the increasing average age and changes in food habits (5,11,12). In this age group, the prevalence of stones which cannot be cleared with a single attempt has also been increasing. In many patients, stenting is required to prevent prolonged ERCP procedure risks resulting from anatomical difficulties, such as juxtapapillary diverticulum, difficult CBD stones, and increased frequency of cholangitis. The success rate of repeated ERCP interventions were reported to be higher with more satisfactory results being achieved (6,7,13,14). The aim of this study was to determine the conditions in which the need for repeated ERCP increases in patients who have undergone ERCP for bile duct stones.

METHODS

In this study, the files of patients who had undergone ERCP by the same endoscopist in different health institutions for CBD stones between 2005 and 2020 were retrospectively reviewed. The patients were evaluated according to age, gender, pre-procedural laboratory tests, imaging methods, anatomopathological conditions, bile duct factors, and stone conditions. Pre-procedural complaints (pain, icterus, fever, and chills), cholangitis, and a history of biliary pancreatitis were investigated to evaluate whether they had any effect on repeated ERCP.

All laboratory tests related to biliary tract pathologies were performed. The differences between the laboratory tests of the two groups were investigated. Pre-procedural USG and MRCP examinations were performed for the detection of CBD stones. In non-emergency situations, the patients sent to our reference hospital were subjected to MRCP for a detailed detection of pancreatic and biliary tract pathologies. In patients with acute biliary pancreatitis, early ERCP was planned if findings of acute cholangitis were present, while in the absence of these findings, the procedure was delayed until the patient's general condition improved.

The condition of the papilla, presence of juxtapapillary diverticulum, appearance of the papilla, presence of very rarely observed findings of choledochoduodenal fistula, and cannulation success were defined. Needle-knife sphincterotomy was the method of choice in patients who were unsuitable for early selective cannulation, especially in the presence of papillary protrusion. However, if cannulation was not present, the procedure was suspended to be repeated. Contrast material was administered after confirming the selective cannulation of the CBD with a guidewire or through the aspiration of bile. In the endoscopic examination, the diameter of the CBD was determined using the image of the extrahepatic biliary tract axis, and the CBD angulation was measured. Extraction of stone/sludge/pus during the procedure was also investigated. The diameter and localization of the stones were recorded. Single stones >15 mm, multiple stones <15 mm, enclaved CBD stones, distal stenosis of the CBD, and stones requiring mechanical lithotripsy were considered as difficult CBD stones. Patients with choledochoduodenal fistula, T-tube *in situ*, or intraprocedural basket impaction were also included in this group. Patients with intrahepatic stones and modified anatomy were not included in this study. All these anatomopathological factors were evaluated in both groups. These factors may be summarized as the presence of juxtapapillary diverticulum, unsuccessful cannulation, and presence of pre-cut sphincterotomy and difficult CBD stones.

Endoscopic biliary stenting was performed in cases where adequate clearing of the stones could not be achieved despite prolongation of the procedure, especially in those with concomitant cholangitis. Our first choice was a 10-F Amsterdam-type plastic stent. However, in patients with severe cholangitis, a dilated CBD, and multiple stones, we preferred a pigtail stent.

Procedural complications included inadequate ERCP, difficult CBD stones, residual stones, and cholangitis. Two groups were formed with 100 patients each, who were selected consecutively; the single ERCP group, in which the initial attempt of stone clearance was successful and repeated ERCP was not required in the early period, and the repeated ERCP group, in which a second procedure was required within a month of the initial procedure due to inadequate stone clearance, stenting, failed cannulation, or basket impaction.

Statistical Analysis

Descriptive statistics of the data used the mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The distribution of variables was determined with the Kolmogorov-Smirnov test. The independent-samples t-test and Mann-Whitney U test were used for the analysis of continuous

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independent data. The chi-square test was conducted for the analysis of categorical independent data, and Fisher's Exact test was used when the chi-square test criteria were not achieved. The effect levels of the factors were investigated with univariate and multivariate logistic regression analyses. SPSS v. 27.0 software package was used in all statistical analyses.

RESULTS

Of the total 200 cases, 128 were female, and 72 were male. The age of patients in the repeated ERCP group were significantly higher ($p<0.05$) than that of patients in the single ERCP group (Table 1).

There was no significant difference in gender distribution between the repeated and single ERCP groups ($p>0.05$). Similarly, the rate of complaints in terms of pain, jaundice, and the presence of gallstones were not significantly different between the two groups ($p>0.05$). The repeated and single ERCP groups did not differ significantly in terms of the duration of complaints ($p>0.05$). The length of complaints did not differ with regard to the number of ERCPs (Table 2).

Compared to the single ERCP group, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were significantly higher in repeat ERCP group ($p<0.05$). The gamma glutamyl transferase, alkaline phosphatase, amylase, and indirect bilirubin levels showed a significant difference between the two groups ($p<0.05$). However, the repeated and single ERCP groups did not differ significantly in terms of the number of gallstones ($p>0.05$). Although juxtapapillary diverticulum was commonly observed in the repeated ERCP group, the difference was not significant between the groups (Table 2).

Compared to the single ERCP group, the presence of pre-procedural biliary pancreatitis and the prevalence of difficult CBD stones were significantly higher in the group with repeated ERCP ($p<0.05$ for both). Additional factors other than the size and number of stones, including age, presence of fever and chills, biliary pancreatitis, cholangitis, white blood cell (WBC), AST, ALT, and total and direct bilirubin levels were also increased with the difficulty of the procedure ($p<0.05$) (Table 2).

Similarly, when we compared the two groups according to the anatomical structure of the biliary system and disease-related variables, the width of the CBD and the number of V-type CBDs were significantly higher in the repeated ERCP group than in the single ERCP group ($p<0.05$). Moreover, CBD angulation was significantly smaller in the repeated ERCP group compared to that in the single ERCP group ($p<0.05$) (Table 3).

The single and repeated ERCP groups did not show a significant difference in terms of the intraprocedural complications ($p>0.05$). Intraprocedural and post-ERCP complications are presented in Table 3. During the procedure, only 14 of the 200 patients had minimal hemorrhage that did not require blood transfusion. The cases that developed hemorrhage were managed using balloon tamponade and injection control. Basket impaction developed in three of our patients, of whom two were treated endoscopically and one was treated by open surgery.

The complication rate was significantly higher in the repeated ERCP group than in the single ERCP group ($p<0.05$) (Table 3). Post-procedural pancreatitis was detected in a patient of the single ERCP group and in five cases of the repeated ERCP group. In addition, the repeated ERCP group comprised 16 patients who developed cholangitis requiring temporary or early ERCP intervention. However, mortality was not observed in these patients.

Imaging performed under endoscopy generally revealed three different types of CBD courses. The straight course was mainly seen in the young patients with a smaller number of stones, V-type angulation was observed in 71 patients, and the S-type CBD course was predominantly observed in elderly patients with larger and more stones (Table 4).

Table 1. Demographic status, complaints, blood test results, and the number of ERCPs of the sample

		Mean ± SD/n-%
Age		61.1±16.5
Gender	Female	128/64.0%
	Male	72/36.0%
Complaint		
Pain		194/97.0%
Jaundice		142/71.0%
Fever-chills		62/31.0%
Biliary pancreatitis		55/27.5%
Cholangitis		118/59.0%
Gallstone		136/68.0%
Duration of complaint		16.8±28.4
WBC (μLx10³)		10.6±4.1
AST (U/L)		211.1±219.3
ALT (U/L)		271.9±226.4
GGT (U/L)		521.6±381.1
ALP (U/L)		453.8±323.2
Amylase (U/L)		343.6±685.3
Total bilirubin mg/dL		5.5±4.1
Direct bilirubin mg/dL		4.1±3.3
Indirect bilirubin mg/dL		1.4±1.5
Number of ERCPs	1	100/50.0%
	2	73/36.5%
	3	24/12.0%
	4	2/1.0%
	5	1/0.5%

SD: standard deviation, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, ALP: alkaline phosphatase, ERCP: endoscopic retrograde cholangiopancreatography

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In the prediction of single and repeated ERCP using the univariate model, a significant association was observed between post-ERCP complications and age, WBC, AST, ALT, total bilirubin, direct bilirubin, width of CBD, angulation of CBD, fever and chills, biliary pancreatitis, cholangitis, difficult stones, and shape of the CBD ($p<0.05$). In the prediction of single and repeated ERCP using the multivariate model, there was a significant association between post-ERCP complications and AST, fever and chills, biliary pancreatitis, and the presence of difficult stones ($p<0.05$) (Table 5).

