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Example: Müller C, Büttner HJ, Petersen J, Roskomun H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. Circulation 2000; 101: 590-3.

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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.

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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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Original Investigations

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A Biomechanical Comparison of Tendon Repair with a Knotless Barbed Suture and a Conventional Monofilament Suture Material: An *ex-vivo* Animal Experiment

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ABSTRACT

Objective: Our aim is to compare the ultimate tensile strength and stiffness of a 2/0 barbed suture and a 3/0 polypropylene monofilament suture in a porcine tendon repair model.

Methods: Sixteen porcine Achilles tendons were transected and separated into two groups. In group I tendons were repaired with a modified knotless four-strand Kessler technique using a 2/0 V-Loc barbed suture. In group II tendons were repaired with a four-strand Kessler technique using a 3/0 monofilament conventional suture and knots were tied. All specimens were biomechanically tested for ultimate tensile strength (UTS) and stiffness. Mode of failure was also noted.

Results: Five specimens in group I failed by stripping of the suture from the tendon tissue, three failed due to suture breakage. In group II two out of eight tendons failed by stripping of the suture and remaining six failed by suture breakage. Median UTS value was found to be 85.96 N (range: 63.24) in group I and 64.29 N (range: 56.84) in group II. Median stiffness value of the samples in group I was found to be 5.67 N/mm (range: 4.32) and in group II it was found to be 4.53 N/mm (range: 6.23). The statistical analysis of UTS and stiffness values revealed no significant difference between the groups (p=0.17 and p=0.56 respectively).

Conclusion: A knotless Kessler tendon repair made with a 2/0 barbed suture is biomechanically equivalent to a knotted Kessler tendon repair made with a 3/0 conventional polypropylene suture in *ex-vivo* conditions.

Keywords: Tendon repair, barbed suture, Kessler

INTRODUCTION

The ideal tendon repair should be strong enough to enable early range of motion exercises, should be easily performed, should minimize injury to tendon vasculature and should not be bulky to facilitate smooth gliding of the tendon (1-3). However, the higher the number of strands that cross the tendon, the more manipulation needed to put them in the tendons and the greater number of knots needed to tie them off which eventually results in a bulky construct.

The recently introduced barbed sutures have properties which render them very different from conventional sutures and yet they have not been extensively tested for tendon repair scenarios. The evenly distributed micro spikes on the barbed suture helps it with unidirectional anchoring all across the suture trajectory, thus they do not require complex trajectories and knots for tissue grasping and friction (4,5). These spikes generate homogenous and steady friction against slippage throughout suture trajectory in the opposite direction of the suture introduction. Increased tissue friction generated by this behavior of the barbed suture represents itself as a theoretical advantage for tendon repair scenarios since it eliminates the necessity for complex suture trajectories, locking loops and tying knots which are all proven to be mechanical and inflammatory stress risers (4,5). Yet, the same spikes also represent

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a mechanical disadvantage. The spikes in a barbed suture are created by generating cuts on the body of a monofilament suture which decreases the effective diameter of the barbed suture. Therefore, these evenly distributed cuts through the body of the suture create mechanical stress risers which render them weaker than a conventional monofilament suture of the same material and diameter (6-8).

All these differences between the barbed sutures and conventional monofilament suture materials create a basis for extensive investigation of barbed sutures' role and performance in tendon repair scenarios. Currently, the evidence on barbed suture as a tendon repair device is limited and it is still not clear if their disadvantage of being weaker at the location of spikes are compensated by not being dependent on afore mentioned stress risers. Therefore, in this study, we aim to compare the ultimate tensile strength (UTS) and stiffness of a 2/0 barbed suture and a 3/0 conventional polypropylene monofilament suture in an *ex-vivo* porcine Achilles tendon repair model.

METHODS

Experimental Method

All *ex-vivo* specimen used in the study were obtained from animals which were euthanized for endoscopic education purposes at our institution, thus no ethics committee approval was obtained. Sixteen porcine Achilles tendons were surgically extracted from freshly euthanized animals and were fresh frozen in an industrial fridge at -21 centigrade for later use. On the experiment day, the tendons were thawed at room temperature and divided into two groups of 8 tendons. All tendons were cut in the middle with a sharp scalpel blade (Figure 1). The tendons were repaired by two separate (four strand) modified Kessler core sutures (Figure 2a and 2b). In group 1, a 2/0 barbed polypropylene (V-Loc PBT Non-Absorbable Wound Closure Device, Covidien Deutschland GmbH, Neustadt, Germany) was used for the repair (Figure 3) and sutures were left untied. In group II, a 3/0 polypropylene monofilament suture (Prolene, Ethicon, Somerville, N.J., USA) was used and two separate knots were tied. A suture purchase length of 1 cm was devised for the repairs in both groups.

Biomechanical Test

A 3kN MTS Acumen 3 testing machine (MTS Corp., Shenzhen, China) was used to assess UTS of the constructs. The both ends of the samples were mounted directly to the clamps of the mechanical testing device making sure that the samples were parallel to the pull direction of the device (Figure 4). After mounting, specimens were axially preloaded with 1 N of force. The specimens were pulled with a speed of 20 mm/minute until failure was confirmed on the stress strain graph on the screen of the mechanical testing device or visual conformation of suture failure by breakage or pull out. The mode of failure was also noted for samples.

Statistical Analysis

Inter group differences for UTS and stiffness were analyzed with the Mann-Whitney U test at 95% confidence interval, using SPSS 21.0 for Windows (Release 21.0, SPSS Inc, Chicago, IL, USA) computer software.

RESULTS

Five specimens (62.5%) in group 1 failed by stripping of suture from the tendon tissue, three (37.5%) failed due to suture breakage. In group 2, two out of eight tendons (25%) failed by stripping of the suture and remaining six (75%) failed by the breakage of which 4 (50%) were adjacent to the knot.

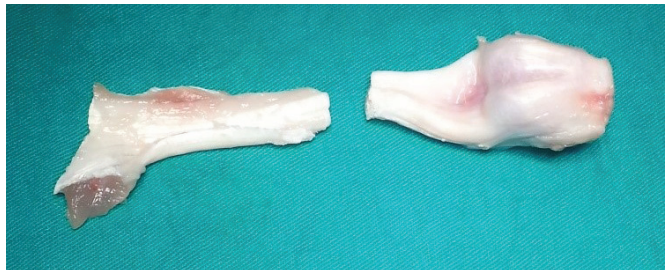

Figure 1. A transected tendon sample

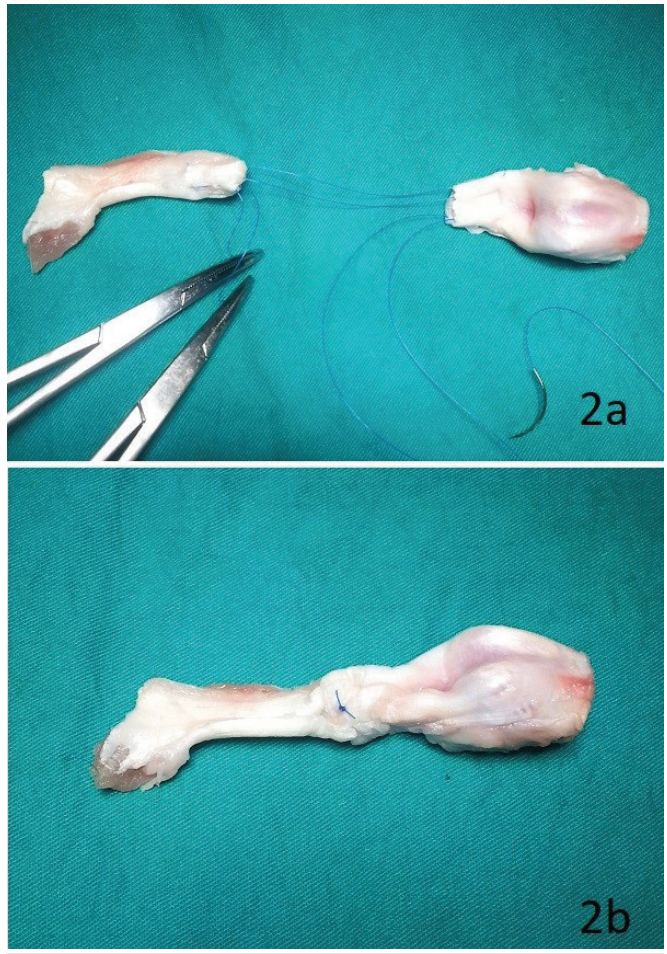

Figure 2 a) Photograph showing application of the dual Kessler sutures to the cut tendon before approximation
Figure 2 b) Photograph showing application of the dual Kessler sutures to the cut tendon after approximation

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The median UTS value was found to be 85.96 N (range: 63.24) in group 1 and 64.29 N (range: 56.84) in group 2. The median stiffness value of the samples in group 1 was found to be 5.67 N/mm (range: 4.32) and in group 2, it was found to be 4.53 N/mm (range: 6.23). A box-plot graphics is provided for better visualization of the UTS and stiffness values (Figure 5, 6). The homogeneity of variance for both UTS and stiffness variables between groups were tested and both variables were found to have similar distribution between the groups. The statistical analysis of UTS values with the Mann-Whitney U test revealed that there was no significant difference between the groups (Mann-Whitney U test: 19, p=0.17 two-tailed). The statistical analysis of the stiffness values of the groups with the Mann-Whitney U test also showed that there was no significant difference between these two groups (Mann-Whitney U test: 26.5, p=0.56 two-tailed).

Figure 3. Close up photograph of the V-loc barbed suture depicting micro anchors

Figure 4. Photograph showing a sample mounted on the mechanical test device for biomechanical testing

DISCUSSION

The findings of our study provide new data to the literature in the field of research of barbed sutures for tendon repair scenarios. In this biomechanical study, our comparison of a barbed suture and a conventional monofilament suture for UTS and stiffness revealed that there was no statistically significant difference between the groups.

The specification sheets of the barbed sutures and previous studies state that tensile properties of the barbed sutures of a certain diameter are comparable to unbarbed sutures of one size smaller diameter conventional monofilament sutures in a straight-pull test as a result of decreased effective diameter caused by the methodology for creating barbs (6-8). Therefore, in this study, we compared a 2/0 barbed suture to a 3/0 monofilament suture. Yet, previous studies prove that repair site thickness of tendons repaired with barbed sutures of one size larger

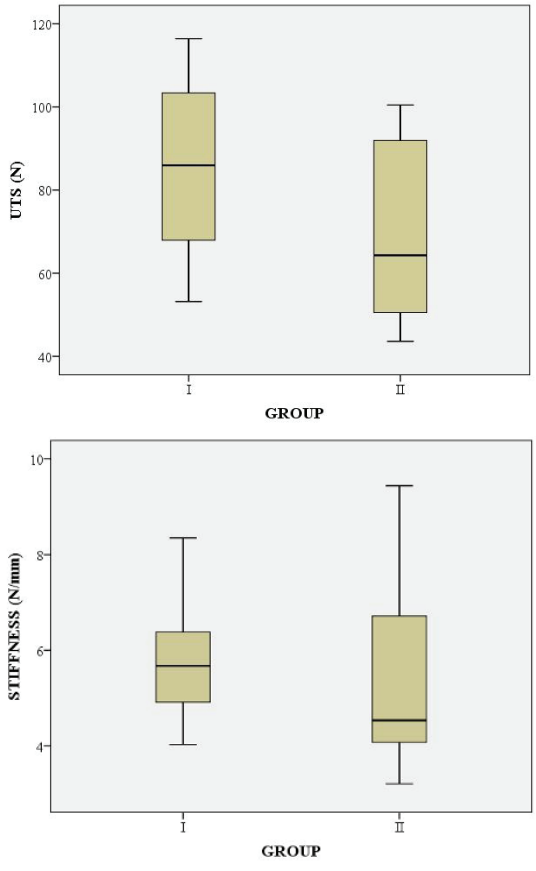

Figure 5, 6: Box-plot charts depicting the minimum-maximum values of UTS and stiffness values for easy visualization of study data

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diameter is comparable or thinner than the tendons repaired with conventional sutures of one size smaller diameter for the fact that they do not require bulky knots to be tied (7-9).

When we compare our findings to the literature, we can see that our findings show parallelism to some similar studies in the literature. The previous studies also do suggest that tendon repair made with the barbed suture which is one size larger by diameter than the compared conventional monofilament suture displays identical UTS and stiffness properties (6-8,10).

Joyce et al. (7) have investigated a novel four strand suture technique with 2/0 barbed suture to a four strand Adelaide technique with 3/0 conventional monofilament suture. Their results showed that the mean ultimate strength of the barbed repairs was 54.51 N while that of the Adelaide repairs was 53.17 N and statistical analysis of their data showed no difference for UTS between the groups. On the other hand, their measurements of 2 mm gap forming force which represents stiffness of the construct favored the barbed group over conventional suture group, which we believe is a result of the new technique they devised for the barbed suture group. In another study by Clemente et al. (8) which investigated a four-strand new technique with 2/0 barbed sutures to two strand modified Kessler technique with 3/0 conventional monofilament sutures, they found identical UTS and 2 mm gap formation forces when the results were corrected for the number of strands in the repair. Yet the study by Marrero-Amadeo et al. (6) also confirms these findings that 2/0 barbed suture performs biomechanically similar to 3/0 conventional monofilament suture.

Contrary to our findings which showed the barbed suture to be biomechanically equivalent to the conventional monofilament sutures, there are studies which have found them to be inferior and superior to the conventional sutures (9,11-14). Trocchia et al. (11) reported that Kessler tendon repair done with a 2/0 barbed suture was biomechanically inferior to the repair done with a 3/0 non-absorbable braided conventional suture. McClellan et al. (12) investigated the ultimate tensile strengths of three different tendon repairs. In the first group, repairs were made using a 3/0 Ethibond modified Kessler 2-strand repair, in the second group a 3-0 Ethibond modified Savage repair and in the third group a unique knotless 4-0 novel barbed suture. They reported that the Savage and knotless repair groups performed significantly better as compared to the modified Kessler repair group. Peltz et al. (13) compared three groups of different tendon repairs, in which one group consisted of a four-strand Adelaide 3-0 Ticron traditional repair, the other a novel four-strand 3-0 Ticron suture repair and the final group with the same novel four-strand technique as in group 2 but with a 3-0 V-Loc barbed suture instead. Their results indicate significantly better ultimate tensile strengths favoring the barbed V-Loc over the other techniques and sutures.

It is critical that a tendon repair suture should not fail prematurely before reaching strength values close to the suture material's simple straight pull test yield values. Suture failing by pull-out is an example of premature failing since the suture does not break, meaning that the force required to fail is less than the suture material's yield strength. Suture breakage adjacent to the knots is another example of premature failure since knots create a weak point in the filament. As a result, the ideal mode of suture failure is suture breakage in the continuum of the filament where there is no mechanical stress riser.

In our study, five specimens in the barbed suture group failed by stripping of suture from the tendon tissue and the remaining three failed due to suture breakage in the continuum of the filament. In the non-barbed suture group, two out of eight tendons failed by stripping and six by suture breakage of which four were adjacent to the knots. The analysis of the failure modes in our study suggests that Kessler suture technique may not be the most suitable for tendon repair with the barbed suture since most of the specimens (67.5%) in this group failed by suture slippage. We believe that modern tenorrhaphy techniques including Kessler have evolved for conventional non-barbed sutures through years of basic and clinical research. Therefore, new research efforts on tendon repair investigating barbed suture's role should concentrate on new techniques which are customized for barbed sutures. Yet, our results confirm that knots do create weak points in the filament forming stress riser areas since four out of eight (50%) specimens in the non-barbed group failed by breakage adjacent to the knot. Studies with similar methodology to ours confirm similar modes of failure data.

Marrero-Amadeo et al. (6) reported that repairs with conventional monofilament sutures with knots failed 65% by suture rupture and the remaining repairs failed by the suture knot unraveling, whereas repairs made with the barbed sutures failed 67% by suture pull-out, and the remaining repairs failed by suture rupture. Joyce et al. (7) also found comparable results about the mode of suture failure. They have reported that the cause of suture failure for the barbed group was breakage in 60% of the cases and pullout in the remainder. For the non-barbed group, they have reported a suture failure mode of pull out by 60% and suture breakage by 40% noting that seven out of eight suture breakage cases occurred adjacent to the knot.

Although we believe that our study fulfills a role in providing additional data on barbed suture's role in the tendon repair scenarios, our study has its own limitations as well. Firstly, the sample size for the groups of our study is the minimum limit for such a study to be relevant. Another limitation to our study is that no measurements of tendon repair site diameter was made, which is often useful to speculate on tendon gliding performance. Next, our study like many other similar ones in the literature compares the biomechanical performance of a barbed suture to a non-barbed suture with a suture technique which has evolved for non-barbed sutures, thus theoretical advantages of the barbed suture are dwindled by this move. Finally, as being an *ex-vivo* biomechanical study, our findings lack the strong evidence which can only be provided by randomized controlled in-vivo studies.

CONCLUSION

Our study confirms some of the previous findings of the literature indicating that the knotless tendon repair made with a one size

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larger diameter barbed suture is biomechanically equivalent to the knotted tendon repair made with a one size smaller diameter conventional monofilament suture *in-vitro* conditions. With the theoretical advantages of the barbed suture such as easy application, no dependency on complex trajectories, locking loops and knots, these sutures may prove to be beneficial for tendon repair scenarios. Yet, further research with potentially advantageous suture techniques and *in-vivo* studies are needed to assess barbed suture's role in tendon repair.

Ethics Committee Approval: All *ex-vivo* specimen used in the study were obtained from animals which were euthanized for endoscopic education purposes at our institution, thus no ethics committee approval was obtained.

Informed Consent: Patient approval has not been obtained as it is performed on animals.

Peer-review: Externally peer-reviewed.

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Prevalence of Intra-spinal Pathologies in Adolescent Idiopathic Scoliosis Patients

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ABSTRACT

Objective: To evaluate the prevalence of intra-spinal pathologies (ISP) in adolescent idiopathic scoliosis patients.

Methods: We retrospectively reviewed all adolescent idiopathic scoliosis cases surgically treated in our institution between 2012 and 2015. Patients aged less than 10 years and older than 20 years were excluded, in addition to those with no hospital records of pre-operative magnetic resonance imaging (MRI) scans or abnormal neurological examination findings. Patients who underwent revision surgery were also excluded. An experienced spinal surgeon measured curvature magnitudes in the coronal plane and thoracic kyphosis angles using the Cobb method, and a radiologist evaluated the MRI scans. The patients were then divided into an ISP group and non-ISP group and compared.

Results: After applying the exclusion criteria, 124 patients with adolescent idiopathic scoliosis were included in the study. Ten (8%) patients had ISP. Eight patients had syringomyelia in the thoracic region, one had a Chiari malformation with syringomyelia, and one had a tethered cord. There were no statistically significant differences between the groups in terms of age, sex, magnitude of thoracic kyphosis angle, magnitude of major coronal curve or direction of the main curve in patients with AIS ($p>0.05$). Of the 10 patients, two with ISP, one with a tethered cord and one with a Chiari malformation required additional neurosurgical procedures prior to corrective surgery.

Conclusion: The prevalence of ISPs in AIS patients was 8%. Given the risk of neurological complications, we recommend that MRI should be routinely performed in all adolescent idiopathic scoliosis patients scheduled for corrective surgery.

Keywords: Syringomyelia, adolescent idiopathic scoliosis, intra-spinal pathology, posterior instrumentation

INTRODUCTION

Scoliosis is defined as a lateral deviation of more than 10° on the coronal plane. Several types of scoliosis, including congenital, neuromuscular, and idiopathic, are recognized according to etiologic factors. In the absence of any underlying etiologic factor, idiopathic scoliosis is diagnosed. Idiopathic scoliosis is subdivided into three groups according to age: infantile, juvenile or adolescent (1,2). Idiopathic scoliosis is the most common type of scoliosis, and 80% of idiopathic scoliosis cases are of adolescent age (3). Posterior instrumentation and fusion with segmental pedicle screw placement are the preferred methods for surgical treatment (3,4). Despite advances in technology and surgical techniques, neurological complications continue to be a major problem in corrective surgery.

According to the literature, magnetic resonance imaging (MRI) should be routinely performed for pre-operative evaluations of spinal corrective surgery for all types of scoliosis, although there is controversy about the need for MRI in AIS. MRI is considered important for several reasons, such as surgical planning, determining the surgical risk and even determining the type of scoliosis. Increased use of MRI has led to the discovery of varying rates of intra-spinal pathologies (ISPs), even in asymptomatic patients. These ISPs include syringomyelia, tethered cords, Arnold-Chiari malformations, diastematomyelia, lipomas, teratomas, dermoids and epidermoid cysts (5,6). The spinal cord may be

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compressed or tethered during corrective manoeuvres in scoliosis, and the presence of an ISP poses a potentially high post-operative risk of neurological complications in spinal surgery (7) (Figure 1).

The purpose of this study was to evaluate the prevalence of ISPs in AIS patients and to determine whether MRI was necessary for pre-operative evaluation.

METHODS

After obtaining the approval of the local ethics committee, we retrospectively reviewed all AIS cases surgically treated in our institution between 2012 and 2015. Written informed consent, approved by our institutional review board, was obtained from all patient. Indications for surgery were a coronal curvature magnitude greater than 40° and progressive deformity, with no response to conservative treatment. Patients with no hospital records of pre-operative MRI scans and plain radiographs were excluded, in addition to those aged more than 20 years and less than 10 years with abnormal neurological examination findings, such as asymmetric abdominal reflexes, and patients who underwent revision surgery. After applying the exclusion criteria, 124 patients with AIS were included in the study. An experienced spinal surgeon measured curvature magnitudes in the coronal plane and thoracic kyphosis angles using the Cobb method. MRI scans, including T1- and T2-weighted sagittal, axial, and coronal images, were performed in all patients using a 1.5-Tesla MRI scanner and evaluated by a radiologist. The patients were then divided into an ISP group and non-ISP group and compared according to the age, sex, magnitude of thoracic kyphosis angle, magnitude of major coronal curve and the direction of the main curve.

The same senior surgeon performed the surgery, using the same technique for all patients. Motor evoked potentials and somatosensory evoked potentials were routinely monitored during the surgery. Segmental pedicle screws were placed bilaterally under fluoroscopy, using the free-hand technique (Figure 2). Partial facetectomy was performed at all levels of instrumentation to increase the correction, and the deformity was corrected by the direct rod derotation technique. The amount of correction was increased using compression and distraction manoeuvres. Bone allografts and autografts obtained during screwing were used for fusion after decortication. All the patients were mobilized the day after the surgery.

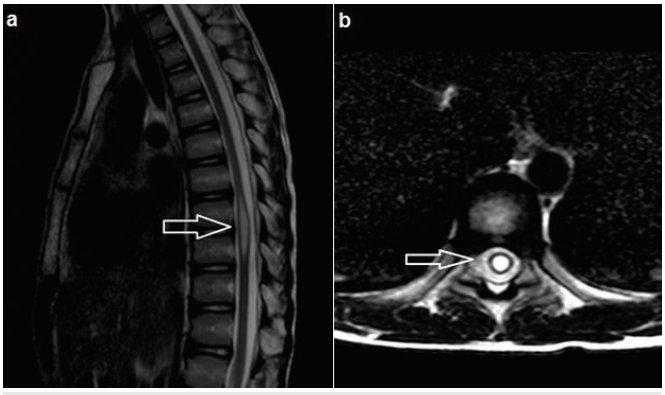

Figure 1. Syringomyelia in thoracic region which may lead to a high postoperative risk of neurological complications in corrective surgery for scoliosis. a) sagittal section, b) axial section

Statistical Analysis

The SPSS, version 19 (SPSS Inc., Chicago, IL) was used. Categorical data were compared using the Fisher's exact test, and continuous data were compared using the Student's t test. A p value of <0.05 was considered to denote statistical significance.

RESULTS

Of 154 patients, 124 were included in the study. Of these, 27 were males and 97 were females. Their mean age was 15.2 (range: 11-20) years. Ten (8%) patients had ISPs. Eight patients had syringomyelia in the thoracic region, one had a Chiari malformation with syringomyelia, and one had a tethered cord (Table 1).

The mean magnitude of the major coronal curve was 49.9°, and the mean thoracic kyphosis angle was 29.2. In 110 patients, the apex of the major curve was on the right side, and it was on the left side in the other 14 patients. Sixty-three of the deformities were type 1, four were type 2, eight were type 3, one was type 4, thirty-three were type 5, and fifteen were type 6 according to the Lenke classification.

When the two groups were compared, there were no statistically significant differences in age, sex, magnitude of thoracic kyphosis angle or magnitude of major coronal curve in patients with AIS ($p>0.05$). The direction of the main curve had no effect on the presence of ISPs in AIS patients ($p>0.05$) (Table 2).

Two of the 10 patients with ISPs required additional neurosurgical procedures prior to corrective surgery due to the presence of a tethered cord and Chiari malformation. Detethering of the cord and decompression of the Chiari malformation were performed by neurosurgeons. Motor evoked potentials and somatosensory evoked potentials were normal throughout the corrective surgery in all the patients. There were no complications in the perioperative period, and none of the patients developed post-operative neurological deficits.

DISCUSSION

In this study, the prevalence of ISPs (syringomyelia, n=8; tethered cord, n=1; Chiari malformation, n=1) in AIS patients was 8%

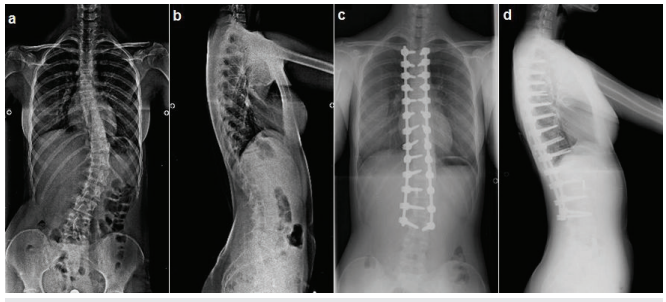

Figure 2. Preoperative and postoperative radiographs of an adolescent idiopathic scoliosis patient who underwent posterior instrumentation and fusion with segmental pedicle screws. a) preoperative anteroposterior view, b) preoperative lateral view, c) postoperative anteroposterior view, d) postoperative lateral view

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(10/124). Prior to corrective surgery for scoliosis, the patients with the tethered cord and Chiari malformation were operated by neurosurgeons to prevent neurological complications. No neurosurgical intervention was required in eight patients with syringomyelia only.

Previous research demonstrated that ISPs increased the risk of neurological complications after scoliosis surgery (7). Many studies have investigated the prevalence of ISPs in different types of scoliosis (8,9). According to these studies, the prevalence differs markedly, depending on the type of scoliosis. The rate was lower in cases of idiopathic scoliosis, especially among adolescents, although it was higher in cases that showed rapid progression due to underlying pathologies such as congenital and neuromuscular scoliosis. Although a pre-operative evaluation by MRI is routinely recommended for all types of scoliosis, there is no consensus in the literature regarding the need for a pre-operative MRI evaluation for ISPs in AIS.

Rajasekaran et al. (10) studied 177 patients younger than 21 years. They divided the patients into three groups according to the type of scoliosis: congenital scoliosis, presumed idiopathic scoliosis, and scoliosis secondary to neurofibramatosis and neuromuscular and connective tissue disorders. They reported a prevalence of ISPs as 35% in congenital scoliosis, 16% in idiopathic scoliosis and 22% in scoliosis associated with neurofibramatosis, neuromuscular and connective tissue disorders. When they examined the subgroups of idiopathic scoliosis, the prevalence of ISPs was 14% in adolescents, 27% in juveniles and 25% in infants. In their study, young age, abnormal neurological findings and thoracic kyphosis were associated with ISPs. They recommended routine use of MRI for pre-operative evaluations in these patients.

Singhal et al. (11) retrospectively examined 206 idiopathic scoliosis patients who underwent deformity correction. Without subdividing the patient group according to age, 20 (9.7%) of the patients had ISPs (a syrinx only, n=7; a syrinx with a Chiari type 1 malformation, n=4; a Chiari malformation only, n=4; a tethered cord, n=2; a split spinal cord, n=1; an intra-spinal tumour, n=1; and an arteriovenous fistula, n=21. All the patients with ISPs underwent an evaluation by a neurosurgeon as part of pre-operative planning. Eleven of 20 patients required a neurosurgical intervention prior to corrective surgery. Given the high number of patients requiring surgical interventions (11/20), Singhal et al. (11) emphasized the need for MRI in the pre-operative evaluation of idiopathic scoliosis patients.

On the other hand, in a study by Winter et al. (12), of 140 AIS patients with ISPs (a syrinx in the thoracic region, n=4; a Chiari type 1 malformation, n=3) who underwent MRI before surgery, none of the patients required a neurosurgical intervention for the ISP. In this study, all the patients underwent corrective surgery without any complications. Therefore, Winter et al. (12) suggested that when the findings of a neurological examination were normal in AIS patients, there was no need for a pre-operative evaluation with MRI. Shen et al. (13) performed MRI in 72 AIS patients before corrective surgery. In their study, only two patients had ISPs, both of which were type 1 Chiari malformations. Neither of these patients required any neurosurgical intervention, and both underwent surgery for scoliosis without complications. Therefore, Shen et al. (13) advocated that there was no need for a pre-operative MRI evaluation in AIS patients before corrective surgery. On the other hand, in a study of 249 AIS patients by Ozturk et al. (14), 20 (8%) patients had ISPs. Of these, 15 patients had syringomyelia, three

Table 1. Demographics of patients with an abnormal magnetic resonance imaging

	Age	Sex	Pathology	Lenke	Main curve direction	Main curve magnitude
1	18	F	Syringomyelia	Type 5	Right	46
2	18	F	Syringomyelia	Type 6	Right	44
3	14	M	Syringomyelia	Type 1	Right	52
4	12	F	Tethered cord	Type 1	Right	53
5	15	F	Syringomyelia	Type 6	Right	46
6	16	F	Syringomyelia	Type 5	Right	42
7	17	F	Syringomyelia	Type 6	Right	50
8	18	F	Syringomyelia	Type 1	Right	40
9	12	F	Syringoöyelia	Type 1	Right	47
10	14	F	Chiari type 1	Type 1	Right	60

F: Female, M: male

Table 2. Demographic comparison of patients with normal and abnormal magnetic resonance imaging findings

	Sex	Age	Direction of major curve	Major curve cobb angle	Thoracic kyphosis angle
Non-ISP group	M: 26 F: 88	15.25±0.57 (range: 11-20)	Left: 14 Right: 100	50.16±0.96 (range: 38-98)	29.58±0.99 (range: 12-68)
ISP group	M: 1 F: 9	15.40±0.17 (range: 12-18)	Left: 0 Right: 10	48.00±1.86 (range: 40-60)	25.20±2.40 range: 15-42
p	0.689	0.616	0.602	0.516	0.205

ISP: Intra-spinal pathologies, M: male, F: female

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patients had syringomyelia with a type 1 Chiari malformation, and two patients had a type 1 Chiari malformation. The three patients with syringomyelia and a type 1 Chiari malformation required neurosurgical decompression prior to corrective surgery. Therefore, in contrast to the literature, they advocated that routine MRI scanning was warranted in AIS patients, even in asymptomatic cases with no neurological complications. In the present study, the prevalence of ISPs in AIS patients scheduled for corrective surgery was 8%. Two of 10 patients with ISPs (one with a type 1 Chiari malformation and one with a tethered cord) required a neurosurgical intervention before corrective surgery. Thus, we also advocate that routine MRI scanning is important for pre-operative evaluations of AIS patients.

CONCLUSION

According to the literature, all scoliosis patients should undergo a pre-operative spinal evaluation using MRI, but there is a controversy about the need for MRI in AIS patients prior to corrective surgery. In the present study, all the AIS patients were asymptomatic, with normal findings in a neurological examination. As shown by MRI, 8% of the patient population had ISPs, and two of 10 patients with ISPs required a neurosurgical intervention prior to corrective surgery. Although the prevalence of ISPs appears to be low in AIS patients, we recommend that MRI should be routinely performed in all patients scheduled for corrective surgery due to the risk of neurological complications and the widespread availability of MRI today.

Ethics Committee Approval: Retrospective study.

Informed Consent: Written informed consent, approved by our institutional review board, was obtained from all patient.

Peer-review: Externally peer-reviewed.

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

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

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The Retrospective Evaluation of The Local Tumor Control and Adverse Effects of Treatment in Patients Treated Using Cyberknife Stereotactic Radiotherapy in Vestibular Schwannomas

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ABSTRACT

Objective: Although the most common tumors of the cerebellopontin angle of the vestibular schwannomas (VS) are benign tumors and are rarely fatal due to their localizations, the symptoms of the disease decreases the quality of life. The aim of the present study was to evaluate the local tumor control, hearing functions, and the adverse effects of treatment of radiotherapy using Cyberknife® device which is a recently popular non-invasive procedure causing minimum toxicity in the neighboring tissues with sharp dose decreases in the treatment of patients with VS particularly in intracranial tumors.

Methods: Cyberknife® radiosurgery was administered to 28 patients diagnosed with VS in the present study. The patients were followed-up with routine radiologic screening, audiologic tests, and with the evaluation of the neurologic functions. The study was performed retrospectively, and the data of the patients were obtained from the archive files.

Results: CyberKnife® stereotactic radiotherapy was administered to 28 patients diagnosed with VS. The mean follow-up time was 40.25 months. Local control rate was found as 100% in the follow-ups, the rate of protection of hearing in patients with adequate level of hearing was 73.6%, and the protection rates of the facial and trigeminal nerves was found as 100%. No statistically significant difference was detected in the distribution of the age, treatment dose, and tumor sizes in patients in accordance with the deterioration of hearing after treatment. Conformity index (CI), and coverage were found as the predictive factors in the protection of hearing.

Conclusion: The investigation of the stereotactic results of VSs in the literature showed that local control and hearing functions were moderately protected, and cranial nerve associated toxicity was found in moderate levels. The treatment parameters of CI and coverage were found as the predictive values in the protection of functional hearing after treatment. Randomized controlled prospective studies in patient groups with longer follow-up periods were required for ultimately determining the reliability of this treatment modality.

Keywords: Vestibular schwannoma, CyberKnife®, radiosurgery, radiotherapy, stereotaxy

INTRODUCTION

The aim was to evaluate the tumor local control rates, hearing functions, and adverse effects of treatment in patients with clinically or radiologically proven cerebellopontin angle (CPA) tumor [vestibular schwannoma (VS) or meningioma], who were treated using the stereotactic radiosurgery (SRS) or fractionated radiosurgery (FSRT) method in Radiation Oncology CyberKnife® unit in Okmeydanı Training and Research Hospital between July 2012 and October 2014. Patients with tumor size higher than 3 cm or patients who had a history of previous surgical treatment were excluded from the study.

Approximately 10% of all intracranial tumors stemmed from the CPA, and VSs constituted the majority of the tumors of this region (1,2). These tumors, previously known as VS, constituted

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6-8% of the primary intracranial brain tumors and 60-78% of the CPA tumors. Although benign, the results may be vexing. The prevalence rate was 1 in 100.000.

Approximately 2 mm/year growth of tumor in the internal auditory canal was evaluated as "gradual growth", and the growth higher than 10 mm/year was evaluated as "the rapid growth" of the tumor. 43% of the cases were in tendency of growth, 51% were stable, and 6% became smaller without any treatment in a collection of 21 literature studies consisting of 1345 patients who were followed up due to VS and the longer follow-up period was 3.2 years (3).

Radiosurgery treatment technique enables a noninvasive treatment option with similar local control rates, and with better protection of hearing and the better protection of the 5th and 7th cranial nerves compared to the surgical treatment (4), and the damage is reduced (5). Therefore, Cyberknife®, a non-invasive radiotherapy technique with sharp dose decreases has recently become popular in VS, and in other benign cranial pathologies compared to surgical treatment particularly with gamma knife. The recent data showed that higher local control and lower adverse effects could be obtained with 12-13 Gy dose in VS (6-9).

METHODS

Ethics committee approval was received for this study from the Ethics Committe of Okmeydanı Training and Research Hospital (approval number: 267, date: 03.02.2015). This is a retrospective study. Patient data were taken from the files.

Patients from all ages and sex, who were diagnosed with clinically and radiologically proven CPA tumor and who underwent CyberKnife® treatment in Okmeydanı Training and Research Hospital between 2012 and 2014 constituted the sampling of the study. Patients with CPA tumor, who were recommended follow-up or who underwent surgery in Okmeydanı Training and Research Hospital between 2012 and 2014, were excluded from the study. All patients included in the study were diagnosed with VS, and the diagnosis was put in a council consisting of the physicians of radiation oncology, radiology, otorhinolaryngology, neurosurgery, and pathology. The decision of stereotactic radiation treatment was taken after discussion with patients who were thought to be suitable for CyberKnife® treatment in tumor council. A total of 28 patients consisting of 17 women and 11 men were included. Physical and neurologic examinations were performed before the treatment. Hearing tests and 5th and 7th cranial nerve examinations using the Gardner-Robertson hearing scale were performed before the treatment in patients diagnosed with VS.

Different fraction schemas were selected as the treatment dose in accordance with the tumor diameter, volume, and the proximity to the neighboring tissue in the present study. 3 (10.7%) patients received radiosurgery under 1x12 Gy irradiation and 11 (39.2%) received 3x6 Gy (18 Gy), 2 (7.1 %) patients received 3x7.5 (22.5 Gy), 1 (3.5%) patient received 3x8 Gy (24 Gy), and 11 (39.2%) patients received 5x5 Gy (25 Gy) radiation treatment. 1x12 Gy radiosurgery was administered for 3 patients who had a tumor diameter smaller than 1 cm, and a total of 18-25 Gy radiation was administered in 3 to 5 fractions for the tumors larger in diameter than 1 cm (10-12).

The hearing functions of all patients before and after CyberKnife® treatment were evaluated using audiometry. Pure tone threshold audiogram, the average pure tone, speech recognition threshold, and Speech Discrimination score were investigated in pure tone audiometry. Gardner-Robertson class for each patient was identified using the pure tone average, and speech discrimination scores (13). The patient group in class 1 was able to speak on the phone with the affected side. The patient group in class 2 (with pure tone audiogram threshold lower than 50 dB, and speech discrimination score higher than 50%) was accepted in the critical threshold for hearing. The hearing levels of patients in class 1 and 2 were evaluated as moderate levels. The hearing levels of patients in class 3 and in poor levels were evaluated as inadequate and/or poor.

Diagnosis of all patients were performed using the radiologic screening. Magnetic resonance imaging (MRI) and computed tomography (CT) were used in radiologic screening. CT and contrast enhanced MRI screening of all patients were performed before the treatment, and tumor size and tumor localization were identified. Post-treatment local tumor control follow-up was performed using the contrast enhanced MRI. The tumor was contoured in each axial section over these images, and tumor diameter and tumor volume were measured.

The 5th, 7th, and 8th nerves were clinically evaluated before and after the treatment. The House & Brackmann classification was used in the clinical evaluation of the facial nerve function. Trigeminal nerve functions were evaluated as the normal, increased, or decreased sense using a semiquantitative scale. The functions of the other cranial nerves were recorded as temporary and permanent deficit.

The symptoms of all patients before and after the treatment (headache, tinnitus, ataxia, vertigo, etc.) were questioned and recorded to the clinical files. Scoring of headache could not be performed; however, the presence or absence of headache was evaluated. The symptoms were recorded as maintained, disappeared in the routine follow-ups.

Statistical Analysis

The IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used in the statistical analysis of the data. The compliance of parameters to normal distribution was evaluated using the Shapiro-Wilks test. Student's t-test was used in the comparison of parameters in normal distribution, and The Mann-Whitney U test was used in the comparison of non-normal distribution between two groups in the quantitative comparison of data, in addition to the descriptive statistical methods (mean, standard deviation, and frequency) in the evaluation of the study data. The paired sample t-test was used in the pretreatment-posttreatment comparisons of the normal distribution parameters, and the Wilcoxon signed test was used in the comparisons of the non-normal distribution parameters. The McNemar test was used in the comparison of

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the qualitative data. Pearson's correlation analysis was used in investigating the association between the parameters in normal distribution, and the Spearman's rho correlation analysis was used in the investigation of the association of parameters in non-normal distribution. The significance was evaluated in $p<0.05$ level.

RESULTS

The present study was performed with 28 patients diagnosed with VS, who were administered Cyberknife® stereotactic radiotherapy between July 2012 and October 2014.

The patient characteristics, tumor, and treatment parameters are summarized in Table 1. The comparison of the pretreatment tumor diameter and volume and hearing tests with post-treatment values were not statistically significantly different between the mean tumor diameter before the treatment and after the treatment ($p>0.05$). There was no statistically significant difference between the tumor volumes before the treatment and after the treatment ($p>0.05$). No statistically significant difference was detected in tumor diameter and volume in the mean 40.25±7.68 (30-54 months) months follow-up after the treatment, and the local control rate was 100%.

Table 1. Patient, tumor, and treatment characteristics

	Minimum-maximum	Mean ± SD
Age (year)	26-71	50.14±12.71
Sex (n%)		
Woman	17	60.7
Man	11	39.3
Age groups (n%)		
Below 60 years	23	82.1
60 years and above	5	17.9
Follow-uptime (month)	30-54	40.25±7.68
Pre-treatment tumor diameter (mm)	11-29	17.89±5.65
Post-treatment tumor diameter (mm)	10-28	17.61±5.45
Pre-treatment tumor volume	360-12600	3206.93±3500.68
Post-treatment tumor volume	359-12591	3203.75±3496.02
Pre-treatment SSA score	0-92	40.46±26.58
Post-treatment SSA score	8-92	48.89±25.81
Pre-treatment speech discrimination score	4-100	59.07±31.29
Post-treatment speech discrimination score	6-94	54.21±28.06
Pre-treatment GR score	1-5	2.04±1.07
Post-treatment GR score	1-5	2.18±1.19
CI	1.18-1.85	1.32±0.14
HI	1.13-1.55	1.25±0.08
Coverage	95.2-99.9	98.35±1.16
Mean cochlear dose	98-2305	1177.04±594.42

SD: Standard deviation, SSA: sensorineural audiogram, GR: gardner-robertson, CI: Conformity index, HI: Homogeneity index

The increase in the mean sensorineural audiogram (SSA) score after the treatment was found to be statistically significant compared to the score before the treatment ($p=0.001$; $p<0.01$, respectively). The decrease in the mean speech discrimination score after the treatment was found to be statistically significant compared to the value before the treatment ($p=0.024$; $p<0.05$, respectively). No statistically significant difference was detected in Gardner-Robertson scores before and after the treatment ($p>0.05$).

There was a statistically significant association to negative direction between the CI and the change differences in SSA scores before and after the treatment in 57.3% levels ($r=-0.573$; $p=0.001$; $p<0.01$). There was a statistically significant association in positive direction between the coverage values and the change differences of SSA scores before and after the treatment in 59.6% levels ($r=0.596$; $p=0.001$; $p<0.01$).

The correlation of the change in speech discrimination in accordance with the tumor size and treatment parameters was statistically significantly associated with positive direction between the CI values and the change differences in the speech discrimination scores before and after the treatment in 38% levels ($r=0.380$; $p=0.046$; $p<0.05$).

The effects of age and sex on the speech discrimination were demonstrated in Table 2.

The rate of the protection of hearing was found as 73.6% in the study. Deterioration was detected in hearing functions of 5 patients who had pretreatment functional hearing.

No toxicity associated with facial, trigeminal, and other cranial nerves was detected before and after the treatment. The protection rate of the facial and trigeminal nerve functions was found as 100% in the present study.

No pseudoprogression was detected in the routine radiological follow-up of the patients in the study.

The decrease in the rate of ataxia after the treatment (3.6%) was found to be statistically significant compared to the rate of ataxia before the treatment (25%) ($p=0.031$; $p<0.05$). The decrease in the detection rate of headache after the treatment (32.1%) was found

Table 2. The effects of age, and sex on the speech discrimination

		Pretreatment-post treatment speech discrimination score	p
		Mean ± SD (median)	
Sex	Woman	-1.06±22.84 (-3)	0.220
	Man	-10.73±14.13 (-7)	
Age groups	Below 60 years	-4.83±22.15 (-3)	0.928
	Sixty years and above	-5±6.67 (-3)	

Mann-Whitney U test, SD: standard deviation

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Table 3. A summary of the other studies in the literature and of our study

Author	No of patients	Dose (Gy)	Fraction	Local control rate (%)	Hearing protection rate (%)	Facial nerve protection rate (%)	Trigeminal nerve protection rate (%)	Follow-up (month)
Murphy and Suh (14)	117	13	1	91	Unknown	95	99	38
Chopra et al. (24)	216	13	1	92	44	100	95	68
Noren (13)	669	Unknown	1	95	65-70	Unknown	Unknown	Unknown
Kondziolka et al. (12)	162	16	1	98	51	79	73	60-120
Iwai et al. (30)	25	12	1	96	64	96	100	89
Szumacher et al. (31)	39	50	25	95	68	95	95	22
Maire et al. (32)	45	50.4	28	86	78	100	100	80
Fuss et al. (33)	51	57.6	32	98	85	100	96	42
Shirato et al. (34)[2]	65	50	25	92	Unknown	Unknown	Unknown	37
Henze et al. (35)	39	54	Unknown	95	Unknown	Unknown	Unknown	36
Kapoor et al. (36)	385	25	5	97	Unknown	98	97	52
Meijer et al. (25)	80	25	5	94	61	97	98	33
Sakanaka et al. (37)	12	20	5	92	80	100	100	40
Williams al. (38)	125	25	5	100	Unknown	100	98	22
Chang et al. (16)	61	18	3	98	74	100	97	48
Poen et al. (39)	31	21	3	97	77	97	84	24
Ishihara et al. (40)	28	17	3	94	93	100	100	32
Our study	28	12-25	1-5	100	73.6	100	100	40

to be statistically significant compared to the detection rate of headache (60.7%) before the treatment ($p=0.021$; $p<0.05$).

DISCUSSION

VSs constitute 6-8% of primary intracranial brain tumors and 60-78% of CPA tumors (13). The prevalence is 1 in 100.000 (14). In parallel with the developments in radiologic screening, the diagnosis of VS may be accomplished when the tumor size is smaller. The studies which evaluated the treatment in VS were retrospective, and the evidence level of the studies were level 3 or smaller (15). Therefore, there is a lack of evidence-based guide in treatment. The increase of the treatment options in VS and the scarce number of randomized and controlled studies of treatment options led the physicians to interdisciplinary study, and to evaluation in the diagnosis and treatment of the disease. VS is rarely life-threatening, thus the main target in treatment is to provide local tumor control and to protect the moderate hearing and organ functions. The tumor size, age, the general condition of the patient, whether the hearing will be protected, the chance of the protection of the 5th and 7th nerves, tumor growth rate, the presence of neurofibromatosis type 2, the adequate local tumor control, and the treatment associated adverse events are considered in the selection of the treatment. The current treatment approaches are close follow-up, SRS, fractioned radiotherapy, and microsurgery resection. The aim in the CyberKnife® radiosurgery and FSRT treatment techniques is to pause the tumor growth or to minimize the tumor by administrating radiation in a single or several sessions. CyberKnife® functions in the guidance of the real time screening, and rigid immobilization of patient is not required. The comparison of the treatment results of CyberKnife® radiosurgery (steorotactic radiosurgery) and FSRT with surgical treatment showed that similar local control rates were obtained. In addition, this method provides a noninvasive treatment option with the possibility of the better protection of the 5th and 7th cranial nerves (16).

Three patients were administered CyberKnife® radiosurgery at 12 Gy, and 25 patients were administered FSRT between 18 and 25 Gy in the present study. Local control rate was found as 100%. The treatment doses and local control rates in our study were parallel with the doses and local control rates of the other researchers; however, the mean follow-up period was between 5 and 10 years in the studies in the literature, and our mean follow-up time was 40 (40.25±7.68 months) months. Therefore, the possible progressions in our longer period follow-ups may cause lower local control rates.

Pseudoprogression is generally detected in the first 2 years after radiosurgery. Hathout showed that the pseudoprogression rate was higher in patients who underwent previous surgery before SRS (17). Therefore, treatment should not be regarded unsuccessful before the month 24 of the treatment, and treatment approach should not be changed before the month 36 unless there is a clinical requirement (18). We detected no pseudoprogression in the patients in our study group, which may be explained by that the patients who underwent previous surgery were excluded from the study.

The use of fractioned stereotactic radiotherapy for VSs minimizes the radiation associated damage of the neighboring cranial

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nerves compared to the use of single fraction radiosurgery. The facial and trigeminal toxicity rate was found as 5% in the 4- year follow-up of 37 patients who were administered CyberKnife® FSRT (10-12). The facial nerve protection rate was reported as 74-100%, and the trigeminal nerve protection rate was reported as 73-100% in an analysis which evaluated 17 studies in the literature (19). We detected no toxicity associated with facial and trigeminal nerves in patients who were administered SRS or FSRT in our study. The protection rate of cranial nerves was 100%, which was similar with the results in the literature.

A summary of the other studies in the literature and of our study is presented in Table 3 (7,20-23). As Cyberknife® is a relatively new device in our country, there are not enough studies on this subject yet.

Our study was similar to the studies in the literature regarding the local control, moderate hearing, and cranial nerves protection rates (20,24-26). There were differences in the studies investigating the predictive factors demonstrating the moderate hearing level after the treatment. No significant association of factors such as age, sex, tumor size, tumor volume, mean cochlear dose, and Homogeneity index was found with the hearing protection in our study (27-29). The moderate CI and coverage rates in treatment were found as the predictive values for hearing protection.

CONCLUSION

The investigation of the stereotactic radiotherapy results of VSs showed that local control was obtained, hearing functions were protected in moderate levels, and cranial nerve-associated toxicity was in moderate levels. CyberKnife® stereotactic radiotherapy is a good treatment option in VS patients particularly with tumor diameter smaller than 3 cm. Randomized controlled prospective studies in patient groups with longer follow-up period are required for the ultimate identification of the reliability of this treatment modality and for preparing a guideline.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committe of Okmeydanı Training and Research Hospital (approval number: 267, date: 03.02.2015).

Informed Consent: This is a retrospective study. Patient data were taken from the files.

Peer-review: Internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - T.B.; Concept - T.B.; Design - T.B.; Data Collection and/or Processing - T.B.; Analysis and/ or Interpretation - T.B., S.G.; Literature Search - T.B., S.G.; Writing Manuscript - T.B.

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Dosimetric Comparison of Radiotherapy Techniques for Treating Early-stage Glottic Larynx Cancer

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ABSTRACT

Objective: As early-stage larynx carcinoma is considered curable, we have investigated the possible differences among treatments with the contribution of advanced technology for maximum prevention of the development of secondary malignancies, and for the long-term quality of life. We compared the doses to the organs at risk, the Conformity indexes (CI), and the total monitor units of patients with early-stage glottic laryngeal cancer with the patients' physical planning for 3-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and volumetric modulated arc radiotherapy (VMAT) using the Eclipse treatment planning system.

Methods: Radiotherapy planning tomography sections of patients with early-stage (T1N0M0) glottic larynx cancer who underwent only radiotherapy were used. The sections were used for target volume and critical organ descriptions. Plans for 3DCRT, VMAT, 5-field IMRT, and 7-field IMRT were made and were compared after the procedures. The patients did not receive elective nodal irradiation. A total of 63 Gy in 28 fractions was described for all patients for the planning target volume (PTV).

Results: There was no difference between the mean PTV dose for VMAT and 5-field and 7-field IMRT. VMAT had the best results for the heterogeneity index and CI; 7-field IMRT had the best results for the mean dose and carotid artery volume receiving (V35 Gy) values. Although very low doses were detected for the medulla spinalis for 3DCRT, the doses of the other three plans were acceptable.

Conclusion: Due to the higher conformality and better protection of the critical organs, VMAT or IMRT is more appropriate rather than 3DCRT in RT treatment of early-stage glottic larynx cancer. The use of 7-field IMRT yields positive results, particularly for the carotid arteries.

Keywords: Dosimetric comparison, early-stage glottic larynx cancer, volumetric arc radiotherapy, intensity-modulated radiotherapy

INTRODUCTION

Larynx cancer constitutes 2% of all cancers and is the second most common cancer after skin cancer in the head-neck region (1). Tobacco use greatly influences the development of larynx cancer (2). Larynx cancers are most frequently detected in the glottic region. The primary treatment of early-stage glottic larynx cancer is surgical treatment or radiotherapy (RT). RT is a singly performed primary treatment in early-stage glottic larynx cancer. It has the advantages of organ protection and enables better voice quality compared to the surgical treatment (3-6). Recently, there has been increased use and preference for treatments that enable larynx protection with increased quality of life. Owing to the functional importance of the larynx, completing treatment with minimal function loss in cancer control has become one of the most important treatment targets (7,8). Factors such as anterior commissure involvement, tumor field size, daily fraction and total dose, total treatment time, beam energy, male gender, and pre-treatment hemoglobin level determine the tumor control of RT in larynx cancer (9-11). RT causes acute and chronic toxicities based on the treated region. To decrease these toxicities, RT for treating

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larynx cancer targets the regions in critical structures neighboring the larynx, such as the carotid arteries, thyroid gland, and medulla spinalis, and normal tissue regions exposed to the radiation dose. Here, we evaluated patients who received only RT for early-stage glottic larynx cancer to identify the approach that would yield the best appropriate tumor and critical organ dose. New volumes were created and physical plans were made using four planning techniques, and the plans were compared on system-recorded computed tomography (CT) sections of patients with pathologically and clinically proven early-stage larynx cancer and who received only RT. We evaluated a total of 20 patients who had been diagnosed with early-stage (T1N0M0) glottic larynx cancer. The study was planned as a prospective study. To enable 63 Gy in 28 fractions for each patient for planning target volume (PTV), we made physical plans that were compatible with 3-dimensional conformal RT (3DCRT), 5-field intensity-modulated radiotherapy (IMRT), 7-field IMRT, and volumetric modulated arc RT (VMAT). A total of 80 plans were prepared. The patients received no elective nodal irradiation.

METHODS

Ethics committee approval was received for this study from the Ethics Committee of Okmeydanı Training and Research Hospital (approval number: 524, date: 25.10.2016). This is a retrospective study. Patient data were taken from the files.

Twenty patients (1 woman, 19 men) with pathologically proven squamous cell epithelial carcinoma larynx cancer with early-stage glottic tumor, and who received only RT indication for treatment between 2013 and 2015 at Okmeydanı Training and Research Hospital Clinic of Radiation Oncology were included in the study. The patients had not received previous treatment, and CT images performed for RT planning were recorded in the system. The mean patient age was 55 (minimum: 33, maximum: 69) years. A prospective study method was planned.

The staging of the patients was conducted after direct laryngoscopy, CT, or magnetic resonance imaging scanning. All patients were diagnosed with T1N0M0 larynx cancer. The CT images previously recorded in the system were used in the study. Each patient was immobilized using thermoplastic head-neck masks when obtaining the images. The CT planning data were obtained using a Philips Brilliance wide-bore, 16-slice CT scanner (Philips Healthcare, Stockholm, Sweden). Image sections were taken from the vertex to underneath the clavicle at 3 mm intervals. Then, the images were transferred to the Eclipse 10.0 treatment planning system. Each patient was drawn compatibly with the following newly identified volume protocols:

- Clinical target volume (CTV): Cricoid cartilage, arytenoid cartilage, false vocal cords, anterior and posterior commissures, true vocal cords, and 1-1.5 cm of subglottis from above the hyoid bone to the end of the cricoid cartilage,

- PTV: CTV + symmetric 0.7 cm safety margin in each direction,

Dose: 63 Gy/28 fractions.

The carotid arteries (right and left), medulla spinalis, and thyroid gland were contoured as the organs at risk (OAR). The medulla spinalis and carotid arteries were drawn in the space determined via the addition of 1 cm to the upper and lower borders of the PTV. The thyroid gland was described to involve the entire organ. In addition, the body sections outside the PTV receiving doses of 5 Gy (D5) and >5 Gy were described. Four plans were prepared using the RapidArc Millennium 120 MLC device on the Eclipse 10.0 system to provide 63 Gy/28 fractions to all of the patients. The 3DCRT used two opposite lateral fields; IMRT planning used 5- and 7-field techniques; VMAT planning used the double arc method. All plans used a 6-MV photon beam. The data were obtained using dose-volume histograms.

Statistical Analysis

The data were prepared using the Microsoft Excel 2013 program. We compared the OAR doses; total treatment times; tumor dose coverage; Conformity index (CI); Homogeneity index (HI); total monitor units administered; and the low, median, and high dose volumes of the normal tissues rather than the target volume among the four dosimetric plans. The statistical analyses were performed using the SPSS 22 program.

RESULTS

Target Volume Dose Contents

The PTV63 volume levels were between 71.4 and 89.3 mL (mean: 77.4 mL). There was a statistically significant difference between the mean PTV and mean dose measurements of the RT techniques ($p=0.003$).

The mean PTV and D5 (Gy) of VMAT was significantly lower than that of 5-field IMRT ($p=0.000$), 7-field IMRT ($p=0.000$), and 3DCRT ($p=0.000$) ($p<0.05$). There was no statistically significant difference between the mean PTV and D5 (Gy) of 5-field IMRT and 7-field IMRT ($p>0.05$). There was no statistically significant difference between the mean PTV and D5 (Gy) measurements ($p=0.837$). There was a statistically significant difference between the mean PTV of the methods and the HI ($p=0.001$) and between the mean PTV and the CI of the methods ($p=0.001$) (Table 1, 2).

Doses in Organs at Risk

The carotid arteries, medulla spinalis, and thyroid gland involved in the treatment region were described as the OAR and were evaluated.

Carotid Arteries

The mean carotid artery doses and the mean dose measurements were statistically significantly different ($p=0.001$).

There was a statistically significant difference between the mean carotid artery dose and minimum dose (Gy) measurements ($p=0.001$). Paired comparisons showed that the mean carotid artery dose and the minimum dose (Gy) of 3DCRT were significantly higher than those of VMAT ($p=0.000$), 5-field IMRT ($p=0.000$), and

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7-field IMRT (p=0.000) (p<0.05). The mean carotid artery dose and the minimum dose (Gy) of VMAT were significantly higher than those of 7-field IMRT (p=0.003) (p<0.05). The mean carotid artery dose and minimum dose (Gy) of the 5-field IMRT and 7-field IMRT were not statistically significantly different (p>0.05). The mean carotid artery dose and the minimum dose (Gy) of the 5-field IMRT and VMAT were not statistically significantly different (p>0.05).

There was a statistically significant difference between the mean carotid artery dose and the maximum dose (Gy) measurements of the RT techniques (p=0.001). Paired comparisons demonstrated that the mean carotid artery dose and the maximum dose (Gy) measurement of 3DCRT were significantly higher than those of VMAT (p=0.000), 5-field IMRT (p=0.019), and 7-field IMRT (p=0.000) (p<0.05).

There was a statistically significant difference between the mean carotid artery dose and the V35 (cm^3, volume receiving 35 Gy) measurements (p=0.001) and between the mean carotid artery dose and the V50 (cm^3) measurements (p=0.001) of the RT techniques (Table 3, 4).

Table 1. The evaluation of the planning target volume measurements

	VMAT	IMRT 5-field	IMRT 7-field	3DCRT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
PTV - mean dose	65.14±0.74	65.52±0.2	65.51±0.27	66±0.56	[1]0.003*
PTV - D5 (Gy)	66.41±0.41	67.26±0.18	67.17±0.32	67.88±0.49	[1]0.001*
PTV - D95 (Gy) (median)	62.95±0.06 (63)	62.97±0.05 (63)	62.96±0.05 (63)	62.96±0.05 (63)	[2]0.837
PTV - HI (median)	0.047±0.007 (0.05)	0.061±0.005 (0.06)	0.059±0.005 (0.06)	0.068±0.009 (0.07)	[2]0.001*
PTV - CI (median)	0.97±0.05 (1)	1.21±0.13 (1.2)	1.27±0.16 (1.2)	2.22±0.31 (2.2)	[2]0.001*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, PTV: planning target volume, SD: standard deviation, HI: Heterogeneity index, CI: Conformity index

Table 2. The evaluation of the compatibility of planning target volume measurements to the plans

	VMAT/IMRT 5-field	VMAT/IMRT 7-field	VMAT/3DCRT	IMRT-5 field/ IMRT-7 field	IMRT 5-field/3DCRT	IMRT 5-field/3DCRT
[1]PTV - mean dose	0.378	0.210	0.002*	1.000	0.022*	0.004*
[1]PTV - D5 (Gy)	0.000*	0.000*	0.000*	1.000	0.000*	0.000*
[2]PTV - HI (median)	0.000*	0.000*	0.000*	0.157	0.007*	0.000*
[2]PTV - CI (median)	0.000*	0.000*	0.000*	0.221	0.000*	0.000*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, PTV: planning target volume, HI: Heterogeneity index, CI: Conformity index

Table 3. The evaluation of the measurements of the carotid artery

	VMAT	IMRT 5-field	IMRT 7-field	3DCRT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Carotid artery - mean dose	32.69±3.79	35.51±5.58	29.2±3.72	61.99±1.30	0.001*
Carotid artery - min dose (Gy)	4.53±0.51	4.45±0.96	4.09±0.46	26.16±4.14	0.001*
Carotid artery - max dose (Gy)	64.59±1.51	66.84±1.01	65.78±1.04	67.73±0.81	0.001*
Carotid artery - V35 (cm^3)	3.47±1.16	3.98±1.54	3.14±0.84	7.74±1.62	0.001*
Carotid artery - V50 (cm^3)	1.11±0.57	1.7±1.38	1.01±0.34	7.11±1.6	0.001*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, SD: standard deviation

Table 4. The evaluation of the compatibility of the carotid artery measurements to the plans

	VMAT/ IMRT 5-field	VMAT/ IMRT 7-field	VMAT/ 3DCRT	IMRT 5-field/ IMRT 7-field	IMRT 5-field/ 3DCRT	IMRT 5-field/ 3DCRT
Carotid artery - mean dose	0.297	0.034*	0.000*	0.000*	0.000*	0.000*
Carotid artery - min dose (Gy)	1.000	0.003*	0.000*	0.321	0.000*	0.000*
Carotid artery - max dose (Gy)	0.000*	0.033*	0.000*	0.065	0.019*	0.000*
Carotid artery - V35 (cm^3)	0.111	0.765	0.000*	0.020*	0.000*	0.000*
Carotid artery - V50 (cm^3)	0.137	1.000	0.000*	0.172	0.000*	0.000*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy

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Thyroid Gland and Medulla Spinalis

There was a statistically significant difference between the mean thyroid gland dose and the mean dose measurements of the RT techniques (p=0.001). Paired comparisons showed that the mean thyroid gland dose and the mean dose of 3DCRT were significantly higher than those of VMAT (p=0.000), 5-field IMRT (p=0.000), and 7-field IMRT (p=0.000) (p<0.05). There was no statistically significant difference between the mean thyroid gland dose and the mean dose measurements of VMAT, 5-field IMRT, and 7-field IMRT (p>0.05).

There was a statistically significant difference between the mean medulla spinalis dose and the maximum dose measurements of the RT techniques (p=0.001). Paired comparisons showed that the mean medulla spinalis dose and the maximum dose of 3DCRT were significantly lower than those of VMAT (p=0.000), 5-field IMRT (p=0.000), and 7-field IMRT (p=0.000) (p<0.05). There was no statistically significant difference between the mean medulla spinalis dose and the maximum dose of VMAT, 5-field IMRT, and 7-field IMRT (p>0.05) (Table 5, 6).

Organs at Risk Outside the Planning Target Volume

Evaluation of the low and median doses of normal tissues outside the PTV63 exposed to radiation revealed a significant difference for V5, V10, V20, V30, and V40 (Table 7).

Monitor Unit Values

There was a statistically significant difference between the mean monitor unit measurements of the RT techniques (p=0.001). As expected, the mean monitor unit values of the 3DCRT plans were significantly lower than those of the VMAT, 5-field IMRT, and 7-field IMRT plans (Table 8).

Treatment Times

There was a statistically significant difference in the mean treatment times of the RT techniques (p=0.001). The mean treatment time of the VMAT, 5-field IMRT, 7-field IMRT, and 3DCRT plans was 2.6±0.29 minutes, 2.62±0.19 minutes, 2.83±0.21 minutes, and 2.52±0.19 minutes, respectively. However, data obtained using QA for the total treatment times showed that

Table 5. The evaluation of the thyroid gland-mean dose, and medulla spinalis-max dose measurements

	VMAT	IMRT 5-field	IMRT 7-field	3DCRT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Thyroid gland - mean dose	20.54±4.83	22.91±4.52	21.05±3.42	34.41±5.93	0.001*
Medulla spinalis - max dose	24.96±2.93	24.67±4.75	26.88±3.45	4.23±1.2	0.001*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, SD: standard deviation

Table 6. The evaluation of the compatibility of the medulla spinalis and thyroid gland measurements in accordance with the plans

	VMAT/ IMRT 5-field	VMAT/ IMRT 7-field	VMAT/ 3DCRT	IMRT 5-field/ IMRT 7-field	IMRT 5-field/ 3DCRT	IMRT 5-field/ 3DCRT
Thyroid gland-mean dose	0.351	1.000	0.000*	0.066	0.000*	0.000*
Medulla spinalis-max dose	1.000	0.215	0.000*	0.450	0.000*	0.000-

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy

Table 7. The evaluation of the the means of the organs at risk (CC) measurements in accordance with the plans

OAR volume	VMAT	IMRT 5 field	IMRT 7 field	3CRRT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
V5	17.17±4.83	16.54±4.52	17.32±5.02	11.03±3.93	0.001*
V10	9.73±1.68	12.51±2.95	12.78±3.15	10.21±1.93	0.001*
V20	3.83±1.21	7.66±1.89	6.84±1.67	5.31±1.44	0.001*
V30	2.5±0.87	3.15±1.11	3.19±1.14	4.2±1.35	0.002*
V40	1.81±0.7	2.03±0.74	2.07±0.76	3.64±1.16	0.001*

OAR: organs at risk, VMAT: volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, SD: standard deviation

Table 8. The evaluation of the means of the monitor unit measurements in accordance with the plans

	VMAT	IMRT 5-field	IMRT 7-field	3CRRT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Monitor unit	503±45.6	792±114.4	941±139.4	271±23.5	0.001*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, SD: standard deviation

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the 3DCRT plans were superior. The total treatment times were as follows: VMAT plans, 3.69±0.31 minutes; 5-field IMRT plans, 6.92±0.61 minutes; 7-field IMRT plans, 8.21±0.74 minutes; and 3DCRT plans, 2.82±0.22 minutes.

DISCUSSION

The primary aim of treatment of early-stage glottic larynx cancer is protecting the larynx function in particular, and protecting voice quality (11,12). Therefore, RT has become the first treatment option in early-stage glottic larynx cancer, considering the relatively lower toxicity with good tumor control, and the organ-protective approach as compared to the surgical treatment (13,14). Over time, RT techniques that reduce the potential adverse effects and morbidity risk have become research areas of interest (15,16).

In early-stage glottic larynx cancer, RT treatment with two opposite fields enables greater tumor control. Patients have been treated with this method for years. However, there has been increased prevalence of atherosclerosis, carotid artery wall thickening, and cerebrovascular accident, as the carotid arteries are innately located in the treatment field. In recent years, the convenience of novel RT techniques such as IMRT and VMAT for treating early-stage glottic larynx cancer has been investigated. The main aim in these advanced technologies is to enable more conformal dose distribution in the target volumes and maximum protection of the surrounding tissues. Modern techniques with higher conformal RT planning and administration systems have the potential to decrease the early and late adverse effects that result from the limitation in tumor dose determination by reducing the dose to which the carotid arteries and surrounding tissues will be exposed. In addition, tumor control may be increased by enabling an increased dose to the target field using more conformal RT techniques.

IMRT provides dose distribution that may create a concave/convex isodose line in the target tissues. The benefit of this modality is the possibility of reducing the early and late adverse effects by decreasing the distribution of high doses to the critical organs.

Many researchers have investigated VMAT for treating local advanced larynx cancer; however, the number of studies investigating VMAT for treating early-stage glottic larynx cancer is inadequate.

The publications on early-stage glottic larynx cancer in which VMAT is used are scarce (17,18), as are comparison studies investigating VMAT and IMRT (19-22).

One advantage of VMAT is the shorter treatment time (23). There is no time loss in the form of a waiting period for the gantry to reach the expected state, as the radiation in VMAT is administered when the gantry is mobile. However, there is a waiting time for IMRT, which is a significant reason for the longer treatment periods (23,24). Rosenthal et al. (25) showed that the treatment times for IMRT and 3DCRT are similar (26).

Lower doses may be obtained in VMAT, as the shorter treatment time will reduce organ movement. Atalar et al. (22) reported that VMAT had the shortest treatment time and lowest carotid artery dose.

However, the shortest treatment time recorded in the present study was for 3DCRT; VMAT had shorter treatment times compared to 5-field and 7-field IMRT. The advantage of the rapid treatment time is that the risk of missing the field is reduced by minimizing organ movement.

In the present study, double arc VMAT was preferred. Comparison studies of single and double arc VMAT have reported higher PTV involvement and critical organ protection rates in favor of double arc VMAT (27). Moreover, a study using double arc VMAT reported better parotid gland protection (28). However, discussion of the accurate VMAT technique is ongoing.

Maximum doses of decrease to the medulla spinalis may be enabled by identifying the angles of the IMRT regions from the anterior surface of the larynx; however, this increases the doses to the carotid artery (22,29).

Although the medulla spinalis doses were within the tolerance doses for VMAT and IMRT, they were higher compared to 3DCRT ($p<0.001$).

The primary aim of the present study was to identify the PTV involvement rate and to identify a limit dose for the critical organs (30). The lowest mean dose for the carotid arteries was, in the order of lowest to highest, from VMAT, IMRT, and 3DCRT. Thus, using VMAT would reduce the risk of cerebrovascular accident. However, it is unclear which dose limitations should be used in RT treatment of the carotid arteries. Therefore, it is possible that more prospective clinical studies will identify the clinical benefit of such dose reduction.

Rosenthal et al. (25) have recommended that decreased carotid artery doses are required, particularly in young patients with carotid artery pathology.

Martin et al. (31) found that a carotid artery vascular wall dose of ≥35-50 Gy was significant. The values obtained in their study were higher than those of other studies. The reason could be the 7 mm safety margin given to the CTV in PTV identification.

Similar to carotid arteries, the thyroid gland is anatomically located in the neighboring region of the PTV. The use of RT for treating head-neck cancers may cause adverse effects such as hypothyroidism, Graves' disease, and various thyroid malignancies (32).

CONCLUSION

RT treatment of head-neck cancers gives rise to risk factors for carotid artery atherosclerosis, cerebrovascular accident, and thyroid dysfunction.

Here, using planning images, we devised 3DCRT, 5-field IMRT, 7-field IMRT, and VMAT plans for patients with early-stage glottic larynx cancer who were treated using only RT. Then, the plans were compared using dosimetric parameters. The 7-field IMRT was

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the best for protecting the carotid arteries; however, the VMAT plan was the best for the CI and HI. These dosimetric advantages may be useful for patients with a history of ischemic stroke with atherosclerotic changes in the carotid arteries. The best technique for medulla spinalis doses was 3DCRT, and the doses obtained for the other three techniques were at acceptable levels. The mean thyroid gland doses were higher in 3DCRT compared to the doses in the other three plans. The 3DCRT plans were the best for treatment times and total monitor units, and VMAT plans enabled shorter treatment times, treatment with monitor units, and better patient comfort compared to the IMRT plans (5- and 7-field).

RT planning systems such as IMRT and VMAT, which were developed after 3DCRT, currently provide better results for both dose distribution and dosimetrically. However, the efficacy, applicability, and dosimetric superiority of the systems in accordance with the treated region are controversial. In addition, there may be differences in CTV contouring among clinicians. In such cases, changes are expected for the dosimetric results.

The main advantage of the IMRT and VMAT plans is the possibility of high-level protection for the surrounding OAR in addition to enabling high doses to the target tissue. Similar studies are required for planning the options for patients with early-stage glottic larynx cancer in clinics that have both planning systems. The best option for RT is treatment conducted using the best available plan.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Okmeydanı Training and Research Hospital (approval number: 524, date: 25.10.2016).

Informed Consent: This is a retrospective study. Patient data were taken from the files.

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The Effect of Smoking on Serum Nesfatin-1 Levels on Women Who are in Follicular Phase: A Pilot Study

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ABSTRACT

Objective: Nesfatin-1, derived from NEFA/nucleobindin 2, is a hormone that suppresses food intake via melanocortin system in hypothalamus and has role on ovarian development. In this study, we aimed to determine the effect of smoking on serum nesfatin-1 levels on women who were in early follicular phase.

Methods: This study included 32 female participants, as smokers (n=11) and non-smokers (n=21). Nesfatin-1, fasting blood glucose, low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol and tryglicerides, follicule stimulating hormone (FSH), luteinizing hormone (LH), anti-müllerian hormone (AMH) and estradiol levels were measured from the blood samples in early follicular phase and they were compared.

Results: 34,3% (n=11) of participants were smokers and according to the Fagerström Nicotine Dependence Scale whose nicotine dependence levels were >7 while 65.6% (n=21) were non-smokers. Serum nesfatin-1 levels in smokers were (81±0.1 pg/mL) found significantly lower than non-smokers (125±0.1 pg/mL) (p=0.007). No significant differences were found between these two groups about the levels of fasting blood glucose, LDL, HDL, total cholesterol, triglycerides, FSH, LH, AMH and estradiol.

Conclusion: The levels of serum nesfatin-1 was found significantly lower in female smokers than the non-smokers in early follicular phase.

Keywords: Nesfatin-1, smoking, follicular, nicotine, ovarian reserve

INTRODUCTION

Obesity causes important health problems in our country and in the world. Due to the rapidly increasing obesity rates in the society, many studies are conducted to understand the biochemical mechanisms that govern our dietary behavior. Nesfatin-1 precursor protein, the first identified effect of which is to suppress appetite, is a polypeptide consisting of 82 amino acids synthesized from nucleobindin (NUCB-2) (1). Nicotine, which is responsible for most of the metabolic effects of smoking, also suppresses appetite, such as nesfatin-1 (2), and takes part in energy metabolism (3).

In addition to suppressing appetite, it has been shown in animal studies that it slows gastric emptying (4), increases glucose-stimulated insulin release and sensitivity (5), lowers lipid levels in blood and suppresses lipogenesis (6). In different studies nesfatin-1 levels have been shown to vary significantly in pregnant women (7), women who are breastfeeding (8), women with menstrual irregularities (21-35 days/2-7 days/a part from women menstruating with 3-4 pads per day) (2); in women with ovarian cyst (3), endometriosis (9), myoma uterus (10), polycystic ovarian syndrome (11), endocrine disease [diabetes mellitus (DM), Cushing disease, adrenal diseases, diseases of the thyroid gland, prolactinoma] (12), epilepsy (13) sleep apnea (14), depression (15), liver and kidney failure (16), and hypertension (17); gastrointestinal system diseases including dyspepsia and previous gastrointestinal

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surgery history (18), women with previous ovarian surgery history and suspicion of malignancy (19); women (20) who use medication, including oral contraceptives, and women who regularly exercise intensely (3 times a week and more than 30 minutes) (21). The saturation molecule nesfatin-1 also takes part in the triggering of puberty and in the development of ovaries (22). It has been shown to be elevated in polycystic ovarian patients and is thought to affect the hypothalamus-pituitary-ovarian axis (23). This suggested that the nesfatin-1 molecule had a role in gonadal development.

Numerous studies have been conducted in the literature that reveal the relationship between nesfatin-1 levels and many biochemical parameters. Nesfatin-1 has been related with ovarian functions, and ovarian diseases and nesfatin-1 levels have been associated. However, in the literature review we have made we have not found a publication about how smoking changes nesfatin-1 levels. Predicting that intensive nicotine stimulation in smokers will change the levels of nesfatin in the blood, we measured serum nesfatin-1 levels in the early follicular phase in the 3rd day of menstruation, along with ovarian reserve tests, in women who smoke and do not smoke.

Our primary goal in this study is to determine how smoking affects nesfatin-1 levels. Our secondary goal is to compare the ovarian reserve tests and nesfatin-1 levels to reveal the relationship between them.

METHODS

This study included women who applied to University of Health Sciences Turkey Gaziosmanpaşa Training and Research Hospital, Gynecology and Obstetrics Clinic policlinics and Smoking Cessation policlinic between 15 August and 30 October 2018. A signed informed consent form was obtained from each woman participating in the study. Anamnesis of each volunteer was taken and a physical examination was performed in order to determine whether the volunteer individuals had an obstacle to the study. The age, height and weight information obtained were recorded and body mass indexes (BMI) were calculated. Women of childbearing age (18-45 years) were included in the study. Women with pregnancies, breastfeeding women, menstrual irregularities (21-35 days/2-7 days/apart from women who menstruate 3-4 pads daily); women with ovarian cyst, endometriosis, myoma uterus, polycystic ovarian syndrome, endocrine disease (DM, Cushing disease, adrenal diseases, diseases of the thyroid gland, prolactinoma), epilepsy, sleep apnea, depression, liver and kidney failure, hypertension; women with gastrointestinal system diseases including dyspepsia and previous history of gastrointestinal surgery, history of previous ovarian surgery, and suspicion of malignancy; Women with drug use, including oral contraceptives, and women who regularly exercise intensely (3 times a week and more than 30 minutes) were not included. The exclusion criteria were created with the cases whose effect on nesfatin-1 was determined by searching the literature.

Volunteers were divided into two groups as smokers and non-smokers. According to the Fagerstörm nicotine addiction test, women with a high level of smoking dependence (≥7) were included in the smoker group, and volunteers with low test results were excluded from the study. Eleven smokers and 21 non-smoker volunteers participated in this preliminary study. Venous blood samples were taken from all volunteers in the early follicular phase of the menstrual cycle (3rd-4th day of menstruation) between 10.00-11.00 after 8-12 hours of fasting. Blood glucose and blood lipid measurements [total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides] were taken from the samples and ovarian function tests [follicule stimulating hormone (FSH), luteinizing hormone (LH), anti-Müllerian hormone (AMH), Estradiol] were studied. Nesfatin-1 levels from samples were measured by ELISA method with commercial kits (Phoenix Pharmaceutical, INC, California, USA).

All procedures were carried out in accordance with the Helsinki declaration. Before starting the study, necessary permission was obtained from the Gaziosmanpaşa Training and Research Hospital Ethics Committee (approval number: 72, date: 08.08.2018).

Statistical Analysis

The normality control of demographic data and blood measurements was done by drawing the Shapiro-Wilk test, histogram, Q-Q plot and box plot charts. Data were given as median, minimum and maximum. The measurement variables between the two groups were analyzed with the Mann-Whitney U test. The limit of significance was taken as $p<0.05$ and bidirectional. The analyzes were done using NCSS 10 (2015. Kaysville, Utah, USA) software program.

RESULTS

While 34.3% (n=11) of the study participants were smokers and high-level (≥7) cigarette addict women according to Fagerstörm nicotine addiction test, 65.7% (n=21) were non-smoker women. All of the volunteers were women of childbearing age between the ages of 18-45, and their mean age was 31.5. The median value of the non-smoker group was 27 and the smoker group was 33, and there was no statistically significant difference between the two groups. While the BMI median value in the smoker group was 26.2, it was 22.7 in the smoker group. Considering the fertility data of the volunteers who participated in the study, 13 of 32 women were women who had never experienced a pregnancy (gravida: 0), and 3 were grand multipa (gravida ≥5). The demographic characteristics of both groups are given in the table (Table 1).

There was no significant difference in the evaluation in terms of fasting blood glucose, LDL, HDL, total cholesterol, triglyceride, FSH, LH, AMH and estradiol levels from blood samples taken from both volunteer groups ($p>0.05$) (Table 2).

Serum nesfatin-1 levels were significantly lower in the smoker group (median value: 81±0.1 pg/mL) compared to the non-smoker group (median value: 125±0.1 pg/mL) ($p=0.007$).

DISCUSSION

In a study conducted by Kim et al. (24), saturation molecule nesfatin-1 was detected in teka and interstitial cells in mouse

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Table 1. Features of smoking and non-smoking group

Variables	Median value (minimum-maximum)		p*
	In non-smokers	In smokers	
Age (year)	27 (18-44)	33 (21-45)	0.099
Body mass index (kg/m^2)	26.2 (19.1-33.9)	22.7 (18.8-39.1)	0.293
Gravida	1 (0-5)	2 (0-5)	0.308
Parity	1 (0-5)	2 (0-5)	0.439

*Mann-Whitney U Test

Table 2. Results of smoking and non-smoking group

Variables	Median value (minimum-maximum)		p*
	In non-smokers	In smokers	
Fasting blood glucose (mg/dL)	83 (64-92)	85 (64-106)	0.551
LDL (mg/dL)	102 (33-168)	109 (53-120)	0.662
HDL (mg/dL)	48 (35-78)	43 (36-111)	0.606
Total cholesterol (mg/dL)	167 (87-263)	170 (104-192)	0.691
Triglyceride (mg/dL)	77 (28-232)	77 (35-217)	0.606
FSH (mIU/mL)	6.7 (4,1-9.6)	6 (5-72)	0.331
LH (mIU/mL)	4.9 (2-9.9)	6 (2-41)	0.383
Estradiol (pg/mL)	47 (20-174)	66 (20-253)	0.565
AMH (ng/mL)	2.2 (0.6-4.8)	2 (0-6)	0.19
Nesfatin-1 (pg/mL)	125.2 (48.7-3098.6)	81 (46-235)	0.007

*Mann-Whitney U Test, LDL: low density lipoprotein, HDL: high density lipoprotein, FSH: follicle-stimulating hormone, LH: luteinizing hormone, AMH: anti-mullerian hormone

ovarian tissue. Nesfatin-1 is also involved in triggering puberty and in the development of ovaries. It has been shown to be elevated in patients with polycystic ovaries (13) and is thought to affect the hypothalamus-pituitary-ovarian axis. This suggested that the nesfatin-1 molecule had a role in gonadal development.

The increase in pubertal transition period and premature telarchy supports the role of nesfatin-1 molecule in gonadal development (25). In another study conducted in rats, it was observed that when nasfatin-1 was given intravenously, gonadotropins increased and when antidote was given, ovarian volume decreased, which is a symptom of delayed puberty (7). This information suggests that the nesfatin-1 molecule can give an idea about the fertility age female ovarian reserve. In our study, we compared nesfatin-1 levels and basal FSH, estradiol, and AMH levels, which were measured on the third day of menstruation with ovarian reserve markers.

In our study, AMH values showing ovarian reserve were found to be lower in the smoker group, although not statistically significant. In addition, nesfatin-1 values were significantly lower in the smoker group. This result may be due to the relative deficiency of our number of cases.

In the study of 477 women of childbearing age examined by Kline et al. (26); it has been determined that there is an increase of approximately 15% in FSH values in women who smoke. In our study, although FSH levels were found to be increased in the smoker group, the difference was not statistically significant. In the same study, AMH values were found to be decreased in the smoker group. However, the difference is not statistically significant. In our study, AMH values were found lower in the smoker group (2.2 vs 2.0, p=0.19). This may be due to the insufficient number of volunteers in our study.

In a study by Ayada et al. (27), it was shown that nesfatin-1 expression increased in puberty and an increase in LH was observed in parallel with this increase. In addition, in another study by García-Galiano et al. (22) it was found that high nesfatin-1 levels increased hypothalamic NUCB-2 protein content and serum LH levels. In parallel with the studies conducted, LH values in our study were found to be higher in the non-smoking group with higher levels of nesfatin-1 serum, but not statistically.

Another effect of nicotine in cigarette is that it negatively affects sex hormone levels such as plasma testosterone and estrogen (27). In a study conducted by Park et al. (28) to demonstrate the effects of smoking on sex hormone levels and sexual functions, it was found that smoking had a negative effect on testosterone levels as expected in men and caused a significant decrease in sexual functions, but did not cause a significant decrease in estrogen levels in women. However, although there is no significant decrease in blood estrogen levels, it has been reported that there is a loss in sexual functions and cigarette has an antiestrogenic effect in the genital system. In our study, blood estrogen levels were higher in the smoker group.

Multiple studies have been conducted to determine the link between the Nesfatin-1 level and the BMI. In a study conducted by Abaci et al. (29) on children, the serum nesfatin-1 level of obese children was found to be significantly lower than the control group. The study by Ramanjaneya et al. (30) on adults showed that there was a positive correlation between plasma nesfatin-1 levels and BMI in patients with a BMI between 22.3 and 27.67 kg/m^2. In our study, we did not find a statistically significant change between BMI and nesfatin-1 levels.

CONCLUSION

Serum nesfatin-1 values measured in the early follicular phase were found to be significantly lower in smoking women compared to non-smoking women (p=0.007).

This study shows the relationship between nesfatin-1 and smoking, but it is not enough to explain the mechanism by which smoking caused a decrease in nesfatin-1 level. More research is needed to explain this relationship.

As a preliminary study, after a sufficient number of volunteers are included in the study, other data that we foresee to be meaningful such as ovarian functions and nesfatin-1 relationship can be accessed along with the decrease in standard deviations. Voluntary recruitment continues for our preliminary study, in which we present the results. After the number of volunteers is increased

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for both groups and sufficient volunteers are reached, the results will be presented again.

Available data on the effect of cigarette addiction and nicotine on nesfatin-1 are very limited. Considering that Nesfatin-1 draws attention as an effective therapeutic agent for various diseases, we think it is important to know more about nesfatin-1 from different perspectives.

Ethics Committee Approval: Before starting the study, necessary permission was obtained from the Gaziosmanpaşa Training and Research Hospital Ethics Committee (approval number: 72, date: 08.08.2018).

Informed Consent: A signed informed consent form was obtained from each woman participating in the study.

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Evaluation of Nutritional Status in Children Consulted to Polyclinics

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ABSTRACT

Objective: We aimed to determine the nutritional status of children who applied to polyclinic for any reason.

Methods: Anthropometric measurements of 1022 subjects aged between one month and eighteen years were evaluated prospectively between February 2017 and May 2017. According to the Gomez and Waterlow classifications, these measurements were calculated and malnutrition degrees were determined in this respect. Patients were evaluated according to relative weight and body mass index (BMI) in obesity measurement. Some patient groups were not included in the study consciously. These were patients with a birth weight of less than 2.500 g and a history of premature birth, and patients with chronic diseases were not included in the study.

Results: The mean age of the patients was 5.7±3.9 years, 501 (49%) were female and 521 (51%) were male. Malnutrition was found in 22.3% (n=228) of the cases. According to the Gomez classification, 172 (16.8%) of them were mild, 53 (5.2%) were moderate, 3 (0.3%) were severe malnutrition. According to the Waterlow classification, 2.7% (n=28) of the cases were diagnosed as acute, 4.2% (n=44) as chronic and 1.8% (n=18) as acute-chronic malnutrition. In the first 6 months, there was no patient with malnutrition before the start of additional food. According to the relative weight, 171 (16.8%) of the cases were above 110%; 1.1% of them (n=12) were under 2 years of age. Of the cases younger than 2 years of age, 0.78% (n=8) were overweight and 0.39% (n=4) were obese. Of the 159 (15.6%) patients with a relative weight above 110%, the rate of BMI was 4.8% (n=50) over 85th percentile, ie overweight, 7.7% (n=78), 95th percentile. ie, obese and 3% (n=31) were within normal limits.

Conclusion: According to our study, anthropometric measurements of the patients should be made and their nutrition should be questioned because of the high probability of detecting nutritional disorder. To any patient who came to pediatrics clinic, the importance of breastfeeding should be emphasized, and nutritional disorder rates will decrease with the introduction of additional food at the right time. Moreover, with the explanation of right food and the general nutrition rules, it is believed that the rates of nutritional disorders will decrease.

Keywords: Malnutrition, obesity, child

INTRODUCTION

Malnutrition is a change in normal body composition due to nutritional deficiency, and it can be prevented or treated (1). Protein energy malnutrition (PEM) is an important problem in undeveloped and developing countries. It is responsible for 60% of the deaths under the age of five years (2).

The presence of malnutrition in children increases the risk of death in gastroenteritis and respiratory tract by approximately twice. Symptoms varies according to duration and severity of nutritional deficiency, nutritional quality, and personal factors such as age and the presence of infection. While heavy malnutrition is easily diagnosed, it may be difficult to identify patients with mild or moderate malnutrition. Therefore, the diet of patients should be questioned well, calorie deficit should be determined, anthropometric measurements and biochemical parameters should be reviewed (3).

While PEM is observed after various diseases, trauma or surgical interventions in developed countries (4,5), malnutrition is generally detected due to malnutrition or dietary errors or as a result of common infections, especially gastroenteritis in developing

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countries (6). Patients suspected to have PEM are evaluated according to the Gomez and Waterlow classifications (7-11).

Obesity in childhood is a health problem that needs to be approached carefully because it continues as adult obesity in the future, it causes insulin resistance, lipid metabolism disorder, high blood pressure and severe psychological stress, causes high morbidity and mortality rates, and most importantly it can be prevented (12,13).