DISCUSSION

In this study, the age of the patients was significantly higher in the repeated ERCP group than in the single ERCP group. There are two possible reasons for this: First, the prevalence of problematic stones increases as the median age increases. In a study investigating the effectiveness and reliability of ERCP in patients ≥85 years, larger stones were detected in the elderly group (15). In some studies, the total clearance of stones was significantly limited in the elderly population (8,15,16). Second, in elderly patients, procedures are often delayed until second intervention to avoid the complications of prolonged ERCP and anesthesia (17).

Although a higher number of repeated ERCP procedures are performed in the elderly, non-significant differences in gender, patient complaints, and duration of the complaints were expected. Especially, fever and chills, elevated WBC, and increased total and direct bilirubin values were found to be significantly higher when evaluated together. These findings represent cholangitis cases,

Table 2. Comparison of demographic status, complaints, and blood test results of the single and repeated ERCP groups

		Single ERCP	Repeated ERCP	
		Mean ± SD/ n-%	Mean ± SD/ n-%	p
Age		57.8±17.5	64.4±14.9	0.007[m]
Gender	Female	70/70.0%	58/58.0%	0.077[X²]
	Male	30/30.0%	42/42.0%	
Complaint				
Pain		99/99.0%	95/95.0%	0.097[X²]
Jaundice		67/67.0%	75/75.0%	0.213[X²]
Fever-chills		21/21.0%	41/41.0%	0.002[X²]
Biliary pancreatitis		35/35.0%	20/20.0%	0.018[X²]
Cholangitis		51/51.0%	67/67.0%	0.021[X²]
Gallstone		70/70.0%	66/66.0%	0.544[X²]
Complaint duration		13.4±10.8	20.2±38.5	0.076[m]
WBC (μLx10³)		9.8±3.7	11.4±4.3	0.004[m]
AST (U/L)		258.7±268.6	163.5±141.4	0.002[m]
ALT (U/L)		321.2±249.0	222.6±190.1	0.001[m]
GGT (U/L)		517.2±393.7	526.0±370.1	0.782[m]
ALP (U/L)		441.5±314.0	466.2±333.3	0.327[m]
Amylase (U/L)		467.2±870.5	219.9±394.1	0.164[m]
Total bilirubin mg/dL		4.7±3.6	6.2±4.6	0.006[m]
Direct bilirubin mg/dL		3.6±3.3	4.6±3.3	0.013[m]
Indirect bilirubin mg/dL		1.3±1.0	1.6±1.9	0.269[m]

[m]Mann-Whitney U test, [X²]chi-square test (Fisher's Exact test), SD: standard deviation, WBC: white blood cell count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, ALP: alkaline phosphatase, ERCP: endoscopic retrograde cholangiopancreatography

Table 3. Comparison of CBD anatomical features, stones, and procedure-related parameters of the single and repeated ERCP groups

		Single ERCP	Repeat ERCP	
		Mean ± SD/n-%	Mean ± SD/n-%	p
CBD width		12.3±4.3	15.2±5.0	0.000[m]
CBD width	<10 mm	44/44.0%	22/22.0%	0.001[X²]
	10-20 mm	46/46.0%	53/53.0%	
	>20 mm	10/10.0%	25/25.0%	
CBD angulation		288.9±38.7	273.7±36.9	0.001[m]
CBD angulation	<250°	20/20.0%	32/32.0%	0.008[X²]
	250°-300°	32/32.0%	41/41.0%	
	⇒300°	48/48.0%	27/27.0%	
Number of gallstones	Several	58/58.0%	50/50.0%	0.467[X²]
	Single	3/3.0%	5/5.0%	
	None	39/39.0%	45/45.0%	
Stone difficulty	Sludge	28/28.0%	3/3.0%	0.000[X²]
	<10 mm	50/50.0%	24/24.0%	
	10-14 mm single stone	9/9.0%	21/21.0%	
	8-12 mm multiple stones	13/13.0%	52/52.0%	
CBD shape	Straight	7/7.0%	6/6.0%	0.042[X²]
	V-type	27/27.0%	44/44.0%	
	S-type	66/66.0%	50/50.0%	
ERCP complication	(-)	95/95.0%	88/88.0%	0.128[X²]
	(+)	5/5.0%	12/12.0%	
	Hemorrhage	5/5.0%	9/9.0%	
	Basket impaction	0/0.0%	3/3.0%	
Post-ERCP complication	(–)	99/99.0%	79/79.0%	0.000[X²]
	(+)	1/1.0%	21/21.0%	
	Pancreatitis	1/1.0%	5/5.0%	
	Cholangitis	0/0.0%	16/16.0%	

[m]Mann-Whitney U test, [X²]chi-square test (Fisher's Exact test) SD: standard deviation, CBD: common bile duct, WBC: white blood cell count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, ALP: alkaline phosphatase, ERCP: endoscopic retrograde cholangiopancreatography

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which constitute the most common ERCP group. Cholangitis is a systemic infection with a high mortality rate that requires emergency treatment (6,18,19). In this condition, complaints of pain, fever, and jaundice (Charcot's triad) are accompanied by lethargy and shock (Reynolds' pentad), which is termed as acute obstructive suppurative cholangitis, and requires emergency biliary decompression (6,18,20). The aim of the treatment in cholangitis is to achieve biliary decompression and save the life of the patient, which explains the increased number of stenting procedures in this group. However, the stenting procedure itself is a risk factor for repeated ERCP interventions (6,17,21).

In our study, compared to the single ERCP group, the cholestasis enzyme levels were significantly higher in the repeated ERCP group. The increase in these values is a predictor of the need for ERCP and the presence of CBD stones. However, these factors do not have a predictive value in estimating the difficulty of the procedure and whether a repeated intervention may be necessary.

Table 4. Stone-related and local anatomical changes and ERCP complications

		Mean ± SD/n-%
CBD width		13.8±4.9
CBD width	<10 mm	66/33.0%
	10-20 mm	99/49.5%
	>20 mm	35/17.5%
		281.3±38.5
CBD angulation	<250°	52/26.0%
	250-300°	73/36.5%
	>300°	75/37.5%
Number of gallstones	Several	108/54.0%
	Single	8/4.0%
	None	84/42.0%
Stone difficulty	Sludge	31/15.5%
	<10 mm	74/37.0%
	10-14 mm single stone	30/15.0%
	8-12 mm multiple stones	65/32.5%
Shape of CBD	Straight	13/6.5%
	V-type	71/35.5%
	S-type	116/58.0%
ERCP complication	(-)	183/91.5%
	(+)	17/8.5%
	Hemorrhage	14/7.0%
	Basket impaction	3/1.5%
Post-ERCP complication	(-)	177/88.5%
	(+)	22/11.0%
	Pancreatitis	6/3.0%
	Cholangitis	16/8.0%

SD: standard deviation, ERCP: endoscopic retrograde cholangiopancreatography, CBD: common bile duct

Juxtapapillary diverticulum was more commonly observed in the repeated ERCP group. There are many studies demonstrating that recurrent CBD stones develop more frequently in the presence of diverticula. Moreover, cholangitis, pancreatitis, and deformation in the choledochal axis are highly prevalent when a duodenal diverticulum is present (2-4,13).

It is generally accepted that ERCP is more challenging in cases with acute pancreatitis. The presence of enclaved CBD stones and a duodenal diverticulum is highly prevalent in cases of acute biliary pancreatitis (7). Increased pressure at the distal end of the CBD due to the developing edema may cause biliary tract obstruction and cholangitis. In case of acute pancreatitis, if there is an obstructing stone that causes acute cholangitis, early ERCP should be planned. Otherwise, unnecessary interventions may increase the severity of pancreatitis. The pathology of such cases should be demonstrated using MRCP or EUS (6,22-24). In late-stage biliary pancreatitis cases, the presence of stones should be investigated with MRCP. Difficulty of CBD cannulation during ERCP increases in patients with acute pancreatitis, and if accompanied by an enclaved stone, stone clearance becomes complicated. The frequency of pre-cut sphincterotomy is high in these patients, which further increases the risk of post-ERCP complications.

Pre-cut access to the CBD is more efficient in cases with enclaved CBD stones. Although these stones are typically difficult to treat, it is possible to easily remove the stone and perform selective cannulation through the efficient sphincterotomy. Pre-cut sphincterotomy can be successfully performed in patients undergoing ERCP, especially in experienced hands. It is required in 10% of all cases (13,25,26). If cannulation cannot be performed in patients with a pre-cut sphincterotomy, extending the duration of ERCP increases the rate of post-procedural complications (25). Pavlides et al. (26) reported a 78% success rate in cannulation when they repeated ERCP within an average of four days in 89 cases for whom successful selective cannulation could not be achieved despite the pre-cut procedure.

In the current study, patients with difficult CBD stones had a significantly higher requirement for repeated ERCP, as expected. In addition, the presence of choledochoduodenal fistula, a wide CBD, and use of mechanical lithotripsy during the procedure increased the number of repeated ERCPs (27). It should be kept in mind that most elderly patients have a wide CBD and a high number of stones, often accompanied by cholangitis (2-4,15,18,19,28). The presence of large and difficult stones in ERCP complicates stone removal. In such cases, repeated ERCP may be undertaken by performing sphincterotomy and stenting (5). It is extremely important to perform adequate sphincterotomy and ensure adequate stone clearance to reduce the number of repeated ERCPs and minimize residual and recurrent stones in the late period (5,28).

An increase in the diameter of CBD is detected in proportion to the increasing difficulty and size of CBD stones. The increase in the width of CBD is greater in elderly patients when the diameter

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Table 5. Univariate and multivariate analyses of the relationship between repeated ERCP and variables related to the patients' demographic status, complaints, and blood test results

	Univariate model			Multivariate model		
	OR	95% Confidence interval	p	OR	95% Confidence interval	p
Age	1.03	1.01-1.04	0.005	-	-	-
WBC	1.00	1.00-1.00	0.007	-	-	-
AST	1.00	1.00-1.00	0.005	1.00	0.99-1.00	0.008
ALT	1.00	1.00-1.00	0.003	-	-	-
Total bilirubin	1.10	1.02-1.19	0.014	-	-	-
Direct bilirubin	1.10	1.00-1.20	0.048	-	-	-
CBD width	1.15	1.07-1.23	0.000	-	-	-
CBD angulation	0.99	0.98-1.00	0.006	-	-	-
Fever-chills	2.61	1.40-4.88	0.003	3.36	1.47-7.63	0.004
Biliary pancreatitis	0.46	0.92-0.88	0.019	0.34	0.15-0.80	0.013
Cholangitis	1.95	1.10-3.46	0.022	-	-	-
Stone difficulty	3.20	2.29-4.48	0.000	3.45	2.33-5.11	0.000
CBD shape	1.73	1.06-2.83	0.030	-	-	-
Post-ERCP complication	36.3	3.5-200	0.002			
CBD width	2.25	1.46-3.47	0.000	6.02	1.32-27.03	0.020
CBD angulation	0.58	0.40-0.84	0.003			

Forward logistic regression. OR: odds ratio, WBC: white blood cell count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CBD: common bile duct, ERCP: endoscopic retrograde cholangiopancreatography

of the stone is large, the stone is enclaved, or the number of stones is high, all of which contribute to the possibility of repeated ERCP. The width of CBD is also a significant factor in the recurrence of CBD stones in the long-term. In many studies, post-ERCP follow-up results have demonstrated that CBD width was a significant factor in the long-term recurrence of CBD stones (6,7,28).

In studies concerning the shape and angulation of the CBD, significant results have been obtained, especially regarding recurrent CBD stones. It was reported that late-stage recurrent stones are more frequently observed, mainly in the S-type CBD structure (28-30). In our study, the need for repeated ERCP attempts was increased by the location, size, and number of stones, rather than the shape of the CBD or the presence of cholangitis.

In the literature, papillary hemorrhage (1.4%) and retroperitoneal duodenal perforation (0.69%) were reported as the most frequent complications observed during invasive ERCP (6,31,32). Among our cases, complications encountered during the procedure were like those reported in the literature. The frequency of mechanical lithotripsy and related complications increase with difficult CBD stones. The most important and challenging complication was basket impaction. In two of our patients, this complication was resolved by the repeated endoscopic intervention, while the remaining patient required open surgery. In case a large stone is detected during the pre-procedural examination, a lithotripter basket should be used while seeking other appropriate solutions to prevent complications (6,7,13,14).

In our study, compared to the single ERCP group, the complication rate in the repeated ERCP group was significantly higher. The most common post-ERCP complication is pancreatitis, with a prevalence of 1.6-15.7% (3,11,33,34). Etiological factors of this complication include the use of electrocauterization in sphincterotomy, edema in the sphincter of Oddi and the pancreatic sphincter, pre-cut sphincterotomy, increased hydrostatic pressure in the pancreatic duct due to excessive contrast injection, and contamination of the pancreatic ductal system with duodenal content (26,32). All these etiological factors increase with repeated ERCP and naturally result in a significantly higher rate of post-ERCP complications. Biliary septic complications, including cholangitis and cholecystitis are also observed in the post-ERCP period (1,5,32,35-37). The clinical follow-up of these patients is very important, since cholangitis may develop frequently in patients with difficult CBD stones due to inadequate sphincterotomy, overlooked stones, and non-functioning stenting.

Study Limitations

The study had some limitations. The present study was conducted with ERCP records of a single endoscopist which may cause bias due to personalization of the data. Additionally, there might have been some patients who had undergone repeated ERCP in a different center that we missed during the study period. On the

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other hand, the most important strength of this study that to the best of our knowledge, this is the first study in the literature to include such a large number of patients with a noticeable amount of data and follow-up period.

ERCP is the gold standard in gallstone treatment; therefore, it should be considered as the first-line treatment. However, due to its invasive nature, its risk of complications is high, even in experienced hands. Along with experience, pre-procedural patient selection is a very important factor for reducing complications (34,36).

CONCLUSION

ERCP is the most important, invasive, endoscopic procedure for the clearance of bile duct stones. It is known that several factors may interfere with a positive outcome in the first attempt. It is important for the endoscopist and the patient to be able to predict under which circumstances a repeat intervention may be required. The diameter of the CBD and the number of stones was increased in elderly patients. On the other hand, the presence of stenosis, enclaved stones in the CBD, and accompanying pancreatitis increased the need for repeated ERCP in young patients. The need for stenting was higher in both age groups when cholangitis was present. The success rate of ERCP was not affected by a single factor, but by all clinical and pathological factors that increase the difficulty of the procedure.

Ethics Committee Approval: Ethical approval was not sought for the present study because this study did not involve a prospective evaluation, did not involve laboratory animals, and only involved the records of ERCP procedures of different health centers at which Dr. Murat Akaydın had been working.