In studies conducted in different times and provinces in our country, it is stated that the frequency of malnutrition decreases and obesity increases in children, but today, malnutrition and obesity are important health problems that can be prevented for both healthy children and hospitalized children (14). For this reason, in our study, we aimed to evaluate the nutritional status in patients who applied to the pediatric outpatient clinic of our hospital for any reason.

METHODS

Between the years of February 2017 and May 2017, 1022 patients between the ages of 1 month and 18 years, who were admitted to our hospital's general child outpatient clinic, were included in our study. Patients with a birth weight below 2.500 grams and a preterm birth history, patients with chronic disease, patients with post-surgical short bowel syndrome and malabsorption were not included in the study because they had the risk factors for the development of malnutrition. Ethics committee approval was received for this study from the Ethic Committee of Taksim Training and Research Hospital (approval number: 11, date: 22.02.2017). Consent was obtained from the parents of the patients. Anthropometric measurements of the cases were evaluated prospectively. Measurements are made by the same healthcare professional with the same weight and height measuring device. Weight and height measurements were evaluated according to the references. Weight by age, height by age and weight by height were determined. According to the Gomez classification, the ratio of current weighing to weighing that should be according to age was calculated. According to age, those with the weights of 90-110% were evaluated as normal, those with the weights of 75-89% as mild, those with the weights of 60-74% as moderate, and those below 60% as severe malnutrition. According to the Waterlow classification, those with a weight less than 90% by height and with a height greater than 95% by age were defined to have acute malnutrition. Those with a weight greater than 90% by height and with a height less than 95% by age were defined to have chronic malnutrition. And, those with a weight less than 90% by height and with a height less than 95% by age were defined as acute malnutrition in the chronic base.

In the evaluation of obesity, the patients were separately evaluated according to relative weight (weight by height) and body mass index (BMI). Children under 2 years of age were classified using relative weight. Considering weight by height, those with 110-120% were evaluated as overweight, and those over 120% were considered as obese. In children older than two years of age, those with BMI of 85. percentile and above were evaluated as overweight and those with BMI of 95. percentile and above were evaluated as obese.

Statistical Analysis

The statistical analysis of the data was done with the 11.0 version of the SPSS program.

RESULTS

The average age of the patients in our study was 5.7±3.9 years, 501 (49%) were girls and 521 (51%) were boys. Malnutrition was observed in 22.3% (n=228) of the cases. The distribution of our patients who are included in the study according to their age (month) and gender is as in Table 1. According to the Gomez classification, 171 (18%) of malnutrition patients were mild, 54 (5.2%) were moderate and 3 (0.3%) had severe malnutrition (Table 2). One of our patients with severe malnutrition was 14 years old and girl; others were boys aged 2 and 15 years. According to the Waterlow classification, 2.7% (n=28) of the cases were defined as acute, 4.3% (n=44) as chronic, 1.7% (n=18) as acute malnutrition in the chronic base (Table 3). We did not have any patients with malnutrition in the first 6 months, before the initiation of supplementary food.

According to the relative weight, 171 (16.8%) of the patients were above 110%; 1.1% (n=12) of them were under 2 years old. The relative weight of 12 of the cases under the age of two years (n=237) was above 110%, 8 of them (3.3%) were over 85. percentile, in other words overweight, according to BMI, and 4 (1,7%) were over 95. percentile, in other words obese. 4.8% (n=50) of 159 patients (15.6%) with a relative weight above 110% and age above two years were above the 85. percentile, that is, overweight; 7.7% (n=78) were above the 95. percentile, that is, obese; and 3% (n=31) were within normal limits Table 4. While 60% (n=30) of overweight patients were male, 46.1% (n=36) of obese patients were male.

DISCUSSION

Malnutrition is kept responsible for more than half of child deaths in the world. Nearly 13 million children under the age of 5 years die each year due to malnutrition (15-17). Malnutrition is still an important problem, especially for developing countries like us. In addition, early detection and early treatment of malnutrition is of great importance. While it is easier to detect the presence of heavy malnutrition, it may be difficult to find the presence of moderate and mild malnutrition. Early diagnosis reduces mortality and morbidity, as well as decreases the cost by decreasing hospitalization rate. In Turkey, the presence of many factors such as low socio-economic status and level of education, wrong eating habits and lack of proper hygiene conditions leads to the occurrence of malnutrition. Improper environmental conditions and accompanying infections make malnutrition more evident (3). Our hospital provides health services to a socioeconomically low and medium population. In patients who apply to general child polyclinic, it is believed that malnutrition rates will decrease

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by emphasizing the importance of breastfeeding, starting supplementary food with the right food at the right time and explaining the general hygiene rules.

In our study, we detected 22.3% malnutrition in patients who applied to our hospital for other reasons. In addition to the Gomez classification, we also used the Waterlow classification as it includes height measurement and can also display chronic malnutrition in detecting and classifying malnutrition. According to Gomez, 18% of our cases had mild, 5.2% had moderate and 0.3% had severe malnutrition. According to Waterlow; 2.7% were evaluated as acute, 4.3% as chronic, 1.7% as acute malnutrition in the chronic base. In our country, according to the values determined by the Turkey Nutrition and Health Survey (TNHS) conducted in 2010, 10.3% of children under 5 years of age were lower weight and 5.6% were found to be have severe malnutrition (18).

When the values we found in our study were compared with the TNHS data, it was seen that the malnutrition rate was higher. Our study values' being higher than TNHS values can be resulted from the fact that the children in our sample were from the population with low socio-economic status.

In our study, we did not have any patients who were found to have malnutrition in the first 6 months, before starting additional food. The supplementary food onset is a critical period for childhood. Low birth weight, delay of baby's time to meet with breast milk, cesarean delivery, high income level, multiparity and use of pacifier are the factors that increase the tendency to start supplementary foods in the first 6 months. The early introduction of additional food causes decreased breast milk, thereby reducing the absorption of certain nutrients, especially iron. In newborns and infants whose digestive system is not fully developed, early switching to additional food increases the likelihood of allergies, especially to cow's milk.

Starting additional food late, as well as starting early, has a negative impact on the child's growth and development. Accordingly, problems such as slowing of growth and development,

Table 1. Distribution of cases by age and gender

	≤6 months		6-24 months		25 months-6 years		6 months-12 years		12 years-18 years	
	n	%	n	%	n	%	n	%	n	%
Girl	23	2.2	99	9.6	180	17.6	154	15	45	4.4
Boy	18	1.7	97	9.4	207	20.2	173	16.9	26	2.54
Total	41	4	196	19.1	387	37.8	327	32	71	7

Table 2. Distribution of malnutrition levels according to ages and Gomez classification of cases

Gomez	≤6 months		6-24 months		25 months-6 years		6 months-12 years		12 years-18 years		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Normal	38	3.7	140	13.6	316	30	247	24.1	53	5.1	794	76.5
Mild	1	0.1	47	4.7	64	7.6	50	4.8	9	0.8	171	18
Moderate	1	0.1	10	1	6	0.5	30	2.9	7	0.7	54	5.2
Severe	0	0	0	0	1	0.1	0	0	2	0.2	3	0.3
Total	40	3.9	197	19.3	387	38.2	327	31.8	71	6.8	1022	100

Table 3. Distribution of malnutrition types by age and Waterlow classification of cases

Waterlow	≤6 months		6-24 months		25 months- 6 years		6 years-12 years		12 years-18 years		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Normal	39	3.8	182	17.9	361	35.3	288	28.1	62	6	932	91.3
Acute	1	0.09	6	0.6	7	0.7	13	1.3	1	0.09	28	2.7
Chronic	1	0.09	4	0.4	14	1.4	18	1.7	7	0.7	44	4.3
Acute in the chronic base	0	0	3	0.3	5	0.5	8	0.8	2	0.2	18	1.7
Total	41	4	195	19.2	387	37.9	327	31.9	72	7	1022	100

Table 4. Distribution of cases according to relative weight

Relative weight >%110	Normal		Overweight		Obese		Total	
	n	%	n	%	n	%	n	%
<2 years	0	0	8	4.6	4	2.3	12	7
>2 years	31	18.1	50	29.2	78	45.6	159	93
Total	31	18.1	58	33.8	82	47.9	171	100

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malnutrition, various vitamin mineral deficiencies, immune deficiency, infectious diseases and micronutrient deficiencies may occur.

The frequency of malnutrition in non-sick children may differ among countries, even among cities in the same country. While the presence of malnutrition in healthy children in Turkey was reported between 15 and 25% in some studies (19-21), it was found between 2.2% and 14.9% considering cross-sectional studies on children below the age of 5 years in various cities in the study of Tezcan et al. (22) between 1989 and 1996.

In other countries, malnutrition rate was 31% mild, 9% moderate, and 1.6% severe in Jamaica (23), 7.4% acute and 60.7% chronic (24) in Nigeria, 16.5% acute and 38.2% chronic in North Korea (25). In a study conducted to investigate nutritional problems in a private school in Ankara, 15.1% malnutrition was found (26). The rate found shows that the frequency of malnutrition (20,21) determined between 1983 and 1993 is at similar levels in 2007. The frequency of malnutrition varies and increases with the different quality of life of the countries, poor diet habits and low education levels, variable population growth, poor nutritional distribution, and inadequate food quality and quantity. In addition, accompanying infections aggravate malnutrition.

Children's dietary habits are closely related to the country's nutritional culture. Obviously, obesity is found at increasing levels in pediatric patients in developed and developing countries. Various factors such as having familial predisposition, skipping meals, especially breakfast, having snacks between meals and lack of physical activity are seen to be effective in the development of obesity (27,28).

There are also differences in terms of frequency of obesity in children according to countries. However, it is seen that it is common to all countries that the rate of obesity increases in parallel with the increase in the level of development and the habits of consuming ready-to-eat food. Studies showing the increase in obesity rates in children are still insufficient (29). In our study, 16.8% (n=171) of the patients were above 110% according to the relative weight, 8% (n=82) were above the 95. percentile, that is, obese. While 60% (n=30) of overweight patients were male, 46.1% (n=36) of obese patients were male. In a study, among 4.260 children between the ages of 6-15 years in Muğla province, it was observed that the rate of overweight or obese ones was 7.6% in girls and 9.1% in boys (28).

In a study conducted in a private school with a high socio-economic level in İstanbul in 2003, the frequency of obesity was 8.4% and the frequency of overweight was 26.7% in 299 children aged between 6 and 15 years (30).

In a study performed in Ankara, in which 180 children between the ages of 1 and 11 years were included, it was found that 44.4% of males and 31% of females from 56 cases over 5 years of age were above normal weight values (31).

CONCLUSION

According to the results of our study, there is a high probability of detecting nutritional disorders among patients who apply to the outpatient clinic with any complaints. Malnutrition is a serious health problem for our country. Obesity is also increasingly seen in children. For this reason, anthropometric measurements of patients admitted to our polyclinic must be made and their nutrition must be questioned. We believe that the nutritional disorder rates will decrease by emphasizing the importance of breastfeeding, starting supplementary food with the right food at the right time and explaining the general nutrition rules to the families.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethic Committee of Taksim Training and Research Hospital (approval number: 11, date: 22.02.2017).

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

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Comparison of Short Segment Pedicle Screw Fixation Including the Fractured Vertebra Versus Long Segment Fixation in Thoracolumbar Fractures

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ABSTRACT

Objective: To compare the radiologic outcomes of short-segment fixation (SSF-P) with screw insertion into the fractured vertebra versus long-segment fixation (LSF), without fractured-level screw for the treatment of unstable thoracolumbar fractures.

Methods: Radiological parameters of 17 patients who had SSF-P or LSF for the treatment of unstable thoracolumbar fractures and had at least one-year fallow-up duration were retrospectively evaluated. Local kyphosis (LK) angle and anterior vertebral height (AVH) value were measured from the preoperative, early postoperative and follow-up radiographs; intergroup comparisons were performed.

Results: The mean age of the patients (male: 12, female: 5) was 50.1±12.8 years and the mean follow-up duration was 15.7±6.4 months. Fracture levels were L1 (n=8), L2 (n=5), T12 (n=2), L3 (n=1) and L4 (n=1). SSF-P was performed for 9 patients and LSF for 8 patients. The mean preoperative LK angles were 17.4±10.6° in the SSF-P group and 16.5±5.8° in the LSF group (p=0.83). In early postoperative measurements, the mean LK angles were 6.9±5.6° in the SSF-P group and 10.3±7.3° in the LSF group (p=0.14). In the follow-up evaluation, they were 8.8±5.8° and 12.0±7.2°, respectively (p=0.36). Preoperative mean AVH values were 72.4±14.5% in the SSF-P group and 56.4±14.8% in the LSF group (p=0.05). In early postoperative measurements, AVH values were 88.5±9.5% in the SSF-P group and 75.6±18.5% in the LSF group (p=0.13). In the follow-up evaluation, they were 86.6±11.3% and 69.1±19.5%, respectively (p=0.06).

Conclusion: Radiological outcomes of SSF-P were similar to LSF in the treatment of unstable thoracolumbar burst fractures. We recommend the SSF-P method, which provides a stable fixation without sacrificing mobile segments, in the treatment of unstable burst fractures.

Keywords: Thoracolumbar fracture, instrumentation, pedicle screw, trauma

INTRODUCTION

Posterior instrumentation with pedicle screws is the most commonly used method in the treatment of unstable thoracolumbar fractures. It is possible to detect all three columns of the spine and correct the deformity caused by the fracture without experiencing potential complications of anterior surgery (1). With the short segment posterior pedicle screw fixation short-segment fixation (SSF), it is aimed to protect the movable segments by placing screws on the upper and lower level of the fracture line. However, with this method, high rates of failure and related progressive kyphosis have been reported in many studies (2,3). While it is possible to provide a more stable fixation with long segment posterior pedicle screw fixation (LSF), movable segments are sacrificed (3).

In order to increase the stability of SSF, placing screws on pedicles in the broken spine is a method recommended in biomechanical

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studies (4,5). However, although successful results are generally reported in clinical studies, their effects on radiological and clinical results in the long term are not clear (6-8). The aim of this study is to compare the radiological results of SSF (SSF-P) applied by placing a pedicle screw on the broken spine with LSF.

METHODS

This study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013). Ethics committee approval was received for this study from the Ethics Committee of the Clinical Researches of University of Health Sciences, Taksim Training and Research Hospital (approval number: 121, date: 16.01.2019).

The records of patients who had posterior instrumentation due to unstable fractures of the thoracolumbar region in 2 different centers were reviewed retrospectively. Seventeen patients with no neurological deficit, fracture type A4 or B2 according to the AOSpine thoracolumbar fracture classification and at least 1-year follow-up were included in the study. Patients with multiple levels of fractures, neurological deficits and undergoing decompression were excluded from the study.

The demographic characteristics (age, gender, type of trauma) and clinical data (pre-and postoperative neurological conditions, complications) of the patients were recorded. Fracture morphology of patients who underwent direct radiographic imaging, computed tomography and magnetic resonance imaging before surgery were evaluated according to the AOSpine thoracolumbar fracture classification and load sharing classification (9,10).

Local kyphosis (LK) angle (wedge angle) and anterior vertebral height (AVH) values were measured by two independent surgeons on preoperative, early postoperative and final follow-up radiographs. LK angle is the Cobb angle value between the upper and lower surfaces of the broken vertebra in lateral X-ray. For the AVH, the anterior wall height of the broken vertebra was measured; this value was divided by the anterior height average of the adjacent vertebrae at an upper and lower level (6). The obtained value was recorded in percentage (Figure 1). Screw breakage, loosening and rod breakage were evaluated as implant failure.

Surgical technique: All patients in the study were applied posterior midline approach in prone position under general anesthesia. After checking the level of fracture under scopy, monoaxial and/or polyaxial pedicle screws were placed bilaterally. Fracture reduction was achieved with compression and distraction forces and using appropriate contoured rods. Local bone material was used for fusion.

Statistical Analysis

Microsoft Excel for Mac 2011 program was used for statistical evaluations. Preoperative, postoperative and follow-up values obtained by radiological measurements were given as mean ± standard deviation. The Student's t-test was used for statistical analysis. The degree of significance was determined as $p<0.05$.

RESULTS

Of the 17 patients, 12 were male and 5 were female. Their mean age was 50.1±12.8 years and mean follow-up time was 15.7±6.4 months. Nine patients had concomitant extremity, pelvis, and/or rib fractures. The fracture level was L1 in 8 patients, L2 in 5 patients, T12 in 2 patients, and L3 in one patient, and L4 in one patient. According to the AOSpine thoracolumbar fracture classification, 9 cases were evaluated as type A4, 8 cases were evaluated as type B2. According to the load sharing classification, while the mean score of all patients was 6.2±1.0, it was 5.5±0.5 in the SSF-P group and 6.0±1 in the LSF group (p=0.11). SSF-P was applied to 9 patients and LSF was applied to 8 patients (Table 1) (Figure 2, 3).

While the mean LK angle value before surgery was 17.4±10.6 degrees in the SSF-P group, it was 16.5±5.8 degrees in the LSF group (p=0.83). AVH value was measured as 72.4±14.5% in the SSF-P group and 56.4±14.8% in the LSF group (p=0.05). In the early postoperative period, the mean LK angle value was 6.9±5.6 degrees in the SSF-P group and 10.3±7.3 degrees in the LSF group. Decreased LK angle values observed in the postoperative period were statistically significant for both groups (p=0.003 and p=0.001). Significant improvements in AVH values were also observed. The mean value was 88.5±9.5% in the SSF-P group and 75.6±18.5% in the LSF group (p=0.01 and p=0.03). When the LK angle and AVH values between the SSF-P and LSF groups were compared in the early postoperative period, the differences were

Table 1. Details of patients' demographic and fracture features

	Age	Gender	Fracture level	AOSpine	Load sharing	Type of fixation
1	56	M	L3	A4	5	SSF-P
2	37	M	L2	B2	7	SSF-P
3	61	F	L2	A4	6	SSF-P
4	50	M	L1	A4	6	SSF-P
5	29	M	L4	A4	6	SSF-P
6	51	M	L2	B2	4	SSF-P
7	34	M	L1	B2	5	SSF-P
8	23	M	L1	A4	7	SSF-P
9	59	M	L1	A4	6	SSF-P
10	38	M	L2	B2	7	LSF
11	67	F	L1	B2	7	LSF
12	61	M	L2	A4	7	LSF
13	61	F	L1	B2	7	LSF
14	58	F	L1	A4	7	LSF
15	51	M	T12	B2	8	LSF
16	50	F	T12	B2	5	LSF
17	65	M	L1	A4	5	LSF

M: Male, F: female, SSF: short-segment fixation, LSF: fractured-level screw

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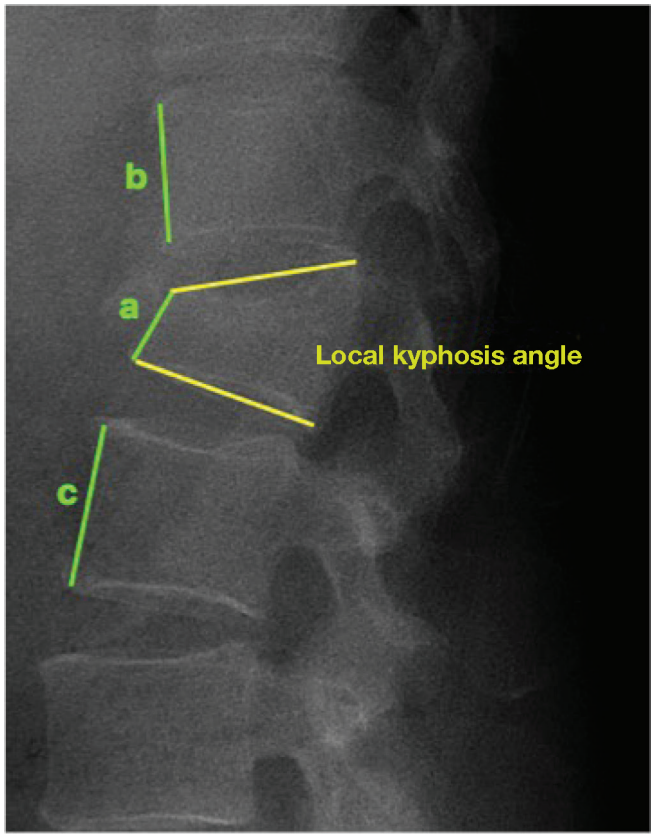

Figure 1. Values measured on the lateral graph a: Local kyphosis angle: Cobb angle between the upper and lower surfaces of the broken vertebra b: Anterior vertebral height (%): a/[(b+c)/2] x100

not statistically significant (p=0.14 and p=0.13) (Table 2).

The LK angle values measured in the last follow-up graphs of the patients were 8.8±5.8 degrees in the SSF-P group and 12.0±7.2 degrees in the LSF group. These increases observed according to the early postoperative values were found statistically significant (p=0.006 and p=0.001). In follow-up radiographs, AVH value was measured as 86.6±11.3% in the SSF-P group and 69.1±19.5% in the LSF group. Changes in these values were not significant for both groups compared to the early postoperative period (p=0.05 and p=0.09). When the LK angle and AVH values measured in the last follow-up graphs in the SSF-P and LSF groups were compared, the differences were not statistically significant (p=0.36 and p=0.06) (Table 2).

Neurological complications and implant failure did not develop in any patient in the postoperative period. One patient had superficial infection, which was treated with local wound care and antibiotics, and one patient had a resistant infection that required removal of the implants in the late period.

DISCUSSION

Our study reveals that in unstable thoracolumbar burst fractures, the radiological results of SSF and LSF applied with the insertion of screws to the pedicles at the broken level are not different in the early postoperative and mid-term follow-up.

Table 2. Comparison of radiological data between groups

	SSF-P	LSF	p
Local kyphosis angle (°)			
Preop	17.4±10.6	16.5±5.8	0.83
Postop	6.9±5.6	10.3±7.3	0.14
Follow-up	8.8±5.8	12.0±7.2	0.36
Anterior vertebra height (%)			
Preop	72.4±14.5	56.4±14.8	0.05
Postop	88.5±9.5	75.6±18.5	0.13
Follow-up	86.6±11.3	69.1±19.5	0.06

SSF: Short-segment fixation, LSF: fractured-level screw

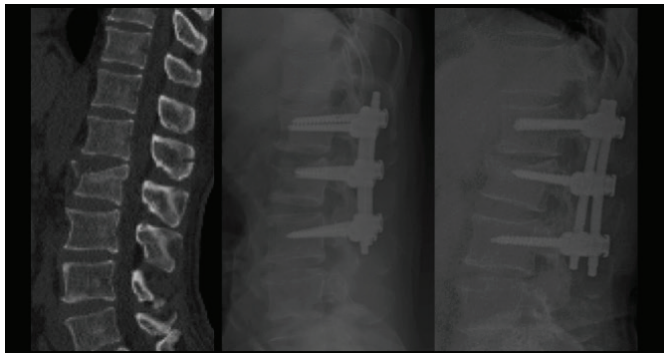

Figure 2. Preop, early postoperative and 12th month follow-up images of a 51-year-old male patient with an L2 burst fracture (AOSpine type B2, load sharing score 4)

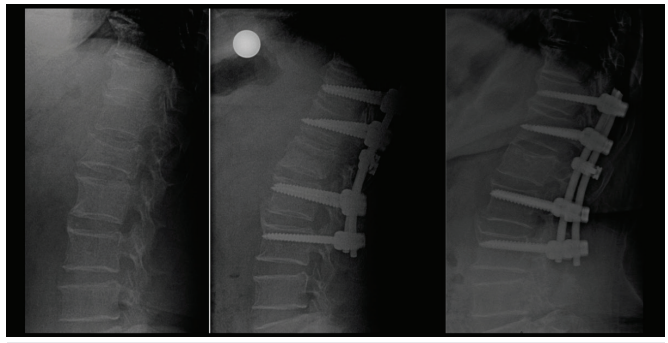

Figure 3. Preop, early postoperative and 18th month follow-up images of a 58-year-old woman with L1 burst fracture (AOSpine type A4, load sharing score 7)

Our results are compatible with similar studies in the literature. In the study of Pellisé et al. (6), evaluating the radiological results of 72 patients, they reported that 6-screw fixation was sufficient for the treatment of burst fractures of the thoracolumbar region. In patients with load bearing scores ≥7, they detected an increase in LK angle less than 5° in the first 6 months. In our study, LK angle values in both the SSF-P and LSF groups increased by 1.9 and 1.7 degrees, respectively, compared to the early postoperative period in the last follow-up graphs. This increase was found statistically significant. Changes in AVH values were not found significant. However, there was no significant difference in the follow-up LK angle values of both groups with similar load bearing scores.

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Kanna et al. (7) reported that even reductions of unstable fractures with load sharing scores ≥7 could be successfully achieved and maintained by SSF-P. In the recent follow-up graphs, they detected an increase of approximately 1.2° in the LK angle.

Farrokhi et al. (11) compared SSF-P and SSF results, and they reported that instrument insufficiency was more frequent with SSF, kyphosis could be corrected better with SSF-P, and clinical results were similar.

Guven et al. (12) reported in the series of 72 cases that, in the treatment of thoracolumbar burst fractures, kyphosis could be better corrected and protected by short or long segment screw fixation placed at the level of the fracture. They emphasized that this effect was more pronounced with SSF-P. Dobran et al. (13) compared SSF-P with LSF in thoracolumbar transition region fractures, and they reported that LK could be corrected with SSF-P similar to LSF and sagittal alignment could be maintained. In our study, no implant failure was observed in the SSF-P and LSF groups. Improvements in LK angle and AVH values were found significant in both groups. When the postoperative values were compared between the groups, improvements in LK angle and AVH value were obtained in the SSF-P group, similar to the LSF group. No significant difference was found between the radiological values measured in the follow-up radiographs.

The fact that our study is based on radiological parameters and does not include clinical results of patients can be considered as its weakness. The retrospective character of the study did not make this evaluation possible. Another weakness is that the number of patients is relatively low. The fact that it included only certain types of burst fractures and relatively rare fixation types was considered as the reason for this situation.

CONCLUSION

In unstable thoracolumbar burst fractures, radiological results similar to long segment pedicle screw fixation were obtained with short segment posterior pedicle screw fixation applied by placing a pedicle screw on the broken spine. We think that this method, which makes it possible to obtain a stable fixation without sacrificing the mobile segments, should be preferred in the treatment of unstable thoracolumbar burst fractures.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Clinical Researches of University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital (approval number: 121, date: 16.01.2019).

Informed Consent: This is a retrospective study.

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The Comparison of Adjustable Single-incision Mini Sling and Transobturator Tape for the Treatment of Stress Urinary Incontinence

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ABSTRACT

Objective: The aim of the study was to compare the efficacy and complications of adjustable single-incision mini-sling (A-SIMS) with transobturator tape (TOT) in surgical management of female urinary incontinence.

Methods: The results of 54 patients performed A-SIMS and TOT were evaluated retrospectively. Inclusion criteria were stress urinary incontinence with valsava leak point pressure <60 cm H2O and at least one-year follow-up. Exclusion criteria were pelvic organ prolapsus, concominant or previous genitourinary surgery and patients without urodynamic assessment. Patients were enrolled into two groups as A-SIMS and TOT, each group included 27 patients. Results of the operations (postoperative hemoglobin decrease, operation time, perioperative complication, urinary retention, postoperative pain) and efficacy of the surgery (objective cure rate, subjective cure rate, failure rate) were compared.

Results: Both of the groups were similar according to the patients characteristics. The mean follow-up period was 21.5 and 17.7 months in TOT and A-SIMS groups, respectively. The difference between the two groups according to objective cure rate, subjective cure rate and failure rate was not statistically significant. Postoperative hemoglobin decrease and operation time in the A-SIMS group were significantly lower than in the TOT group. Five patients had postoperative pain in the TOT group. However, no pain was revealed in the A-SIMS group. Besides, no perioperative complication was revealed in both of the groups.

Conclusion: In short-term period, A-SIMS is as effective and safe as TOT in the surgical management of female urinary incontinence. However, A-SIMS may be superior as a simple procedure having shorter operation time.

Keywords: Mini-sling, tot, stress urinary incontinence

INTRODUCTION

Stress urinary incontinence (SUI) complaint is defined as involuntary urinary incontinence with exertion, exercise, sneezing or coughing (1-3). Urinary incontinence in women causes distress and negatively affects their daily lives. Urinary incontinence incidence varies between 10 and 40% (4,5). This problem affecting approximately 50% of incontinent women all over the world is primarily treated conservatively and medically (6). However, failed conservative treatments often make surgical treatment necessary. Surgical treatment is somewhat developed and aimed at correcting urethral hypermobility that causes SUI (7). Incontinence is more common in older women than in younger women (4). Obesity and childbirth are seen as general risk factors in SUI (8,9). Stress is the gold standard midurethral sling operation in the treatment of urinary incontinence and has a cure rate of 70-90% when considering the long-term results (10). Transobturator tape (TOT), tension-free vaginal tape (TVT) or adjustable single-incision mini-sling (A-SIMS) can be successfully applied according

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to the experience and choice of the surgeon who will apply them as surgical treatment options in SUI treatment (10-12). These surgical procedures can be performed with the approach from the rertopubic region or with the transobturator approach (13). Although sling operations are performed retrobupically and they are minimally invasive procedures, all of these surgical procedures involve complications in the intraoperative or postoperative period (14). During retropubic procedures, voiding dysfunction, bladder injury, and vascular injury can occur. In the transobturator approach, risks in reropubic processes can be avoided, while more pain arises (13).

SIMS are at the last point in the search for safe and effective minimally invasive surgery. In the first SIMS (MiniArc), the braid, which is shorter than the midurethral sling, is inserted through a single vaginal incision and bilaterally binded to the obturator muscle (such as Ajust, Altis, TFS). The latest developed Adjustible SIMS (A-SIMS) are designed without anchors (such as Contasure, Ophira). Because the SIMS are less invasive and easier to apply, while outpatient approach, short operation and recovery time and fewer perioperative complications are expected, its superiority to standard MUSs (TVT, TOT, TVT-O) in terms of efficacy and safety has not been clarified in the literature (11,15,16).

When the studies comparing TOT and mini sling operations are examined, it is seen that both methods are successful in preventing SUI, while less invasive procedure with mini-sling and therefore lower pain and complaints are reported in the postoperative period (9).

We also aimed to evaluate the efficacy and safety of contasure-needleness application, a new generation A-SIMS, in patients undergoing surgery for SUI, by comparing it with TOT application with the literature.

METHODS

Study Group

A total of 54 patients, including 27 patients who received TOT for SUI in the gynecology service of our hospital between March 2015 and April 2017 and 27 patients who underwent A-SIMS, were included in the study. Ethics committee approval was not obtained since the required data were obtained by retrospectively examining patient records.

In the urodynamic evaluation of all operated patients, valsava leak point pressure <60 cm H_2O and at least 1-year postoperative follow-up were determined as inclusion criteria. Informed consent was ontained. Genital prolapse, concomitant or previous genitourinary surgery, and the absence of preoperative urodynamic evaluation were accepted as exclusion criteria.

Age, parity, body mass index (BMI), type and number of births, if any, smoking and menopausal status of all patients were evaluated as patient characteristics.

Hemoglobin levels before and after the operation, operation and hospitalization times, perioperative complications, urinary retention after operation, and postoperative pain information were evaluated as the results of the application.

In order to evaluate the effectiveness of the application, the objective treatment, subjective treatment, and inadequate treatment criteria recorded in the patients' most recent controls (16-30 months) were used. Objective therapy was defined as the negative cough stress pad test (CSPT) and bladder volume of 150 cc and above, and subjective treatment was defined as CSPT positive and bladder volume less than 150 cc. Continuation of incontinence was accepted as inadequate treatment.

The authors declared that the study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Surgical Technique

All operations were performed under spinal anesthesia and by two different surgeons. In TOT application, with Supro SUI (Klas Medikal, Turkey), one side of the groin was inserted with the aid of a 1.2 cm wide monoflament polypropylene knitting needle, using standard outward-inward technique. The obturator foramen was passed and it was placed in the periurethral area prepared previously. The other end of the knitting was taken out of the other groin in the same way. The knitting ends were cut under the skin to allow tension-free application. A-SIMS application was performed as described by Petros and Richardson (17). In A-SIMS, the knitting is the same type but shorter and is applied through a single vaginal incision. The contasure-needleness (Neomedic Int., Spain) sling used in this study has no anchor and has facial pockets on both ends that provide post-insertion stabilization.

Statistical Analysis

SPSS v. 16.0 package program (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of the data. The normal distribution of data in both groups was evaluated with the Kolmogorov-Simirnov test. Comparison of numerical data with normal distribution between groups was performed with the Student's t-test and comparison of non-normally distributed numerical data was performed by using the Mann-Witney U test. The chi-square test was used for categorical variables. Average and standard deviation values of both groups were calculated separately. Values of $p<0.05$ were considered statistically significant.

RESULTS

Demographic data of 54 patients included in the study are shown in Table 1. There was no significant difference between the groups in terms of age, BMI, parity, menopausal status and smoking. When we evaluated the ages of the patients, the mean age of the A-SIMS group was 47.41±10.89 years, while the mean age of the TOT group was 52.22±10.98 years. While the mean age was higher in the TOT group, the difference between the groups was not found to be statistically significant (p=0.112). When the parity numbers of the patients were analyzed, it was 3.26±1.99

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in the mini-sling group and 2.74±2.29 in the TOT group. In both groups, the number of births of the patients was more than 2, but the difference between the groups was found to be statistically insignificant after comparing the groups (p=0.380). Vaginal delivery in the TOT group was higher than in the A-SIMS group. In the A-SIMS group, cesarean delivery was higher than in the TOT group.

When the operation results were evaluated in both groups, the operation time was found to be significantly shorter in the SIMS group (p<0.001). Similarly, the decrease in postoperative hemoglobin was found to be significantly higher in the A-SIMS group (p<0.007). In the TOT group, 3 patients had urinary retention and 5 patients developed early postoperative groin pain. No other perioperative complications developed in both groups. No significant difference was found between the groups in terms of length of stay (Table 2).

The effectiveness of the treatments applied was evaluated by the examination performed at the last control of the patients. The shortest follow-up was 16 months, and the longest was 30 months. The mean follow-up time was 21.5 months in the TOT group and 17.7 months in the A-SIMS group. When we evaluated the objective treatment, subjective treatment, and inadequate treatment rates, it was found that there was no significant difference between the two groups (Table 3).

Table 1. Demographic data of patients

	A-SIMS** (n=27)	TOT*** (n=27)	p
Age	47.41±10.89	52.22±10.98	0.112
BMI****	30.00±4.53	28.92±6.03	0.461
Parity	3.26±1.99	2.74±2.29	0.380
Vaginal delivery	21 (77.8%)	26 (96.3%)	**0.043***
Caesarean	6 (22.2%)	1 (3.7%)	**0.043***
Post menopause	13 (48%)	16 (59.3%)	0.115
Smoking	12 (54.5%)	10 (45.5%)	0.413

*p<0,05, **A-SIMS: adjustable single-incision mini-sling, ***TOT: transobturator tape, ****BMI: body mass index

Table 2. Operative results

	A-SIMS** (n=27)	TOT*** (n=27)	p
Duration of operation (minutes)	15,81±3,58	25.41±6.82	<0.001*
Length of hospitalization (day)	2,85±0,90	3.52±1.52	0.057
Perioperative complication	0	0	-
Decreased postoperative hemoglobin level (g/dL)	1,31±0,60	1.78±0.61	0.007*
Urinary retention	0	3 (11.1%)	0.075
Postoperative pain	0	5 (18.5)	0.019

*p<0,05, **A-SIMS: adjustable single-incision mini-sling, ***TOT: transobturator tape

DISCUSSION

In our study, TOT and A-SIMS procedures applied to patients with urinary incontinence due to SUI were evaluated. When the data of our study were evaluated, the superiority of both methods to each other could not be determined statistically in the comparison of the A-SIMS procedure and the TOT procedure. In the literature, many studies evaluating patients undergoing anti-incontinence surgery due to SUI have been conducted (18,19). In a study by Pascom et al. (2), 130 women undergoing mini-sling (SIMS) and TOT operations from a single incision were followed up for 36 months. In the study, they determined that both surgical procedures had a similar effect in improving the quality of life. In the study, they also determined that the mini-sling operation required more revision procedures compared to the TOT operation. In addition, after 3-year follow-up in the group of patients who underwent TOT, they determined less persistence in SUI. As a result, they reported that although both groups had similar satisfaction rates for surgery in the postoperative 36-month follow-up, TOT operation had higher treatment rates in SUI compared to A-SIMS operation.

In our study, TOT and A-SIMS were applied to patients with similar characteristics (age, BMI, number of vaginal births) as SUI surgery, the results of the patients were evaluated, and no statistically significant difference was found regarding the results of both groups.

In a study by Schellart et al. (14), 225 patients who underwent mini-sling and TOT were followed for 24 months and the results of the patients were compared with each other at the end of the study. The study was started with 225 patients, and 32 patients refused to participate in the study and the study continued with 193 patients. 20 patients after the first year follow-up and 32 patients after the second year of follow-up were excluded. The study ended with 141 patients. The age, BMI, parity and postmenopausal status of the patients were evaluated and no difference was found between the groups. In the study, the treatment rates of TOT and mini-sling patients were similar in the first and second years, and the side effects were similar. In the study, the superiority of TOT or mini-sling to each other could not be determined after 2 years. In our study, we could not determine the superiority of both methods to each other.

In a meta-analysis by Zhang et al. (9), they compared mini-sling and TOT surgery in female SUI surgery. In the study, 154 studies were evaluated and meta-analysis was completed with 5 randomized controlled studies. As a result of the study, they found that the mini-sling operation was safe and effective in SUI in women. In

Table 3. Effectiveness of treatment

	A-SIMS* (n=27)	TOT** (n=27)	p
Objective therapy	25 (92.6%)	23 (85.2%)	0.386
Subjective therapy	3 (11.1%)	2 (7.4%)	0.639
Inadequate therapy	1 (3.7%)	1 (3.7%)	0.755

*A-SIMS: Adjustable single-incision mini-sling, **TOT: transobturator tape

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comparison with TOT and TVT, they stated that they had the same rate of treatment effects and that there were few perioperative complications. In addition, although they reported that mini-sling operations caused shorter operation time and less pain in meta-analysis, they reported that the studies had short follow-up time and the results should be examined again by having a longer follow-up time. Our study also showed that there was no difference between A-SIMS and TOT procedures in women operated for SUI, as in meta-analysis by Zhang et al. (9).

In the review of Nambiar et al. (20), which included 3290 women and 31 studies, they compared A-SIMS and transobturator or retropubic sling operation. They reported in the review that there was not enough evidence to show that both operations were better than each other, and studies involving longer periods should be done. They also stated clearly that the difference in fixation mechanisms desired to be achieved by operation might affect success. Our study also shows similar results.

In our study, patients with BMI 30 and below were evaluated. There are also studies in the literature evaluating anti-incontinence surgeries applied to obese patients (BMI >30) with SUI. In a study conducted by Kokanalı et al. (21), TOT and TVT performed for SUI were divided into two groups as obese and non-obese and the results of the surgery were compared. TOT was applied to 69 obese (31 patients) and non-obese (38) patients in the study; TVT was applied to 120 obese (62 patients) and non-obese (58 patients) patients. As a result of the study, successful results were obtained in both obese and non-obese women with TOT and TVT procedures. Considering the short term results, they determined that they were successful in obese women with SUI. They reported that they achieved similar and successful results in obese and non-obese groups although voiding dysfunction and bladder injury were slightly observed as a complication, but a little more in the TVT group.

There are also studies evaluating pain after TOT and mini-sling operations. In a study by Thomas et al. (13), data from 597 patients were evaluated and the timing of pain and resolution after the transobturator and retropubic sling operation were evaluated. They determined that suprapubic pain was more frequent in transoburator operations, and groin pain was higher in retropubic operations, but they did not find a difference among pain caused by surgery, pain intensity, and drug use for pain.

In the literature, there are also studies involving surgical application and results for SUI, which occurred during pregnancy and continued in the postpartum period. Twelve female patients were evaluated in a study conducted by Cavkaytar et al. (4) As a result of the study, they stated that the SUI with ongoing postpartum was independent of the way of delivery. They reported that patients with urinary incontinence during pregnancy might be a risk factor for incontinence seen after delivery.

In recent studies, successful results have been obtained by applying TOT or TVT procedure in cases where medical treatment fails in women with mixed urinary incontinence other than SUI (22).

In our study, after 1-year follow-up of the patients, the objective and subjective treatment rates in the A-SIMS group were higher than the TOT group (92.6%-11.1% versus 85%-7.4%), but there was no statistically significant difference between the two groups. Our results are similar to the study done by Sivaslıoglu et al. (15) In this study, the objective treatment rates obtained at the end of the 3-year follow-up in the TOT and A-SIMS (TFS) groups were reported as 90% and 84%, respectively, and no statistically significant difference was found.

In the first studies comparing SIMS and traditional MUSs, SIMSs were found to be lower according to objective treatment rates (11). However, these studies included third generation MUSs, called TVT-secure, that were withdrawn from the market in 2013 due to poor clinical results. After that, promising results were obtained in studies that excluded TVT-secure (16,23). In two separate meta-analyzes (6.9) that included five randomized controlled trials comparing A-SIMS and MUSs in 2015 and eight studies in 2018, A-SIMS was reported to be as effective as MUS when considering short-term results (12 months).

This result may be due to the fact that both techniques were developed with the same surgical principle. However, it has been reported that SIMS application does not show perioperative complications in standard MUS applications and its operation time is shorter because it is less invasive and easy (9).

In our study, shorter operation times ($p<0.001$) and higher postoperative hemoglobin decrease ($p=0.007$) were found statistically significant in the A-SIMS group. Although the duration of hospitalization in the A-SIMS group was shorter, there was no statistically significant difference in terms of length of stay between the two groups ($p=0.057$). Perioperative complications did not develop in both groups.

In TOT application, bladder, obturator nerve and vessels can be injured during the transition from obturator foramen. Similarly, passage through the adductor tendons and skin is thought to cause postoperative groin and thigh pain (13). In the literature, it has been reported that postoperative pain formation with SIMS is much less than transobturator slings (14). The absence of transition from the obturator foramen and exit from the skin in SIMS application prevents these complications and reduces the possibility of postoperative pain.

In our study, postoperative groin pain was observed in 5 patients (18.5%) in the TOT group. In addition, although 3 patients (11.1%) developed postoperative urinary retention, pain and urinary retention were not observed in the A-SIMS group.

Considering the limitations of our study, it is remarkable that it is retrospective and the number of cases is not very high. However, the fact that the data of the study are single-centered and that surgical procedures are performed by the same surgeons are among the advantages of our study.

CONCLUSION

A-SIMS or TOT procedures applied in the treatment of SUI are successful and have not been proven to be superior to each other.

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Although advantages such as the mini-sling procedure's being less invasive and short length of hospital stay are short, we are of the opinion that patient-related risks should be discussed before decision-making for the selection of surgical procedure and type in addition to the experience of surgeon.

Ethics Committee Approval: Ethics committee approval was not obtained since the required data were obtained by retrospectively examining patient records.

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - S.K.; Concept - T.Ç.; Design - Me.T.; Supervision - B.Ç.; Resources - B.Ç.; Data Collection and/or Processing - M.T.; Analysis and/ or Interpretation - T.Ç.; Literature Search - A.E.Y.; Writing Manuscript - S.K., M.T., T.Ç., M.T., A.E.Y.

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

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Is the Probiotic Mixture Effective in the Treatment of TNBS-induced Experimental Colitis?

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ABSTRACT

Objective: Inflammatory bowel disease (IBD) is an idiopathic disease associated with changes in the immune system and in the intestinal microbiota. The most accepted hypothesis of IBD pathogenesis is thought to be the abnormal immunological response and chronic intestinal inflammation, which is caused by the complex interactions between genetic, environmental factors and the host immune system. Microbial flora is important in the maturation of the immune system. Dysbiosis is defined as changes in intestinal microbiota composition and function. Clinical and experimental studies support that dysbiosis plays a significant role in the etiopathogenesis of IBD. Probiotics are useful live microorganisms that provide the intestinal balance in the host.

In this study, we aimed to evaluate the anti-inflammatory and anti-oxidant activities of *Enterococcus faecium, Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium bifidum* and *Bifidobacterium longum* bacteria in the experimental colitis model.