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

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REFERENCES

1. Ramirez FC, Dennert B, Sanowski RA. Success of repeat ERCP by the same endoscopist. Gastrointest Endosc 1999; 49: 58-61.
2. Lu J, Cheng Y, Xiong XZ, Lin YX, Wu SJ, Cheng NS. Two- stage vs single -stage management for concominant gallstones and common bile duct stones. World J Gastroenterol 2012; 8: 3156-66.
3. Collins C, Maguire D, Ireland A, Fitzgerald E, O'Sullivan GC. A prospective study of common bile duct calculi in patients undergoing laparoscopic cholecystectomy: natural history of choledocholithiasis revisited. Ann Surg 2004; 239: 28-33.
4. Bansal VK, Misra MC, Garg P, Prabhu M. A prospective randomized trial comparing two-stage versus single-stage management of patients with gallstone disease and common bile duct stones. Surg Endosc 2010; 24: 1986-9.
5. Wu Y, Xu CJ, Xu SF. Advances in risk factors for recurrence of common bile duct stones. Int J Med Sci 2021; 18: 1067-74.
6. Manes G, Paspatis G, Aabakken L, Anderloni A, Arvanitakis M, Ah-Soune P, et al. Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2019; 51: 472-91.
7. Lujian P, Xianneng C, Lei Z. Risk factors of stone recurrence after endoscopic retrograde cholangiopancreatography for common bile duct stones. Medicine (Baltimore) 2020; 99: e20412.
8. Aranovich D, Zilbermints V, Goldberg N, Kaminsky O. Detection of common bile duct stones in mild acute biliary pancreatitis using magnetic resonance cholangiopancreatography. Surg Res Pract 2018; 2018: 5216089. doi: 10.1155/2018/5216089.
9. Molvar C, Glaenzer B. Choledocholithiasis: evaluation, treatment, and outcomes. Semin Intervent Radiol 2016; 33: 268-76.
10. Ramirez FC, Dennert B, Sanowski RA. Success of repeat ERCP by the same endoscopist Gastrointest Endosc 1999; 46: 58-61.
11. Vaira D, Ainsley C, Williams S, Cairns S, Salmon P, Russell C, et al. Endoscopic sphincterotomy in 1000 consecutive patients. Lancet 1989; 2: 431-4.
12. Deng F, Zhou M, Liu PP, Hong JB, Li GH, Zhou XJ, et al. Causes associated with recurrent choledocholithiasis following therapeutic endoscopic retrograde cholangiopancreatography: A large sample sized retrospective study. World J Clin Cases 2019; 7: 1028-37.
13. Stefanidis G, Christodoulou C, Manolakopoulos S, Chuttani R. Endoscopic extraction of large common bile duct stones: A review article. World J Gastrointest Endosc 2012; 4: 167-79.
14. Trikudanathan G, Navaneethan U, Parsi MA. Endoscopic management of difficult common bile duct Stones. World J Gastroenterol 2013; 19: 165-73.
15. Lida T, Kaneto H, Wagatsuma K, Sasaki H, Naganawa Y, Nakagaki S, et al. Efficacy and safety of endoscopic procedures for common bile duct stones in patients aged 85 years or older: A retrospective study. PLoS One 2018; 13: e0190665. doi: 10.1371/journal.pone.0190665.
16. Obana T, Fujita N, Noda Y, Kobayashi G, Ito K, Horaguchi J, et al. Efficacy and safety of therapeutic ERCP for the elderly with choledocholithiasis: Comparison with younger patients. Internal Med 2010; 49: 1935-41.
17. Tohda G, Ohtani M, Dochin M. Efficacy and safety of emergency endoscopic retrograde cholangiopancreatography for acute cholangitis in the elderly. World J Gastroenterol 2016; 22: 8382-8.
18. Kimura Y, Takada T, Kawarada Y, Nimura Y, Hirata K, Sekimoto M, et al. Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo Guidelines J Hepatobiliary Pancreat Surg 2007; 14: 15-26.
19. Lai EC, Tam PC, Paterson IA, Ng MM, Fan ST, Choi TK, et al. Emergency surgery for severe acute cholangitis. The high-risk patients. Ann Surg 1990; 211: 55-9.
20. Mulki R, Shah R, Qayed E. Early vs late endoscopic retrograde cholangiopancreatography in patients with acute cholangitis: a nationwide analysis. World J Gastrointest Endosc 2019; 11: 41-53.
21. Dedemadi G, Nikolopoulos M, Kalaitzopoulos I, Sgourakis G. Management of patients after recovering from acute severe biliary pancreatitis. World J Gastroenterol 2016; 22: 7708-17.
22. Petrescu I, Bratu AM, Petrescu S, Popa BV, Cristian D, Burcos T. CT vs. MRCP in choledocholithiasis jaundice. J Med Life 2015; 8: 226-31.
23. Mustafa A, Begaj I, Dcakin M, Durkin D, Corless DJ, Wilson R, et al. Long term effectiveness of cholecystectomy and endoscopic sphincteretomy in the management of gallstone pancreatitis. Surg Endosc 2014; 28: 127-33.
24. Hazem ZM. Acute biliary pancreatitis: diagnosis and treatment. Saudi J Gastroenterol 2009; 15: 147-55.
25. Saritas U, Ustundag Y, Harmandar F. Precut sphincterotomy: a reliable salvage for difficult biliary cannulation. World J Gastroenterol 2013; 19: 1-7.
26. Pavlides M, Barnabas A, Fernandopulle N, Bailey AA, Collier J, Phillips-Hughes J, et al. Repeat endoscopic retrograde cholangiopancreaticogarphy after failed initial precut sphincterotomy for biliary cannulation. World J Gastroenterol 2014; 20: 13153-8.
27. Akaydin M, Demiray O, Ferlengez E, Erozgen F, Ersoy YE, Er M. Importance of spontaneous choledochoduodenal fistulas detected during ERCP procedure. Indian J Surg 2018; 80: 216-20.
28. Konstantakis C, Triantos C, Theopistos V, Theocharis G, Maroulis I, Diamantopoulou G, et al. Recurrence of choledocholithiasis following endoscopic bile duct clearance: long term results and factors associated with recurrent bile duct stones. World J Gastrointest Endosc 2017; 9: 26-33.

J Acad Res Med 2021;11(2):219-26

29. Seo DB, Bang BW, Jeong S, Lee DH, Jeon YS, Lee JW, et al. Does the bile duct angulation affect recurrence of choledocholithiasis? World J Gastroenterol 2011; 17: 4118-23.
30. Ryu S, Jo IH, Kim S, Kim YJ, Chung WC. Clinical impact of common bile duct angulation on the recurrence of common bile duct stone: a meta-analysis and review. Korean J Gastroenterol 2020; 76: 199-205.
31. Baek YH, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, et al. [Risk factors for recurrent bile duct stones after endoscopic clearance of common bile duct stones]. Korean J Gastroenterol 2009; 54: 36-4.
32. Iorgulescu A, Sandu I, Turcu F, Iordache N. Post-ERCP acute pancreatitis and its risk factors. J Med Life 2013; 6: 109-13
33. Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, et al. Incidence rates of postERCP complications: a systematic survey of prospective studies. Am J Gastroenterol 2007; 102: 1781.
34. Anderson MA, Fisher L, Sharaf RN, Shergill AK, Dominitz JA, Appalaneni V, et al. Complications of ERCP. Gastrointest Endosc 2012; 75: 467-73.
35. Li GZ, Wang F, Fang J, Zha H, Zhao Q. Risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis: evidence from 1786 cases. Med Sci Monit 2018; 24: 8544-52.
36. Silviera ML, Seamon MJ, Porshinsky B, Prosciak MP, Doraiswamy VA, Wang CF, et al. Complications related to endoscopic retrograde cholangiopancreatography: a comprehensive clinical review. J Gastrointestin Liver Dis 2009; 18: 73-82.
37. Minaga K, Kitano M, Imai H, Yamao K, Kamata K, Miyata T, et al. Urgent endoscopic ultrasound-guided choledochoduodenostomy for acute obstructive suppurative cholangitis-induced sepsis. World J Gastroenterol 2016; 22: 4264-9.

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Successful Treatment of Chemotherapy-induced Symptoms with Granisetron as Alternative for Ondansetron Allergy

Öner Özdemir[1], Olena Erkun[2]

[1]Sakarya University Faculty of Medicine; Sakarya Training and Research Hospital, Department of Pediatrics, Division of Allergy and Immunology, Sakarya, Turkey
[2]Sakarya Training and Research Hospital, Clinic of Pediatrics, Sakarya, Turkey

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ABSTRACT

Ondansetron is a selective 5-hydroxy-tryptamine 3 receptor antagonist that is widely used as an antiemetic agent, especially for the preventive treatment of chemotherapy-induced nausea and vomiting. Side effects of ondansetron are headache, dizziness, constipation, diarrhoea and hypersensitivity reactions such as anaphylaxis, which are very rarely described in the literature. Herein, we present a patient with Hodgkin lymphoma who developed urticaria secondary to ondansetron intake, had been receiving chemotherapy and has safely used granisetron as alternative. Granisetron appears to be a safer potent alternative to ondansetron in patients with cancer receiving chemotherapy.

Keywords: Hypersensitivity, urticaria, drug hypersensitivity, ondansetron, granisetron

INTRODUCTION

Ondansetron is a selective 5-hydroxy-tryptamine 3 (5-HT3) receptor antagonist that is widely used in haematology and oncology wards. Ondansetron has highly antiemetic (anti-emetogenic) effect (1). Thus, ondansetron is often used for the prevention and treatment of chemotherapy-induced nausea and vomiting (1). Ondansetron has several common side effects, which include headache, dizziness, diarrhoea, fever and constipation (1). There were reports of electrocardiographic changes in some patients (2). However, IgE- or non-IgE-mediated hypersensitivity reactions such as urticaria, anaphylaxis and anaphylactoid reactions are very rarely reported side effects of ondansetron (3-7).

Herein, we present the case of a patient with Hodgkin lymphoma who developed urticaria following ondansetron intake and was later successfully treated with granisetron for chemotherapy-induced nausea and vomiting.

CASE PRESENTATION

A 9-year-old boy was scheduled to undergo chemotherapy for nodular sclerosing Hodgkin lymphoma, which constitutes a combination of four drugs, namely, vinblastin, dacarbazine, doxorubicin and bleomycin, as well as ondansetron for prevention of nausea and vomiting. Within the last 6 months, the patient has been receiving chemotherapy and using ondansetron as prophylaxis for severe nausea. He had no known history of hypersensitivity reactions to any food and/or drug allergens, including ondansetron. During the intravenous administration of the first dose of ondansetron (0.15 mg/kg; total, 4 mg) at the last chemotherapy course, after 2-3 min, the patient developed redness (flare) and wheals along with urticaria (Figure 1). There

ORCID IDs of the authors: Ö.Ö. 0000-0002-5338-9561; O.E. 0000-0003-3067-3794.

Corresponding Author: Öner Özdemir,
E-mail: ozdemir_oner@hotmail.com

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was no accompanying bronchospasm or hypotension. The patient was immediately treated with intravenous administration of 30 mg pheniramine (1 mg/kg). The reaction disappeared within a few minutes. The patient did not complain of any other symptoms and was discharged after a couple of hours of observation. He was asymptomatic within 24 h of follow-up.

According to the patient's mother, during the past one session of chemotherapy, the patient also demonstrated redness, swelling and mild rash over the body after injection of ondansetron. The patient has no individual or family history of atopy and asthma, but he has a history of common variable immunodeficiency disease. Thus, he has been receiving intravenous treatment with immunoglobulin.

After allergy consultation, the skin prick test to undiluted ondansetron (2 mg/mL concentration) with commercial product was performed, and the result was negative. Moreover, intradermal test showed a positive response to 0.02 mg/mL (100 times dilution of ondansetron) concentration, and a positive flare and wheal reaction were observed (hyperaemia, 35 mm; wheal, 20 mm) (Figure 2). Because of this positive response, intradermal test to 10 times dilution of ondansetron was not performed. Furthermore, the skin prick test and intradermal tests with an alternative drug granisetron (1 mg/mL, undiluted) were performed similarly for granisetron (1:100 and 1:10 dilution), and all test results were negative. The prick and intradermal test concentrations for both ondansetron and granisetron were defined based on previous clinical reports (5,8). All skin prick and intradermal tests were performed with original commercial preparations including excipients. Since our patient needed one of the 5-HT3 receptor antagonists, we provoked him the same day with granisetron as an alternative. He was given intravenously cumulative doses of granisetron at 20-min intervals under strict scrutiny, beginning with 1 mg up to the therapy dose of 100 mg, as described earlier (9). As a result, granisetron was successfully administered to the patient for prevention of chemotherapy-induced nausea and vomiting.

Verbal and written informed consents were obtained from the patient's parents for publication of this case report and any accompanying images.

DISCUSSION

The 5-HT3 receptor antagonists (ondansetron, tropisetron, granisetron, dolasetron and palonosetron) are well-tolerated, potent antiemetic drugs that are used for the prevention of chemotherapy-induced nausea and vomiting. They are highly safe and have rare side effects, such as dizziness, headache, dystonia, constipation, chest pain and prolongation of the QT period on electrocardiogram (1,2). In our case, the side effect was a localised urticarial wheal near the injection site. It was successfully treated with administration of antihistaminic drug without any need of further medications such as epinephrine and/or prednisolone.

In the literature, hypersensitivity reaction induced by ondansetron has been reported in patients with cancer, who are undergoing chemotherapy with a prior history of ondansetron exposure (3-10). However, some authors hypothesise that hypersensitivity may be a class effect, while some others suggest that it is drug-specific effect as long as ondansetron and tropisetron contain indole