Methods: Twenty-four female Wistar-Albino rats and 30 mg 0.5 mL trinitrobenzenesulfonic acid (TNBS) dissolved in 50% ethanol which induced colitis by intrarectal installation. Rats were divided into four groups; healthy control (sham: group A), TNBS colitis (group B), (TNBS + methylprednisolone: group C) and probiotic (TNBS + P: group D). The rats were sacrificed on the 8th day. Macroscopic and microscopic scores, tissue myeloperoxidase (MPO), malondialdehyde (MDA) and superoxide dismutase (SOD) levels were measured.

Results: Macroscopic and microscopic scores levels in group A were significantly lower than in group B, C and D. Macroscopic and microscopic scores levels in group C were significantly lower than in group B. Macroscopic scores were statistically similar between group C and D. There was a statistically significant difference between the groups in terms of median MDA levels and median SOD levels ($p<0.001$). There was no statistically significant difference between the groups in terms of median MPO levels ($p=0.114$). Median MPO levels were 0.27 (0.15-0.30) in group A, 0.44 (0.22-0.61) in group B, 0.28 (0.25-0.50) in group C, and 0.30 (0.25-0.37) in group D ($p=0.114$). Median MDA levels were 1.1 (1.0-2.8) in group A, 4.3 (3.1-5.5) in group B, 3.8 (3.2-4.2) in group C, and 3.9 (3.1-4.2) in group D ($p<0.001$). Median SOD levels were 160.7 (150.1-161.7) in group A, 141.6 (137.9-147.3) in group B, 157.6 (155.2-167.7) in group C, and 164.7 (160.3-168.3) in group D ($p<0.001$). MDA levels were statistically significantly different between each group. These levels were significantly higher in group B, C and D than in group A; statistically similar in group C and D; and statistically higher in group B than in group C and D ($p<0.001$ & $p=0.047$). SOD levels were statistically significantly different between each group. They were significantly lower in group B, C and D than in group B; statistically significantly different in group A, C and D; and statistically higher in group D than in group A and C.

Conclusion: Our study showed that probiotics regulate the balance between anti-oxidant and oxidant systems. Therefore, probiotics can be used as a supportive treatment in inflammatory bowel diseases if promoted by clinical trials.

Keywords: IBD, MDA, MPO, SOD, probiotics

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INTRODUCTION

Probiotics are useful living microorganisms that provide intestinal balance in the host where they are located. The gastrointestinal tract is the colonization site of millions of beneficial or harmful bacteria. Because of its acidic fluid and protective secretions, the stomach contains a small number of bacteria, but certain types of bacteria migrate through the gastrointestinal tract and settle in the intestines, especially the colon (1). 20% of faeces are bacteria mostly from the colon. Bacteria make up most of the flora and more than 60% of the dry weight of the faeces in the columns of normal people. The main bacterial species in the colon are *Lactobacillus, Bifidobacterium, Eubacterium, Streptococcus, Coliforms, Clostridium* and Saccharomyces. A healthy individual has about 100 trillion bacteria in their intestines. Although they are widely consumed with yogurt and fermented foods in the world, it is found and used in different forms such as various dietary supplements and functional foods (2). The microbial flora contributes to the maturation of the immune system and to the formation of the ability to recognize and destroy pathogenic microorganisms taken from food and from outside. It has an important role in the formation of colonic morphology and control of continuous inflammatory response. By creating a barrier to the colonic mucosa, it prevents the entry of microorganisms and allergens into the body (3,4).

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases. It has two major types, ulcerative colitis and Crohn's disease. About 3.5 million people are affected in Europe and the United States. Although the incidence of both diseases has increased all over the world, their etiologies remain uncertain and no treatment method providing cure has yet been found (5). The accepted hypothesis of IBD pathogenesis is that complex interactions between genetics, environmental factors and the host immune system lead to abnormal immune responses and chronic intestinal inflammation. Dysbiosis has been described as changes in intestinal microbiota composition and function. Clinical and experimental studies support that dysbiosis plays an important role in the etiopathogenesis of IBD (6). Recently, the replacement of the intestinal microbiota composition with probiotics or fecal transplantation has been the focus of attention among the supportive and therapeutic methods.

In this study, it was aimed to evaluate the anti-inflammatory and antioxidant activities of the bacteria of *Enterococcus Faecium, Lactobacillus Acidophilus, Lactobacillus Rhamnosus, Bifidobacterium Bifidum, Bifidobacterium Longum* in the experimentally created colitis model and the treatment success of probiotics compared to steroid.

METHODS

This study was carried out in Gazi University Faculty of Medicine Experimental Animals Laboratory. Pathological examinations were carried out in Gazi University Faculty of Medicine, Department of Pathology. In this study, a total of 24 Wistar-Albino female rats with the weight of 200-250 grams were used. All animals were fed with standard feed and water before the experiment.

Four different groups were created with 6 rats in each group. The animals were kept in standard humidity, light (12 hours daylight/12 hours dark) and heat conditions (22-24 °C) during the experiment and fed with standard rat food. Wire pads were placed inside the cage to prevent coprophagy. Rats were placed in single cages to determine the amount of food and liquid consumed by each rat. Weights of the rats were recorded every day throughout the study to determine weight changes.

Anesthesia to the rats was provided by injecting intramuscular Ketaminehydrochloride (Ketalar, Parke Davis and Eczacıbaşı, İstanbul) at a dose of 50 mg/kg + Xylazinehydrochloride (Rompun, Bayer HealthCare) at a dose of 5 mg/kg. To create experimental colitis, a mixture of 30 mg (80 mg/kg) trinitrobenzenesulfonic acid (TNBS) (92823, picrylsulfonicacidsolution) + 50% ethanol was used. TNBS was purchased from Sigma (Sigma, La Verpaille-re, France).

Group A (n=6): Sham group; The group receiving intrarectal 2 mL of saline for 7 days,

Group B (n=6): The group developing colitis with TNBS and receiving no treatment,

Group C (n=6): The group given oral Prednisol 2mg/day 24 hours after the development of colitis with TNBS,

Group D (n=6): Twenty-four hours after the development of colitis with TNBS, 1 sachet of oral probiotic per day (*E. Faecium, L. Acidophilus, L. Rhamnosus, B. Bifidum, B. Longum* were given as 3 doses a day with gavage for 7 days.

Monitoring the symptoms: After the animal model was established, rat feces were collected daily. The overall condition of the rats including feces, blood, activity, fur, food intake, and weight was observed.

Surgical method: After anesthesia, which was achieved by applying 50 mg/kg ketamine + 5 mg/kg xylazine intramuscularly, laparotomy was performed with xifopubic median incision in the colitis models and control group, and exploration was performed. Subsequently, transection was performed from the distal of the rectum from the middle of the transverse colon at the lowest possible level and approximately 10 cm colon segment was removed. The removed colon tissue was divided into two equal parts longutidinally. A part of the column sample was detected in 10% formaldehyde. The other half was stored in -80 °C freezer (Sanyo MDF-U70V) until the day of the procedure. Under deep anesthesia (ketamine 45 mg/kg + xylasin 5mg/kg IM intracardiac), 5 cc blood was collected and the rats were sacrificed.

Histopathological Examination Methods

Macroscopic evaluation: Following the longitudinal opening of the removed intestinal sections, they were rapidly washed with normal saline and their macroscopic scorings were done by a pathologist blinded to the groups and treatment for each subject

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individually, as described by Millar et al. (7) and group averages were calculated.

0 = normal mucosa,

1 = mucosal erythema only,

2 = mild mucosal edema, minor bleeding or minor erosions,

3 = moderate edema, bleeding ulcer or erosion,

4 = severe ulcer, erosion, edema and presence of tissue necrosis.

Microscopic evaluation: Colon segments fixed in 10% formalin were embedded in paraffin blocks. Sections taken from these blocks with a thickness of 5 µ were stained with hematoxylin-eosin. The prepared preparates were examined for the groups by a blind pathologist under the light microscope and microscopic scoring was performed. The scoring system used by Ackerman et al. (8) was modified and calculated separately for each animal and the average score of each group was obtained.

A: Necrosis depth: none = 0; mucosal = 1; mucosal and submucosal = 2; mucosal, submucosal and muscularispropria = 3; in the entire colon wall = 4,

B: Width of necrosis: none = 0; a small area = 1; a moderate area = 2; a large area = 3; common = 4,

C: The degree of inflammation: none = 0; minimal = 1; mild = 2; moderate = 3; serious = 4,

D: Width of inflammation: none = 0; mucosal = 1; mucosal and submucosal = 2; in mucosal, submucosal and muscularispropria = 3; in the entire colon wall = 4.

Preparation of Tissues for Tissue Myeloperoxidase Activity and Myeloperoxidase Measurment

It is based on the oxidation of H_2O_2 by homogenate and the reduction of O-dianicide and measuring the reduced O-dianicide at 410 nm. 130 mg intestinal mucosa was homogenized with 1.3 mL cold 20 mM EDTA. 1 mL of the homogenate is taken and placed in eppendorf tubes and centrifuged at +4 degrees for 15 minutes at 20.000 g. Supernatant was discarded and it was sonicated for 60 seconds with PELLET 1.3 mL of 50 mM buffer (pH 6), then centrifuged again at +4 degrees at 20.000 g for 15 minutes. The supernatant was transferred to new eppendorfs. The myeloperoxidase (MPO) level was studied from this supernatant. Optical density at 410 nm was read against the blind. That occurring at 1 Unit = min at 37 °C was accepted as optical density change. Specific activity was evaluated as = U/g tissue.

Malondialdehit Level, Homogenizing Tissue Samples for Superoxide Dismutase Activity

Tissue samples were homogenized in ice with 1/10 phosphate buffer saline (pH: 7.4) in cold. Homogenates were centrifuged at 15.000 rpm for 15 minutes in a cooled centrifuge, and tissue malondialdehyde level and tissue superoxide dismutase (SOD) activity were determined from supernatants.

Intestinal Tissue Malondialdehyde Analysis

Tissue malondialdehyde (MDA) levels were determined according to the method described by Ohkawa et al. The principle of this method; After the binding of the homogenate proteins with sodium dodecyl sulfate, the MDA in the sample was performed according to the spectrophotometric measurement of the red color connected to the complex formed by thiobarbituric acid under ambient pH of 3.5.

Superoxide Dismutase Analysis in Colon Mucosa Tissue

The SOD activity was measured spectrophotometrically by this color intensity, as defined by Yi-Sun, by the formation of $O_2^{\cdot}$- with xanthinxanodinoxidase and forming a colored compound with NBT. The greater the SOD activity in the environment, the less the intensity of the resulting color will be, since it will eliminate $O_2^{\cdot}$-'.

Statistical Analysis

Statistical analysis of the data was done using SPSS v.17.0 (SPSS, Inc., Chicago, IL, USA) software. The Kruskal-Wallis test and Mann-Whitney Utest were used as post-hoc tests for the analysis of macroscopic scores, microscopic scores and biochemical parameters between the groups. Data were expressed as mean ± standard deviation. The means of the variables in the groups were drawn by selecting Boxplot. The value of $p<0.05$ between the results was considered statistically significant.

RESULTS

In group A, there was no weight loss, color change in feathers and stool changes in rats, and food intake was normal during the experiment. After the development of the animal model, decreased appetite, increased stool frequency, bloody stool, and coarse hairy appearance were observed in group B, C, and D.

There was no statistically significant difference between the groups in terms of median MPO levels ($p=0.114$).

There was a statistically significant difference between the groups in terms of median MDA levels ($p=0.002$). When the factors causing this difference were examined, it was found that the median MDA levels of group B, C and D were statistically higher compared to group A ($p<0.001$). At the same time, the median MDA levels of group C and D were statistically lower than group B ($p<0.001$ and $p=0.047$). The median MDA level of group D was statistically higher than group C ($p=0.047$) (Figure 1, 2).

There was a statistically significant difference between the groups in terms of median SOD levels ($p<0.001$). When the conditions causing the difference in question were examined, it was found that the median SOD level of group B was statistically lower compared to group A and the median SOD level of group D was statistically significantly higher ($p<0.001$). At the same time, the median SOD levels of group C and D were statistically higher than group B ($p<0.001$). The median SOD level of group D was statistically higher than group C ($p<0.001$). The median SOD

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levels were statistically similar between group A and group C (p=0.106) (Table 1).

In group A, there was no statistically significant decrease in body weight on the 8th day compared to the 1st day. In group B, there was a statistically significant decrease in body weight on the 8th day compared to the 1st day (p<0.001). There was a statistically significant decrease in body weight on the 8th day compared to the 1st day in group C (p<0.001). In group D, there was a statistically significant decrease in body weight on the 8th day compared to the 1st day (p<0.001).

There was a statistically significant difference among the groups in terms of weight loss (p<0.001). When the factors causing the difference in question were examined, it was found that, the average weight loss in groups B, C and D was statistically higher compared to group A (p<0.001). The mean weight loss between group B and C, group B and D, and group C and D were found to be statistically similar (p=0.550; p=0.077 and p=0.608) (Table 2).

There was a statistically significant difference among the groups in terms of median macroscopy scores (p<0.001). In the investigation of this difference, it was found that the median macroscopy scores of group B, C and D were statistically higher compared to group A (p<0.001). At the same time, the median macroscopy score of group B was statistically higher than that of group C and D (p=0.002 and p<0.001). The median macroscopy scores were statistically similar between group C and D (p=0.093) (Table 3).

DISCUSSION

Probiotics have regulatory effects on the intestinal mucosa. These effects include receptor antagonism, receptor expression, binding and expression of adapter proteins, expression of negative regulator signal molecules, induction of microRNAs, endotoxin tolerance, and stimulation of the secretion of

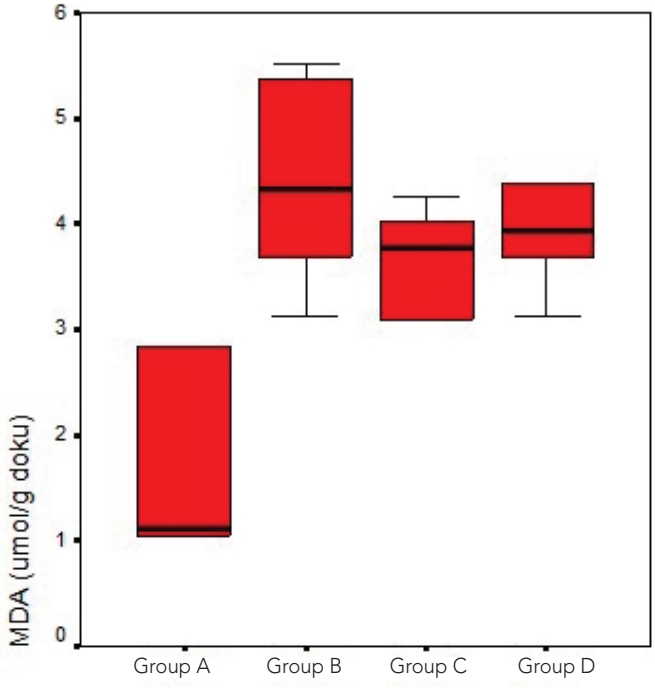

Figure 1. Malondialdehyde levels according to the groups
MDA: Malondialdehyde

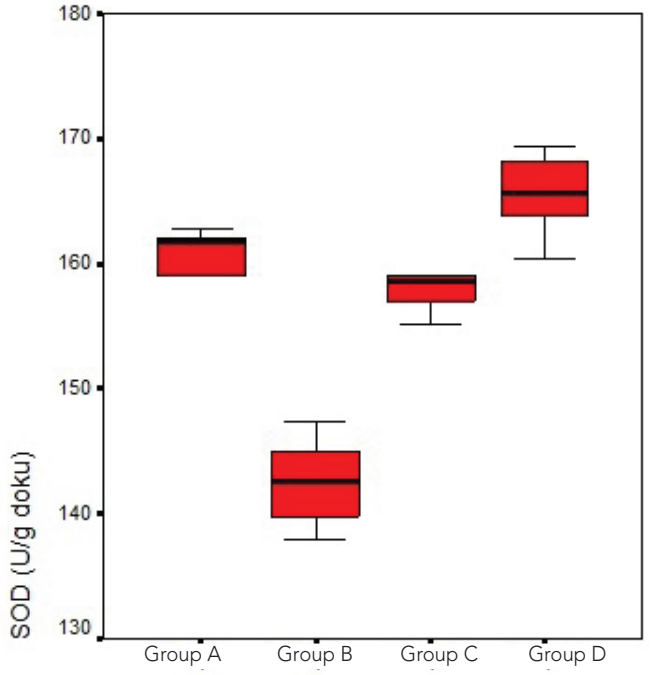

Figure 2. Superoxide dismutase levels according to the groups
SOD: Superoxide dismutase

Table 1. Measurements of inflammation markers according to the groups

Groups	MPO (U/g tissue)	MDA (umol/g tissue)	SOD (U/g tissue)
Group A (control)	0.27 (0.15-0.30)	1.1 (1.0-2.8)[a,b,c]	160.7 (150.1-161.7)[a,c]
Group B (TNBS)	0.44 (0.22-0.61)	4.3 (3.1-5.5)[a,d,e]	141.6 (137.9-147.3)[a,d,e]
Group C (TNBS + MP)	0.28 (0.25-0.50)	3.8 (3.2-4.2)[b,d,f]	157.6 (155.2-167.7)[d,f]
Group D (TNBS + P)	0.30 (0.25-0.37)	3.9 (3.1-4.2)[c,e,f]	164.7 (160.3-168.3)[c,e,f]
p	0.114†	**0.002†**	**<0.001†**

†Kruskal-Wallis test, [a]The difference between group A and B is statistically significant (p<0.001), [b]The difference between group A and C is statistically significant (p<0.001), [c]The difference between group A and D is statistically significant (p<0.001), [d]The difference between group B and group C is statistically significant (p<0.001), [e]The difference between group B and group D is statistically significant (p<0.05), [f]The difference between group C and D is statistically significant (p<0.05).
MPO: Myeloperoxidase, MDA: malondialdehyde, SOD: superoxide dismutase, MP: methylprednisolone, P: probiotic

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immunomodulatory proteins, lipids and metabolites to modulate the immune system. Probiotics not only have activating effects on the immune system, but they also have a suppressive effect. It can affect hemostasis, inflammation and immunopathology pathways with direct or indirect effect on the immune system (1). Probiotics pass the testinal epithelium and reach the M-cells, which are immunomodulators in the payer plates. M-cells transmit probiotic bacteria and their soluble proteins to mucosalenfoid tissue and initiate immunregulation. Antimicrobial activity increases and as a result, mucosal immunoglobulin A also increases. It activates goblet cells located in the mucosa, stimulates mucous secretion, prevents the pathogens to attach the epithelium and to settle in the tissue. It enhances mucosal integrity by strengthening the connections between epithelial cells. It inhibits the binding of lipopolysaccharides to the CD14 receptor, reducing nuclear factor-κβ activation and the production of proinflammatory cytokines. It has regulatory effects on B and T lymphocyte functions located in laminapropria. They reduce the secretion of tumor necrosis factor-alpha and interferon gamma, which play a central role in the formation of testinal inflammation of probiotics. They stimulate regulatory T-cells via interleukin-10 and transforming growth factor-beta. Thus, they display a regulatory effect on inflammation. Lactobacillus and Bifidobacterium species are quite common probiotic species and they are found naturally in the gastrointestinal tract. These bacteria are beneficial bacteria that help the digestive process (9).

IBD are chronic inflammatory diseases that progress with remission and activation. The etiopathogenesis of IBD is still not fully known. It is accepted that it occurs as a result of genetic and environmental factors, and mutual interaction between luminalmicroflora and immune system. Although antibiotics and immunomodulating drugs have an important role in the treatment of these diseases, the ideal treatment method for IBD is still under discussion. In recent years, doubts about that intestinal microbiota changes trigger susceptibility to many gastrointestinal diseases have increased. As a result, attention has focused on the use of probiotics in treatment.

Numerous studies on colitis models formed with TNBS and on patients with IBD have also confirmed anti-inflammatory activities of probiotics (4,9,10). Although the mechanisms regarding how probiotics reduce IBD symptoms are not known, it is known that they have a role in the change of the composition of bacteria in the gastrointestinal system; they compete in holding the epithelium with pathogenic microorganisms and prevent their infection development; they regulate the function of mucosal immune cells; they stimulate the formation of antimicrobial factors such as bacteriocin, hydrogen peroxide, acetic acid, and lactic acid, and inhibit the proliferation of pathogenic microbes; they increase the barrier functions of the mucosa by increasing the inter-epithelial connections and providing mucosal integrity; and they induce T-cell apoptosis (11).

In this study, we preferred the colitis model formed with TNBS due to the development of chronic inflammation, no occurrence of spontaneous remission, and development of inflammation similar to IBD pathogenesis. Subsequently, we examined the colon samples taken from rats microscopically and macroscopically. Activation of neutrophils, macrophages, lymphocytes, and mast cells for any reason and the formation of reactive oxygen metabolites, which occur as a result of oxidative stress in the tissue, cause mucosal impairment and ulceration, and form the pathogenesis of intestinal inflammation.

Therefore, in this study, we determined the SOD, MPO, and MDA tissue levels, which are inflammation, oxidative stress and fibrotic markers, and compared the groups in terms of the tissue levels of these molecules. In this way, we investigated the effects of probiotics on inflammatory and antioxidant markers, which are expected to exist on the mucosa at the very early stage of inflammation.

When the sham group (group A), control group (group B), group receiving steroid treatment (group C), and group taking probiotic

Table 3. Macroscopy scores according to the groups

Groups	Macroscopy score
Group A	0 (0-0)[a,b,c]
Group B	3.5 (2-4)[a,d,e]
Group C	2 (1-3)[b,d]
Group D	2 (2-3)[c,e]
p	**<0,001†**

†Kruskal-Wallis test, [a]The difference between group A and B is statistically significant (p<0.001), [b]The difference between group A and C is statistically significant (p<0.001), [c]The difference between group A and D is statistically significant (p<0.001), [d]The difference between group B and C is statistically significant (p=0.002), [e]The difference between group B and D is statistically significant (p<0,001)

Table 2. Body weights on the 1st and 8th days according to the groups

	1st day	8th day	p†	Change	p‡
Body weight	-	-	-	-	**<0.001**
Group A	227.3±6.8	224.0±6.6	0.118	-3.3±1.2[a,b,c]	-
Group B	233.7±9.2	176.7±14.0	**<0.001**	-57.0±14.0[a]	-
Group C	226.1±9.4	178.3±10.2	**<0.001**	-47.8±18.1[b]	-
Group D	230.0±8.9	190.7±13.0	**<0.001**	-39.3±6.0[c]	-

†Dependent t-test, comparisons of body weights on the 1st and 8th days among the groups, ‡One-way ANOVA, comparisons among the groups in terms of changes in body weight on the 8th day compared to the 1st day, [a]The difference between group A and group B is statistically significant (p<0.001), [b]The difference between group A and group C is statistically significant (p<0.001), [c]The difference between group A and group D is statistically significant (p<0.001)

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(group D) were compared in terms of weight differences on the 1st and 8th days, there was a statistically significant difference among the groups in the weight measurements on the 1st and 8th days. When the groups were compared among themselves, while there was a significant difference in weight loss between the sham group and colitis forming groups, the weight loss was statistically similar among the control group, standard group and test group. This supported the subjects to be selected homogeneously. This may be due to the fact that the rats were not fed 24 hours before the colitis induction and the oral intake of rats receiving anesthesia was reduced because they were administered IR TNBS.

Compared to the sham group, colitis formed groups showed a marked difference in the macroscopic appearance of the colon. In colitis-formed groups, the colon was necrozed, edematous, and rigid, and wall thickness was increased. In groups with colitis, the uterus was adhered to the colon, the spleen was small in size, and the pancreas was hyperemic. In the sham group, the colon was completely normal in macroscopic and microscopic appearance, and the pathological features observed in the groups where colitis was formed in the uterus, spleen and pancreas were not found. While there was microscopically prominent colonic inflammation, erosion, ulceration, necrosis in colitis groups, no pathological findings were found in preparates belonging to the sham group. This difference confirmed us that TNBS was an effective chemical agent in creating a chronic colitis model.

Inflammatory process in IBD and experimental colitis occurs by infiltration of leukocytes such as neutrophils, monocytes and lymphocytes into the colon mucosa. Leukocytes are the main source of free oxygen radicals. Reactive oxygen radicals cause cell and tissue level damage by doing peroxidation of lipid membranes, protein denaturation and DNA damage. MPO is the most frequently released enzyme from azurophilic granules, found in neutrophils (12). Neutrophil infiltration in inflamed tissue facilitates the emergence of potent cytotoxic oxidants through the MPO enzyme (13). Studies have shown that MPO activity correlates with the severity of tissue damage in TNBS colitis and increases more in the colitis groups than in the control groups, and is also a marker of infiltration of neutrophils (13,14). Domek et al. (15) investigated MPO activities in the treatment groups according to colitis groups in the rats that they formed as colitis model and suggested that neutrophil infiltration and activation played an important role and this was determined by the level of MPO in the tissue. Karmeli et al. (16) compared the effects of cyclooxygenase-2 inhibitors in the colitis model in rats and stated that with treatment, MPO activities decreased 61% compared to subjects in the colitis model. In our study, the MPO levels of the group receiving steroid and the group receiving probiotics were very close to the sham group. The MPO level of the group taking probiotics was higher than the group taking steroids. Although MPO level was higher in the experimental colitis model compared to other groups, no statistically significant difference was found. Although there was no significant difference in MPO values among the groups, MPO values were lower in the sham and treatment groups than in the colitis model.

MDA increase is the most important laboratory indicator of lipid peroxidation in tissues in clinical and experimental studies (17). In acute inflammation, activated neutrophils leave the circulation and enter the mucosa and submucosa of the intestine, causing excessive production of lipid mediators, lactoferrin, proteases, reactive oxygen and nitrogen derivatives that contribute to inflammatory damage (18). Aytac et al. (19) showed that ilioprost significantly reduced tissue MDA levels in the colitis model they formed with acetic acid. In our study, the MDA level was significantly higher in the colitis group and the groups that formed colitis and received treatment compared to the sham group, and the MDA level was lower in the probiotic group compared to the steroid group, and this was statistically significant. When MPO and MDA levels were evaluated, low values compared to the control group supported the probability of probiotics to have anti-inflammatory activity, but not as much as steroid.

SOD is the major defense system against superoxide anions. SOD catalyzes the conversion of superoxide to hydrogen peroxide. It is the primary protector against oxidant molecules. Three types of SOD have been identified; those located in mitochondria-SOD, in cytosol [(Cu), Zn-SOD], and in extracellular matrix [(EC)-SOD]. EC-SOD is released from endothelial and stromal cells. It tends to decrease in IBD patients. Cu, Zn-SOD is released from the epithelium dominantly and decreases in inflammation. Plasma and tissue levels are low in IBD patients. SOD activity in normal intestinal mucosa is lower than in the liver and lung. This level decreases even more in inflammatory conditions (20). Kuralay et al. (21) showed that SOD levels decreased in response to oxidative stress in the experimental colitis model. Grisham et al. (22) found low SOD activity in the colitis model they created with TNBS. Patel et al. (23), in an experimental study, they compared the sham group given 3 groups as 500 mg/kg, 1 mg/kg, 5 mg/kg IR in the colitis model stimulated with PAR-2 agonistitrypsin TNBS and the groups given only TNBS and they examined MPO, MDA, SOD levels. While oxidative enzymes, macroscopic score and microscopic score were high in the group applied 5 mg/kg, antioxidant enzyme levels were low.

In our study, a statistically significant difference was detected among the groups in terms of SOD levels. Compared to the sham group, the median SOD level was statistically lower in the colitis-formed group not receiving treatment. The median SOD level of the probioticic receiving group was statistically higher than the other groups. Also, remarkably, the SOD level was higher in the probiotic group than the sham group. This situation supported the antioxidant activity of probiotics.

Our study supports that probiotics regulate the balance between antioxidant and oxidant systems.

CONCLUSION

As a result, probiotics can be used as supportive therapy to classical therapy with their antioxidant effects. However, clinical studies are needed to show that probiotics regulate mucosal defense systems with changes in microbiota and may be effective in treatment.

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Ethics Committee Approval: This study was carried out in Gazi University Faculty of Medicine Experimental Animals Laboratory.

Informed Consent: Patient approval has not been obtained as it is performed on animals.

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Original Investigation

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Radiological and Clinical Comparison of the Results of Patients with Fusion and Unfusion Cervical Anterior Microdiscectomy with the Help of Cases and Literature

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ABSTRACT

Objective: In this study, we aimed to show the superiority of fused anterior cervical discectomy and fusion (ACDF) with fuseless ACD by comparing the clinical and radiological follow-up results of patients with ACD and ACDF.

Methods: Between 2001 and 2005, 67 patients with cervical disc disease, who underwent anterior cervical intervention, were included in this study. Fifty patients underwent ACD. In 31 cases, cage system and osteoinductive graft material (demineralized bone matrix, KOP) were used and 11 cases were treated with plate anterior cervical discectomy in addition to cage system. The mean follow-up period was 12 months (6 months-18 months) in the ACD group. The mean follow-up period in the ACDF group was 12 months (6 months-18 months). All ACD and ACDF patients were evaluated according to the criteria of direct cervical grafillary and Odem criteria taken at the postoperative early period, 6 months and 12 months.

Results: Fifty-five patients with ACD and 42 patients with ACDF were included in the study group. The mean age of the patients in the ACD group was 41 years (the youngest was 29, the oldest was 59 years old) and the mean age of the ACDF group was 46 years (the youngest was 30, the oldest was 69 years old). The difference was not statistically significant ($p>0.05$). There was no decrease in intervertebral disc height and foramen height in patients undergoing ACDF. No kyphosis was seen in ACDF patients.

Conclusion: According to the patient group who underwent ACD and ACDF and followed for 24 months, it was seen that the intervertebral disc height, foramen height and cervical lordosis were preserved in ACDF. No intervertebral cage was seen in the cervical corpus in any patient of ACDF. Clinical and radiological findings showed that clinical and radiological outcomes of patients with ACDF were better than ACD patients. The necessity of fusion of the anterior cervical discectomy and the use of instrumentation are discussed in the literature. Because of this reason, the results of our study will be meaningful in terms of contributing to future research.

Keywords: Cervical disc herniation, anterior cervical discectomy, fusion, cage

INTRODUCTION

Cervical disc hernia (CDH) is a disease that affects the spinal cord and roots and is most frequently encountered in the thirties of life. CDH can cause the development of radiculopathy/myelopathy (1,2). The first surgical treatment for this disease was implemented by Sir Victor Horsley in 1895 with a posterior approach, but later anterior approaches became more popular and successful. Smith and Robinson first described the anterior cervical discectomy and fusion (ACDF) method in 1955 and Cloward in 1958. After this period, the anterior approach has become preferable in CDH (2). However, in 1960, Hirch's successful results by applying ACD

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without fusion caused some controversy about the need for fusion (2,3).

In recent years, when instability has developed in the cervical vertebra, instrumentations developed for stabilization and fusion by placing cervical plaque from the anterior to the cervical vertebra has started a new era in CDH surgery. Whether or not there is a need for fusion after ACD have carried on the discussions about the indications and suitability of the materials (autografts, allografts, etc.) to date (2,4).

In this study, patients who underwent ACD and ACDF surgery for CDH between 2001-2005 were evaluated retrospectively. In both surgical methods, preoperatively and postoperatively conducted 4-way direct cervical radiographs of the patients were compared and the results were discussed in the light of the current literature.

METHODS

This study consists of 67 patients who were operated with the diagnosis of CDH in Bakırköy Mental and Neurological Diseases Hospital, Clinic of Neurosurgery between 2001-2005. After the data of these patients were evaluated retrospectively, they were found to be appropriate for our study and included. Patients who developed fracture, dislocation, and instability after cervical trauma were not included in our study. Preoperative neurological examination information, radiological examinations and surgical reports of all patients included in this study were examined. Patients who underwent single and double level surgery and ACD and ACDF were included in the study. Patients operated with the posterior approach were not included in this study. Written consent was obtained from patients participating in the study to add their records to the study. The examinations were collected in accordance with the Helsinki Ethics Committee Declaration. Since our research is a retrospective study, the ethics committee permission has not been obtained.

According to the clinical evaluation results, the cases in our study were divided into 3 groups. The group with radicular pain and motor-sensory and reflex disorders was named as radiculopathy group. Patients with spastic paresis, walking problem, muscle atrophy, bladder dysfunction constituted the myelopathy group. The patients whose two symptoms were detected at the same time were named as radiculomyelopathy group. In their neurological examination, patients with symptoms of 2nd motor neuron in one or more root areas such as radicular pain (unilateral or bilateral), paresis, decreased deep tendon reflexes (DTR), dermatomal sensory damage, and atrophy were evaluated in the radiculopathy group. In their examinations, patients with 1st motor neuron findings such as pain in the neck and interscapular area, increase in DTRs regardless of radicular pain, pathological reflex, patella or achilles clone, and muscle tone prominence were evaluated in the myelopathy group. In the myeloradiculopathy group, myelopathy and radiculopathy symptoms were associated. All patients underwent 4-way cervical radiography and preop cervical magnetic resonance imaging before surgery. Some patients underwent preop cervical computed tomography and electromyography to ensure the level of clinical origin. When the surgical reports were examined, soft intervertebral disc was detected in one group of patients, while spondylosis was detected in others. In postoperative direct cervical radiography, lordosis loss, anterior opening, narrowing of the foramen, reduction in intervertebral space, superior end plate (Sup-EP), inferior end plate (Inf-EP) length and osteophytes were evaluated.

In the lateral cervical x-ray examination, the angle formed by the posterior line of the C2 spine corpus and the posterior line of the C7 spine corpus was used to calculate the cervical angle (Figure 1). If the axis is <0°, it is considered kyphosis, if the axis is 0° - 10° it is flat, and if the axis is >10 ° it is considered lordosis. When the angle between the posterior line of the spine corpus above the space from the CDH and the posterior line of the corpus below was calculated and it gave the segmental angle. If the axis was <0°, it was considered kyphosis, and if the axis was >1° it was considered lordosis.

The angle to the anterior was assessed by the Gore method and the Martins rating system was adopted (3,5). Martins divided the patients into 4 groups according to the cervical vertebra line after surgery. It was considered excellent if normal cervical lordosis developed, if lordosis decreased and anterior angle was 5°< it was considered good, if anterior angle was 5°-15° it was moderate and if it was 15°> it was considered bad. 25 of the patients included in our study had ACD and 42 of them had ACDF. Anterior cervical plate implant was also present in 11 of the ACDF cases. The surgical indications for both groups were the same.

The surgical approach was ACD in both groups. Osteophytes were routinely taken in surgeries and posterior longitudinal ligament (PLL) was opened. In the ACDF group, titanium and peek cage implants were placed for fusion. Demineralized bone matrix, bone chips, synthetic graft were applied to create bone fusion. Following surgery, patients were advised to use cervical collar for 6-8 weeks. Routine cervical direct radiography was performed at regular intervals during the observation interval (1 month-36 months). Surgical satisfaction results of the cases were reported using the Odom criteria (2).

Statistical Analysis

SPSS 21.0 package program was used in the statistical analysis of the data obtained (SPSS, Chicago, IL, USA). Continuous data are summarized as mean ± standard deviation, while categorical data are summarized in numbers and percentages. For comparisons between groups, chi-square test (χ^2) was used to evaluate two categorical independent groups. $P<0.05$ value was taken as statistical significance level.

RESULTS

Twenty-five of 67 cases, which constituted the population of our study, were treated with ACD, and 42 with ACDF. In 11 cases from the ACDF group, fusion with anterior cervical plate was also present. Twenty-two patients from the ACD group were treated from a single space and 3 patients from 2 spaces. From the

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ACDF group; 23 patients were treated from a single space and 19 patients from 2 spaces. The mean age of the patients in the ACD group was 41 (29-59), and the mean age of the patients in the ACDF group was 46 (30-69). There was no statistically significant difference (p>0.05). The mean age of all patients was calculated as 45 (29-69). Thirty of the cases were male (44.7%) and 37 were female (55.2%) (Figure 2).

While there were 13 female patients in the ACD group, the mean age of the female patients in this group was 42. The number of female patients in the ACDF group was 24 and the mean age was 43. The number of men in the ACD group was 12, and the mean age was 44. In the ADCF group there were 18 males and the mean age was 42 (Figure 3).

The complaint detected in all cases was in the form of pain hitting left, right or two arms. Neck pain was the most common additional complaint (92%). According to the order of accompanying complaints; in 50% of the cases, there was numbness in the arms, in 41%, there was a loss of strength in the arms, and in 1%, headache.

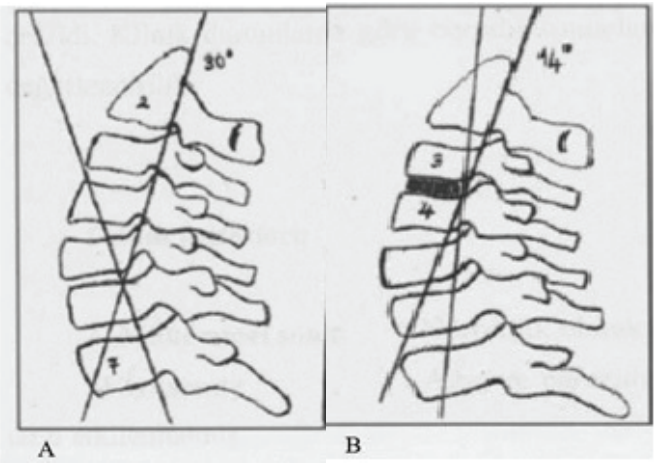

Figure 1. (4,5) Calculation of the angle formed by the lines drawn from the posterior border of the C2 vertebra corpus and the posterior border of the C7 vertebra corpus. A) Evaluation of cervical angulation by lateral cervical radiography in the neutral position (measuring the angle of C2-7 is shown schematically 30°). B) Evaluation of the segmental angulation with the lateral cervical radiography in the neutral position (C3-4 segmental angulation is shown schematically 14°)

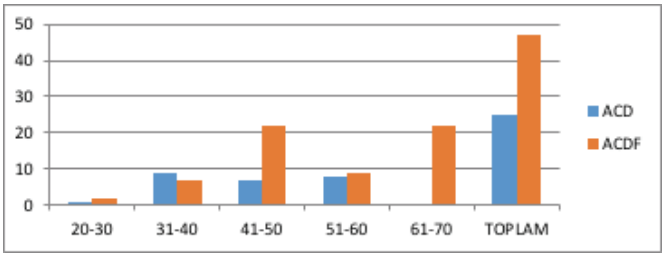

Figure 2: Age distribution of patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups
ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

The cases were evaluated in 3 different groups according to their neurological symptoms. Fifty-five (82%) cases were evaluated in radiculopathy, 1 (1.49%) case was myelopathy and 11 (16.4%) cases were evaluated in myeloradiculopathy group (Table 1).

Neurological and physical examination of all cases were done in detail. In the first examination of cases in the ACD and ACDF group; dermatomal sensory defect was detected in 40 (60%) patients, reflex changes in 36 (54%) cases, and varying degrees of paresis in 34 (51%) cases (Table 2).

Routine two-way cervical direct radiographs were performed for preoperative and postoperative follow-ups as radiological examinations. In preoperative evaluation, no cervical listhesis was detected in the ACD group. Cervical listhesis was detected in 10 patients (23.8%) in the ACDF group. Loss of lordosis was detected in 12 patients (48%) in the ACD group and 40 patients (95.2%) in the ACDF group. Osteophyte was detected in 17 (68%) patients in the ACD group, and 38 patients (90.4%) in the ADCF group. Narrowing foramen was observed in 10 cases (40%) in the ACD group and 26 cases (61.9%) in the ACDF group (Table 3).

Before the operation, all patients received anti-inflammatory and analgesic therapy, 30 patients received cervical collar support for 2-4 weeks, and 27 patients received physical therapy and rehabilitation treatment. However, despite all these treatments, there was no significant improvement in their complaints.

Forty-four of the cases were diagnosed as single and 23 of them had two levels CDH. It was determined that the C5-C6 disc space was the most treated level in both groups. The C6-C7 level was the second frequently treated level. The levels C4-C5 and C3-C4 were treated, respectively. The number of levels operated with the diagnosis of CDH was 100 (Table 4).

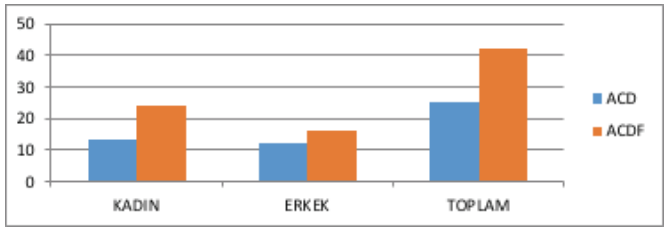

Figure 3: Gender distribution of patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups
ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

Table 1. Proportion of clinical findings of patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups

Clinical Finding	ACD		ACDF		Total	
	n	%	n	%	n	%
Radiculopathy	22	88%	33	78.5%	55	82.08%
Myelopathy	0	0%	1	2.3%	1	1.49%
Myeloradiculopathy	3	12%	8	19.2%	11	16.41%
Total	25	100%	42	100%	67	100%

ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

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The herniations were either midline or laterally located, in the form of a hard or soft disc. Twenty-five patients received ACD and 42 patients received ACDF. Of the 67 patients, 46 patients were single level and 21 patients were two level, and 88 intervertebral disc spaces were operated with an anterior approach. Thirty-one patients in the ACDF group had a cage system for fusion, 11 patients had cage and plaque.

The length of hospitalization after the intervention was the same in the ACD and ACDF group and was on average 2 days. The mean follow-up duration was 12 months (6 months-18 months) in both groups. All patients who underwent ACD and ACDF were evaluated with postoperative early period (postoperative within the first two days), cervical direct radiographs performed at the end of 6th and 12th months and according to Odom's criteria.

Table 2. Physical examination findings of patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups

Physical examination findings	ACD		ACDF		Total	
	n	%	n	%	n	%
Paresis						
Paresis on the arm	12	48%	22	52.3%	34	50.7%
Hemiparesis	0	0%	0	0%	0	0%
Quadriparesis	0	0%	0	0%	0	0%
Reflex						
Hypoactive	10	40%	17	40.4%	27	40.2%
Hyperactive	3	12%	6	14.2%	9	13.4%
Normoactive	12	48%	17	40.4%	39	58.2%
Cannot be taken	0	0%	1	2.3%	1	1.4%
Pathological reflex						
Hoffman	3	12%	9	21.4%	12	17.9%
Clonus	0	0%	1	2.3%	1	1.4%
Babinski	0	0%	0	0%	0	0%
Sensory defect	10	40%	30	71.4%	40	59.7%
Atrophy	2	8%	6	14.2%	8	11.9%
Walking disorder	0	0%	1	2.3%	1	1.4%
Sphincter defect	0	0%	1	2.3%	1	1.4%

ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

Table 3. Preoperative direct cervical X-ray findings of patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups

Preoperative direct graph findings	ACD		ACDF		Total	
	n	%	n	%	n	%
Narrowing in the space	12	48%	28	66.6%	40	59.7%
Osteophyte presence	17	68%	38	90.4%	32	82%
Foramen stenosis	10	40%	26	61.9%	36	53.7%
Loss of lordosis	12	48%	40	90.4%	52	77.6%
Cervical slip	0	0%	10	23.8%	10	14.9%

ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

While the excellent postoperative early outcome rate in the ACDF group was 28.5%, it was 20% in the ACD group. However, the rate of good evaluation in the ACDF group was 57.1%, while it was 60% in the ACD group. The "excellent + good" result rate was 85.7% in the ACDF group and 80% in the ACD group (Table 5).

While the excellent outcome rate in the ACDF group at the 6th month was 33.3%, it was 12% in the ACD group. At the same time, the rate of good evaluation of the ACDF group was 59.5%, while it was 68% in the ACD group. The "excellent + good" result rate was 92.8% in the ACDF group and 80% in the ACD group (Table 6).

While the excellent outcome rate in the ACDF group at the postoperative 12th month was 35.7%, it was 12% in the ACD group. At the same time, the good outcome of the ACDF group was 62%, while it was 72% in the ACD group. The "excellent + good" result rate was 97.6% in the ACDF group and 84% in the ACD group (Table 7).

The measurements of preoperative and postoperative 7 parameters were taken using cervical direct graphs (Figure 4).