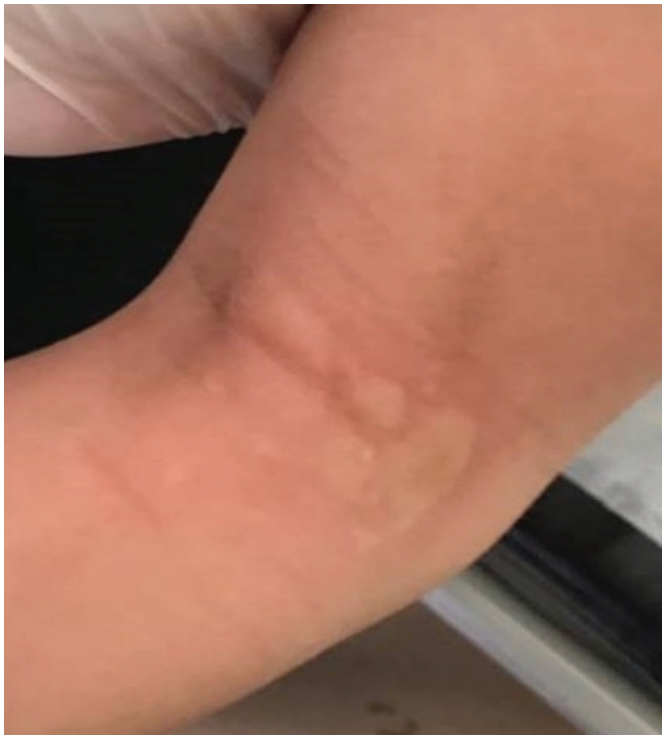

Figure 1. Redness and wheals after administration of ondansetron

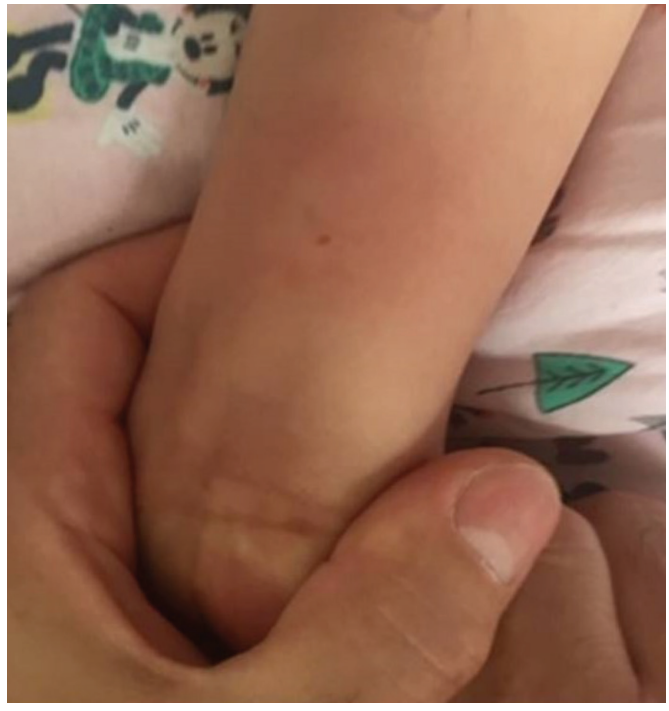

Figure 2. Positive result to intradermal test with 0.02 mg/mL (100 times dilution) of ondansetron (hyperaemia, 35 mm; wheal, 20 mm)

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ring, whereas granisetron does not (5). Thereby, some authors advise avoidance of all 5-HT3 antagonists after developing hypersensitivity to ondansetron. Others have demonstrated the successful utilisation of granisetron (9,10).

Before giving a substitute drug to a patient with drug allergy, it is compulsory to first learn possible cross-reactivity by performing skin tests and provocation tests (6). Granisetron might be an alternative antiemetic agent for patients with cancer who are undergoing chemotherapy (9,10).

In conclusion, we describe a rare case of IgE-mediated type I hypersensitivity to ondansetron that presents as isolated urticaria (9). In consistent with the literature, granisetron can be considered a safer potent alternative to ondansetron in patients with cancer who are receiving chemotherapy.

Informed Consent: Verbal and written informed consents were obtained from the patient's parents for publication of this case report and any accompanying images.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Chaudhary NK, John RR, Boddu D, Mahasampath G, Nesadeepam N, Mathew LG. Palonosetron is a better choice compared with ondansetron for the prevention of chemotherapy-induced nausea and vomiting (CINV) in a resource-limited pediatric oncology center: results from a randomized control trial. J Pediatr Hematol Oncol 2019; 41: 294-7.
2. Krammes SK, Jacobs T, Clark JM, Lutes RE. Effect of intravenous ondansetron on the QT interval of patients' electrocardiograms. Pediatr Emerg Care 2018; 34: 38-41.
3. Kataja V, de Bruijn KM. Hypersensitivity reactions associated with 5-hydroxytryptamine (3)-receptor antagonists: a class effect? Lancet 1996; 2: 584-5.
4. Mehra KK, Gogtay NJ, Ainchwar R, Bichile LS. Hypersensitivity to intravenous ondansetron: a case report. J Med Case Rep 2008; 2: 274.
5. García Núñez I, Algaba Mármol MA, Reina Ariza E. Ondansetron hypersensitivity: a clinical diagnosis protocol and cross-reactivity study. J Investig Allergol Clin Immunol 2015; 25: 221-2.
6. Ross AK, Ferrero-Conover D. Anaphylactoid reaction due to the administration of ondansetron in a pediatric neurosurgical patient. Anesth Analg 1998; 87: 779-80.
7. Weiss KS. Anaphylactic reaction to ondansetron. Arch Intern Med 2001; 161: 2263.
8. Fernando SL, Broadfoot AJ. Ondansetron anaphylaxis: a case report and protocol for skin testing. J Med Case Rep2009; 102: 285-6.
9. Bousquet PJ, Co-Minh HB, Demoly P. Isolated urticaria to ondansetron and successful treatment with granisetron. Allergy 2005; 60: 543-4.
10. Demir AH. Anaphylactic reaction owing to ondansetron administration in a child with neuroblastoma and safe use of granisetron: a case report. J Pediatr Hematol Oncol 2010; 32: e341-2.

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A Rare Cause of Rectal Bleeding in Children Mimicking Rectal Cancer

Burçin Aygün Coşarpınar[1], Nafiye Urgancı[2], Ramazan Uçak[3], Hüseyin Alkım[4]

[1]University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatric, İstanbul, Turkey
[2]University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatric Gastroenterology, İstanbul, Turkey
[3]University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey
[4]University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Gastroenterology, İstanbul, Turkey

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ABSTRACT

Solitary rectal ulcer syndrome is a rare lower gastrointestinal system disease that mainly manifests as rectal bleeding, tenesmus, chronic constipation, straining, and incomplete evacuation. It is usually diagnosed by histopathological examination via biopsy. The lesion takes on various sizes and shapes, ranging from mucosal erythema to single or multiple ulcers, ulcer-nodular lesions, or a polypoid mass. The colonoscopic findings may mimic rectal cancer and inflammatory bowel disease. Treatment of solitary rectal ulcer depends on the severity of the disease and ranges from behavioral therapy to lifestyle modification in mild cases, and medical and surgical procedures in severe refractory cases. Herein, we report on a 17-year-old male patient who presented with rectal bleeding, tenesmus, and constipation and was diagnosed with solitary rectal ulcer.

Keywords: Rectal bleeding, solitary rectal ulcer, rectal tumor

INTRODUCTION

Rectal bleeding is a common symptom of gastrointestinal diseases. The etiology can be classified according to age group. The most common causes are anal fissure, food allergy (allergic colitis), Meckel's diverticulitis, inflammatory bowel disease, colon polyps, vascular malformations, amebiasis, malignancies, bleeding disorders, volvulus, intussusception, Henoch-Schönlein purpura, hemorrhoids, and solitary rectal ulcer (1,2).

Solitary rectal ulcer syndrome (SRUS) is a rare benign disease, which is generally characterized by rectal bleeding, constipation, difficulty in defecation, abdominal pain, mucus discharge, tenesmus, rectal prolapse, and anemia due to chronic rectal bleeding (3). The estimated incidence of solitary rectal ulcer is approximately 1/100,000 in adults, but rarely it may affect pediatric patients (4). Twenty-six percent of cases are asymptomatic (1,4). A limited number of cases have been reported in the literature, with variable clinical findings (5-7).

Due to the diagnostic challenge posed by SRUS, endoscopic and histological findings are important in suspected cases, in addition to clinical symptoms. Generally, SRUS develops in the anterior rectal wall in about two-thirds of cases. The ulcer can be single, multiple, or circumferential and is usually superficial and non-penetrating. Ulcers become hyperemic and edematous, strict bordered and not extremely superficial in the inner surface of the anal canal. Colonoscopy reveals varying numbers of ulcers or tumoral masses resembling polypoid lesions. Fibromuscular

ORCID IDs of the authors: B.A.C. 0000-0002-4744-1108; N.U. 0000-0003-4854-507X; R.U. 0000-0002-2999-7495; H.A. 0000-0001-7875-0627.

Corresponding Author: Nafiye Urgancı,
E-mail: nafiyeurganci@yahoo.com

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hyperplasia, smooth muscle cells and collagen infiltration in the lamina propria, thickening of the muscularis mucosa, and crypt structure disruptions on histopathological examination are the main findings that help to distinguish SRUS from ulcerative colitis (1,8,9).

Herein, we present a 17-year-old male patient admitted with rectal bleeding, tenesmus, and constipation, diagnosed with solitary rectal ulcer.

CASE PRESENTATION

A 17-year-old male patient was admitted to the emergency department with a 7-month history of weakness and recent rectal bleeding. Based on his medical history, he had progressively increasing amounts of rectal bleeding and intermittent difficulty in passing stool for the last 5 months, recently accompanied by tenesmus, constipation, and abdominal pain. His weight was 57 kg (<3 p), and his height was 162 cm (3-10 p). His general condition was well, and his vital signs were normal. No pathological findings were detected on physical examination. In the initial evaluation, the abdomen was soft, bowel sounds were normal, and there was no hepatosplenomegaly.

Initial laboratory findings were normal (Hemoglobin: 14.8 mg/dL, hematocrit: 43.4, white blood cells: 8,450 10^6/L, ferritin: 17 ug/L, vitamin B12: 210 ng/L, folic acid: 8.64 ug/L, total protein: 6.2 g/L, albumin: 3.8 g/L). Additionally, liver and kidney function tests, IgA: 167 mg/L, IgG: 1,030 mg/L, IgM: 87 mg/L, tissue transglutaminase IgA: (-), fecal calprotectin: 1,466 µg/g, C-reactive protein, and coagulation profile were also normal.

Colonoscopic examination revealed a cauliflower-like lobular polypoid formation, which was large enough to fill the lumen up to 10 cm, extending from the anal canal to the lower rectum. The upper parts of the polypoid formations were ulcerated and partially bleeding (Figure 1). Histopathological examination revealed fibromuscular tissue proliferation in the lamina propria indicating a solitary rectal ulcer (Figures 2 and 3).

The patient was conservatively treated with a high-fiber diet, a laxative (lactulose 1 cc/kg/day divided into three doses), defecation training and a mixture of 5-aminosalicyclic acid (ASA) (50 mg/kg/day, 2 doses), sucralfate (5 cc/dose, two doses/day), and methylprednisolone (10 mg/dose, two doses). The rectal bleeding started to decrease following treatment. A follow-up rectosigmoidoscopy was performed after 3 months, and the lesion had improved markedly (Figure 4). When compared with the initial colonoscopic examination, the lesion had shrunk approximately 3x3 cm, and clinical symptoms improved after treatment (Figure 5). The rectal enema treatment was continued as a single dose. He is still under follow-up in the pediatric gastroenterology clinic.

DISCUSSION

SRUS is a rare, benign disease of childhood and is generally characterized by rectal bleeding, constipation, tenesmus, abdominal pain, or localized pain in the perineal region. It was first described by Cruveilhier (3) in 1830, and detailed clinical and histopathological characteristics were reported by Madigan and Morson in 1969. The pathogenesis of SRUS is not yet clearly understood. Pressure necrosis of the rectal mucosa due to high intrarectal pressure caused by paradoxical contraction of the pelvic floor, puborectal muscle contractions and rectal mucosal blockage as a result edema and ulcer formation are proposed mechanisms (4,7). Common clinical findings of SRUS are rectal bleeding, mucous passage, tenesmus, and constipation. It is more common in male than in female patients (1-7).

The lack of typical clinical symptoms or atypical signs and symptoms can cause a delayed diagnosis or even misdiagnosis, such as rectal tumoral mass (6-8,10). The diagnosis of SRUS is established by symptoms together with endoscopic and histopathological findings. Since it is quite rare in children, and symptoms are not characteristic, clinicians and pathologists should keep SRUS in mind to prevent diagnostic delays.

The mean duration between symptom onset and diagnosis is 3.2 years and varies between 1.2 and 5 years in pediatric patients, which is shorter than that in adult patients (1,4). Like other similar cases in the literature, our case was also a male patient admitted with rectal bleeding and a recent history of straining and defecation. Different treatment methods were suggested to him, especially for constipation and preliminary diagnosis of anal fissure.

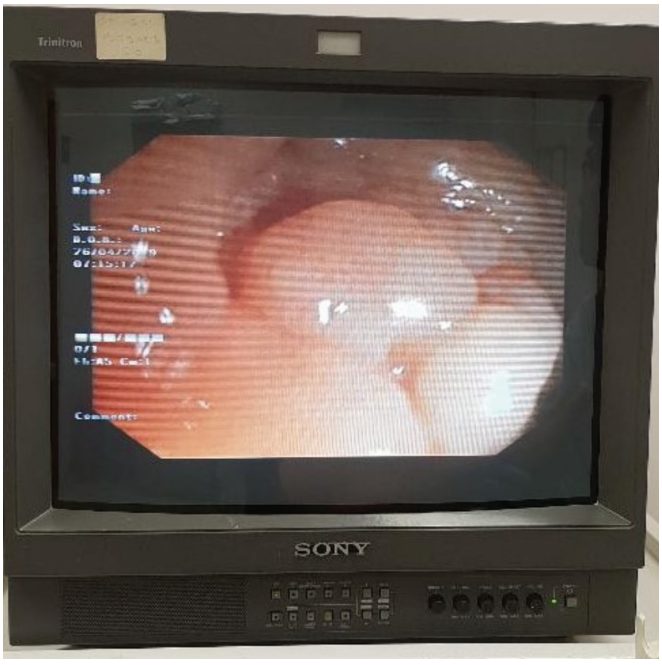

Figure 1. First colonoscopic view with different polypoid lesions

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The sigmoendoscopic findings of SRUS can be detected in three macroscopic types: Ulcerative, polypoid, and hyperemic. The ulcer site does not differ between the three types. The ulcerative form is the most common type in pediatric patients (60%), and the most frequent sites are the anterior or anterolateral wall of the rectum, 5-10 cm proximal to the dentate line. Ulcers are usually 1-1.5 cm and encircled with hyperemic and edematous mucosa. SRUS cases with a macroscopic polypoid appearance can be misdiagnosed with inflammatory polyp, hyperplastic polyps, or rectal cancer (1,7-9). Since we observed lobular, cauliflower-like, hyperemic surrounded formations in different sizes, starting from the anal canal and filling the lumen up to 10 cm in the colonic examination of our case, we thought it might be a tumoral mass. The histopathological examination of biopsy material revealed fibromuscular proliferation in the lamina propria, and a diagnosis of solitary rectal ulcer was made based on clinical, colonoscopic findings and histopathological evaluation.

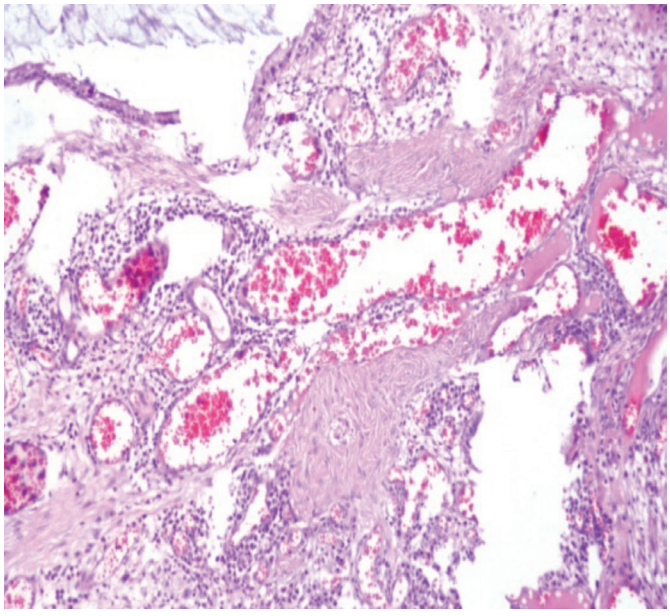

Figure 2. Nonorganized colonic crypts, enlarged vessels, hyperplasia of the lamina propria. Hematoxylin and eosin (H&E), 100×