Intervertebral disc space	1st measurement
Foramen height	2nd measurement
Superior end plate	3rd measurement
Inferior end plate	4th measurement
Loss of lordosis	5th measurement
Presence of osteophyte	6th measurement

Figure 4. Parameters evaluated in the study

Table 4. Classification of patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups according to operated disc spaces

Operated disc spaces	ACD		ACDF		Total	
	n	%	n	%	n	%
Single level						
C3-4	0	0%	1	2.3%	1	1.4%
C4-C5	4	16%	3	7.1%	7	10.4%
C5-C6	8	32%	13	30.9%	21	31.3%
C6-C7	10	40%	4	9.5%	14	20.8%
C7-T1	0	0%	1	2.3%	1	1.1%
Two level						
C3-C4/C5-C6	0	0%	1	2.3%	1	1.4%
C3-C4/C4-C5	0	0%	0	0%	0	0%
C4-C5/C5-C6	1	4%	4	9.5%	5	7.4%
C5-C6/C6-C7	2	8%	15	35.7%	17	25.3%
Total	25	100%	42	100%	67	100%

ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

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Preoperative osteophyte, segmental angle presence and lordosis loss are significantly higher in ACDF group than ACD group ($p<0.05$). There was no statistically significant difference between the groups in terms of early postoperative osteophyte, lordosis loss and segmental angle ($p>0.05$). It was found that 12th month lordosis loss and segmental angle presence were significantly higher in ACD group than ACDF group ($p<0.05$ and $p<0.001$) (Table 8).

The ACDF group's early postoperative, mean 6th and 12th month disc space were significantly higher than that of the ACD group. When the means of preoperative disc space of both groups were calculated, there was no statistically significant difference ($p>0.05$). The mean preoperative foramen height of the ACD group was found to be significantly higher than that of the ACDF group ($p<0.05$). There was no statistically significant difference between groups in terms of preoperative, early postoperative, 6th and 12th month Sup-

Table 5. Postoperative early satisfaction results of patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups

Postoperative early period	Excellent		Good		Medium		Poor		Total	
	n	%	n	%	n	%	n	%	n	%
ACD (dingle level)	4	18.1%	14	63.7%	3	13.6%	1	4.6%	22	100%
ACD (double level)	1	33%	1	33%	1	33%	0	0%	3	100%
ACDF (fusion with cage) (Single Level)	7	36.8%	11	57.8%	1	5.3%	0	0%	19	100%
ACDF (fusion with cage) (two levels)	4	33.3%	5	41.7%	2	16.7%	1	8.3%	12	100%
ACDF (fusion with cage + plate) (single level)	0	0%	1	100%	0	0%	0	0%	1	100%
ACDF (fusion with cage + plate) (two levels)	1	12.5%	6	75%	1	12.5%	0	0%	8	100%
Anterior cervical corpectomy + cylindrical cage + plate	0	0%	1	50%	1	50%	0	0%	2	100%

Odom's Criteria (1958)
ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

Table 6. Postoperative 6th month satisfaction results of the patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups

Postoperative 6th month	Excellent		Good		Medium		Poor		Total	
	n	%	n	%	n	%	n	%	n	%
ACD (single level)	3	13.6%	15	68.2%	4	18.2%	0	0%	22	100%
ACD (double level)	0	0%	2	66.7%	1	33.3%	0	0%	3	100%
ACDF (fusion with cage) (single level)	7	36.9%	12	63.1%	0	0%	0	0%	19	100%
ACDF (fusion with cage) (two levels)	5	41.7%	6	50%	1	8.3%	0	0%	12	100%
ACDF (fusion with cage + plate) (single level)	0	0%	1	100%	0	0%	0	0%	1	100%
ACDF (fusion with cage + plate) (two levels)	2	25%	5	62.5%	1	12.5%	0	0%	8	100%
Anterior cervical corpectomy + cylindrical cage + plate	0	0%	1	50%	1	50%	0	0%	2	100%

Odom's Criteria (1958)
ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

Table 7. Postoperative 12th month satisfaction results of patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups

Postoperative 12th month	Excellent		Good		Medium		Poor		Total	
	n	%	n	%	n	%	n	%	n	%
ACD (single level)	3	13.6%	16	72.8%	3	13.6%	0	0%	22	100%
ACD (double level)	0	0%	2	66.7%	1	33.3%	0	0%	3	100%
ACDF (fusion with cage) (single level)	7	36.8%	12	63.2%	0	0%	0	0%	19	100%
ACDF (fusion with cage) (two levels)	5	41.7%	7	58.3%	0	0%	0	0%	12	100%
ACDF (fusion with cage + plate) (single level)	1	100%	0	0%	0	0%	0	0%	1	100%
ACDF (fusion with cage + plate) (two levels)	2	25%	5	62.5%	1	12.5%	0	0%	8	100%
Anterior cervical corpectomy + cylindrical cage + plate	0	0%	2	100%	0	0%	0	0%	2	100%

Odom's Criteria (1958)
ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

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EP means (p>0.05). There was no statistically significant difference between groups in terms of preoperative, early postoperative, 6th and 12th month Inf-EP means (p>0.05) (Table 9).

In the ACD group, early postop disc space and foramen height values were found to be significantly decreased compared to preoperative status (p<0.00l). In the ACD group, 6-month evaluation, disc space and foramen height values were found to be significantly decreased compared to preoperative values (p<0.001). In the ACD group, in the 12th month, disc space and foramen height values were found to be significantly decreased compared to preoperative values (p<0.001) (Table 10).

In the ACDF group, early postoperative, 6th, 12th month disc space and foramen height were found to increase significantly (p<0.001). In the ACDF group, early postoperative, 6th, 12th month superior and Inf-EP and foramen height results were found to be significantly decreased when compared with preoperative values (p<0.001) (Table 11).

Complications

Minor complications were seen in ACD and ACDF groups. Although wound site infection was observed in 1 patient in the ACD group and postoperative pain complaint was observed in four of the ACDF patients, these complaints resolved completely between the 3rd day and the 1st week. It was observed that these pains continued for 2 weeks to 3 months in 2 patients in the ACDF group and resolved completely after 3 months. In 8 patients from the ACD group, pain complaints decreased between postoperative week 1 and month 2, and complaints persisted in 3 patients. There was transient hoarseness in 8 patients, 3 in the ACD group and 5 in the ACDF group. However, it was observed that completely healed within the postoperative first month. No major complications such as perioperative dural injury, vascular injury were observed. No surgical mortality was observed. There were no patients who underwent wrong level discectomy in either group. Osteophyte formation was detected in 4 patients from the ACD group at the operation level or adjacent level. No such formation was found in the ACDF group. Postoperative pseudoarthrosis did not develop in either group. In all patients in the ACD group, angulation was detected in 8 patients in the postoperative 1st-3rd month control direct cervical radiographs. In 16 patients from the ACD group, disc height loss was observed in disc space, and in 9 patients, slight height loss was observed. A decrease in lordosis was detected in 12 patients in the ACD group. In the ACDF group, complications such as angulation, decrease in disc space and decrease in lordosis were not encountered. There were no complications related to the materials used for fusion in the ACDF group (Table 12).

Table 8. Comparison of early postoperative and 12th month osteophyte, lordose loss and segmental angle presence of the patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups

Early postoperative	ACD	ACDF	p
	n %	n %	
Loss of lordosis	17 68.0 8 32.0	31 73.8 11 26.2	0.26 0.610
Osteophyte	25 100.0	42 100.0	-
Segmental Angle	25 100.0	60 100.0	-
12th month			
Loss of lordosis	15 60.0 10 40.0	42 97.7 1 2.3	0.000
Osteophyte	25 100.0	43 100.0	-
Segmental Angle	12 42.9 16 57.1	52 86.7 8 13.3	18.47 0.000

ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

DISCUSSION

One of the most important goals of spinal surgery is to maintain or restore the sagittal balance of the spine. The normally expected cervical angle is lordotic, and the angle range is between 10° and 40° (6,7). Recently, ACD has become a more preferred surgical method because it is useful and easier to apply. However, the need for fusion has begun to be discussed (8,9). With the anterior method, neurovascular structures can be decompressed, osteophytes can be removed if fused and the height of the disc space can be maintained. The ligamentum flavum is not expected to fold, and relaxation in the foramen becomes more pronounced.

Table 9. Results of disc space, foramen height, inferior end plate and superior end plate measurement result of preoperative, postoperative 6th and 12th months of patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups

Disc space	ACD		ACDF		p
	Mean	SD	Mean	SD	
Preoperative	6.26	1.10	5.89	1.71	0.300
Postoperative	5.00	1.19	9.67	0.95	0.000***
6th month	4.57	1.03	9.65	0.92	0.000***
12th month	4.11	0.99	9.58	1.00	0.000***
Foramen Height					
Preoperative	11.54	1.45	10.56	2.23	0.036*
Postoperative	10.57	1.57	13.25	2.20	0.000***
6th month	10.25	1.55	13.23	2.17	0.000***
12th month	9.79	1.42	13.13	2.06	0.000***
Sup-EP					
Preoperative	23.07	3.11	23.92	3.03	0.229
Postoperative	22.54	3.31	22.05	2.55	0.460
6th month	22.64	3.27	22.49	2.01	0.793
12th month	23.11	3.13	22.19	2.56	0.155
Inf-EP					
Preoperative	23.29	3.09	23.01	3.08	0.649
Postoperative	22.02	3.13	21.81	2.75	0.131
6th month	23.00	3.10	21.04	2.70	0.055
12th month	23.61	3.01	22.20	2.74	0.043

ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion, SD: standard deviation, Sup-EP: superior end plate, Inf-EP: inferior end plate

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Table 10. Comparison of disc space, foramen height, superior end plate and inferior end plate of the patients in acd group of direct graphies in preoperative-early postoperative preoperative-6th month, preoperative-12th month

Anterior cervical discectomy group											
	Preoperative		Early postoperative			6th month			12th month		
	Mean	SD	Mean	SD	p	Mean	SD	p	Mean	SD	p
Disc space	6.26	1.10	4.56	1.05	0.000***	4.56	1.05	0.000***	4.07	1.00	0.000***
Foramen height	11.54	1.45	10.25	1.55	0.000***	10.25	1.55	0.000***	9.79	1.42	0.000***
Sup-EP	23.07	3.11	22.64	3.27	0.130	22.64	3.27	0.130	23.11	3.13	0.130
Inf-EP	23.29	3.09	23.00	3.10	0.284	23.00	3.10	0.284	23.61	3.01	0.284

ACD: Anterior cervical discectomy, SD: standard deviation, Sup-EP: superior end plate, Inf-EP: inferior end plate

Table 11. Comparison of disc space, foramen height, superior end plate and inferior end plate of the patients in anterior cervical discectomy and fusion group of direct graphies in preoperative-early postoperative preoperative-6th month, preoperative-12th month

Anterior cervical discectomy and fusion group											
	Preoperative		Early postoperative			6th month			12th month		
	Mean	SD	Mean	SD	p	Mean	SD	p	Mean	SD	p
Disc space	6.04	1.67	9.67	0.95	0.000***	9.65	0.92	0.000***	9.58	1.00	0.000***
Foramen height	10.56	2.23	13.25	2.20	0.000***	13.23	2.17	0.000***	13.13	2.06	0.000***
Sup-EP	23.75	3.07	22.05	2.55	0.000***	22.49	2.01	0.000***	22.19	2.56	0.000***
Inf-EP	23.35	2.91	21.81	2.75	0.000***	21.84	2.76	0.000***	22.26	2.74	0.000***

SD: Standard deviation, Sup-EP: superior end plate, Inf-EP: inferior end plate

In a study of complications, Bertalanffy and Eggert (10) found that in some of the reexplorations performed due to postoperative morbidity, pressure on the neural tissue developed due to the expansion and folding of PLL.

In the anterior approach, there are two types of operations, ACD and ACDF, for CDH (11). The opponents that fusion is necessary considers that thanks to the bone implant placed in the intervertebral space; biomechanical stability develops in the early period, fusion is easier, osteophytes regress and foramen are relieved (10). According to the Robinson et al.'s fusion results; solid fusion theoretically eliminates neural irritation by limiting movement at the fusion level, and at the same time, this allows osteophytes to resorb. In addition, they found that spinal cord/nerve root manipulation was not required in the anterior approach, that the bone graft preserved the height of the disc space and expanded the neural foramen. However, in their same study, they also stated that by performing ACDF, it eliminated possible compression to the spinal cord/nerve roots due to folding in PLL and ligamantum flavum (12).

In some studies, they stated that in anterior interventions performed in SDH, kyphosis developed in the late period secondary to closing the disc space after decompression. The necessity of fusion application has been advocated due to the decrease in foramen width after kyphosis and related root findings (13-15). However, segmental kyphosis in ACD develops in many cases. Studies have shown that segmental kyphosis, which may develop after ACD, causes problems in neighboring regions and sagittal angles (16-21).

Table 12. Complication rates in patients in anterior cervical discectomy and anterior cervical discectomy and fusion groups

Complications	ACD	ACDF	Total
	n%	n%	n%
Wound site infection	-	-	-
Postoperative pain	9 (36%)	6 (14.2%)	15 (22.3%)
Temporary hoarseness	2 (8%)	5 (11.9%)	7 (10.4%)
CSF fistula (dura damage)	-	-	-
Hematoma	-	-	-
Vascular injury	-	-	-
Esophagus/tracheal perforation	-	-	-
Wrong space expansion	-	-	-
Graft infection	-	-	-
Mortality	-	-	-
Total	11 (44%)	11 (26.1%)	22 (32.8%)

ACD: Anterior cervical discectomy, ACDF: anterior cervical discectomy and fusion

Cages placed in the intervertebral space for fusion after ACD are used frequently in practice today. Especially easy application, maintaining physiological disc height, providing distraction, correcting angular instability, and fusion with bone implant are considered to be more preferred because it is thought to be superior in the treatment planned (17).

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Cages, which are the cornerstone of fusion surgery, provide reliable clinical and radiological successes, alone or in combination with fixation systems (cervical plates). The most important task of the cages is to create fusion in the vertebral corpus. In addition, they maintain the height of the original disc space and provide resistance to axial weight, which is evident in the first periods (19,20). Based on these important tasks, we found in our study that the disc space intervened, especially in the tests performed after the use of the cage, preserves the physiological dimension and we stated in our study.

In order to evaluate the indications and advantages of cage use, it is necessary to evaluate factors such as the time spent in surgery, painless mobilization, the need to use postoperative cervical collar, the duration of postoperative neck pain, whether there is a loss of disc space after 6 months and fusion time (17). Although these are the criteria we base in our study, the results we obtained are in line with the literature.

Bohlman (22) found that 95% of the patients they operated with the Smith-Robinson method relieved upper extremity pain and 69% neck pain.

Galera and Tovi (23) in their series of 146 cases where they applied ACDF, reported the rate of pain recovery as 78% in the early postoperative period. In addition, Aronson et al. (24) stated the superiority of ACDF in the relief of upper limb pain associated with soft intervertebral disc herniation in patients treated with the ACD technique.

Joint spacing and foramen height are rearranged by ACDF method. Decompression is higher in ACDF patients than ACDF. It is more evident in the ACDF group that the pain complaint passes early. They stated that neural foramen height may decrease in ACD and therefore may cause upper limb pain to continue (25).

96% of the cases in our series applied to our clinic with arm and neck pain. In postoperative early ACD group; It was determined that the pain of 5 patients persisted for a while and it eased slightly compared to preoperative pain. In one patient, his pain was still observed at the 6th month follow-up. In the ACDF group, complaints of pain occurred in 6 patients in the first period and resolved within 1-week. In one case, it was found that this complaint was completely gone after 6 months. These values in our study were found to be compatible with the literature (4,22,24).

It has been stated in the literature that neural foraminal distraction cannot be achieved in ACD and the protrusion of ligamantum flavum to the canal cannot be reduced. In ACD, the disc space is collapsed, and kyphosis develops rapidly. This kyphosis is generally less than 5° and its clinical significance is not fully known. Spontaneous fusion rate varies between 28-100%. In addition, 10% of patients develop painful discogenic syndrome with radiculopathy. A significant portion of these patients may need surgery again (17).

In our series, 22 patients had single level and three patients had two level ACD. Preoperative, early post-operative, post-operative 6th month and post-operative 12th month direct cervical radiographs of all patients were compared. In our study, it was observed that disc spaces collapsed, foramen height was lost, and in some cases, the current lordosis loss continued postoperatively. In the 42 patients forming the ACDF group, preoperative two-way direct cervical and post-operative radiographs were compared. It was determined that there was no collapse in the disc spaces, the disc spaces were distracted, and that the foramen heights were preserved and even increased. In addition, it was observed that existing preoperative lordosis losses, anterior angles and cervical shifts improved in the early post-operative period. Measurements of patients in both groups were compared statistically. The advantage of using cages and plates was that they maintain the intervertebral disc space and foramen height, reduce morbidity, correct deformity, stabilize until arthrodesis, and provide mechanical strength against axial loads.

CONCLUSION

Watters and Levinthal (26) have shown that patients who have received ACDF decreased their current symptoms and complaints compared to those with ACD, and achieved superior results in the late period. Similar results were found in our research. Namely; we found that improvement of our cases started rapidly in the first periods and complaints and symptoms improved completely in late controls. Therefore, we think that intervertebral fusion using single and two-level degenerative disc disease using cage system, plate and bone fusion is a simple and reliable method if performed in accordance with the indications we have specified in our study.

What we would especially like to emphasize in our study is that, as stated in other studies, ACDF maintains the height of physiological disc space, prevents foramen height loss and contraction, thereby preventing nerve compression and reducing morbidity.

Ethics Committee Approval: Since our research is a retrospective study, the ethics committee permission has not been obtained.

Informed Consent: Written consent was obtained from patients participating in the study to add their records to the study.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept - N.K., M.T.; Design - N.K., M.T.; Supervision - S.K.; Resources - Y.A.; Data Collection and/or Processing - N.K.; Analysis and/ or Interpretation - S.K., M.T.; Literature Search - Y.A., G.G.; Writing Manuscript - N.K.; Critical Review - S.K.

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Recurrent Admissions to Psychiatric Emergency Service: What are the Needs of the Elderly in This Area Differing from Young People and What Can be Done? A Retrospective Comparative Study

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ABSTRACT

Objective: Recurrent admissions to psychiatric emergency services (PES) are a multidimensional clinical situation. In this situation, elderly people have different properties and needs compared to younger people. The aim of the present study was to determine the characteristics and needs of the elderly people with recurrent admissions to PES in terms of sociodemographic, clinical characteristics and clinical approach, according to the different features of the youth, and to draw attention to what can be done.

Methods: The files of the patients aged 18 years and over, who had two or more admissions to our hospital's PES between January 2011 and January 2012, were examined by random method (one in 23 patients). A total of 324 patients were included in this retrospective comparative study. The patients were divided into two groups as those aged 65 years and older (elderly group, n=167) and those aged 18-65 years (young group, n=157) and compared as per the findings obtained.

Results: As per the young people, the elderly often applied to the PES with family members; the rate of physical disease was higher; more physical examinations and consultations were requested during the evaluation of the elderly; visual hallucination, memory impairment, and verbal violence were found to be higher in the symptom profiles. The most common diagnoses of the elderly were determined to be psychosis, behavioral and psychological symptoms related to dementia, bipolar mood disorder, depression and anxiety disorder, and the hospitalization was found to be lower in the elderly.

Conclusion: Elderly patients differ from young people in terms of physical disease comorbidity, physical examination, consultation request, symptom profile, diagnosis and treatment plan. The evaluation of the elderly patient will provide a multidisciplinary approach, the formation of professional teams in the field should be the main purpose. In this way, recurrent admissions of elderly people to PES can be prevented.

Keywords: Psychiatric emergency service, recurrent admission, age, psychiatric disease

INTRODUCTION

The proportion of the elderly population (65 years and over) in the total population in our country increased from 7.7% in 2013 to 8.5% in 2017. This rate is estimated to be 16.3% in 2040 (1). In parallel with the increase in the elderly population, psychiatric emergency services (PES) will be an important clinical need to meet the needs of this group of patients.

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The definition of recurrent admission to PES in the literature differs. There are different definitions on 2 admissions to PES within one year, six or more admissions within one year or at least three admissions within one year (2-4). Recurrent admissions constitute 1/3 of PES admissions. A good understanding of the sociodemographic and clinical characteristics of these patients will contribute to the improvement of mental health services (3,5,6). The recurrent admission rate to PES ranges between 5 and 56%. Those with recurrent admissions have more chronic social problems than those with single admissions (7).

Detecting the diagnostic, demographic and social characteristics of PES admissions in the elderly group, who require special interest and knowledge in the field of psychiatry, will better determine the role and structure of future geropsychiatric emergency health care provision (8). Despite the fact that PES is an important point of admission for the elderly in reaching mental health services and researchers in the field of health are working on the adequacy of health care services for the elderly, the general interest in PES is insufficient. Research should be carried out in order to create recommendations that may be a guide in PES planning and implementation. In order to overcome the deficiencies in PES, it is necessary to increase the quality of health services, to increase education in this area, to develop PES, to standardize and to encourage research. In this way, the future crises to be given to the elderly in future mental health services can be prevented (9,10).

Unlike the young people, the reasons for remitting referral to PES and determining the needs in this area are important factors in effective interventions to prevent recurrent admissions, measures to be taken before the admission, management of the admission process and the post-admission is thought to be important in planning health.

METHODS

The files of the patients aged 18 years and over, who had two or more admissions to our hospital's PES between January 2011 and January 2012, were examined by random method (one in 23 patients). A total of 324 patients (167 elderly, 157 young) were included in this retrospective comparative study. Data were recorded to the data screening form prepared by the researchers, which included sociodemographic and clinical characteristics prepared by the researchers (age, gender, education level, marital status, social security, working status, with whom they live, smoking, alcohol, psychoactive substance use, physical illness), admission to PES, evaluation and treatment. In the data screening form including psychiatric diagnoses according to Diagnostic and Statistical Manual of Mental Disorders-4 diagnostic criteria, the characteristics (number of admissions, number of visitors, admission form, admission for drug printing, physical examination, consultation, emergency treatment, treatment plan, treatment arrangement), clinical signs and symptoms and diagnoses were recorded. The patients were divided into two groups as those aged 65 years and older and those aged 18-65 years, and compared with respect to these characteristics. Ethical committee approval was obtained from the Local Ethics Committee of İstanbul Bakırköy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital (approval number: 6779, date: 03.02.2014).

Statistical Analysis

SPSS 18 program was used for statistical analysis of data. To determine the statistical significance between the groups, numerical data were evaluated by the t-test and other data by the chi-square test. The chi-square for normally distributed data and the Fisher's exact for non-normally distributed data were performed. $P<0.05$ was considered statistically significant.

RESULTS

When elderly group and young group were compared in terms of sociodemographic and clinical features, the female gender ratio was higher in the two groups [(57.5% (n=96) in the elderly group and 52.2% (n=82) in the young group]. When the two groups were compared, the rates were as follows in the old and young groups, respectively; 91% vs 58% for those receiving education between 0 and 5 years, 98.8% vs 92.3% for those who had social security, 5.4% vs 33.8% for smoking, 4.2% vs 29.3% for working life, 1.8% vs 10.8% for alcohol use, 3% vs 8.9% for psychoactive substance use, and 50.3% vs 10.8% for additional physical disease. According to the mentioned characteristics, the elderly showed a statistically significant difference ($p<0.05$) than the young. The sociodemographic and clinical characteristics are summarized in Table 1.

When we compared the groups in terms of admission to PES, evaluation and treatment characteristics were as follows: elderly people were more frequency admitted to the emergency unit with family members (82.6% vs 36.9%), had more physical examinations (7.2% vs 1.3%), consultations (19.8% vs 3.2%) and planned outpatient follow-up visits to emergency service (75.4% vs 65.6%). In addition, more recipe was prescribed for the elderly during emergency discharge (68.3% vs 44.6%). According to the mentioned characteristics, the elderly showed a statistically significant difference ($p<0.05$) than the young except planned outpatient follow-up visits ($p<0.052$). According to the mentioned characteristics, the elderly showed a statistically significant difference ($p<0.05$) than the young. The admission to PES, evaluation and treatment characteristics are summarized in Table 2.

When we compared two groups in terms of the symptom profile, it was found that visual hallucinations (7.8% vs 1.3%), memory impairment (7.8% vs 0%), and verbal violence (33.5% vs 17.8%) were significantly higher in the elderly group than in the young group. Disease duration, clinical symptoms and findings are summarized in Table 3.

In turn, the rates of diagnoses in the elderly were 24.6% for psychosis, 23.4% for behavioral and psychological symptoms related to dementia, 19.2% for bipolar mood disorder, 17.4% for depression, 12% for anxiety disorder, 1.8% for adverse effects of drug use, 1.2% for mental retardation and behavior problems, and 0.6% for substance use disorders. The diagnostic distribution

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showed a statistically significant difference between the two groups (p<0.05). The distribution of psychiatric diagnoses is summarized in Table 4.

DISCUSSION

In our study, we defined recurrent admissions as two or more admissions to PES per year. There is no consensus among the researchers about the definition of recurrent admission to PES. This situation does not cause any problem about the definition of recurrent admission in our study. In 2012, the average number of admissions per day to PES of our hospital was 77. Between January 2011 and January 2012, a total of 28359 people were admitted to PES. Among these admissions, the rate of two and more admission is 26.8% (7505). In the studies, the rate of recurrent admission to PES was reported to be between 21 and 65%. Ratios may be affected by variables such as the definition of recurrent admission, region where PES is located, and different cultures (4,7). The ratio we determined was in parallel with the rates in other studies.

The level of education in the elderly was lower than in the young. Among the elderly who were admitted to PES, the rate of those receiving education for seven years and below was reported to be 32%. The level of education may vary according to the region where the study was conducted (11,12). Increasing the level of education can increase the awareness of the patients and provide a more effective solution to the problems. Again, the increased level of education may be effective in the implementation of preventive measures (prevention of diseases such as healthy nutrition, sports, social activity) before admitting to PES.

57% of elderly patients who were admitted to PES were living with their families, 38% were living alone, and only 61% of the elderly group had a supportive environment. It was reported that the rate of admission to emergency service was 60% higher in patients living alone compared to their spouses, and weak social support was found to be determinant in emergency service admissions

Table 1. Socio-demographic and clinical characteristics

		65 years and over (n=167)	Between 18-64 (n=157)	p
Age		72.69±7.35	36.94±10.66	0.001***
Gender	Female	96 (57.5%)	82 (52.2%)	0.342
	Male	71 (42.5%)	75 (47.8)	
Education (years)	0-5	153 (91.6%)	91 (58.0%)	0.001***
	5-10	3 (1.8%)	27 (17.2%)	
	10-15	11 (6.6%)	39 (24.8%)	
Marital status	Married	93 (55.7%)	84 (53.5%)	0.693
	Other (single, widow, divorced)	74 (44.3%)	73 (46.5%)	
Social security	No	2 (1.2%)	14 (8.9%)	0.001***
	Yes	165 (98.8%)	143 (92.3%)	
Working status	Unemployed	160 (95.8%)	111 (70.7%)	0.001***
	Employed	7 (4.2%)	46 (29.3%)	
Who does she/he live with?	Single	13 (7.8%)	7 (4.5%)	0.115
	Family	144 (86.2%)	138 (87.9%)	
	Friends-Relatives	7 (4.2%)	12 (7.6%)	
	Institution-caregiver	3 (1.8%)	0 (0.0%)	
Smoking	No	158 (94.6%)	104 (66.2%)	0.001***
	Yes	9 (5.4%)	53 (33.8%)	
Alcohol	No	164 (98.2%)	140 (89.2%)	0.001***
	Yes	3 (1.8%)	17 (10.8%)	
Use of psychoactive agents	No	162 (97.0%)	143 (91.1%)	0.023*
	Yes	5 (3.0%)	14 (8.9%)	
Physical disease	No	83 (49.7%)	140 (89.2%)	0.001***
	Yes	84 (50.3%)	17 (10.8%)	

Numerical data were evaluated with t-test, other data with chi-square test. *p<0.05, **p<0.01, ***p<0.001

Table 2. Application to psychiatric emergency services, evaluation and treatment characteristics

		65 years and over (n=167)	Between 18-64 (n=157)	p
Number of admissions		2.46±0.99	2.41±0.71	0.356
Accompanying during admission	Single	23 (13.8%)	88 (56.1%)	0.001*
	Family member	138 (82.6%)	58 (36.9%)	
	Other (friends, security staff, etc.)	6 (3.6%)	11 (7.0%)	
Admission type	Direct	155 (92.8%)	154 (98.1%)	0.076
	External referral	5 (3.0%)	1 (0.6%)	
	Consultation	7 (4.2%)	2 (1.3%)	
Admission for prescribing medication	No	164 (98.2%)	153 (97.5%)	0.642
	Yes	3 (1.8%)	4 (2.5%)	
Physical examination	No	155 (92.7%)	155 (98.7%)	0.009*
	Yes	12 (7.2%)	2 (1.3%)	
Consultation	No	134 (80.2%)	152 (96.8%)	0.001*
	Yes	33 (19.8%)	5 (3.2%)	
Treatment at emergency service	No	114 (68.3%)	106 (67.5%)	0.885
	Yes	53 (31.7%)	51 (32.5%)	
Treatment plan	Outpatient	126 (75.4%)	103 (65.6%)	0.052
	Inpatient	41 (24.6%)	54 (34.4%)	
Treatment arrangement	No	53 (31.7%)	87 (55.4%)	0.001*
	Yes	114 (68.3%)	70 (44.6%)	

Numerical data were evaluated with t-test, other data with chi-square test. *p<0.05, **p<0.01, ***p<0.001

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Table 3. Disease duration, clinical symptoms and findings

		65 years and over (n=167)	18-65 years (n=157)	p
Disease period	1-5 years	81 (48.5%)	78 (49.7%)	0.001***
	5-10 years	14 (8.4%)	43 (27.4%)	
	10-20 years	22 (13.2%)	28 (17.8%)	
	20-30 years	24 (14.4%)	7 (4.5%)	
	over 30 years	26 (15.6%)	1 (0.6%)	
Drug refusal	No	150 (89.8%)	130 (82.8%)	0.065
	Yes	27 (10.2%)	17 (17.2%)	
Decrease in sleep	No	97 (58.1%)	82 (52.2%)	0.290
	Yes	70 (41.9%)	75 (47.8%)	
Increase in sleep	No	167 (100%)	156 (99.4%)	0.302
	Yes	0 (0.00%)	1 (0.60%)	
Auditory hallucination	No	147 (88.0%)	138 (87.9%)	0.972
	Yes	20 (12%)	19 (12.1%)	
Visual hallucination	No	154(92.2%)	155 (98.7%)	0.005**
	Yes	13 (7.8%)	2 (1.3%)	
Thought of suicide	No	163 (97.6%)	152 (96.8%)	0.666
	Yes	4 (2.4%)	5 (3.2%)	
Suicide attempt	No	165 (98.8%)	151 (96.2)	0.128
	Yes	2 (1.2%)	6 (3.8%)	
Unhappiness	No	138 (82.6%)	126 (80.3%)	0.582
	Yes	29 (17.4)	31 (19.7%)	
Distress	No	111 (66.5%)	105 (66.9%)	0.937
	Yes	56 (33.5%)	52 (33.1%)	
Fear of death	No	162 (97%)	145 (92.4%)	0.061
	Yes	5 (3%)	12 (7.6%)	
Loss of appetite	No	152 (91.0%)	149 (94.9%)	0.173
	Yes	15 (9.0%)	8 (5.1%)	
Increased appetite	No	167 (100.0%)	157 (100.0%)	-
	Yes	0 (0.0%)	0 (0.0%)	
Somatic complaint	No	140 (83.8%)	106 (67.5%)	0.001***
	Yes	27 (16.2%)	51 (32.5%)	
Social withdrawal	No	161 (96.4%)	151 (96.2%)	0.913
	Yes	6 (3.6%)	6 (3.8%)	
Hyperactivity	No	149 (89.2%)	127 (80.9%)	0.035*
	Yes	18 (10.8%)	30 (19.1%)	
Persecution delusion	No	135 (80.8%)	122 (77.7%)	0.487
	Yes	32 (19.2%)	35 (22.5%)	
Reference delusion	No	165 (98.8%)	148 (94.3%)	0.024*
	Yes	2 (1.2%)	9 (5.7%)	
Jalusic delusion	No	164 (98.2%)	156 (99.4%)	0.345
	Yes	3 (1.8%)	1 (0.6%)	
Nihilistic delusion	No	167 (100.0%)	157 (100.0%)	-
	Yes	0 (0.0%)	0 (0.0%)	
Grandiose delusion	No	165 (98.8%)	152 (96.8%)	0.279
	Yes	2 (1.2%)	5 (3.2%)	
Memory impairment	No	154 (92.2%)	157 (100.0%)	0.001***
	Yes	13 (7.8%)	0 (0.0%)	
Behavioral problem	No	157 (94.0%)	154 (98.1%)	0.062
	Yes	10 (6.0%)	3 (1.9%)	
Verbal violence	No	111 (66.5%)	129 (82.2%)	0.001***
	Yes	56 (33.5%)	28 (17.8%)	
Physical violence	No	134 (80.2%)	123 (78.3%)	0.674
	Yes	33 (19.8%)	34 (21.7%)	

Chi-square and Fisher's exact tests were performed.
*p<0.05, **p<0.01, ***p<0.001

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Table 4. Psychiatric diagnosis distribution

	65 years and over (n=167)	18-65 years (n=157)	p
Depression	29 (17.4%)	37 (23.6%)	0.001***
Anxiety disorder	20 (12.0%)	19 (12.1%)	
Bipolar mood disorder	32 (19.2%)	46 (29.3%)	
Psychosis	41 (24.6%)	44 (28.0%)	
Behavioral and psychological symptoms related to dementia	39 (23.4%)	0 (0.0%)	
Mental retardation and behavior problems	2 (1.2%)	3 (1.9%)	
Alcohol and/or substance use disorder	1 (0.6%)	4 (2.5%)	
Adverse effect due to drug use	3 (1.8%)	4 (2.5%)	

Chi-square test was performed. ***p<0.001

(13). According to the results of our study, the majority of both groups were living with their families. Elderly people with loss of spouse are given care by their relatives (1). Even though the elderly were mostly living with their families, they were admitted to PES as recurrent. It is necessary to establish a system to determine the psychosocial and emotional needs of the elderly and the people with whom they live together, to provide them with education to increase their awareness and to produce the necessary solutions.

In the studies, it was stated that diagnosis and treatment were particularly difficult in elderly people with psychiatric diseases, and that these problems were complicated by comorbid diagnosis, multiple drug use and underlying psychosocial problems. It is emphasized that determination of organic etiological factors is vital (6,14-18). In our study, we found that the rate of comorbidity, physical examination and consultation was higher in the elderly who had recurrent admission to PES compared to the younger ones. While this situation is an indicator of more detailed evaluation and examination in evaluating the elderly patient in PES, the fact that the elderly patient recurrently admitted to PES is questioning the effectiveness of this service. While evaluating the elderly patient in PES, the importance of detailed examination was emphasized in terms of characteristics such as medical condition of the patient, medications used, substance abuse, cognitive functions and behavior changes. It was emphasized that detailed and careful evaluation of the elderly patient was the first step of safe separation from the emergency unit, well-regulated treatment and good results. For elderly patients, it has been reported that PES should be multidisciplinary (such as psychiatrists, internal medicine specialists, family physicians, social workers, specialist nurses often need to be integrated to other health care professionals), and should be linked to medical, psychiatric and social facilities (10,14,17). In PES in our country, the creation of units consisting of trained teams providing special services to the elderly will ensure effective management of admissions and avoid repeated application.

The elderly and young group had similar rates in terms of emergency treatment. The rate of drugs prescribed was higher in the elderly group as a result of emergency psychiatric evaluation. The decision of hospitalization was higher in young people (statistically significant borderline significance). This may indicate that the clinician evaluating the elderly in PES prioritizes the safety of the patient in terms of medical intervention, takes into consideration the service conditions and has difficulty in making the decision of admission. This difficulty may lead the elderly to refer to PES recurrently. Indeed, despite the low rates of admission to PES, it has been reported that the rate of admission is higher in comparison to older patients (16). Elderly patients who are admitted to PES should be established to provide post-emergent hospitalization, multidisciplinary service, effective, adequate safety, focused on solving problems and reliable discharge. In this way, the elderly admitted to PES can be hospitalized to the service when necessary and recurrent admission can be prevented by effective interventions. Our hospital is a private branch hospital and absence of geropsychiatric service can explain the low hospitalization rates.

Specific diagnosis rates of the elderly patients who were admitted to PES were 27-37% for cognitive disorders, 31-39% for mood disorders, 4-14% for anxiety disorders, 8-18% for psychotic disorders, 11-24% for substance use, 3-11% for adjustment disorder and 8% for personality disorders. Cognitive, psychotic and bipolar disorder diagnoses were higher in elderly patients who were admitted to PES (15,19,20). In another study in which the epidemiology of the elderly psychiatric patients admitted to the emergency department was investigated, substance abuse was found to be the most frequently diagnosed disorder with 27%, neuroses with 26% and psychoses with 21%. In another study of 118 elderly patients who presented to PES, 30% organic brain disease and 31% affective disorder-schizophrenia and other psychotic disorders were diagnosed (21). It was reported that the most frequently diagnosed diagnosis was dementia in patients admitted to the emergency department of geropsychiatry and if there is an additional psychiatric diagnosis, the probability of hospitalization is high (16). In elderly patients, behavioral or psychological symptoms related to delirium and/or dementia are the most common causes of PES admission. Urgent safety issues for both patient and staff coexist with diagnostic priorities in a setting not geared the first line non-pharmacological strategies of meetings psychosocial and emotional needs of patients. It has been reported that the development and implementation of successful methods to provide effective support and management

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of patients, their families and psychosocial and emotional problems due to dementia with behavioral and psychological symptoms may reduce the rate of recurrent admission, psychotropic drug use and hospitalization (22). In a study that examined socio-demographic, clinical and discharge status of elderly and young people who were admitted to PES, depression was the most common diagnosis in both groups and it was stated that 19.5% of the patients were diagnosed with dementia, the diagnosis of two or more medical diseases was more common, cognitive impairment was more common and moderate-severe functional impairment was reported (23). According to the results of our study, visual hallucinations, memory impairment and verbal violence are the most common diagnoses in the elderly, and psychosis, behavioral and psychological symptoms related to dementia, bipolar mood disorder, depression and anxiety disorder are the most frequent diagnoses in the elderly. In young people, bipolar mood disorder, psychosis, depression, anxiety disorder, and alcohol and/or substance use disorder are the most common. According to our results and findings, psychotic disorder cognitive problems, behavioral and psychological symptoms related to dementia are prominent in the elderly. However, the distribution of diagnoses in the elderly may very between studies. This difference may be affected by the characteristics of the sample included in the study, the study design (such as retrospective, prospective), the unit in which the study was performed (such as general hospital emergency service, PES), and the country and/or region where the study was conducted.

According to our findings, symptom profile and diagnosis distribution (psychotic disorder, cognitive problems and behavioral and psychological symptoms related to dementia) are compatible with the elderly patients admitted to PES recurrently. This group of patients is recurrently admitted to PES because of psychotic symptoms such as visual hallucinations, cognitive problems such as memory disorders, and behavior problems such as verbal violence. An elderly patient with cognitive impairment, psychotic symptoms and behavioral problems, the clinician and his team in PES conditions, the effective evaluation of the patient, the correct diagnosis, what can and should be done as behavioral or psychological interventions, when, how and what drug should be started and decision to receive an outpatient and/or inpatient treatment may be confronted with many problems such as the safe discharge from PES. Failure to resolve these problems properly may cause the patient and his/her relatives to admit to PES again.

When evaluating the elderly patient in PES, it is important to consider the medical, cognitive, psychiatric, functional and social areas in detail, and to allocate sufficient time for the family interview where the patient and the caregiver will also be evaluated. PES needs to be shaped to meet the needs of the elderly.

Study Limitations

The limitation of our study is that it is carried out from a single center, it is based on retrospective file records and it is based on the records of different evaluators.

CONCLUSION

Our findings and studies, elderly patients differ from young people in terms of physical disease comorbidity, physical examination, consultation request, symptom profile, diagnosis and treatment plan. The evaluation of the elderly patient will provide a multidisciplinary approach, the formation of professional teams in the field should be the main purpose. In this way, recurrent admissions of elderly people to PES can be prevented.

Ethics Committee Approval: Ethical committee approval was obtained from the Local Ethics Committee of İstanbul Bakırköy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital (approval number: 6779, date: 03.02.2014).

Informed Consent: Retrospective study.

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Original Investigation

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Evaluation of Factors Affecting Perioperative Mortality in Newborns with Critical Congenital Heart Disease

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ABSTRACT

Objective: Congenital heart diseases (CHD) are most common malformation group in neonatal period and their frequency ranges from 6 to 8 in 1.000 live births. Critical CHD constitutes approximately 25% of group and results in mortality if not diagnosed and treated in neonatal period. The aim of our study was to determine the factors affecting the perioperative mortality of patients with critical CHD.

Methods: Our study was performed retrospectively between July 2017 and December 2018. The demographic data, echocardiographic diagnosis and comorbidities of the patients were recorded. Patients who were discharged and who were dead were compared in terms of risk factors. In the descriptive analyses, the student's t-test was used for normally distributed numerical variables and the Mann-Whitney U test was used for non-normally distributed variables. Categorical variables were presented in percentages and by using cross tables.

Results: Ninety-two cases were included in the study, 19 were premature and 16 had additional organ anomalies, 23.9% had low birth weight. The rate of antenatal diagnosis was 39.1% and 14.1% of the cases needed resuscitation in the delivery room. During admission, 41 cases needed inotropic agent. Low birth weight, prematurity, resuscitation need, additional organ anomaly and need for inotropic support were found to be statistically significant in the mortality group (p=0.027, 0.026, 0.001, 0.001, 0.022, respectively).

Conclusion: Prematurity, low birth weight, and additional organ anomalies are critical risk factors for cardiac malformation. In addition, patients with active cardiopathy during intrauterine period are more resuscitated in the delivery room, their inotropic needs are higher, and they have higher mortality.

Keywords: Newborn, critical congenital heart disease, mortality

INTRODUCTION

Congenital heart disease (CHD) is the most common malformation group seen in the newborn period and its frequency varies between 6-8 per 1.000 live births (1). This group includes a range of diseases ranging from benign anomalies to severe anomalies in which early diagnosis and treatment are required for the baby to survive. The subgroup of severe anomalies is called critical CHD and its frequency is 1.2/1.000 live births (1,2). Unfortunately, these cases, which are associated with high mortality and morbidity in case of delay in diagnosis, may not give finding until the mother and baby couple are discharged (3).

With the increase in antenatal diagnosis opportunities and the spread of the CHD screening program with pulse oximetry in the postnatal period, the rates of diagnosis were increased before the newborn babies became symptomatic. Although it is a logical approach that a patient with critical CHD may have an antenatal diagnosis and proper perinatal management, its prognosis may be better, contradictory results have been obtained in the studies on the subject. Although some studies have found significant improvements in surgical survival in severe congenital heart anomalies such as hypoplastic left heart syndrome (HLHS), aortic coarctation, and large arterial transposition, other studies have not shown that being diagnosed with antenatal in similar patient

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populations creates a significant advantage (4-8). The reason for this is that antenatal detection rates of anomalies with a much heavier and fatal single ventricle physiology are higher.

Critical CHD mortality in developed countries varies between 15 and 25% and varies according to the type of cardiac defect and time of diagnosis (9-11). Although the prognosis has improved due to the advances in medical and surgical methods, the risk of mortality and morbidity still continues compared to the normal population (12).

In the studies conducted, additional factors such as accompanying major organ anomalies, chromosomal disorders, low birth weight of the case, premature birth and low APGAR score as well as the severity of cardiac anomaly were found to contribute to the surgical mortality of these patients (13,14). However, since these studies did not include cases who were lost before surgery or intervention or whose pathology was not suitable for intervention, they cannot fully demonstrate perioperative risk factors.

The aim of our study is to reveal the risk factors affecting the perioperative mortality of the newborns diagnosed with critical CHD and followed and treated in our center, which is a 3rd level neonatal intensive care and congenital cardiac surgery clinic.

METHODS

Design: Our study was conducted as single-centered by retrospectively examining the files of the patients diagnosed with critical CHD, who were followed up in the neonatal intensive care unit of our hospital in a single-center period in the 18-month period between July 2017 and December 2018.

Definition: Critical CHD is a structural cardiac malformation that progresses with mortality and morbidity, causing cardiovascular insufficiency when not treated in the first 4 weeks of neonatal period. Large artery transposition (LAT), aortic coarctation, intermittent arcus aorta, critical aortic valve stenosis, HLHS, pulmonary atresia/critical pulmonary valve stenosis, tricuspid atresia, Fallot tetralogy which is critical pulmonary outflow stenosis, and single ventricle cases, Ebstein anomaly, truncus arteriosus and total abnormal pulmonary venous return anomaly are included in this group.

Inclusion Criteria

In our study, patients who were referred to our neonatal intensive care unit during the neonatal period (first postnatal 28 days) for the pre-diagnosis of CHD and whose echocardiography revealed critical CHD were included.

Exclusion Criteria

1. Structural congenital malformations (ventricular septal defect, complete atrioventricular septal defect, atrial septal defect, and Fallot tetralogy cases with good pulmonary artery anatomy) that do not require intervention (angiography, cardiac surgery) but require medical follow-up in the neonatal period.

2. Cases of premature ductus arteriosus cases without a response to medical treatment, who were directed to us from external centers for surgical treatment, were not included in the study.

Data of Cases

The centers the cases came from (external center, our hospital), gender, birth weight, gestational week, type of delivery, need for resuscitation in the delivery room (positive pressure ventilation, intubation, chest compression, drug administration), time of diagnosis (before antenatal, postpartum discharge of mother and baby at the hospital, application from the home postnatally), the day of admission to our hospital (for those admitted in the first 24 hours or for cases born in our hospital, the day of admission was recorded as the 1st day), and mechanical ventilator support during the application to our center (non-invasive or invasive) and/or receiving inotropic drugs, day of intervention (angiography, cardiac surgery), pre-intervention period, echocardiography diagnosis, other accompanying organ anomalies, discharge time, whether there was mortality before or after the intervention, if there was mortality, the time and cause were recorded in the prepared forms.

Independent variables were prematurity (gestational week 36+6/7 and smaller), low birth weight (less than 2.500 grams), having an antenatal diagnosis, presence of other organ anomalies, need for resuscitation in the delivery room, need for a mechanical ventilator during admission to our center, and need for inotropic agent at admission.

Dependent variables were pre-intervention mortality and mortality during hospitalization.

Ethics Committee Approval and Patient Consent

Ethics committee approval of our study was obtained from the Ethics Committee for Science, Social and Non-Interventional Health Sciences Research at University of Health Sciences, İstanbul Yeni Yüzyıl University (approval number: 2019/2, date: 04.02.2019). Written consent was obtained from the families of all cases included in the study prior to medical and surgical interventions.

Statistical Analysis

Statistical analyses were performed using SPSS version 13 software. Descriptive analyses were given using the mean and standard deviations for normally distributed numerical variables and compared using the student's t-test. Non-normally distributed variables were given using median and interquartile values and compared using the Mann-Whitney U test. Categorical variables were presented as a percentage and given using cross tables. Whether there was a difference between the groups was compared using the chi-square or Fisher tests. Situations in which the P-value was below 0.05 were considered statistically significant.

RESULTS

Of the 92 cases included in the study, 57 (62%) were male and 19 (20.6%) were preterm babies. The mean gestational week was 37.8±2.1 weeks, and the mean birth weights were 2.986±680 grams. The number of cases with low birth weight (<2.500 grams) was 22 (23.9%). While the rate of having a prenatal diagnosis was 39.1%, 14.1% of the study group needed resuscitation in the delivery room.

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The average day of admission of cases to our clinic was 4.7 days. During the application, 52 cases received mechanical ventilation (42 invasive, 10 non-invasive), and 41 received inotropic agent support. During the clinical follow-up, 6 cases died without any intervention, and 19 cases died during or after the intervention. While the overall mortality of the case group was 27%, intervention mortality was 22%. The demographic and clinical features of the cases are detailed in Table 1.

In 16 of the cases, there were other organ anomalies and genetic disorders accompanying cardiac anomalies. Trisomy 21, renal agenesis/hypoplasia, esophageal atresia were the most common anomaly and genetic disorder with two cases. Genetic and organ anomalies detected in the study group are given in detail in Table 2.

Cyanotic CHD was present in 72 (78.2%) of the cases. According to the frequency of occurrence, 24 cases with HLHS, 18 cases with LAT, and 12 cases with pulmonary atresia were on the first three ranks. The diagnoses of our acyanotic cases were aortic coarctation and intermittent arcus aorta (20 cases in total). Distribution of the cases according to their echocardiographic diagnosis is shown in Table 3.

The majority of the cases lost during their clinical follow-up were followed up with the diagnosis of HLHS (2 before, 10 during and after the intervention). Mortality was observed in 9 cases with a rate of 14% in 64 cases who were diagnosed and attempted other than HLHS. The distribution of lost cases by diagnosis and time of mortality is shown in Table 4.

When the factors affecting the prognosis during clinical follow-up of the cases were examined, the rates of having low birth weight, being born prematurely, the need for resuscitation in the delivery room, other accompanying organ anomalies and the need for an inotropic agent at the time of admission to our clinic were found to be statistically significant in cases that resulted in mortality. Comparative analysis of the two groups is shown in Table 5.

DISCUSSION

CHDs are the most common major birth defect and mostly consist of mild lesions that do not require intervention (small ventricular septal defect, atrial septal defect, mild pulmonary stenosis). However, 1/3-1/4 of the cases are in the critical CHD group that requires early intervention. While children with severe CHD had a 30% chance of getting adult until fifty years ago, success was increased in interventional procedures and a serious improvement in prognosis was observed as a result of increased knowledge in cardiac surgery and cardiology and dizzying technological developments (14). Thanks to the developments in the field of obstetrics and neonatology, recognition of these cases in the fetal period, careful antenatal follow-up, appropriate management of the natal and postnatal period were provided and contributed to the improvement in prognosis.

The main factors that determine surgical mortality in critical CHD are the severity of cardiac malformation, the time of diagnosis and other accompanying features (15,16). In our study, while our perioperative mortality rate was 27%, our intervention mortality was 22% similar to the data of developed countries. We think that our perioperative and surgical mortality increased because of the patients with HLHS at the rate of 26.1% and high mortality of this diagnostic group globally. In the literature, neonatal mortality increases to as high as 68% in patients with HLHS (15). In our case

Table 1. Demographic and clinical features of cases included in the study

Gender, n (%)	
Female	35 (38)
Male	57 (62)
Birth weight (mean ± standard deviation, minimum-maximum)	2986.7±680.8 (920-4810)
Gestational week (mean ± standard deviation, minimum-maximum)	37.8±2.1 (29-41)
Place of birth, n (%)	
External center	85 (92.4)
Our hospital	7 (7.6)
Type of delivery[b], n (%)	
Nsvd	45 (48.9)
Cs	47 (51.1)
Delivery room resuscitation, n (%)	13 (14.1)
Time of diagnosis[ß], n (%)	
Antenatal	36 (39.1)
Postnatal hospital	30 (32.6)
Postnatal home	26 (28.3)
Admission day (mean ± standard deviation, minimum-maximum)	4.7±5.3 (1-26)
Mechanical ventilator support at admission, n (%)	52 (56.5)
Non-invasive, n	10
Invasive, n	42
Inotropic agent need at admission, n (%)	41 (44.6)
Duration of pre-intervention hospitalization (mean ± standard deviation, minimum-maximum)	8.9±8.2 (1-35)
Day of operation (mean ± standard deviation, minimum-maximum)	13.7±8.9 (2-38)
Day of discharge (mean ± standard deviation, minimum-maximum)	37±17.6 (14-88)
Mortality, n/total (%)	25/92 (27%)
Before intervention	6/92 (6.5%)
Intervention and afterwards	19/92 (20.6%)
Intervention mortality, n/total intervention (%)	19/86 (22%)
Mortality day (mean ± standard deviation, minimum-maximum)	26.7±27.1 (2-119)

[b]Nsvd: Normal spontaneous vaginal delivery, Cs: caesarian delivery, [ß]Postnatal Hospital: diagnosis before the discharge of mother and baby, Postnatal home: diagnosis after the emergence of symptoms after mother-baby couple is discharged to home

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group, this rate was 50% perioperatively and 45% postoperatively. The overall mortality of our cases with other echocardiographic diagnoses was 19%.

In our study, besides the severity of heart anomaly, other factors affecting mortality were found to be having low birth weight, preterm birth, need for resuscitation in the delivery room, accompanying other organ anomaly and need for inotropic agents during admission.

When the literature is examined, it was found that the low APGAR score (5th minute score <7) in various studies increased surgical mortality (14). The reason for this was explained in the way that cardiopathy was active in the antenatal period and the supply of nutrients and oxygen to the fetus was insufficient.

In another study involving 439 newborns with an antenatal diagnosis rate of 67%, the fact that the APGAR scores of the case did not correlate with the diagnosis time reinforces this hypothesis (7). In our study, the problem of adaptation to postnatal life, which is a different dimension of this situation, was observed, 13 cases (14.1%) needed resuscitation in the delivery room. The fact that

Table 2. Other organ anomalies and genetic disorders accompanying heart anomaly

Accompanying anomalies, n (%)	**16 (17.4)**
Trisomy 21, n	2
Renal agenesis/hypoplasia, n	2
Esophageal atresia, n	2
Hydrocephalus, n	1
Congenital cataract, n	1
Corpus callosum agenesis, n	1
Sacrococcygeal teratoma, n	1
Posterior urethral valve, n	1
Anal atresia, n	1
Microcephaly, n	1
Bronchomalacia, n	1
Cleft palate, n	1
Biliary atresia, n	1

n: Number

Table 3. Distribution of cases according to echocardiographic diagnoses

	Number of cases (n)	**Ratio to total number of cases (%)**
Cyanotic congenital heart disease	**72**	**78,2**
Hypoplastic left heart syndrome	24	26,1
Great arterial transposition	18	19,6
Pulmonary atresia	12	13
Fallot tetralogy	4	4,3
Total abnormal pulmonary venous return anomaly	4	4,3
Tricuspid Atresia	3	3,3
Double outlet right ventricle + pulmonary stenosis	3	3,3
Critical pulmonary stenosis	3	3,3
Ebstein anomaly	1	1,1
Acyanotic congenital heart disease	**20**	**21,7**
Aorta coarctation	14	15,2
Intermittent arcus aorta	6	6,5
Total	**92**	**100**

Table 4. Distribution of cases resulting in mortality by diagnosis

Echocardiographic Diagnosis	**Pre-intervention mortality**	**During and post interventional mortality**	**Total mortality/ total number of cases, (%)**
Hypoplastic left heart syndrome	2	10	12/24 (50%)
Great arterial transposition	2	2	4/18 (22.2%)
Pulmonary atresia	-	3	3/12 (25%)
Aorta coarctation	-	2	2/14 (14.2%)
Double outlet right ventricle + pulmonary stenosis	-	2	2/3 (66.6%)
Intermittent arcus aorta	1	-	1/6 (16.6%)
Ebstein anomaly	1	-	1/1 (100%)
Total	6	19	25/92 (27.1%)

Table 5. Evaluation of risk factors affecting mortality of cases

Parameter	**Cases resulting in discharge (n=67)**	**Cases resulting in mortality (n=25)**	**p**
Birth weight (mean ± standard deviation)	3073.8±599.9	2753.4±830.3	0.087
Low birth weight (<2500 gram)	12 (17.9%)	10 (40%)	**0.027**
Gestational week (mean ± standard deviation)	38.3±1.6	36.6±2.8	**0.007**
Premature birth (<37 gestational week)	10 (14.9%)	9 (36%)	**0.026**
Absence of antenatal diagnosis	38 (56.7%)	18 (72%)	0.181
Need for resuscitation in the delivery room	3 (4.4%)	10 (40%)	**0.000**
Need for mechanical ventilator at admission	36 (53.7%)	16 (64%)	0.377
Need for inotropic agent at admission	25 (37.3%)	16 (64%)	**0.022**
Accompanying other organ anomaly	6 (8.9%)	10 (40%)	**0.000**

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10 of the resuscitated cases resulted in mortality also showed that cardiopathy, which started in the antenatal period in congenital heart patients and affected postnatal adaptation, was closely related to surgical mortality. Again, in our study, we found that overall mortality was significantly higher in patients who needed inotropy to provide normotension and cardiac contractility before intervention due to this cardiopathic condition.

Studies have shown that low birth weight is an important factor in mortality in congenital cardiac surgery (17-19). In our study, although the birth weight average of the group that resulted in mortality was lower than the group discharged, this difference was not statistically significant (p=0.087). However, the rate of the number of cases below 2.500 grams, which was accepted as the surgical margin in the majority of the studies, was found to be significantly higher in the group resulting in mortality. In addition to increasing the surgical risk, low birth weight increases mortality as an independent risk factor in the pre-intervention period. The low birth weight of 4 of our 6 cases who died before intervention reveals this risk.

Being born prematurely is the cause of low birth weight in addition to immature organ systems and plays an important risk factor for cardiac surgery. In the literature, it has been shown to be an important risk in many studies, and some studies have identified below 39 pregnancy weeks for surgical risk (19-21).

In accordance with the literature, our study found that the mean gestational week was significantly lower in the mortality group (36.6±2.8 gestational weeks versus 38.3±1.6), and the prematurity rate was as high as 36% to 14.9%. Both parameters are statistically significant (p=0.007 and 0.026, respectively). The fact that 50% (n=3) of the cases lost before intervention was preterm shows that being born before 37 weeks of gestation is an independent risk in terms of decreasing the chance of intervention.

It is known that the cause of 20% of CHD cases is a part of chromosome anomalies, single gene disorders and syndromes (22). In our study group, 14 (15.2%) patients had accompanying non-cardiac anomalies, while 2 (2.1%) cases had trisomy 21. Extracardiac anomalies and chromosomal disorders have been shown to increase the risk of mortality in critical CHDs (23). In our study, the frequency of non-cardiac anomalies was found to be significantly higher in the group with mortality. Again, 3 of the 6 cases lost before the intervention were found to have major organ anomalies.

Among the factors affecting the critical CHD prognosis, one of the most studied conditions is the timing of diagnosis. While prenatal diagnosis rates are around 30-40% especially in developed countries in the early 2.000s, this rate has reached the 75-80% band in recent years (6,24). In various studies, cases with antenatal diagnosis were compared with undiagnozed cases in terms of mortality. It is thought that having an antenatal diagnosis allows immediate start of medical treatment for the maintenance of the ductus patency of the newborn baby, thereby preventing metabolic acidosis, hypoxemia and end organ damage and reducing mortality and morbidity. In many case series, it has been shown to reduce the mortality rate in patients with HLHS, LAT, and aortic coarctation (4-6). However, these findings were not repeated in studies with similar case series and no difference was found in terms of mortality and postnatal diagnosis (8,24). This has been attributed to increased frequency of diagnosis of more complex and severe cardiac anomalies such as HLHS with increasing frequency of fetal echocardiography. In the study of Oster et al. (15), early diagnosis and poor prognosis were found to be correlated. The reason for this situation is that the group with antenatal diagnosis has more complex cardiac anomalies, and fetal echocardiography is performed in patients with chromosome anomalies detected in screening tests. In our study, when patients with and without antenatal diagnosis were compared in terms of mortality, no significant effect on survival was shown. Although 18 of 25 cases resulting in mortality did not have antenatal diagnosis, 38 of our 67 cases did not have prenatal diagnosis. In our case group, we think that the most common echocardiographic diagnosis group is those with HLHS and the diagnosis timing does not change the prognosis because the severity of the disease determines surgical mortality in this anomaly. However, none of the 6 cases with mortality in the pre-intervention period had antenatal diagnosis, and this emphasizes the importance of this condition. As soon as the newborn is diagnosed, it is possible to make the necessary interventions in ideal conditions, as well as to prepare the family for the psychological condition and to have them get information about the disease of their babies (25). As a matter of fact, in a metanalysis including 8 studies, it has been found that antenatal diagnosis reduces mortality before planned surgery (10).

CONCLUSION

Being born prematurely, having low birth weight, and additional organ anomaly are risk factors independent of the severity of cardiac malformation in terms of mortality in critical CHD. Apart from these, the patients whose cardiopathies are active in the intrauterine period are more resuscitated in the delivery room, their inotropic needs are higher and progress with higher mortality. With the increase in antenatal diagnosis rates, the patients with this high risk can be given care under more favorable conditions and the mortality rate before the intervention will decrease. We also think that postoperative mortality will decrease as these cases can be intervened in a better clinical condition.

It will be possible to reach the rates in developed countries by combining perinatal centers with cardiac surgery centers for increasing their number and expanding them to all regions in our country, which will shorten the transport time, and by working in close cooperation with newborn clinics and child intensive care specialists in surgical centers.

Ethics Committee Approval: Ethics committee approval of our study was obtained from the Ethics Committee for Science, Social and Non-Interventional Health Sciences Research at University of Health Sciences, İstanbul Yeni Yüzyıl University (approval number: 2019/2, date: 04.02.2019).

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The Comparison of the Management Models for Identifying the Risk of Serious Bacterial Infection in Newborn Infants with a Newly Developed Scale

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ABSTRACT

Objective: We aimed to evaluate the major approach protocols of fever in febrile newborn and to define the incidence of serious bacterial infections (SBI) in febrile newborns.

Methods: This study was designed as a prospective observational cohort study and directed between January 2011 and December 2015. All newborns with a rectal temperature of ≥38 °C and admitted to the neonatal intensive care unit were eligible for participation in the study. Infants were evaluated and classified as low-risk using the Boston criteria, the Philadelphia criteria, and the Rochester criteria, and our newly developed İstanbul criteria. The protocol results were compared regarding calculations of sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and likelihood ratio (LR).

Results: During the study period, 328 infants were enrolled and the frequency of SBI was found as 38.4%. The leading etiology was fever of unknown origin with 43.6%, followed by urinary tract infection, dehydration, and bacteremia, accounting for 15.5%, 14%, and 5.8%, respectively. The highest sensitivity and NPV and the lowest negative LR were noted with the İstanbul protocol. The highest PPV was found in the Philadelphia and Boston protocols.

Conclusion: The low-risk criteria of febrile infant protocols are not sufficiently reliable to exclude the presence of SBI in febrile neonates. The low-risk criteria in our new protocol were detected to be more reliable and may be useful in excluding SBI in the neonatal period.

Keywords: Fever, newborn, management, serious bacterial infections, dehydration, bacteremia

INTRODUCTION

Febrile neonates are at higher risk of serious bacterial infections (SBI). They often need to undergo extensive laboratory investigations and to be hospitalized because if a SBI in a neonate is not diagnosed and treated promptly, it may lead to undesirable consequences. However, the origin of fever in some cases is not infection or other serious diseases, and routine hospitalization or antibiotic treatment are not essential in all neonates. Additionally, iatrogenic complications and emotional stress in parents may increase due to the hospitalization of the infants (1). The widely accepted approach is to determine babies at high risk for SBI and hospitalization, who need intravenous antibiotic treatment, and babies at low risk for SBI, who require treatment on an outpatient basis with or without antibiotics (2-4).

Different approaches for the determination of low-risk neonates

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for SBI have been compared (5,6). There are three studies addressing the efficacy and safety of outpatient management of febrile infants who are considered to be at low risk for SBI (3,6,7). The Philadelphia, Boston, and Rochester protocols can be used for infants aged less than 90 days and with fever, but they are not suitable during the neonatal period (6,8). The universally acknowledged approach is to use the Rochester criteria, which assess clinical and laboratory evidence to identify low-risk and high-risk groups (8). Even though the negative predictive value (NPV) of these criteria for SBI is as high as 95-100%, the protocol is not adopted generally for outpatient follow-up of a newborn with fever (1). It is suggested that low-risk criteria are not satisfactory in excluding the presence of SBI in febrile neonates and all febrile neonates aged ≤28 days should be hospitalized and undergo a complete sepsis evaluation, and empirical intravenous antibiotic therapy should be given (9).

We developed a new protocol for febrile neonates, which differs from other protocols for febrile infants. First, our protocol included only febrile newborn babies (gestational age ≥35 weeks and within 28 days of life). Secondly, we added C-reactive protein (CRP) levels in the laboratory examination. Lastly, we defined dehydration in febrile newborn. The aims of our study were to evaluate the usefulness of our new protocol and to compare it with major protocols used for evaluating febrile infants.

METHODS

This study was designed as a prospective observational cohort study, directed from January 2011 to December 2015 (5 years) at a tertiary care university-affiliated education and research hospital in İstanbul. The study protocol was approved by: Şişli Etfal Training and Research Hospital Ethic Committee (approval number: 745-2011). Written informed consent was obtained from the parents. This is a prospective observational cohort study registered at the NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), with number NCT03183531.

The study consisted of two steps. The first step included the evaluation of the clinical and laboratory characteristics of febrile neonates and described the etiology and causative organisms in febrile neonates, which was published (10). The second step was formed by the data obtained in the first step. We have developed a new protocol that can be applied to febrile newborn babies. In the literature, protocols that evaluate febrile babies include infants in the first 90 days of life, there is not any protocol including only newborn babies. The aim of the second step (present study) was to evaluate the usefulness of our new protocol and major protocols of febrile infants in the assessment of only newborns with fever.

Study Population

All neonates (aged 1 to 28 days) who were admitted to our neonatal clinic with a rectal temperature ≥38 °C (documented at medical evaluation) were eligible for the study. Gestational age <35 weeks, refusal for participation by parents, chromosome anomaly, the presence of a chronic illness, congenital anomaly (e.g., anencephaly, truncus arteriosus), admission to pediatric surgery, antibiotic use before hospitalization, and insufficient records were accepted as exclusion criteria.

Patients Data

The following data were collected from all babies included in the study: The demographic features (birth weight, age and gender), general evaluation (appearing good and ill), medical history, physical examination signs, laboratory analysis results, and exact diagnosis. All patients underwent laboratory examinations containing: blood count, CRP, serum chemistry and blood culture, urine analysis and urine culture (obtained by bladder catheterization). Lumbar puncture and cerebrospinal fluid assessment were performed in the presence of neurological signs. If there was evidence of respiratory tract infection, X-Ray was performed.

Definition of Serious Bacterial Infections

The SBI acceptance criteria were as follows: Firstly, the growth of a known pathogenic bacteria in cultures [bacteremia, meningitis, pneumonia and urinary tract infection (UTI)] and secondly any disease that is often associated with bacterial pathogens such as abscess, mastitis, omphalitis, acute otitis media and cellulitis. The diagnosis of pneumonia was made according to the lung X-Ray findings presented by the radiologist.

All samples were assessed using standard microbiological methods to culture. The sample was not processed for viral cultures. If the organism is known to cause disease in neonate, blood culture isolates are accepted to be pathogenic. The isolation of a single pathogen by catheterization with $>10^4$ colony-forming units/mL in urine was considered UTI. Leukocyte ≥10 cells/mm^3 in uncentrifuged urine or with the dipstick stripe a positive result for nitrite or leucocyte esterase was defined as positive urine analysis.

Viral agent evaluation methods: Newborn with respiratory signs such as runny nose, sneezing or coughing were assessed from nasopharyngeal secretions by influenza-Ag (immunoassay test produced by Dalian Rongbang Medical Healthy Devices, Spain) and respiratory syncytial virus antigen: Rapid immunochromatographic test produced by Prima lab SA, Switzerland).

Definition of dehydration: All neonates were weighed at admission and weight loss was assessed according to the birth weight. Dehydration is defined as the weight loss more than twelve percent with a serum sodium level ≥145 mEq/L.

Our newly proposed protocol (İstanbul) includes: (1) Unremarkable medical history (no perinatal antibiotic use, no chronic disease, no hospitalization longer than the mother); (2) good appearance (unremarkable physical examination); (3) no focal physical signs of infection; (4) CRP level <1 mg/dL; (5) white blood cell count 5000-15.000/mm^3 and immature/total neutrophil ratio (I/T) <0.2; and (6) normal urine analysis.

Infants who met these criteria were considered to be at low risk for SBI. All infants were classified as low risk using the criteria of the Rochester, Boston, Philadelphia and İstanbul protocols. The criteria of the four protocols are presented in Table 1. Our

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newly created protocol is different because of its inclusion of only febrile newborns, the addition of CRP levels in the laboratory examination, and with defined dehydration in febrile newborn features (Table 1).

Statistical Analysis

Statistical analysis was performed with SPSS version 16.0 (SPSS, Chicago, IL, USA). Categorical variables are given in percentages with mean ± standard deviation. The positive predictive value (PPV), NPV, and likelihood ratio (LR) for SBI of the low-risk criteria were calculated using the standard statistical formula. All patients were evaluated according to the Boston, Philadelphia, Rochester, and İstanbul protocols, and the results were compared for sensitivity, specificity, NPV, PPV, and accuracy values for predicting SBI. Statistical significance was accepted as $p<0.05$.

RESULTS

In the study period, 412 febrile newborns aged ≤28 days, who were hospitalized due to fever, were evaluated. The flow diagram of study is presented in Figure 1. A total of 328 infants fulfilled the inclusion criteria of the study. Of 328 infants in the study, 184 (56.1%) were boys. The mean birth weight was 3214±492 gram, gestational age was 39.2±1.4 weeks, mean rectal temperature was 38.3±0.4 °C (lower and upper limit: 38-40 °C), and the mean age during admission to the hospital was 12.5±8.0 days (lower and upper limit 1-28 days). The ratio of SBI was found to be 38.4% during the study period.

Febrile illness with no detectable cause was the most common diagnosis which accounted for 43.6% of all cases. UTI (15.5%), dehydration (14%), bacteremia (5.8%) pneumonia (5.5%), viral respiratory tract infection (4.0%), and meningitis (3.7%) were the next most common diagnoses.

The comparison of sensitivity, specificity, PPV, NPV, and LR for the four protocols is presented in Table 2. The highest sensitivity and NPV and the lowest LR (-) were observed in İstanbul protocol, whereas high specificity and the highest LR (+) were detected in the Boston protocol. The highest PPV was found in the Philadelphia and Boston protocols (Table 2).

DISCUSSION

In current protocols for the evaluation of fever in infants aged ≤3 months, if no risk of severe bacterial infection is determined, infants can be observed without admission with close examination and monitoring. However, this approach is widely deemed as unacceptable in the neonatal period. The main purpose of our

Table 1. Evaluation criteria and differences of Boston, Philadelphia, Rochester and İstanbul protocols

	Boston[6]	Philadelphia[11]	Rochester[8]	İstanbul
Study design	Prospective	Prospective	Prospective	Prospective
Study period	3 years (1987-1990)	5 years (1987-1992)	8 years (1984-1992)	5 years (2011-2015)
Patient group	**28-89 days**	**29-60 days**	**≤60 days**	**≤28 days**
Criteria				
Temperature, rectal, °C	≥38.0	≥38.2	≥38.0	≥38.0
History	No immunization within last 48 hours, No antimicrobial given within 48 hours	Not defined	No perinatal antibiotics, No underlying disease, Not hospitalized longer than the mother	No perinatal antibiotics, No underlying disease, Not hospitalized longer than the mother
Well appearance with unremarkable physical examination and absence of any local infection	**+**	**+**	**+**	**+**
Gestational age	**–**	–	≥37 weeks	**≥35 weeks**
Healthy before	**+**	Not defined	**+**	**+**
Absence of dehydration	**+**	Not defined	Not defined	**+**
Leucocyte count, cells/mm^3	**<20.000**	**<15.000**	**5.000-15.000**	**5.000-15.000**
Band/neutrophil ratio (I/T)	Not defined	**<0.2**	**ABC ≤1.500**	**<0.2**
Urine analysis, WBC/hpf	**<10**	**<10**	**≤10**	**<10**
CSF, leucocyte, cells/mm^3	**<10**	**<8**	**Not defined**	**<10**
Chest radiography	**No infiltration (if obtained)**	**No infiltration**	**No focal infiltration (if clinically indicated)**	**No infiltration (if clinically indicated)**
Stool examination	Not defined	No blood or leucocyte (if indicated)	≤5 leucocyte (if indicated)	<5 leucocyte (if indicated)
CRP	--	--	--	<1 mg/dL

ABC: Absolute band form, WBC: white blood cells, CSF: cerebrospinal fluid, CRP: C-reactive protein

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study was to investigate whether these protocols were suitable for monitoring febrile newborn infants.

The management of febrile illnesses in babies aged <90 days vary considerably among physicians. The reason for this variation is associated with the wide range of management protocols suggested during the last few decades (6-8,11). The current suggestions for the assessment and management of young febrile infants are based on studies conducted in the late 1980s and early 1990s (12). The globally accepted approach is to determine infants at high risk for SBI and in need of hospitalization for intravenous antibiotic treatment, and also to determine infants at low risk, who can safely go through outpatient care with or without antibiotics therapy (4). Three main studies reported the efficacy and safety of outpatient management of febrile infants considered at low risk for SBI (6,8,11). The rate of newborn infants in these three studies was 10-15% of all infants, which is very low. In a comprehensive review on SBI identification in infants younger than 90 days, it was stated that the Boston and Philadelphia protocols were more accurate when applied to older infants rather than neonates. The Rochester protocol, on the other hand, was more accurate for neonates than older infants (12).

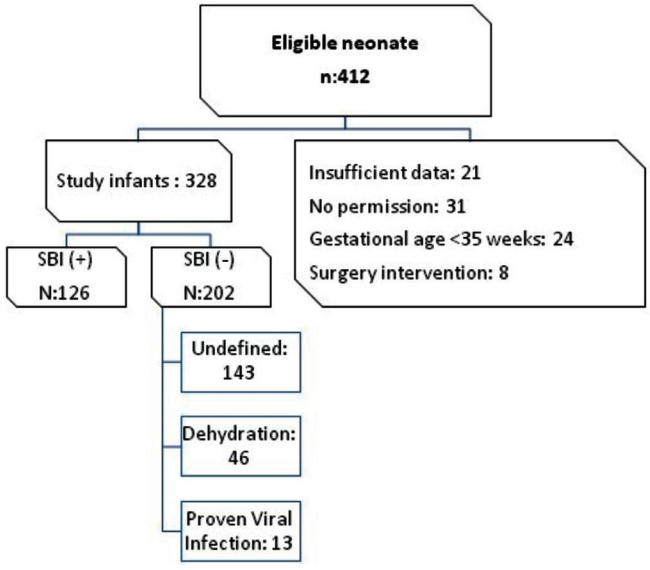

Figure 1. Flow diagram of the study
SBI: Serious bacterial infections

The management and treatment of newborns with fever vary widely among centers (13). These differences indicate the need of national or international guidelines for the evaluation of fever in neonatal period. Accordingly, given that the prevalence of SBI is higher in neonatal period, generally accepted practice in most centers is a full sepsis evaluation and hospitalization (14).

The prevalence of SBI in infants less than 3 months with fever is about 7.1-19.7%. The prevalence of SBI is higher in neonatal period (9-28%) than in infants aged 2-3 months (7.1%) (15-21). Garcia et al. (17) reported SBI prevalence as 31.9%, 33.3%, and 18.3% in infants aged 7-14 days, 15-21 days, and >21 days, respectively. In our study the incidence of SBI was high and our findings supported that SBI was seen more frequently in the newborn babies.

Several protocols that bring clinical and laboratory criteria together to diagnose young infants (<90 days of life) at low risk for SBI, who can be safely managed as outpatients, have been published. The use of these protocols are advised for different age groups of infants (Philadelphia: 29-60 days; Rochester: 60 days or younger; Boston: 28-89 days) (6,8,11). Our protocol was designed to be used only in newborn (0-28 days) babies. The main aim of our study was to evaluate febrile newborns in their first month of life according to these protocols. When evaluated separately, the neonates did not show similar test characteristics with older children or the whole group aged <3 months. The combined laboratory and clinical parameters demonstrated lower sensitivity in neonates as compared to older groups. Likewise, the false-positive rate for SBI tended to be higher in neonates compared to older infants (12). The comparison of different diagnostic tests across the age groups (≤28 days vs >29 days) was possible only for a few selected criteria reported in 14 studies. The Boston criteria and Philadelphia protocol have shown higher sensitivity, lower specificity, smaller PPV, and similar NPV when applied to older infants (age >28 days) compared to newborn babies for overall SBI or bacteremia. Contrarily, the Rochester criteria were more accurate (higher sensitivity, specificity, and PPV) in neonates than in older infants for SBI or bacteremia. The false positive ratio for SBI (i.e., the percentage of infants with SBI classified as low risk) tended to be higher for neonates (1.0% to 6.25%) versus older infants (0% to 5.4%) (12).

Table 2. The effectiveness of the protocols in identifying serious bacterial infections in febrile neonates

Protocols	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	LR (+)	LR (–)
Boston	61.6% (54-68.7)	81.7% (75.1-86.9)	77.1% (69.2-83.5)	68% (61.2-74.1)	71.7% (66.5-76.3)	3.37	0.47
Rochester	47.6% (40.1-55.2)	72% (64.6-78.3)	62.9% (54.1-70.9)	57.8% (51-64.4)	59.8% (54.4-64.9)	1.70	0.73
Philadelphia	67.7% (60.2-74.4)	79.9% (73.1-85.3)	77.1% (69.6-83.2)	71.2% (64.3-77.3)	73.8% (68.8-78.2)	3.36	0.41
İstanbul	81.7% (75.1-86.9)	56.1% (48.4-63.5)	65% (58.3-71.2)	75.4% (67.1-82.2)	68.9% (63.7-73.7)	1.87	0.33

CI: Confidence interval, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio

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Study Limitations

This study has some limitations. The study included only febrile neonates but many more neonates presented with or developed SBI without fever. Neonates with non-febrile sepsis were not included in the study. Further studies with larger patient series are needed to validate our new protocol.

CONCLUSION

In this prospective observational study, we performed a comparison of the results of four protocols (Rochester, Philadelphia, Boston and İstanbul) in 328 febrile neonates. Our study demonstrated that the incidence of SBI in febrile newborns was encountered with higher rates. The most common etiology was UTI in neonates with SBI. The low-risk criteria of the Rochester, Philadelphia, and Boston protocols are not sufficiently reliable to exclude the presence of SBI in febrile neonates. In our study, with the inclusion of CRP, NPV was found at the highest level. The low-risk criteria in our newly created protocol were detected as more reliable and may be useful for excluding SBI in the neonatal period.

Ethics Committee Approval: The study protocol was approved by : Şişli Etfal Training and Research Hospital Ethics Committee (approval number: 745-2011).

Informed Consent: Written informed consent was obtained from the parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.B., L.B., U.Z., S.O., S.U.; Design - A.B., L.B., U.Z., S.O., S.U.; Supervision - A.B., L.B., U.Z., S.O., S.U.; Resource - A.B.; Materials - S.O., U.Z.; Data Collection and/or Processing - L.B., U.Z.; Analysis and/ or Interpretation - L.B., A.B.; Literature Search - S.O., L.B.; Writing Manuscript - L.B.; A.B., S.O.; Critical Reviews - L.B.

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

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Outcomes of Post-traumatic Stiff Elbow Arthrolysis

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ABSTRACT

Objective: In this study, the results of open release surgeries performed for the stiff elbows which were caused by intrinsic, extrinsic or by combination of both factors were evaluated.

Methods: Twenty-three elbows of 22 patients who could not perform functional elbow motions were surgically treated between January 2005 and December 2012. The mean age was 30.6±11.4 years (16 to 67 years), and the average follow-up period was 81 months (58 months to 12 years). Elbow arc of motions was recorded pre- and postoperatively. Patients were evaluated clinically by using quick Disabilities of the Arm, Shoulder and Hand (DASH) self-report questionnaire, and MAYO elbow performance scores.

Results: The mean preoperative elbow arc of motion was 42 degrees (0-90), and it became 109 degrees (70-140) postoperatively after at least 58-month follow-up. The average increase was 67.8±25 degrees (30-125). The mean Quick DASH score was 18.2±12.7 (6.8 to 63.6). According to MAYO elbow rating system, one patient who had experienced infection following the initial fracture treatment had poor result, three patients had fair results, 17 patients had good results, and one patient who had bilateral elbow stiffness had excellent results.

Conclusion: Although good results can be achieved by open release of the stiff elbows, one must keep in mind that preventing the stiffness rather than solving this problem would bring better results. As 15 patients with stiff elbows in this study had a previous surgery performed for an elbow region fracture, stabile fixation, meticulous hemostasis, shorter immobilization period and early rehabilitation can be considered as the most important steps for avoiding elbow stiffness where surgery is indicated.

Keywords: Elbow, stiff, arthrolysis, post-traumatic

INTRODUCTION

The elbow joint is very congruent with three articulations: the ulnohumeral joint, the radiocapitellar joint, and the proximal radioulnar joint. The stability of the elbow is provided by static and dynamic stabilizers. The ulnohumeral articulation, the anterior bundle of the medial collateral ligament, and the lateral collateral ligament complex are acting as the primary static constraints, and the radiocapitellar articulation, the common flexor tendon, the common extensor tendon, and the capsule are acting as secondary static constraints. The dynamic stabilizers are the muscles crossing the elbow (1-3).

Morrey et al. (1) pointed out that 30 to 130 degrees of flexion with 50 degrees pronation and 50 degrees supination may provide

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a functional range of motion (ROM) for most of the daily living activities. We may call the elbow "stiff" if the hand cannot be used functionally due to the loss of elbow motion and this functionality differs for each individual.

The etiology of elbow stiffness must be well understood while planning the treatment. Anatomically the reasons can be classified as extrinsic, intrinsic or combination of both. The intrinsic contracture term is used to determine that the pathology involves the articular surface such as articular adhesions, arthritis, osteophytes, loose bodies, malunions of intra-articular fractures and proliferative synovitis. The extrinsic contracture term defines the periarticular pathologies such as capsule, ligaments, muscles and skin contractures surrounding the joint and also the heterotopic bone formation within these structures. The most common type of elbow contracture is the post-traumatic stiff elbow which usually involves both of the intrinsic and extrinsic pathologies (4,5).

The conservative treatment of stiff elbow includes therapeutic heat application, myofascial soft tissue mobilization, progressive ROM exercises and contracture splinting. Surgery is considered when conservative treatments fail. Surgical treatment options have a spectrum from arthroscopic or open anterior and posterior capsular release to total elbow arthroplasty (6,7). Molecular pathogenesis of the stiffness is still under investigation and immunohistochemical studies warrants further investigation (8,9).

The purpose of this study is to report the functional outcome of the surgically treated stiff elbows.

METHODS

We reviewed 23 stiff elbows of 22 patients who underwent surgical release between January 2005 and December 2012. Conservative treatment methods were tried for at least six months for all of the patients. Surgery was considered for the patients who could not perform functional elbow motions and did not respond to conservative treatment methods. Plain radiographs were obtained to assess the heterotopic bone formations, articular surfaces, hardware positions and the healing of initial fractures. Computerized tomography (CT) scans were also obtained before the treatment to evaluate the articular surfaces more accurately.

The mean age of the patients was 30.6±11.4 years (16 to 67 years), six of the patients were female and 16 were male. The average follow-up period was 81 months (58 months to 12 years). Elbow arc of motions was recorded preoperatively and postoperatively. Patients were evaluated clinically by using quick Disabilities of the Arm, Shoulder and Hand (DASH) self-report questionnaire, and MAYO elbow performance scores.

Only post-traumatic stiff elbows were included in this study; nine patients experienced radial head fractures, four patients had complex elbow fractures (humerus lower end fracture dislocation accompanying ulna or radius fractures), four patients had humerus lower end fractures, three elbows of two patients had heterotopic ossification (HO) due to head and elbow trauma, one patient had olecranon fracture, one patient had radial head chronic luxation, and one patient had radial head fracture with humero-ulnar luxation. Fifteen patients with fractures underwent surgical intervention after the fractures occurred. The mean time elapsed from the initial trauma to surgical release was 21.4 months. No joint instability was observed before and after the treatment. The etiologies of the stiffness were also demonstrated in Table 1.

All surgical arthrolyses were performed by one of the senior hand and upper extremity surgeon at the author's clinic.

All surgeries were performed under regional block anesthesia and indwelling brachial plexus catheters were placed for postoperative pain management. Lateral incisions alone were used in eleven patients, medial incisions alone in four patients, single anterior incisions in three elbows of two patients, medial and lateral incisions were combined in four patients, and a single posterior incision was used for one patient. Anterior capsulectomy (Figure 1) was performed for extension deficit and posterior capsulectomy (Figure 2) was performed to gain flexion (Figure 3, 4). Additionally, radial head excision was also performed for four patients, HO excision for three elbows of two patients, radial head prosthesis excision for three patients, nervus ulnaris anterior transposition (Figure 1) for four patients and nervus ulnaris release for five patients. After soft tissue and heterotopic bone excisions, olecranon fossa and the coronoid fossa were explored to check if any osteophytes or callus formation making a mechanical block remained. If the extension block was due to posterior impingement, widening the olecranon fossa by the help of a high-speed burr and also the excision of the tip of the olecranon while preserving the triceps tendon insertion were generally needed. If there was any hardware to be removed, the removal was performed at the end of the operations. The tourniquets were released, surgical hemostasis was achieved by cauterization. After applying closed suction drainage, skin closures were performed. The degree of flexion/extension and also supination/pronation achieved under anesthesia were measured and noted. The elbow was usually splinted in maximal extension, but if the patient was suffering only for lack of flexion and already had full extension before the operative release, the elbow was splinted in maximal flexion for 24 hours. Progressive passive ROM exercises was started in the following day and the drains were left in place until the drainage stopped, which was usually observed in the third day after surgery. Patients received a therapy program immediately after discharge.

Patients' data were collected with permission, by reviewing the medical records. This study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was received for this study from the ethics committee of University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital (approval number: 125; date: 16.01.2019). Informed consent was obtained.

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Table 1. Patient's descriptive data

Patient No	Age, y Sex side	Pre-op flex/ ext sup/pron	Post-op final flex/ ext sup/ pron	Gained arc of motion (flex/ext)	Approach	Etiology	Pre-op. ulnar neuropathy	DASH score pre-op	DASH scores post-op	MAYO scores Pre-op	MAYO scores post-op
1	40/M/right	140/-50	150/-10	50	Lateral	Radial head fracture	-	50	20.50	70	85
Left elbow of 2	16/M	90/-40	130/0	80	Anterior	Myositis ossificans	-	56.8	27.3	60	100
Right elbow of 2	-	60/no motion (ankylosis)	130/-10	120	Anterior	Myositis ossificans	-	61.4	6.8	50	100
3	27/F/left	80 / -30	130/-10	70	Medial	Radial head fracture	+	54.5	20.50	55	85
4	25/M/left	90 / -40	110/-25	35	Lateral	Radial head + capitellum fracture	-	61.4	34.10	50	65
5	35/M/right	90 / -45	110/0	65	Lateral + Medial	Complex elbow fracture	+	65.9	15.90	50	85
6	44/M/left	90 / -40	130/-20	60	Medial	Humerus lower end fracture	-	63.6	13.6	50	85
7	35/M/left	60 / -40	80 / -10	50	Lateral	Radial head & coronoid fracture	-	81.8	63.6	30	50
8	16/M/right	120/-55	130 / -10	55	Lateral + Medial	Humerus lower end fracture	-	68.2	6.8	65	85
9	36/M/right	110/-40	135 / -10	55	Medial	Olecranon fracture	-	65.9	22.7	70	85
10	29/M/right	70/-40	130/-10	90	Lateral	Radial head fracture	-	70.5	11.4	50	85
11	26/M/left	100/-60	100/-30	30	Lateral	Complex elbow fracture	-	77.3	31.8	40	60
12	32/F/right	90/-70	120/-40	60	Posterior	Complex elbow fracture	-	77.3	29.50	40	60
13	24/M/right	120/-45	135/-20	40	Lateral + Medial	Radial head fracture	-	63.6	11.4	55	85
14	20/M/left	80/-45	120/-20	65	Lateral	Humerus lower end fracture	-	70.5	13.6	50	85
15	47/F/right	110/-50	130/-20	50	Lateral	Radial head fracture	-	63.6	11.4	50	85
16	24/F/right	Fixed at 90 degree flexion	135/-20	115	Anterior	Myositis ossificans	-	77.3	13.6	45	85
17	32/F/right	Fixed at 90 degree flexion	135/-10	125	Lateral + Medial	Humerus lower end fracture	+	79.5	11.4	45	85
18	67/M/right	90/-45	140/-20	75	Medial	Radial head fracture + humero-ulnar luxation	+	81.8	9.1	45	85
19	28/M/left	90/-60	120/-30	60	Lateral	Radial head fracture	-	79.5	13.6	45	80
20	31/F/right	80/-40	130/-20	70	Lateral	Radial head chronic luxation	-	77.3	15.9	50	80
21	30/M/right	100/-50	140/-20	70	Lateral	Radial head fracture	-	50	6.8	50	85
22	24/M/left	110/-50	130/-20	70	Lateral	Complex elbow fracture	-	56.8	9.1	55	85

DASH: Disabilities of the arm, shoulder and hand, M: male, F: female

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Statistical Analysis

We have compared the preoperative and post-operative flexion and extension degrees, DASH scores, and the MAYO elbow performance scores with the Wilcoxon rank-sum test by using SPSS 22.0 (SPSS Inc, IBM, Chicago, IL) software. P-values less than 0.05 were regarded as statistically significant.