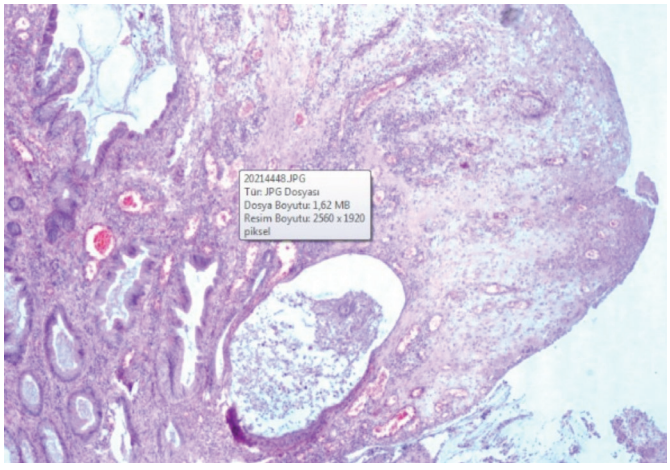

Figure 3. Polypoid granular lesion with ulceration, fibromuscular hyperplasia, filled with mucin and without atypia. H&E, 40×

There is a no standard therapeutic approach for pediatric SRUS patients. The treatment is unique for each patient and the condition quite difficult to manage. Patients and their parents should be informed and convinced that SRUS

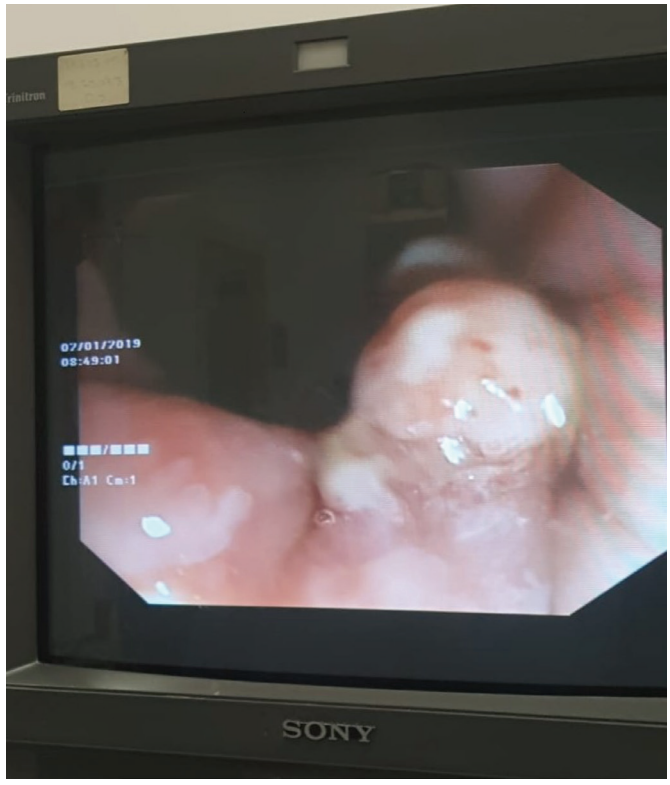

Figure 4. Contraction of the polypoid lesion after 3 months of treatment

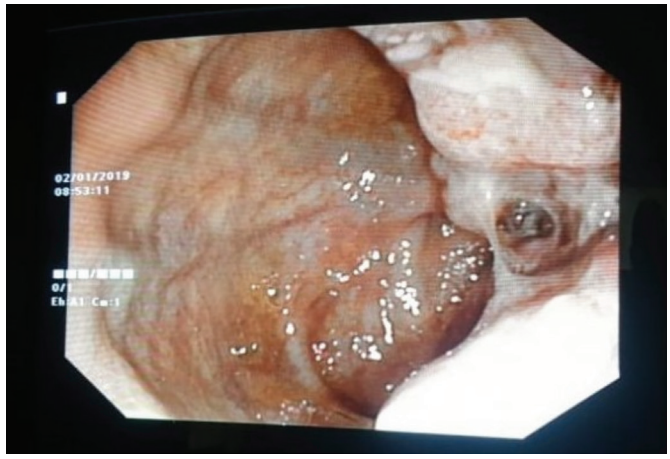

Figure 5. After 6 months of treatment

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is a benign and chronic disease. The goal of treatment is to improve bowel habits and rectal ulcers. The current treatment includes a high-fiber diet, toilet training, bulking agents (lactulose), enemas (steroid and mesalamin), oral 5-ASA, sucralfate, biofeedback, endoscopic steroid injection, laser treatment, argon plasma coagulation and, in selected cases, surgical intervention (rectopexy, ulcer excision) (1,6,8,10). There are studies reporting that local sucralfate, sulfasalazine, or steroid enemas were effective (1,7).

As reported by others in the literature, we obtained recovery in both clinical complaints and endoscopic findings with conservative treatment including a high-fiber diet, defecation training, laxatives and sucralfate, steroids, and 5 ASA enema in our patient 3 months after the onset of the treatment. After treatment, rectal bleeding and partial blockage findings of our case gradually improved.

SRUS is a chronic condition that significantly decreases quality of life. SRUS must be kept in mind in children presenting with chronic rectal bleeding, tenesmus, and constipation who are refractory to treatment. Endoscopic examination is necessary to prevent delayed diagnosis or misdiagnosis.

Informed Consent: The patient agreed the doctors could use and publish his disease related article with personal information deleted.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - N.U., R.U., H.A.; Concept - B.A.C., N.U.; Design - B.A.C., N.U.; Data Collection and/or Processing - B.A.C., N.U., R.U., H.A.; Analysis and/or Interpretation - B.A.C., N.U., R.U., H.A.; Literature Search - B.A.C.; Writing - B.A.C.

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REFERENCES

1. Dehghani SM, Malekpour A, Haghighat M. Solitary rectal ulcer syndrome in children: a literature review. World J Gastroenterol 2012; 18: 6541-5.
2. Wong W, Lai K, Shek TW, Lam S. Self-inflicted rectal ulcer with exuberant granulation that mimics carcinoma. Gastrointest Endosc 2002;55:951-2.
3. Cruveilhier J. Ulcere chronique du rectum. In: Anatomie pathologique du corps humain, JB Bailliere, Paris 1829.
4. Blackburn C, McDermott M, Bourke B. Clinical presentation of and outcome for solitary rectal ulcer syndrome in children. J Pediatr Gastroenterol Nutr 2012; 54: 263-5.
5. Dehghani SM, Haghighat M, Imanieh MH, Geramizadeh B. Solitary rectal ulcer syndrome in children: a prospective study of cases from southern Iran. Eur J Gastroenterol Hepatol 2008; 20: 93-5.
6. Urgancı N, Kalyoncu D, Eken KG. Solitary rectal ulcer syndrome in children: a report of six cases. gut liver 2013; 7: 752-5.
7. Thirumal P, Sumathi B, Nirmala DA. Clinical entity often missed-solitary rectal ulcer syndrome in children. Front Pediatr 2020; 8: 396.
8. Saadah OI, Al-Hubayshi MS, Ghanem AT. Solitary rectal ulcer syndrome presenting aspolypoid mass lesions in a young girl. World J Gastrointest Oncol 2010; 2: 332-4.
9. Brahim N, Al-Awadhi N, Al-Enezi S, Alsurayei S, Ahmad M. Solitary rectal ulcer syndrome: a clinicopathological study of 13 cases. Saudi J Gastroenterol 2009; 15: 188-92.
10. Somani SK, Ghosh A, Avasthi G, Goyal R, Gupta P. Healing of a bleeding solitary rectal ulcer with multiple sessions of argon plasma. Gastrointest Endosc 2010; 71: 578-82.