RESULTS

The mean preoperative elbow flexion was 93.4±19 degrees (ranges from 60 to 140 degrees) and lack of extension was 51±15.2 degrees (30 to 90 degrees). The average postoperative flexion of elbow was 126±14.8 degrees (80 to 150 degrees) and lack of extension was 17±9.4 degrees (0 to 40 degrees) after a mean follow-up period of 81 months. Preoperative mean arc of motion was 42 degrees (0 to 90 degrees), and it became 109.3 degrees (70 to 140 degrees) postoperatively after at least 58-month follow-up. The average increase was 67.8±24.9 degrees (30-125 degrees). The preoperative mean Quick DASH score was 69±9 points, and it was calculated as 18.2±12.7 (6.8 to 63.6) at the last visit. These changes were found statistically significant. According to MAYO elbow rating system, one patient who had experienced infection following the initial surgery for the fracture treatment had poor results, three patients had fair results, 17 patients had good results, and one patient had excellent results for both of his elbows. Ulnar nerve related symptoms of four patients were recovered after anterior transposition of the nerves. No infection, instability or recurrence of HO was observed after the releases.

DISCUSSION

In this study, we described our experience in surgical release of stiff elbows. Before deciding surgical intervention to release the contracture, the pathology and also the expectations of the patient must be well understood and the patient must be aware of the risks of the procedure such as pain, instability, weakness and worsening of the ulnar nerve related symptoms.

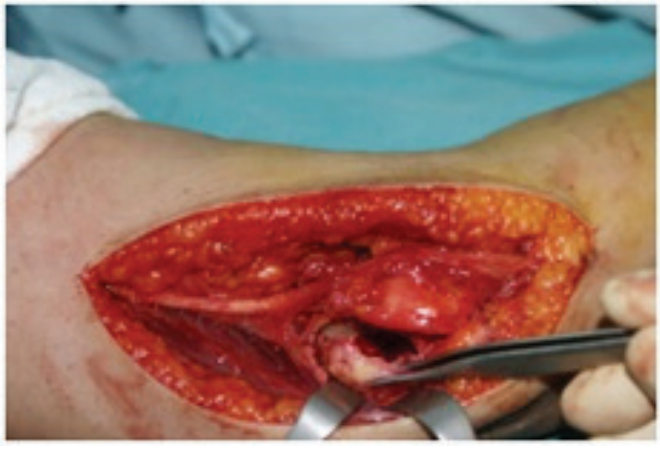

Figure 1. Posterior capsular excision by using the "medial over the top" technique

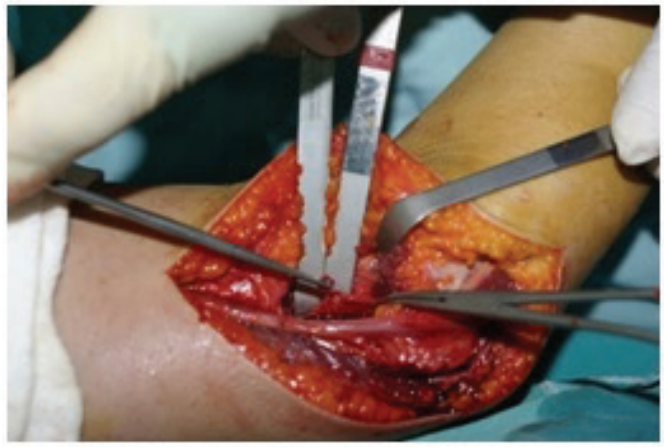

Figure 2. Anterior capsular excision

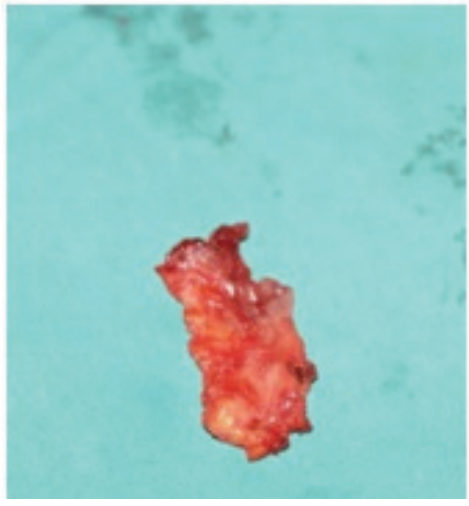

Figure 3. Excised posterior capsule

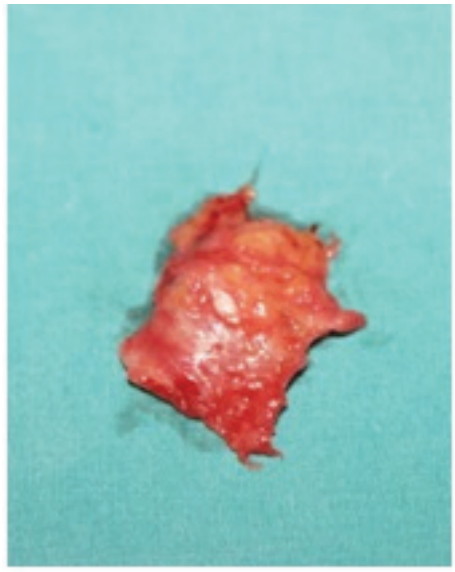

Figure 4. Excised anterior capsule

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Preoperative assessments about the articular cartilage and the congruity of the joint would change the operative procedure from basic capsular release to more complex interventions such as fascial graft interposition. Therefore, CT of the joint must be obtained before making the decision. In our cases, no fascial graft interposition was needed, CT scans were also obtained before the treatment.

Pain would seldom be present with a stiff elbow and if present, it is generally seen at the end of flexion or extension; however, if pain is elicited during the whole arc, it should be associated with joint incongruity, synovitis, loose bodies, and arthrosis (10), and this finding could change the type of operation to be performed. In our study, there was no motion at three elbows of two patients who had HO. And the remaining patients were feeling pain only at the end of the arc of motion.

There are several operative techniques determined for the arthrolysis of the contracted elbows and the surgeon dealing with stiff elbows must be familiar with different types of approaches as one incision should not be enough for an adequate release in some cases (11). Manipulation under anesthesia, elbow arthroscopy, synovectomy, excision of radial head, triceps lengthening, excision of ectopic bones, anterior and posterior capsulectomy, distraction arthroplasty, fascial interposition arthroplasty and total elbow arthroplasty are the described procedures for stiff elbow management (11-13).

Although arthroscopic release of the stiff elbows was reported as a safe and effective method by several authors, the indications are limited and cannot be used for the elbows where the anatomy is altered (14-16). We have not performed any arthroscopic release for the patients who were included in this study.

Operative approaches were varying depending on the preoperative and intraoperative findings. Previous incisions, location of the HO and presence of ulnar neuropathy were some of the factors affecting the decision making about the appropriate approach.

For most of our cases, the lateral column procedure was performed, in which a limited lateral approach was used (4). Medial "over-the-top" approach, which was popularized by Mansat et al. (17), was our preferred approach if ulnar nerve symptoms were present pre-operatively and anterior subcutaneous transpositions of the ulnar nerves were performed in those cases. We prefer release and anterior transposition of the ulnar nerve in patients who have preoperative nerve related symptoms, whose elbows are contracted in an extension position for a long time or the amount of postoperatively expected flexion gain is significant.

Another method is a transhumeral, so-called Outerbridge-Kashiwagi (O-K) method, which was originally described by Kashiwagi in 1978. In this technique, a posterior incision is used and after posterior capsulectomy, the olecranon fossa is fenestrated, then anterior capsulectomy can be performed through this hole (18). Morrey (19) have modified this technique and named it as ulnohumeral arthroplasty (UHA) and used a triceps elevation technique rather than splitting it. Hertel et al. (20) have described a sequential arthrolysis which starts with the standard O-K method and continued with a limited lateral and a limited medial approach if needed for adequate release. Posterior incisions or anterior incisions to address the heterotopic bones can also be used. In our experience, we have found lateral or medial approach useful if the olecranon and its fossa have to be reshaped due to osteophyte formation. Neither O-K method nor UHA was needed in our cases.

For long-standing contractures of the elbow, muscle tightness would also restrict motion and Bhattacharya have suggested triceps and brachialis muscle mobilization as a solution, but this will result in loss of strength and will risk the necessary post-operative rehabilitation program and must be avoided if possible (12). It is also important to preserve the primary constraints of the elbow to avoid laxity and the need for an external fixator device. We did not apply any external fixator to our patients.

If severe arthrosis is the cause of stiffness, releasing the soft tissues would improve the ROM but unfortunately the pain would continue being the most important complaint of the patient and he or she would seek the preoperative condition of the elbow. Therefore, it is important to realize this condition and perform other types of operations like arthrodesis, distraction with fascial interposition arthroplasty or total elbow arthroplasty, which should only be used in some selected patients (13,21,22). Our patient population did not have severe arthrosis; therefore, contracture releases were found to be enough.

Lindenhovius et al. (23) stated that the release in elbows with HO would have better results than the stiff elbows without HO. Our results with HO resections support this statement. In case of total bony ankylosis, the muscle control and strength must be carefully evaluated as these patients would lose the gained arc if they cannot actively flex or extend their elbows after releasing the stiffness.

In a report by Liu et al. (24), the mean improvement in total elbow flexion/extension motions was 80 degrees documented in 11 patients by using combination of lateral and medial approaches and hinged external fixation. In another study performed by Ehsan et al. (25), he documents a total improvement of 58 degrees of elbow flexion/extension motions. Of interest, 68 of 77 patients demonstrated radiographic evidence of HO and 53 patients (69%) achieved a total arc of motion ≥100 degrees. Another report by Kayalar et al. (26) represents an increase of 66 degrees in total flexion/extension arc. The average increase in our study was 67.8 degrees (30-125 degrees), which is comparable with others.

The post-operative physical therapy program of these patients is of paramount importance because maintenance of the gained ROM will affect the overall results. Unfortunately, there is no consensus about the most effective therapy program in the literature (6). Some authors have used immediate postoperative continuous passive motion (CPM), interscalene blocks and corrective splinting modalities but some authors did not ever

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use the CPM (5,15,23,24). In our clinic, we use static splinting for the first post-operative day in an elevated position to decrease the soft tissue swelling, and the position of the elbow in the long arm splint depends on the patient's preoperative findings. If the operation was performed for a flexion contracture with or without lack of flexion, the elbow was splinted in maximal extension position that was gained in the operation room. If the aim was to gain only flexion, the position of the splint was set in flexion. We believe that educating the patient about passive exercises is a very effective method if he/she is compatible and capable of using his/her other upper extremity. After 24 hours, the patient begins passively flexing the elbow to the end point and stands in that position for fifteen minutes. After muscle relaxation, the patient can flex the elbow a little bit more and holds that position for another 15 minutes. Then does the same for extension exercises and wears the splint when got tired. The splints are worn every resting time and after three weeks worn only nightly. Indwelling brachial plexus catheter was used for pain management during the therapy program for two days and followed by non-steroidal anti-inflammatory agents. Indomethacin 25 mg three times daily was preferred if there were ectopic bones.

Charalambous and Morrey (8) emphasized the importance of molecular pathogenesis of the stiffness in a review of posttraumatic elbow stiffness. In a study conducted by Hildebrand et al. (27), anterior capsules of contracted elbows and healthy elbows of organ donors were compared and immunohistochemical study revealed that myofibroblast numbers were significantly elevated in the contracted elbow capsules. Cohen et al. (28) also investigated the contracted capsules and compared to normal capsules of donors and demonstrated that the contracted capsules were thicker and cytokine levels (MMP-1, MMP-2 and MMP-3) were significantly higher than normal capsules, while collagen type III had decreased levels. According to these findings, they stated that the contracture tissue formation mechanism was different than normal wound healing. Hildebrand et al. (9) also assessed joint myofibroblasts, nerve fibers containing neuropeptides and mast cells by immunohistochemistry in another study and found significantly greater expression in the contracture capsules. They suggested that a manipulation to myofibroblast-mast cell-neuropeptide fibrosis link should be a solution which warrants further investigation.

Molecular pathogenesis of the stiffness is still under investigation and immunohistochemical studies warrants further investigation.

CONCLUSION

Although good results can be achieved by open release of the stiff elbows, one must keep in mind that preventing the stiffness rather than solving this problem would bring better results. As 15 patients with stiff elbows among the 23 patients included in our study had a previous surgery performed for an elbow region fracture, we may conclude that stable fixation, meticulous hemostasis, minimal immobilization and early rehabilitation must be achieved for avoiding elbow stiffness where surgical treatment is indicated.

However, any patient with elbow trauma must be informed about the possibility of stiffness. And, we believe that the basic scientific investigations should focus on the prophylaxis of joint stiffness in the future.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital (approval number: 125; date: 16.01.2019).

Informed Consent: It was obtained.

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The Impact of Timing of Surgery and the Anesthesia Technique in Hip Fracture Surgery on In-hospital Mortality and Length of Hospital Stay

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ABSTRACT

Objective: To point the positive impact of early surgery (performed within 48 hours) and non-general anesthesia techniques on early outcomes like in-hospital mortality and length of hospital stay (LOS).

Methods: Seven hundred and ten patients were included in this retrospective study. Patients aged 50 years and over, who were admitted to our hospital with hip fracture, were included, while the patients with pathological fractures or polytraumatic injuries were excluded.

Results: The median age of the patients was 75.8±10,.3 years. Four hundred and sixty-nine (66.1%) patients were female. Six hundred and eighty-two patients (96.1%) were treated surgically, 16 patients (2.25%) received conservative treatment and 12 patients (1.7%) died before scheduled surgery. General anesthesia (n=328), spinal anesthesia (n=268), unilateral spinal anesthesia (n=47), peripheral nerve block (n=29), and combined spinal-epidural (CSE) anesthesia (n=10) were the anesthesia techniques used for surgery. Patients who were treated within 48 hours (G1) had lower in-hospital mortality than the patients who were treated lately (G2) (0.8% vs 4,7%). The LOS for G1 was 8.6 days whereas it was 17.5 days for G2 ($p<0.001$). Mortality rates and median LOS of the anesthesia techniques were 5.5% and 15 days with general anesthesia, 2.2% and 14 days with spinal, and 4.3% and 13 days with unilateral spinal anesthesia. There were no deaths in 10 patients with 11.5 days of LOS, who received CSE anesthesia, while the mortality rate of the peripheral nerve block group was 3.4% with 10 days of LOS.

Conclusion: The results of this study suggest that the surgical repair of the fractured hip should be performed within the first 48 hours, with a non-general anesthesia technique in order to reduce in-hospital mortality and LOS.

Keywords: Hip fracture, mortality, length of stay, timing of surgery, anesthesia technique

INTRODUCTION

Hip fractures are the most common osteoporotic fractures with serious consequences in elderly population. Across the world, the prevalence of hip fractures is 1.6% at the age of 65 years and it increases to 8.9% for individuals older than 90 years (1). Considering the increased lifetime expectancy, these numbers are expected to increase to 2.6 million by the year 2025 and to 4 million by the year 2050 while it was only 1.26 million in the year 1990 (2). Hip fracture impairs the physical function and may lead to loss of independency, thus has a high impact on quality of life along with the consumption of healthcare resources (3,4). Despite the advances in anesthesia and surgical techniques, and perioperative nursing care, hip fractures are still associated with high morbidity and mortality rates and one of the most common

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causes of death with trauma, cardiovascular disease and cancer in the elderly population (5). Consequently, this devastating medical problem has become one of the major issues in healthcare systems. The literature about early and one-year mortality in hip fracture patients is very rich (6-11). One-year mortality rates of hip fracture for all age groups have been reported between 12% and 36% in different studies and up to 50% in extremely older patients (8-12).

Aging of the population, so do the hip fracture patients', causes additional medical problems in acute management of the hip fracture patients. Most of the hip fracture patients undergo surgery and a typical hip fracture patient is confined to bed-rest before surgery. Delay in surgery may cause an increase in the incidence of bed-rest associated complications including atelectasis, thromboembolism, pneumonia, urinary tract infections, pressure sores and delirium, which may increase in the length of hospital stay (LOS) (13). On the other hand, delaying surgery until physiological stabilization will let more time for the correction of dehydration, electrolyte imbalance, anemia and uncontrolled hypertension, arrhythmias, control of hemorrhagic risks in patients taking anticoagulants or antiplatelet agents, uncontrolled diabetes mellitus or treatment of co-existing infections. Although the recent studies suggest early surgery, optimal time of surgical repair of the fractured hip is still one of the most controversial questions in the hip fracture management (7,14,15).

The aim of the present study was to evaluate the impact of timing of surgery and type of anesthesia for surgical treatment of fractured hip on in-hospital mortality and LOS.

METHODS

This retrospective study comprised of patients with a primary diagnosis of hip fracture, who were admitted to İstanbul University, İstanbul Faculty of Medicine, Department of Orthopedics and Traumatology between January 2004 and December 2010.Ethical Committee approval was obtained from Gaziosmanpaşa Taksim Training and Research Hospital (approval number: 2011/809-569). Patients younger than 50 years, patients with pathologic fractures, distal or femoral shaft fractures, bilateral fractures, and multiple trauma patients were excluded.

Seven hundred and ten patients' information including age, gender, discharge diagnoses and procedure codes according to the International Classification of disease-10, time to surgery, LOS and in hospital mortality rates were derived retrospectively from hospital records. Type of treatment [conservative treatment, minimally invasive surgery, open reduction-internal fixation (ORIF) or arthroplasty], type of anesthesia performed during the surgery (general anesthesia, spinal, unilateral spinal, combined spinal-epidural (CSE) anesthesia, peripheral nerve block), and time of surgery were also recorded using a standardized case report form. Mortality was considered as in-hospital mortality. Post-discharge mortality rates (3 months, 6 months and 1 year) were not included. This is a retrospective research; therefore, informed consent was not obtained from the patients.

Statistical Analysis

Number Cruncher Statistical System 2007 & Power Analysis and Sample Size 2008 Statistical Software (Utah, USA) program was used for statistical analyses. Student's t-test was used for the comparison of quantitative data and normally distributed parameters as well as the descriptive statistical methods (mean value, standard deviation, median, frequency, ratio) for the evaluation of the collected data. Mann-Whitney U test and Kruskall-Wallis tests were performed for the two and three group comparisons of the abnormally distributed parameters, respectively. Mann-Whitney U test was also used for the determination of the group responsible for the difference. Pearson chi-square test was performed to compare qualitative data. Fisher's Exact and Yates Continuity Correction tests were used for the determination of the group that makes the difference. Finally, Spearman's Correlation Analysis was used to assess the correlation between the parameters. Statistical significance levels were $p<0.01$ and $p<0.05$.

RESULTS

66.1% (n=469) of the patients were female. The age of the patients ranged between 50 and 109 years (mean 75.8±10.3 years). One hundred thirty of 682 patients (19.06%) received surgical treatment within 48 hours from the admission (group 1) while 552 patients (80.94%) waited more than 48 hours for the surgery (group 2). Surgical fixations were performed between the day of admission and the 28th day (mean: 6.12±412 days) while LOS ranged between 2 and 138 days (mean: 15.63±10.23 days) 54.1% of the patients (n=384) had intertrocanteric fractures, 36.1% (n=256) had femoral neck fractures, and 9.9% (n=70) of the patients had subtrocanteric fractures. Twenty-eight patients (3.9%) were treated conservatively. Surgically treated 682 patients' (96.1%) treatment modalities were given as follows: 63.9% (n=436) had arthroplasty, 32.4% (n=221) of the patients were treated with closed reduction-internal fixation (CRIF) technique, and 3.7% (n=25) were treated with ORIF technique. General anesthesia 48.1% (n=328), spinal anesthesia 39.3% (n=268), unilateral spinal anesthesia 6.9% (n=47), peripheral nerve block 4.2% (n=29) and CSE anesthesia 1.5% (n=10) were the techniques performed for surgery. Mortality rates in patients whose surgery were delayed for more than 48 hours were significantly higher than the patients who had surgery within 48 hours ($p<0.05$). LOS was also significantly longer in this group ($p<0.01$) (Table 1).

Total in-hospital mortality rate of the 710 patients was 5.1% (n=36). The in-hospital mortality rate of the patients who had surgery was 3.4% (n=24) while 1.7% of the patients (n=12) died before the surgery. Statistically significant result was obtained when the effects of general and regional anesthesia techniques were compared with respect to in-hospital mortality ($p=0.049$; $p<0.05$) (Table 2). However, there were no statistically significant

differences between the regional anesthesia techniques when compared (p>0.05).

LOS of different anesthesia technique groups was significantly different (p=0.001; p<0.01). The general anesthesia group had longer LOS than the spinal, peripheral nerve block and unilateral spinal anesthesia groups (p=0.009; p=0.001; p=0.005; p<0.01) (Table 3). Hospitalization was longer in the spinal anesthesia group than the peripheral nerve block group (p=0.004; p<0.01). There was no statistically significant difference between LOS when the other anesthesia techniques were compared (p>0.05).

There was a strong correlation with 32.4% positive ratio (hospitalization lengthens with increased age) between age and LOS (r=0.324; p<0.01) (Table 4) (Figure 1). There was also a strong correlation with 23.8% positive ratio (operation is delayed in elderly patients) between age and time to surgery (r=0.238; p<0.01) (Figure 2).

Table 1. Timing of the surgical procedure (day) and mortality correlation

	Timing of the operation		p
	≤48 hours (n=130)	>48 hours (n=552)	
[c]LOS; Mean ± SD (median)	8.62±3.74 (8.0)	17.55±10.51 (16.0)	[a]0.001**
Mortality; n (%)	1 (0.8%)	26 (4.7%)	[b]0.043*

[a]: Mann-Whitney U test, [b]: pearson chi-square test, [c]: length of hospital stay, *p<0.05, **p<0.01

Table 2. Evaluation of the mortality rates according to different anesthesia modalities

Anesthesia modality (n=682) (%)	[a]Mortality (n= 36); (%)	[a]p
General		
328 (48.1%)	18 (5.5%)	0.049*
Regional		
354 (51.9%)	9 (2.5%)	-
Bilateral spinal		
268 (39.3%)	6 (2.2%)	-
Unilateral spinal		
47 (6,9%)	2 (4.3%)	0.798
[b]CSE		
10 (1,4%)	0	-
[c]PNB		
29 (4,3%)	1 (3.4%)	-

[a]: Pearson chi-square test, [b]: combined spinal epidural anesthesia, [c]: peripheral nerve block, *p<0.05

DISCUSSION

The aim of this study was to evaluate the effects of time to surgery and anesthesia technique performed during the surgical treatment of hip fracture patients on in-hospital mortality and LOS. It was found out that the in-hospital mortality rates and LOS of the patients who had surgical delay for more than 48 hours were significantly higher than the patients who had surgery within 48 hours.

Guidelines point out the favorable effects of early surgical repair of the fractured hip on patient mortality in the literature. The Scottish Intercollegiate Guidelines Network suggest that the surgery should be performed as soon as possible, within safe operating hours, from the admission in medically fit patients, in order to reduce the postoperative mortality (15). Likewise, The British Orthopedic Association guidelines indicate that surgical repair should not be delayed for more than 48 hours from admission unless the patient has clearly reversible medical conditions (16).

Many studies show that a prolonged surgical delay significantly increases the mortality (7,14,17-21). McGuire et al. (18) reported increased mortality rates within 30 days in hip fracture patients who had surgical delay for more than 48 hours. In a recent study, Dailiana et al. (19) pointed out a significant association between delayed surgery (>48 hours) and increased in-hospital mortality. On the other hand, many studies show that early surgery (performed within 48 hours) does not reduce mortality (14,22,23). High mortality rates in these studies are associated with patient's comorbidities and poor medical conditions, but not with surgery time. In a review of 52 published studies involving 291.413 patients, it was found that none of the included studies demonstrated a causal relationship between surgical delay and mortality rates (13). Another comprehensive study including 2.660 patients not surprisingly indicates that delayed surgery patients with comorbidities have 2.5 times more risk of death compared to the delayed surgery patients without comorbidities within thirty

Table 4. Age, LOS and Timing of the operation correlation

	Age (years)	
	r	p
[a]Lenght of hospital stay	0.324	0.001**
[a]Timing of the operation (day)	0.238	0.001**

[a]: Spearman's correlation analysis, **p<0.01

Table 3. Evaluation of the LOS according to different anesthesia techniques

		[a]Anesthesia technique					
		General	Bilateral spinal	Unilateral spinal	[c]CSE	[d]PNB	p
[b]LOS (day)	Mean ± SD Median	17.11±10.75 15.0	15.27±10.36 14.0	13.25±5.59 13.0	16.20±9.31 11.5	11.31±5.76 10.0	0.001**

[a]: Kruskal-Wallis test, [b]: length of hospital stay, [c]: combined spinal epidural anesthesia, [d]: peripheral nerve block, **p<0.01.
SD: standard deviation, LOS: length of hospital stay, CSE: combined spinal epidural anaesthesia, PNB: peripheral nerve block

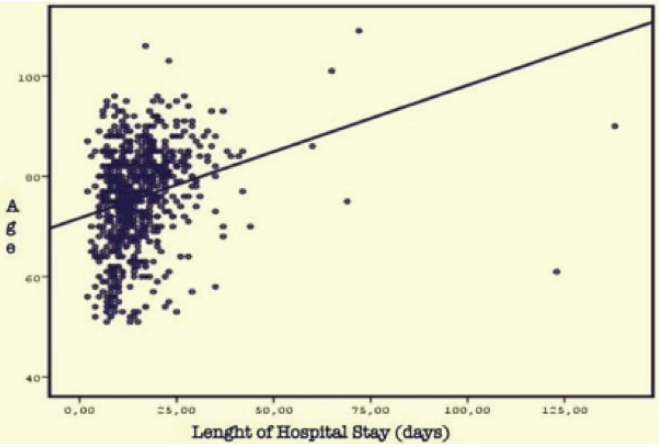

Figure 1. Length of hospital stay (days)

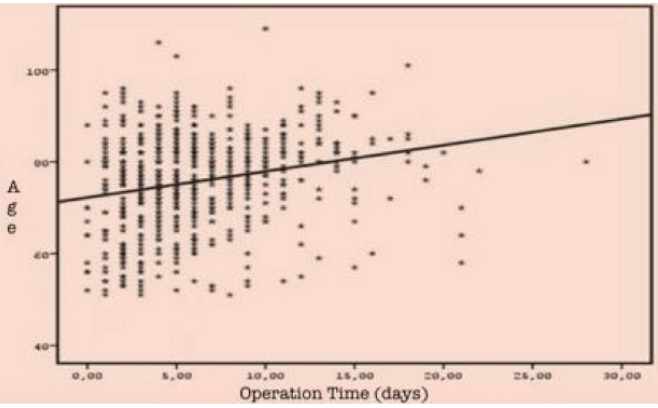

Figure 2. Operation time (days)

days after the surgery. They also showed the delayed surgery up to four days did not increase the mortality of the patients who were fit for the surgery; however, a delay of more than four days significantly increased mortality in these patients (24).

The in-hospital mortality rate in the present study was 5.1% (n=36), concordant with the literature. In a study including 4.633 patients, Novack et al. (25) reported the in-hospital mortality and 30-day mortality rates as 4,5% and 6,1%, respectively. Anwar et al. (26) reported the in-hospital, 30-day and total mortality rates of the surgically treated hip fracture patients as 5.6%, 10.6%, and 16.3%, respectively. Also, the in-hospital mortality rate of men was 11.5% while that of women was 4.3%, 30-day and total mortality rates were 4.6% and 17.9%, respectively, in a recent study performed in Greece (19).

The results of the present study demonstrated that LOS was significantly shorter in patients who had surgery within 48 hours. There are many studies suggesting that the LOS could be improved by shortening the waiting time for surgery (20,27-31). In a recent study conducted in USA, preoperative time to surgery, anesthesia type and procedure type were shown to be three modifiable risk factors for increased LOS (27). Bergeron et al. (28) reported that the delayed surgery lengthens the hospitalizations in their study involving 977 patients. These results might be associated with reduced complications caused by prolonged bed rest and immobilization before surgery, which may lengthen the hospitalization and even increase the mortality rates. However, this relationship is not universally supported, there are also studies suggesting that there is no significant effect of early surgery on LOS (32-34).

Different anesthesia techniques were performed during the surgical fixation of the patients. 48.1% of the patients received general anesthesia while 51.9% received regional anesthesia (spinal anesthesia 46.2%, peripheral nerve block 4.2% and CSE anesthesia 1.5%). Many studies pointed out the association between non-general anesthesia techniques and reduced mortality recently (21,31-33). Rodgers et al. (31) demonstrated that neuroaxial anesthesia techniques reduce postoperative mortality. Luger et al. (32) conducted a wide study including 18.715 patients and reported that the spinal anesthesia reduced early mortality rates and complications like deep venous thrombosis and acute postoperative confusion in geriatric hip fracture patients. However, there are many studies with conflicting results (34-36). O'Hara et al. (34) could not reveal the regional anesthesia technique's positive impact on mortality compared to general anesthesia in their retrospective study including 9425 patients. Le-Wendling et al. (35) reported that there was no difference in in- hospital mortality, postoperative mortality, treatment costs and re-hospitalization when the general anesthesia and regional anesthesia techniques were compared in geriatric hip fracture population. In a retrospective cohort study including 73.284 adults undergoing hip fracture surgery, mortality risk did not differ significantly by anesthesia type (36). Also, in a recent study performed in our country, surgically treated 187 hip fracture patients' 30-day mortality rates according to anesthesia techniques were reported as follows: general anesthesia group 1.4%, spinal anesthesia group 5.9%, and epidural group 5.8%, in which there was no superiority shown for the techniques on each other (37). In contrary with all these results, the in-hospital mortality rates of the regional anesthesia group in the present study were significantly lower when compared to the general anesthesia group while there were no significant differences between the regional techniques, themselves. These results might be related to the choice of regional techniques for less invasive surgery like CRIF or the preference general anesthesia for high-risk patients rather than regional techniques.

There are many studies suggesting that there is no relationship between the anesthesia technique and LOS (31,38). In a study of 217 patients performed by Liu et al. (38), no differences were shown in mortality rates and LOS, when the general anesthesia and peripheral nerve blockage techniques were compared. Also, in a recent study conducted in USA, no superiority was shown for regional techniques to general anesthesia when compared in terms of mortality. On the other hand, LOS of regional anesthesia group was found modestly shorter (39). However, Basques et al. (27) pointed out the non-general anesthesia clinically significantly

increased LOS relation in their recent study including 8.434 surgically treated hip fracture patients. In the present study, we observed significant differences in LOS when the anesthesia techniques were compared. The general anesthesia group had significantly longer hospitalizations when compared to the regional anesthesia groups, and the neuroaxial anesthesia group had significantly longer hospitalizations when compared to the peripheral nerve block group. Lower mortality rates and shorter LOS might be related to known reduced complications of regional anesthesia techniques and earlier ambulation of the patients in this group.

CONCLUSION

It was concluded that hip fracture surgery should be performed as soon as the patient is medically stabilized within 48 hours with regional anesthesia techniques in order to achieve better results of early outcomes like in-hospital mortality and LOS.

Ethics Committee Approval: Ethical Committee approval was obtained from Gaziosmanpaşa Taksim Training and Research Hospital (approval number: 2011/809-569).

Informed Consent: This is a retrospective research; therefore, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

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

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Radioguided Occult Lesion Localization Versus Wire-guided Localization of Nonpalpable Breast Lesions: A Comparative Analysis

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ABSTRACT

Objective: Wire-guided localization (WGL) is the preoperative localization method most commonly used before the surgical excision of non-palpable breast lesions (NPBLs). Recently, radioguided occult lesion localization (ROLL) has emerged as an alternative to WGL. We sought to compare the efficacy of ROLL with that of WGL for the preoperative localization of NPBLs and to assess our experience encountered as ROLL is implemented at our institution.

Methods: We retrospectively identified reports of patients with NPBLs who underwent mammography- or ultrasonography-guided ROLL or WGL between January 2014 and March 2017. Medical records were reviewed to compare radiologic and pathologic findings, rates of accurate localization, specimen volumes, lengths of operation, creation of positive surgical margins, number of simultaneous sentinel lymph node biopsies (SLNB) performed, complication rates, and lengths of hospital stay.

Results: Our search identified 67 women (mean age, 52.7 years; range, 32-69 years) diagnosed with NPBLs during the study period. ROLL was used in 25 patients; WGL was used in 42 patients. Both methods had a high accurate localization rate (ROLL, 96%; WGL, 98%). The length of operation was longer in the ROLL group than in the WGL group (p=0.001), and more SLNBs were performed in the ROLL group than in the WGL group. No significant differences were seen between the groups in terms of radiologic and pathologic findings, specimen volumes, positive surgical margins, complication rates, or lengths of hospital stay.

Conclusion: ROLL is a promising alternative to WGL for preoperative localization of NPBLs. The operation time for ROLL procedures at our institution will likely decrease as clinicians become more familiar with the procedure.

Keywords: Nonpalpable breast lesion, ROLL, WGL

INTRODUCTION

Breast lesions that cannot be palpated on physical examination but are found to have features suggestive of malignancy on imaging studies are known as nonpalpable breast lesions (NPBLs) (1). Over the past 20 years, the detection of NPBLs has increased (1-6); this is important, as early detection of NPBLs can substantially reduce both morbidity and mortality (7-9).

NPBLs must be accurately localized before surgical excision is attempted (1). The main aim of localization is to allow for total excision of the lesion with minimal tissue loss. Wire-guided localization (WGL) is the most commonly used technique for lesion localization (10). However, this method can be complicated by the breakdown of the wire, difficulties with insertion, and wire dislodgement and migration, which can lead to pain and pneumothorax (11-13).

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The radioguided occult lesion localization (ROLL) method is increasingly being used as an alternative to WGL (14) and was just recently introduced at our institution. With the ROLL technique, a radionuclide is injected into the lesion under imaging guidance and the lesion is then surgically excised, with a gamma probe used for intraoperative localization. The ROLL technique has several advantages over the WGL method, including a shorter procedure time, smaller volume of tissue removed, cleaner surgical margins, and less pain and improved comfort for the patient (13,15). Additionally, when ROLL is used, a sentinel lymph node biopsy (SLNB) can be performed simultaneously (16). Although recent studies have showed ROLL is a good method to assess the NPBLs (17-21), there is lack of information regarding the assessment of this method at the learning curve period, when implementing the ROLL technique at an institution. The aim of this study was to compare the efficacy of the ROLL method with that of the WGL technique in localizing NPBLs before surgery and to assess our experience encountered as ROLL is implemented at our institution.

METHODS

Ethics committee approval was received for this study from the ethics committee of University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2017/29). Ethics committee approval and waiver of individual consent of participants were obtained for this retrospective study. Eligible patients were those who had an NPBL <2 cm in diameter with features suggestive of malignancy on mammography and ultrasound [Breast Imaging Reporting and Data System (BI-RADS) score of 4 or 5] and who underwent mammography or breast ultrasonography with breast marking and surgical excision between January 2014 and March 2017. Patients who were pregnant or breastfeeding were not eligible for inclusion. Patients who had been treated with neoadjuvant chemotherapy and clips were also not included in the study. Patients were divided into 2 groups based on the method used for lesion localization (ROLL vs WGL).

The method used for breast marking was chosen by the radiologist. Microcalcification, parenchymal distortion, and asymmetric density were marked with mammography; irregularly shaped, spiculated, solid, and complex cystic lesions were identified with ultrasonography.

In mammography-guided WGL, the radiologist used a Selenia DS mammography device (Hologic, Bedford, MA, USA) and a 20 G/10 cm Hawkins needle (Angiotech Breast Localization Needle; National-Standard Medical Products, Gainesville, FL, USA) to perform breast marking before surgery. First, lateral and craniocaudal images of the mammary gland were obtained. With the patient seated, the breast tissue was exposed to pressure, and the closest distance between the lesion and the skin was determined. The x- and y-coordinates of this area were identified on a perforated plate. Once the desired depth of the lesion was reached with a wire, control graphics were taken from 2 different positions. A wire in the form of a hook was fixed inside the localization needle, and a control chart was used to determine whether the wire was in the lesion. Specimen graphy was also obtained to determine whether the lesion could be surgically excised.

In ultrasonography-guided WGL, an Aplio 500 system (Toshiba Medical Systems Corp., Tokyo, Japan) was used for breast marking. With the patient in the supine position, a local anesthetic was applied to the area near the lesion. Using ultrasonographic guidance, the radiologist advanced the marking needle and then the wire into the lesion, and surgical excision was performed.

The technique used for mammography-guided ROLL was similar to that used for mammography-guided WGL. With ROLL, however, marking was performed via the intrathecal injection of radioactive material through a 20 G needle. The radiologist injected 0.5 mCi Tc-99m-macroaggregate albumin (MAA) in a volume of 0.2 to 0.3 mL. Subsequently, 0.2 mL of water-soluble nonionic contrast material was injected to determine whether the lesion had been accurately localized, and mammography was performed to determine whether the area of suspicion could be surgically excised.

The technique used for ultrasonography-guided ROLL was also similar to that used for ultrasonography-guided WGL. The only difference was that lesions were localized with ultrasonography while the radionuclide was injected to ensure that increased echogenicity in the lesion was seen. For surgical excision with ROLL, general anesthesia was administered to patients in the operating room, and radioactivity was measured as a hot spot with an intraoperative gamma probe (Crystal Probe System SG04; Crystal Photonics, Berlin, Germany). The highest hot spot was then selected for excision on skin that was marked with a marking pen, and this region was excised. Radioactivity control of the excised area was assessed with a gamma probe to ensure that no radioactive tissue remained.

The ROLL and WGL groups were compared in terms of radiologic and pathologic findings, rates of accurate localization, specimen volumes, lengths of operation, creation of positive surgical margins, number of SLNBs performed, complication rates, and lengths of hospital stay.

Evaluation of Lesion Localization Success

For patients undergoing mammography-guided ROLL, successful lesion localization was defined as observation of the radioactive contrast material near the lesion in question. For patients undergoing ultrasonography-guided ROLL, successful localization was defined as an increase in echogenicity in the lesion when radioactive material was administered (Figure 1). Before the surgery, scintigraphic control could be performed to ensure that the radionuclide had not spread (Figure 2); in this study, only one patient had such a scintigraphic image available. In terms of the specimen, lesions localized with mammography were examined by specimen graphy to determine whether the marked lesion was removed during surgery (Figure 3). Lesions localized with ultrasonography were assessed with a gamma probe while the radionuclide was injected to ensure that increased echogenicity

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in the lesion was seen (Figure 4).

For patients undergoing mammography-guided WGL, successful lesion localization was defined as the presence of the wire tip near the lesion in question (<1 cm). For those undergoing ultrasonography-guided WGL, successful lesion localization was defined as the presence of echogenicity of the wire in the lesion. For patients who underwent mammography-guided WGL, observation of the suspicious lesion on specimen control graphy was considered indicative of successful lesion removal (Figure 5). No radiologic examinations of the specimens were performed for patients who underwent ultrasonography-guided WGL.

Statistical Analysis

Mean, standard deviation, and median values for continuous variables and frequency and percentage values for categorical variables were calculated. A chi-square test, Fisher's exact test, and the Fisher-Freeman-Halton exact test were used to assess categorical interrelationships. Normal distribution was assessed with the Kolmogorov-Smirnov test. An independent-samples t-test was used when normal distribution was observed for continuous variables, whereas a Mann-Whitney U-test was used when normal distribution was not observed. For all statistical tests, $p<0.05$ was considered statistically significant.

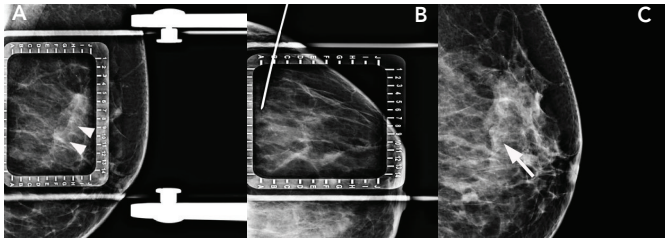

Figure 1. Radioguided occult lesion localization performed with mammographic guidance. **A.** Microcalcifications (arrowheads) can be seen. **B.** Needle can be seen entering the suspected area. **C.** After injection of contrast, increased density can be seen (arrow)

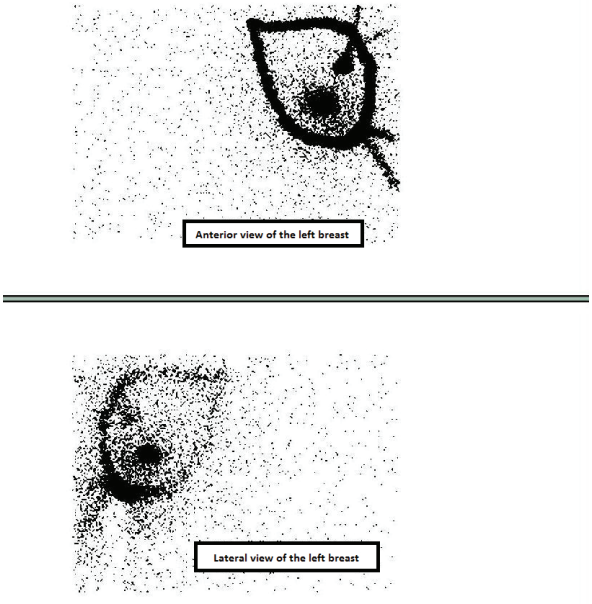

Figure 2. Scintigraphic graphy of lesion obtained using radioguided occult lesion localization under ultrasonographic guidance before surgical excision

RESULTS

Our search identified 67 women (mean age, 52.7 years; range, 32-69 years) who had been diagnosed with NPBL with features suggestive of malignancy during the study period. ROLL was used

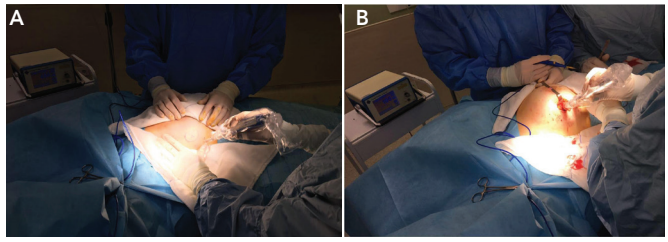

Figure 3. Use of a gamma probe **(A)** before surgical excision to localize the lesion and **(B)** after lesion removal to assess the cavity for evidence of residual lesion tissue

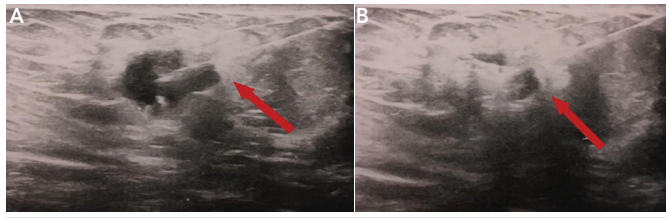

Figure 4. Radioguided occult lesion localization performed with ultrasonographic guidance. **A.** The needle can be seen inside the lesion (red arrow). **B.** After radionuclide injection, there is increased echogenicity in the lesion (red arrow)

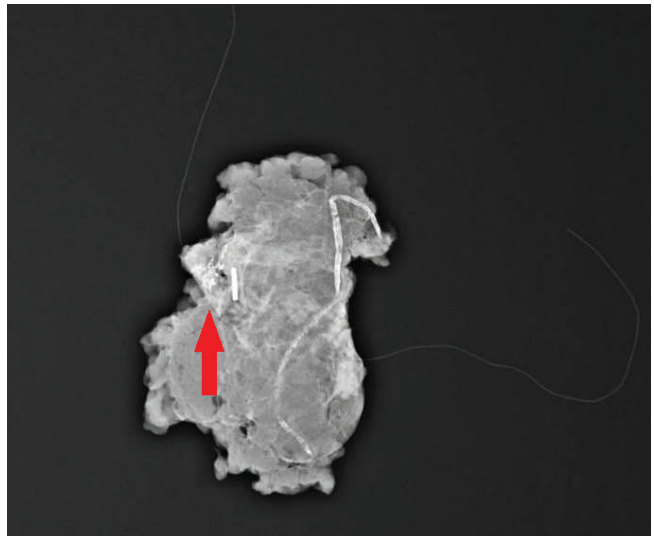

Figure 5. The control graphy for a specimen obtained using wire-guided localization shows the wire in the area of the calcification (red arrow)

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in 25 patients (26 lesions, including 2 separate foci in 1 patient), and WGL was used in 42 patients (44 lesions, with 2 separate foci in 2 patients) (Table 1). There was no significant difference between the groups in terms of age (p=0.09) or in terms of lesion location in the right or left breast (p=0.378). Nine of the patients in the ROLL group (36%) and 34 of the patients in the WGL group (81%) underwent mammography-guided breast marking; 16 of the patients in the ROLL group (64%) and 8 (19%) of the patients in the WGL group underwent ultrasonography-guided breast marking. Simultaneous SLNB was performed in 13 patients in the ROLL group and in 4 patients in the WGL group.

Images obtained before ROLL or WGL was performed demonstrated evidence of microcalcifications in 34 patients (79%) in the WGL group and in 9 patients (20%) in the ROLL group; a mass was observed in 8 patients (33%) in the WGL group and in 16 patients (66%) in the ROLL group. Pathologic analysis demonstrated that in the WGL group, 15 of 39 BI-RADS 4 lesions and 2 of 5 BI-RADS 5 lesions were malignant; in the ROLL group, 4 of 11 BI-RADS 4 lesions and 13 of 15 BI-RADS 5 lesions were malignant.

In the ROLL group, the lesion was accurately localized in 24 of 25 patients (96%). The one patient in the ROLL group without accurate localization demonstrated diffuse increased echogenicity on ultrasonography after Tc-99m-MAA injection; this finding was further evaluated on intraoperative ultrasonography, and the lesion was found and excised. In the WGL group, the lesion was accurately localized in 41 of 42 patients (98%). In the one patient without accurate localization, the wire was dislodged out of the lesion.

No significant difference was observed between the groups in terms of the median specimen volume (p=0.202). There were also no significant differences between the groups in terms of complication rates, lengths of hospital stay, and creation of positive surgical margins. The length of operation was significantly longer in the ROLL group than in the WGL group (ROLL: 96.40±37.54 minutes; WGL: 60.21±20.21 minutes) (p=0.0001).

DISCUSSION

In this study, we found that ROLL was as effective as WGL in preoperatively localizing NPBLs. This accurate preoperative localization should lead to improved success rates for the surgical excision of NPBLs.

Table 1. Image guidance for non-palpable breast lesions localization in the radioguided occult lesion localization and wire-guided localization groups

	Guidance techniques for localization	
	Mammography	Ultrasound
	n (*)	n (*)
ROLL	9	16
WGL	34	8

*Number of patients, ROLL: radioguided occult lesion localization, WGL: wire-guided localization

The WGL method of lesion localization has been used successfully for many years. In this study, we assessed whether the ROLL technique, just recently introduced at our institution, could provide safe and effective lesion localization, and we found that ROLL accurately localized NPBLs in 96% of patients, a rate similar to that seen with WGL (98%). These rates are also comparable to the localization rates of 89% to 100% reported in previous studies (17-22).

Accurate lesion localization and early surgical excision of NPBLs are important, as NPBLs are malignant in 10% to 30% of patients. BI-RADS 4 and 5 lesions carry the highest risk of malignancy (16,23,24). In this study of patients with BI-RADS 4 or 5 lesions, BI-RADS 4 lesions demonstrated heterogeneous distribution of malignancy risk in both the ROLL and WGL groups. The American College of Radiology states that the BI-RADS subgroups of 4a, 4b, and 4c have malignancy risks of 6%, 15%, and 53%, respectively (25), but the radiologic reports for lesions in this study did not include BI-RADS 4 subclassifications. For patients with BI-RADS 5 lesions, the malignancy rates in both the ROLL and WGL groups were consistent with rates previously reported (25).

We observed no difference between the groups in the creation of positive surgical margins and in the size of specimens obtained. In previous studies, the ROLL procedure was associated with less involved margins and smaller surgical specimens than the WGL technique (20,25-29). Because the surgeons at our institution have just begun using ROLL, a larger excision than usual may have been made, leading to larger specimen sizes. The size of the margins created is also dependent on lesion size and histologic grade; more involved margins are seen more frequently with cases of large ductal carcinoma in situ and lobular carcinoma in situ (28,30). The suggested protocol for creating surgical margins in patients with NPBLs is to use a gamma probe to trace the radioactivity in the center of the lesion and then assess the excision site to ensure that no residual lesion tissue remains (15,17,18,31,32), as we did in this study. However, some authors recommend excising an additional 1 to 2 cm of tissue around the maximal radioactive site (20,33).

The length of the operation was longer with ROLL than with WGL in our study. These results again contrast with those of previous studies, which reported shorter surgery times with ROLL than with WGL (17,18,27,32). This difference may again be partly explained by the learning curve required when implementing the ROLL technique. Additionally, more patients in the ROLL group than in the WGL group underwent SLNB, which may have added to the procedure time.

Complication rates and lengths of hospital stay were similar for the 2 groups and were similar to results from previous studies (17). Complications such as breakdown of the markers, syncope, pain, and pneumothorax have previously been reported with WGL (10-12), but a meta-analysis found that no major complications have been reported with either WGL or ROLL (27).

In this study, most of the ROLL procedures were guided by ultrasonography; this choice was determined by the radiologist.

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In general, the choice of imaging guidance depends on the availability of the technique and on the lesion characteristics. Mammography is recommended for assessing microcalcifications, whereas ultrasonography is recommended for evaluating solid and cystic lesions (18). Additionally, the choice of imaging used for guidance should be based on the type of imaging that first demonstrated the lesion (34).

In both the WGL and ROLL groups, SLNB was performed in only certain patients. However, more patients in the ROLL group underwent SLNB, perhaps because benign lesions were more common in the WGL group and lesions in the ROLL group were more likely to be mass-like. Histopathologic analysis of SLNB results was not included in this study.

Our study had several limitations. The main limitation of this study was that it was a retrospective study with small sample size, which limited our ability to include more lesions. Prospective data are needed to confirm these findings. On the other hand, study patients were treated by various radiologists and surgeons who had different degrees of experience with the procedures involved. These variations may have affected our analysis regarding accurate localization of lesions. Nuclear medicine at our institution has been a promising deparment which has provided us radionuclide material for ROLL. Collaboration of the departments of radiology and nuclear medicine has given us more chance to implement this new technique in our institution. This study was our first experience of this collaboration with some difficulties including low number of scintigraphic controls after ROLL procedures. Another limitation was that we could not evaluate the patient's comfort because of the retrospective design of the study.

CONCLUSION

In conclusion, this study demonstrated that the ROLL technique is a safe and effective method for preoperatively localizing NPBLs, thus allowing accurate surgical excision of potentially malignant lesions. The ROLL technique may therefore serve as an alternative to WGL for the localization of NPBLs, as this technique is simple to perform (even for inexperienced operators) and provides satisfactory results.

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Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences Turkey İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2017/29).

Informed Consent: Informed consent was not taken from patients due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - C.Ç., S.K., A.K.; Concept - C.Ç., F.Ç.Y., S.K., A.K., E.İ.; Design - C.Ç., S.K., A.K., E.İ.; Data Collection or Processing - C.Ç., F.Ç.Y., S.K., A.K.; Analysis or Interpretation - C.Ç., F.Ç.Y., S.K., A.K., E.İ.; Literature Search - C.Ç., F.Ç.Y.; Writing - C.Ç., S.K., A.K., E.İ.

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Case Report

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High SUV_{max} Value of Ovarian Tubercular Mass: Conflict in Diagnosis

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ABSTRACT

Abdomino-peritoneal tuberculosis is a commonly encountered infectious disease especially in endemic areas. Abdomino-peritoneal tuberculosis should be kept in mind in assessing patients with elevated blood CA125 levels, abdominal ascites and adnexal mass since these signs may indicate both advanced ovarian cancer and ovarian tuberculosis as a known dilemma. In the literature, standardized uptake values (SUV) of malignant ovarian tumors and inflammatory/infectious conditions of ovaries on Positron emission tomography/computed tomography (PET/CT) scan have been demonstrated so far.

In this case report, we present a 13-year-old female patient who was living in an endemic area for tuberculosis and complaining of abdominal distention and blunt abdominal and back pain, and whose F-18 Fluorodeoxyglucose (FDG)-PET scan revealed adnexal mass with avid FDG uptake with the SUV_{max} value of 16.6 which was highly suggestive for ovarian cancer.

Keywords: Abdomino-peritoneal tuberculosis, ovarian tuberculosis, standardized uptake value

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium Tuberculosis*. TB occurs all part of the world (1). Approximately 8 million new cases and more than 2 million deaths arise due to TB each year (2). The lifetime risk of developing active TB in people who have active TB is about 5-15%. This rate increases in immunocompromised patients such as those infected with human immunodeficiency virus, malnutrition status, diabetes, tobacco usage, and diseases that repress the immune system. Even TB affects mainly lungs and mediastinal lymph nodes, it may involve all systems in the body causing wide variety of symptoms. The peritoneal or abdominopelvic tuberculosis is a form of abdominal tuberculosis that involves the liver, spleen, female genital tract, omentum and visceral and parietal peritoneum. Peritoneal TB is the sixth most common site for extrapulmonary TB which accounts 1-2% of all forms of tuberculosis (3,4). Abdomino-peritoneal tuberculosis should be kept in mind in assessing patients with elevated blood CA125 levels, abdominal ascites and adnexal mass since these signs may indicate both advanced ovarian cancer and ovarian tuberculosis. To keep abdomino-peritoneal TB in mind is essential for proper diagnosis and accurate and rapid treatment.

Ultrasound is the first choice and mainly used as the imaging modality for the characterization of tuboovarian tubercular mass. It is widely available and there is no exposure to radiation. Computerized tomography (CT) may be helpful but generally gives nonspecific information. Magnetic resonance imaging (MRI) characterizes tubo-ovarian masses better than CT and ultrasound do. 2-deoxy-2-(18) fluoro-D-glucose- positron emission tomography (F-18 FDG-PET) combined with CT detects

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malignant lesions and inflammatory masses and differentiates active and inactive disease process by demonstrating increased FDG uptake (3).

We presented a case of abdomino-peritoneal tuberculosis referred from the periphery as ovarian carcinoma. As shown in our case, preoperative definitive diagnosis is still a problem in ovarian cancer and ovarian TB. We also wanted to emphasize that the maximum standardized uptake values (SUV_{max}) on (F-18 FDG-PET) may also be misleading in differential diagnosis.

CASE PRESENTATION

A 13-year-old female patient was referred to our hospital from the periphery as ovarian carcinoma. She was complaining of abdominal distention, lower abdominal pain and low back pain for over two months. Physical examination revealed only lower abdominal tenderness by palpation. She had no sexual history. Her past medical history was unremarkable. In blood analysis, white blood cell count was 13.000 (1/mm^3), hematocrit level was 34.3, B-human chorionic gonadotropin was below 0.5 mU/mL, carcinoembrionic antigen (CEA) level was 0.23 (ng/mL) and preoperative CA125 was 500.6 (U/mL). The sedimentation rate was increased (89 mm/hr). Ultrasound was performed as the initial diagnostic modality and bilateral adnexal masses of 5x4 centimeter on the right and 4x4 centimeter on the left, with cystic and solid components, were noted. On performed MRI, bilateral mass like lesions with soft tissue and hemorrhagic cystic components were noted with sizes of 47x32x41 and 39x43x33 mm, respectively. High attenuation was observed in both of the lesions after intravenous contrast administration. The MRI findings were reported as suggestive for ovarian carcinoma and further evaluation with F-18 FDG-PET was recommended. On F-18 FDG-PET imaging combined with CT, bilateral adnexal mass lesions with cystic and solid components were noted (Figure 1). Solid parts of the masses had intense hypermetabolism with 16.6 SUV_{max} value, which is also very suggestive for malignity rather than infectious processes. There were also multiple lymph nodes in abdominal cavity with increased FDG uptake which were evaluated as metastasis (Figure 2), a nodular lesion in the superior lobe posterior segment of the right lung that showed increased FDG uptake with the 1.3 SUV_{max} value (Figure 3) and multiple soft tissue lesions with increased FDG uptake spread in the abdominal cavity in which the highest size was up to 2.5 centimeter in diameter and 13.5 SUV_{max} value, which were evaluated as peritoneal implants. Also increased FDG uptake was observed in the left quadratus lumborum muscle and evaluated also as tumor implant. Metastatic ovarian carcinoma was considered by blood tests and imaging. Transabdominal ultrasound guided biopsy of the adnexal masses was planned to attain histopathological diagnosis and to start possible chemotherapy rapidly. Biopsy was performed under ultrasound with 20 Gauge biopsy needle from the right ovary and intra-abdominal free fluid was aspirated for characterization concomitantly. Pathology report revealed necrosis and inflammatory cell proliferation. Ehrlich Ziehl Neelsen staining of the samples was unremarkable. On performed abdominal free fluid analysis, there was increased glucose (79 mg/dL), microprotein (8.850 mg/dL), leucocyte (11.200/mm^3) and erythrocyte (33.600/mm^3) levels. Unfortunately, no bacterial reproduction could be observed. After these steps for final diagnosis, laparoscopic biopsy was planned. During the operation, wedge biopsy from the right ovary was performed and aspirated abdominal fluid was collected for culture. The biopsy specimen revealed chronic granulomatous inflammatory infiltration with caseification necrosis. *M. Tuberculosis* bacteria reproduction was obtained in culture specimen. Four drug fixed dose combination of anti-TB regimen was initiated to patient. Written informed consent from the patient's relative was taken for this case presentation.

DISCUSSION

Abdomino-peritoneal tuberculosis generally presents with nonspecific symptoms like dull abdominal pain, menstrual cycle

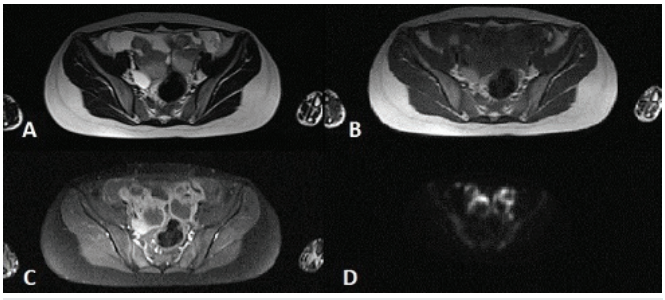

Figure 1. Bilateral ovarian mass lesions with cystic and soft tissue components. Peripheric enhancement after intravenous contrast injection and avid fluorodeoxyglucose (FDG) uptake in adnexal masses are seen. A) Axial pre-contrast T2-weighted (T2-W) sequence. B) Axial pre-contrast T1-W sequence. C) Axial post-contrast T1-W sequence. D) Fluoro-18 FDG-positron emission tomography imaging

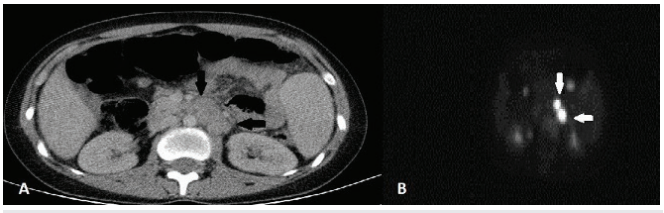

Figure 2. Paraaortic enlarged lymph nodes are seen (arrows). A) Axial computed tomography imaging. B) Axial fluoro-18 fluorodeoxyglucose-positron emission tomography imaging

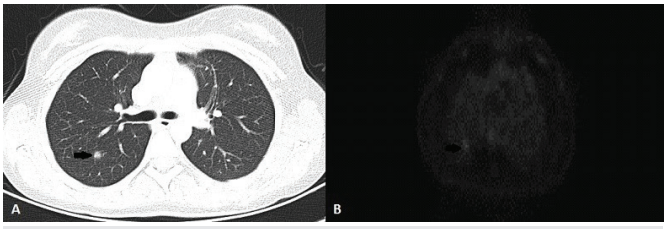

Figure 3. Solid nodule with peripheric ground-glass opacities in the lower lobe superior segment of the right lung is seen. A) Axial CT imaging B) Axial fluoro-18 fluorodeoxyglucose-positron emission tomography imaging

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abnormalities, and infertility problems (3-5). Abdominopelvic mass and ascites may be present and accompanied by an increase in serum Ca125 level. These findings may mimic ovarian cancer. Preoperative diagnosis of ovarian cancer and abdomino-peritoneal tuberculosis can be a challenging issue at times. Definitive diagnosis is made by tissue biopsy. To attain the tissue sample, diagnostic laparotomy/laparoscopy or ultrasound guided biopsy can be performed (4). There is no pathognomonic marker in the differentiation of abdominopelvic tuberculosis and advanced ovarian cancer, as a known dilemma. In our case, patient history and physical examination were unremarkable and all symptoms were non-specific. In blood analysis, preoperative CEA-125 was elevated (500.6 (U/mL), which may accompany ovarian cancer and also many benign conditions like peritoneal TB and malign conditions other than ovarian cancer. Ultrasound and MRI showed bilateral ovarian mass, abdominal ascites, mass like peritoneal thickening and multiple enlarged lymph nodes. These imaging features could be observed in both advanced ovarian carcinoma and peritoneal tuberculosis as well. The F-18 FDG-PET imaging revealed bilateral adnexal masses with cystic and solid components and intense hypermetabolism with 16.6 SUV_{max} value which was very suggestive for malignancy rather than infectious processes. There was also a nodular lesion in the superior lobe posterior segment of the right lung, multiple lymph nodes in abdominal cavity, multiple soft tissue lesions spread in abdominal cavity, and a mass like lesion evaluated as an implant in the left quadratus lumborum muscle, and all showed increased FDG uptake.

To our knowledge, there is no study which points out the maximum standardized uptake value (SUV_{max}) of ovarian masses secondary to tuberculosis. Chen et al. (6) performed a retrospective analysis of F-18 FDG-PET of 103 patients with peritoneal thickening. They showed that there was no significant difference of SUV_{max} values between benign and malignant peritoneal thickening with P value of 0.12. On the other hand, SUV_{max} value of malignant peritoneal thickening was higher than non-tuberculous etiologies of benign peritoneal thickening (p=0.02). They also showed that peritoneal thickening secondary to tuberculosis had SUV_{max} values similar to malignant peritoneal thickening within a range of 1.7 to 8.6 (6). In another study, Sharma et al. (7) obtained F-18 FDG-PET of 17 patients with tubercular tubo-ovarian masses to assess the role of F-18 FDG-PET scan in preoperative diagnosis. They classified tubo-ovarian masses according to masses that uptake glucose or not. The ratio of unilateral tubo-ovarian mass with glucose uptake was 35.3% and the ratio of bilateral tubo-ovarian masses with glucose uptake was 23.5%. They did not mention about the SUV_{max} values quantitatively in this study.

CONCLUSION

Abdominopelvic tuberculosis needs to be considered in young women diagnosed as ovarian cancer, who come from low socioeconomic backgrounds and live in endemic areas of tuberculosis. Even though the role F-18 FDG-PET scan cannot be denied in confirming malignant and benign inflammatory or infectious lesions, it has limited performance in distinguishing abdomino-peritoneal tuberculosis from advanced ovarian cancer or peritoneal carcinomatosis. Ultrasound-guided fine needle biopsy, as a relatively new method, and laparoscopic biopsy are still needed for final histopathologic diagnosis of abdomino-peritoneal tuberculosis.

Informed Consent: Written consent from the patient's relative was taken for this case presentation.

Peer-review: Internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - D.T.M.; Concept - B.A.Ü.; Design - B.A.Ü., D.T.M.; Data Collection and/or Processing - E.Ö.; Analysis and/or Interpretation - E.Ö., Ş.M.E.; Literature Search - B.A.Ü.; Writing Manuscript - B.A.Ü., Ş.M.E.

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

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Sitagliptin/Metformin Related Cutaneous Leukocytoclastic Vasculitis in a Patient with Type-2 Diabetes Mellitus

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ABSTRACT

Small vessel vasculitis is characterized by the involvement of arterioles, capillaries, and venules. The most common cutaneous finding of small vessel vasculitis is palpable purpura, and urticaria, petechiae, erythema, vesicles, and pustules may also be seen. It may be related to malignancies, connective tissue diseases, infections, and drugs such as penicillin, sulphonamides, allopurinol, antithyroid drugs but it is often idiopathic. Drug-related vasculitis is seen in 7 to 21 days after the onset of the drug and systemic findings are usually absent. Both metformin and sitagliptin are frequently used in the treatment of diabetes. However, skin reactions to these drugs are rare. In this case report, our aim is to present a 70-year-old female patient with the diagnosis of type 2 diabetes mellitus, and metformin/sitagliptin-induced cutaneous leukocytoclastic vasculitis.

Keywords: Sitagliptin/metformin, cutaneous leukocytoclastic vasculitis, type 2 diabetes mellitus

INTRODUCTION

Leukocytoclastic vasculitis (LCV) is a small vessel vasculitis characterized by the involvement of arterioles, venules, capillaries with inflammation and necrosis. It may be related to malignancies (<5%), connective tissue diseases (15-20%), infections (15-20%), and drugs such as penicillin, sulphonamides, allopurinol, and antithyroid drugs (10-15%) but it is often idiopathic (50%) (1). Also, tartrazine, insecticides, herbicide, diphenylhydantoin, acetylsalicylic acid, naproxen, and furosemide cause LCV (2). Skin biopsy is needed to diagnose LCV and to exclude mimicking causes, and drug-related LCV is an exclusion diagnosis. Dipeptidyl peptidase (DPP)-4 inhibitors are new generation oral anti-diabetic drugs developed for type 2 diabetes mellitus (DM) and the mechanism of action is to inhibit the degradation of incretins (3). Common side effects of DPP-4 inhibitors include nausea, abdominal pain, diarrhea, and rarely pancreatitis (3,4). However, there are studies reporting that sitagliptin has no association with vomiting, nausea, and diarrhea (5).

Sitagliptin and its metabolites- related hypersensitivity reactions and generalized skin eruption have been reported (3,4,6). However, LCV associated with sitagliptin is extremely rare (4). The most common side effects of metformin are dyspeptic symptoms such as flatulence, nausea, and vomiting but skin reactions are rare. Metformin-associated psoriasiform drug eruption and LCV have been reported in the literature (6,7). Here, we aimed to present a female patient with metformin plus sitagliptin-induced cutaneous LCV.

CASE PRESENTATION

A 70-year-old female patient was admitted to our clinic with a complaint of rashes on her legs. On physical examination, the patient was morbidly obese and there were symmetrical

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erythematous papules and palpable purpura on both lower extremities (Figure 1). There was no medical history of smoking or alcohol use. She had hypertension for 15 years, type 2 DM for 14 years, asthma for 20 years, and was taking insulin aspart (fast-acting insulin analog), insulin detemir (long-acting human insulin analog), metformin, inhale glycopyrronium bromide (long-acting muscarinic antagonist as a bronchodilator β1 receptor blocker) and nebivolol (nitric oxide-potentiating vasodilator). Metformin was withdrawn and therapy was continued with sitagliptin/metformin due to impaired blood glucose regulation 10 days before. The blood results were as following: hemoglobin: 14.3 g/dL, hematocrit: 44,6%, mean corpuscular volume: 92 fL, leukocyte: 9.230/mm^3, platelet: 249.000/mm^3, C-reactive protein: 34.4 mg/L, sedimentation: 44 mm/h, Urinalysis and stool analysis were normal. The anti-nuclear antibody and anti-neutrophilic cytoplasmic antibody were negative. And, rheumatoid factor, anti-cyclic citrullinated peptide, immunoglobulins, and complement levels were within normal ranges. Hepatomegaly/hepatosteatosis was detected by abdominal ultrasonography and chest X-ray was normal. Left ventricular diameter and motions were normal by echocardiography. Skin biopsy revealed LCV with neutrophilic inflammation, fragmented neutrophilic nuclei, and fibrinoid necrosis. It was considered to be associated with sitagliptin. The suspected drug was discontinued and 0.5-1 mg/kg prednisolone was started. In the follow-up, the rashes of the patient disappeared within one week. Written informed consent was obtained from the patient.

DISCUSSION

In the histopathological examination of cutaneous vasculitis, neutrophilic transmural inflammation and fibrinoid necrosis, extravasation of erythrocytes, granulocyte debris are seen on the vessel wall, and granulomatous or lymphocytic infiltration and immunoreactant deposition may also be seen according to etiology (1). Drug-related vasculitis is seen in 7 to 21 days after the onset of the drug and systemic findings are usually absent. Diagnosis is usually made by questioning time of exposure to the suspected drug and excluding other causes such as infections, connective tissue diseases and malignancies (1). We have not found infections, connective tissue diseases, and malignancies as underlying causes in our patient. Due to the recent addition of sitagliptin plus metformin to the treatment of the patient, it was thought to be drug-induced LCV.

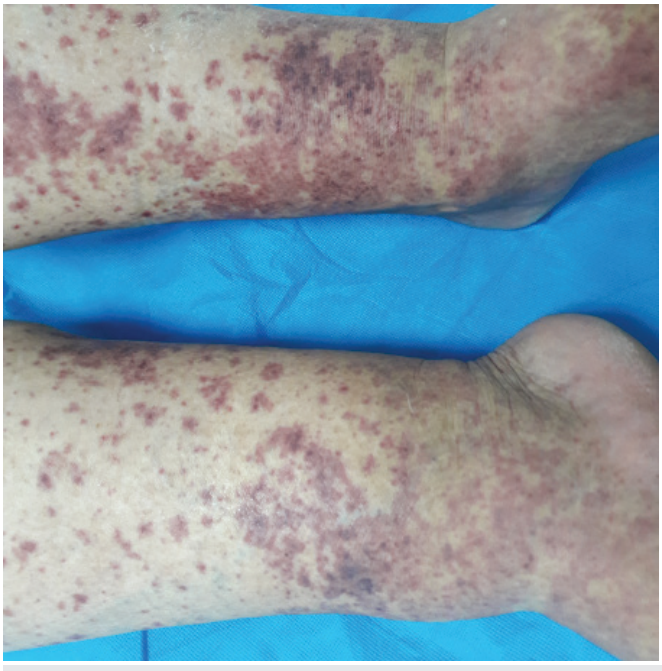

Figure 1. Symmetrical erythematous papules and palpable purpuras on both lower extremities

Metformin is widely used in tip 2 DM. Rash, urticaria, bullous pemphigoid, psoriasiform drug eruption, LCV, lichen planus, and acute alopecia have been reported as metformin-induced skin eruptions (7,8). In the literature, there are few cases on metformin-induced LKV. Ben Salem et al. (8) described a case of LKV that developed after metformin in a 33-year-old female patient. She started self-treatment with metformin twice one month apart, but at both times, maculopapular rash and petechial lesions developed on her lower extremities after metformin 850 mg treatment. Lesions resolved by discontinuation metformin and biopsy showed LCV.

Sitagliptin is a new generation oral antidiabetic drug used in the treatment of type 2 DM. Dyspeptic symptoms and hypersensitivity reactions may occur with sitagliptin (3,4). Anaphylaxis and angioedema may occur due to the use of a DPP-4 inhibitor (4). Sitagliptin-associated skin and subcutaneous diseases were found to be 1.3 per 100 patient-years (3). It has been reported that gliptins may cause serious reactions such as toxic epidermal necrolysis and Steven Jonhson's syndrome (4).

There are also gliptin-related bullous pemphigoid case reports and case series (9). In a case report of Attaway et al. (9), 70 year-old male patients with type 2 DM developed bullous eruption and urticaria one year after the start of sitagliptin therapy. Skin biopsy revealed bullous pemphigoid, healed within two to three days with the discontinuation of sitagliptin and initiation of steroids. Authors did not find a strong association with bullous pemphigoid and other drugs of the patient (9). In the review of the case reports, 64% of the patients were using vildagliptin and 36% were using sitagliptin, the mean age was 72 years with male predominance and the mean interval between bullous pemphigoid and drug initiation was found to be 6 months (9).

Uçan et al. (10) reported sitagliptin-induced LCV in a 46-year-old male patient. He was followed up for 6 years with type 2 DM and was using 2000 mg of metformin and 100 mg of sitagliptin was added to the treatment. Fifteen days after sitagliptin initiated, bilateral rashes appeared on his legs. There was no evidence of systemic involvement and skin biopsy revealed LCV. Within 10 days after the discontinuation of sitagliptin treatment, the patient's rashes disappeared. In another case, generalized skin eruption was reported in a patient using sitagliptin plus metformin (6). In a 66-year-old male with untreated type 2 DM, treatment was

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started with sitagliptin 50 mg + metformin 500 mg. Six months later a rash occurred on the upper limbs of the patient and then spread to the chest, back, abdomen and thigh. The skin lesions did not respond to steroid treatment but resolved immediately after sitagliptin discontinuation. The authors did not perform skin biopsy, and they considered sitagliptin-induced allergic reaction in their differential diagnosis. Other hypersensitivity reactions reported with sitagliptin are erythema, urticaria, and angioedema (3,4).

CONCLUSION

Cutaneous vasculitis cases due to both metformin and sitagliptin are rare. The combination of sitagliptin/metformin is frequently used in the treatment of diabetes. It should be kept in mind that metformin plus sitagliptin may cause cutaneous LCV.

Informed Consent: Written informed consent was obtained from the patient.

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Treatment of Sympathetic Nerve Neurofibroma of the Neck and Approach to the Postoperative Pain

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ABSTRACT

Peripheral nerve sheath tumors (PNST) are a kind of neuro-ectodermal tumors. Neurofibromas are benign PNST originating from Schwann cells, fibroblast-like cells, and perineural cells. The origin of symptomatic neurofibromas may be many parts of the body, but about 25% of them originate from the head and neck region. Postoperative pain is a quite common condition in these tumors of which primary treatment is surgical excision. Postoperative treatment of this neuropathic pain which is unresponsive to many painkillers is still an important problem. In this case study, we discussed our applications and results of a 64-year-old female patient with sympathetic nerve neurofibroma to relieve the postoperative pain.

Keywords: Sympathetic nerve, neurofibroma, postoperative pain

INTRODUCTION

Peripheral nerve sheath tumors (PNST) are tumors of neuroectodermal origin (1). Neurofibromas are benign PNST originating from Schwann cells, fibroblast-like cells and perineural cells (2). Neurofibromas can originate from any peripheral nerve. Symptomatic neurofibromas can be seen in many parts of the body, but they can be seen in the head and neck region at the rate of about 25%. (3). These tumors are usually asymptomatic until they reach the size that will cause discomfort or deformity. Approximately half of neurofibromas are manifested by pain (4). The characteristic physical examination finding of PNST is a mass that cannot be manipulated up and down but moves only laterally. Although the majority of neurofibromas in the head and neck are benign, slowly growing tumors, it has been reported that malignant degeneration may also occur (5).

The purpose of the treatment of these tumors is to provide resection by maintaining the function of the nerve. Intracapsular enucleation of PNST is defined as a surgical technique that can limit the risk of nerve damage without increasing the risk of tumor recurrence (6). However, post-surgical pain is a common condition in these tumors. Elimination of this neuropathic pain that remains unresponsive to many painkillers continues to be an important problem. In this study, we discussed the practices performed to relieve pain after surgery and their results in a 64-year-old female patient with sympathetic nerve neurofibroma.

CASE PRESENTATION

Our patient was a 64-year-old woman who first noticed a mass in her neck 3 months ago. The patient applied to our clinic because she felt that the mass was growing constantly and at

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admission, she had no pain or sensitivity. He did not show the symptoms of dysphagia, dysphonia, hearing changes, cranial nerve, and brachial plexus. On physical examination, it was observed that there was a hard mass that was localized in the left anterior cervical region and that was mobile with palpation. In magnetic resonance imaging (MRI), a mass deeply well confined with the left sternocleidomastoid muscle (SCM), hyperintense in T2 sequences, and isointense in T1 sequences was detected (Figure 1). The mass showed heterogeneous enhancement and its dimensions were measured as 4.0x4.4x6.2 cm. Diffusion imaging showed a mass with an apparent diffusion coefficient of 2x10 -3 mm2/sec. Imaging findings were consistent with a neurofibroma. Upon the decision of surgical treatment, informed consent was obtained from the patient after giving detailed information about the operation. In addition, she was informed about that a case presentation regarding all diagnosis-treatment stages that would be applied to the patient and their results would be prepared and presented to the literature, and her approval was obtained.

The patient was operated under general anesthesia. After endotracheal intubation, a skin incision was made at the anterior border of the SCM from top to bottom and the subplatysmal skin flap was elevated to both sides. The mass was revealed by palpating and dissecting from surrounding tissues (Figure 2). The mass lateralized the internal jugular vein (IJV) and was causing compression. Likewise, the vagus nerve and carotid artery lateralized by pushing from below. Dissection was continued along the lower margin of the mass and the XI. cranial nerve was identified; The XII. cranial nerve was on the upper edge of the mass. The mass extended to the prevertebral muscles and the base of the skull over the deep cervical fascia. When the lower part of the tumor was determined and followed, it was observed that the mass separated from the vagus and originated from the sympathetic nerve. Later, IJV and carotid artery were isolated from the mass by blunt dissection. The mass was resected by maintaining the vagus. Histopathological examination was reported as neurofibroma (Figure 3).

The patient who had no postoperative complications was discharged in good condition. However, in the following period, unbearable pain occurred in the patient, which radiated to the neck and increased during eating. The given non-steroidal painkillers did not eliminate pain. The patient was consulted to the pain outpatient clinic, 25 mg of amitriptyline once a day and 150 mg of pregabalin, one in the morning in the first week and one in the morning and in the evening in the second week, were initiated. Although the pain decreased with these treatments, it did not disappear completely. 4 cc injection consisting of 1 cc prednisolone and 3 cc bupivacaine combination was applied to the resection region of the patient, who insistently stated that she felt pain especially during eating, by interventional radiology. After the injection, the patient's pain decreased, and the pain disappeared over time. The patient, who come for intermittent control, has not had pain for 4 months.

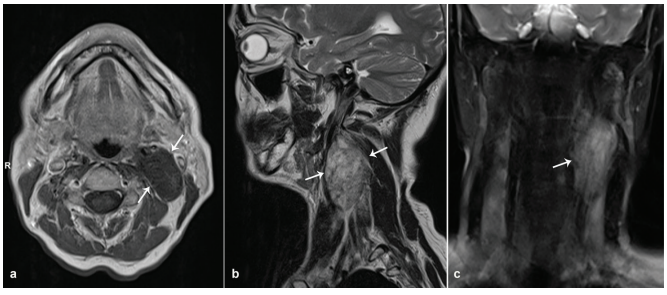

Figure 1. Magnetic resonance imaging. a) Isointense image of the mass in T1 sequence axial section, b) hyperintense view of the mass in T2 sequence sagittal section, c) T2 sequence coronal section

DISCUSSION

Serious pain after neurofibroma excision is a fairly common condition. In the treatment of postoperative pain, besides medical treatments with a multidisciplinary approach, interventional

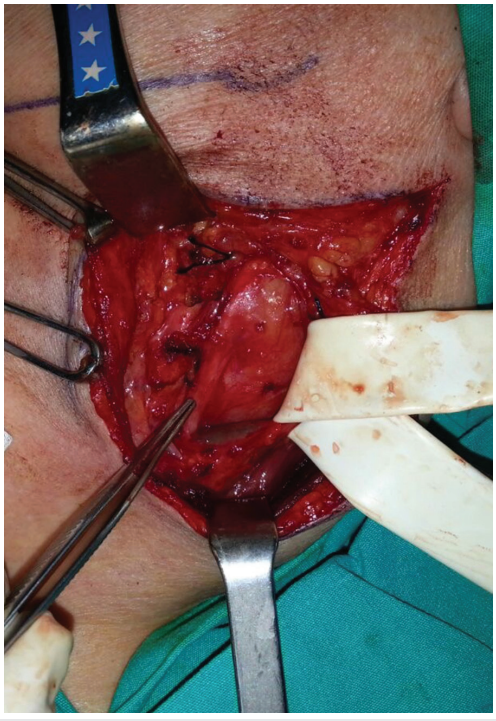

Figure 2. Intraoperative view

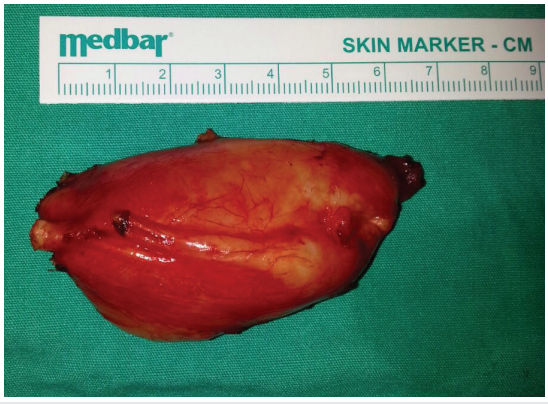

Figure 3. View after excision

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procedures may also be required. If a PNST is suspected with history and physical examination/ultrasonography (USG) findings, it would be reasonable to obtain an MR image of the mass in the next step. MRI is considered as the best imaging method to characterize PNST (7,8). In our case, the location and dimensions of the mass were first determined by USG, and it was revealed that there was a solid mass. Afterwards, MRI was performed to reveal its relationship with surrounding tissues and blood supply status and to rule out a possible carotid body tumor. As shown in this case report, neurofibromas are usually isointense in T1 sequences and hyperintense in T2 sequences, and they are observed heterogeneously in T1 after gadolinium contrast (7,8). Benign and malignant primary nerve sheath tumors exhibit overlapping features such as T2 hyperintensity, focal enlargement and strengthening in MRI. In our case, we determined that the mass might be a tumor of nerve origin with MRI.

Nerve tumors can be either benign or malignant. Malignant tumors are generally larger than benign tumors. While myxoid, cystic and hyaline changes are associated with benign tumors, necrosis, bleeding and mitotic activity were observed in malignant tumors (1). Also, while it is benign first, malignant change can be observed over time. In the literature, a case of solitary-sclerotic neurofibroma showing malignant transformation following three recurrences has been reported (9).

While there is a nerve fiber that enters and exits the tumor in the schwannomas, multiple fibers pass through the tumor mass in the neurofibroma. The basis of neurofibroma treatment is based on the resection of the tumor with the preservation of the function of these nerves, which may be associated with the tumor to varying degrees. Donner et al. (10) recommended intracapsular enucleation of neurofibroma in surgical treatment. They reported that more than 10% of patients developed pain syndromes related to the sensory area in which the operated nerve spread. In such cases, reaching the mass completely is an important problem. An improper exposition can cause injury to other vital organs. Therefore, in our case, an incision from the mastoid tip to the calvicula in front of the SCM was made to create a large surgical area. This was critical to prevent damage to important neurovascular structures that crossed the mass. Imaging is helpful in diagnosis and can also reveal safe surgical corridors for the surgeon. For safe tumor resection, electromyography, which evaluates nerve action potentials in the intraoperative period, can also be used (2).

The primary goal of both surgical and radiosurgery treatment of nerve tumors in the craniocervical junction is the preservation or restoration of the functions of the underlying cranial nerves. However, after treatment, head and neck pain may occur. In patients with nerve sheath tumors in the neck region, pain can be observed before surgery, and in the occipital region, in the right parietal and temporal areas, there may be pain radiating to the neck and shoulder. In our case, there was a very mild pain that was not disturbing before the operation, while severe pain occurred after the operation. Before, simple painkillers were given considering that as the pain of the surgical site. However, when the pain did not ease, support was obtained from the pain and anesthesia polyclinic. Despite the pregabalin treatment initiated by the pain and anesthesia outpatient clinic, the pain did not disappear completely, and interventional radiology blocked the exposed nerve fibers in the resection area of the patient.

Even if the nerve sheath tumors are benign, complete excision after the operation can sometimes lead to very severe pain. In these cases, firstly, simple painkillers should be tried parenterally or orally, and in cases which gives no response, support should be obtained from the pain outpatient clinic. A nerve blockage application that will be applied by interventional radiology can be considered as a last resort.

Informed Consent: Informed consent was obtained from the patient after giving detailed information about the operation.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - G.Y., A.B.S., K.M.Ö.; Concept - Ö.H., C.S.; Design - C.S.; Analysis and/or Interpretation - Ö.H., C.S., A.B.S.; Literature Search - G.Y., K.M.Ö.; Writing Manuscript - G.Y., Ö.H.

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

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A Case of Nodular Cystic Acne Treated with Systemic Dapsone

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ABSTRACT

Dapsone is an aniline derivative from synthetic sulfones. The mechanism of action of dapsone is obscure in inflammatory diseases; however, it is suggested to inhibit neutrophil chemotaxis and lysosomal enzymes. Acne vulgaris (AV) is a chronic inflammatory disorder of the pilo-sebaceous unit.

Herein we report a pediatric patient who was started systemic isotretionin due to severe nodular cystic AV but could not continue due to elevated liver enzymes and well response to systemic dapsone treatment. We consider that per-oral dapsone treatment may be a well-tolerated and effective treatment option in patients with moderate/severe, frequently recurring AV which is irresponsive to conventional therapies and may a good alternative to isotretionin particularly in pediatric cases.

Keywords: Dapsone, isotretinoin, nodulocytic acne

INTRODUCTION

Dapsone (4,4'-diamino diphenyl sulfone) is an aniline derivative from synthetic sulfones, which has both anti-bacterial and anti-inflammatory effects. It was first used for the treatment of leprosy in 1940 and for the treatment of dermatitis herpetiformis and non-infectious inflammatory dermatoses thereafter (1).

Acne vulgaris (AV) is a chronic inflammatory disorder of the pilo-sebaceous unit, which is characterized by open and closed comedones, inflammatory papules, pustulae, nodules and cysts, which may lead to scar formation and altered pigmentation (2). Abnormal follicular keratinization, increased sebum production, Propionibacterium acnes colonization and inflammation are accused for the pathogenesis of AV (2).

Herein we report a pediatric patient who was started systemic isotretionin due to severe nodular cystic AV but could not continue due to elevated liver enzymes and well response to systemic dapsone treatment.

CASE PRESENTATION

A 14-year-old male patient was admitted to Dermatology Clinic due to widespread nodular cystic acne. Dermatologic examination revealed widespread nodular cystic acne lesions on the face, shoulders, and anterior side of the trunk (Figure 1). It was learned that he did not respond to systemic and local antibiotic therapies given due to nodular cystic AV.

He was planned to commence isotretionin 20 mg daily and increase gradually; however, the dose was decreased to 10 mg daily due to elevated liver enzymes at the first month of therapy. Isotretonin was discontinued at the control two weeks later due to the detection of aspartate aminotransferase 192 U/L, alanine aminotransferase 406 U/L and gastro-enterology consultation was made. Viral panel results and auto-antibody test results (anti-nuclear antibodies, anti-mitochondrial antibodies, anti-smooth muscle antibodies) were negative. Elevated liver enzymes were suggested to be associated with isotretionin and turned to normal after the cessation of the drug.

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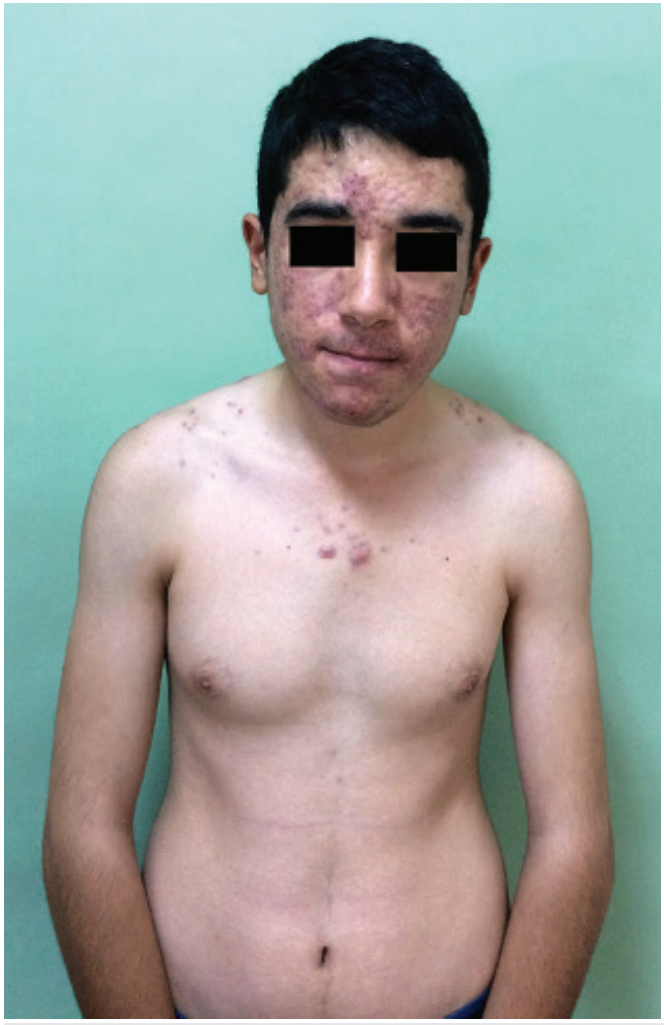

Figure 1. Widespread nodular cystic acne lesions on the face, shoulders, anterior side of the trunk

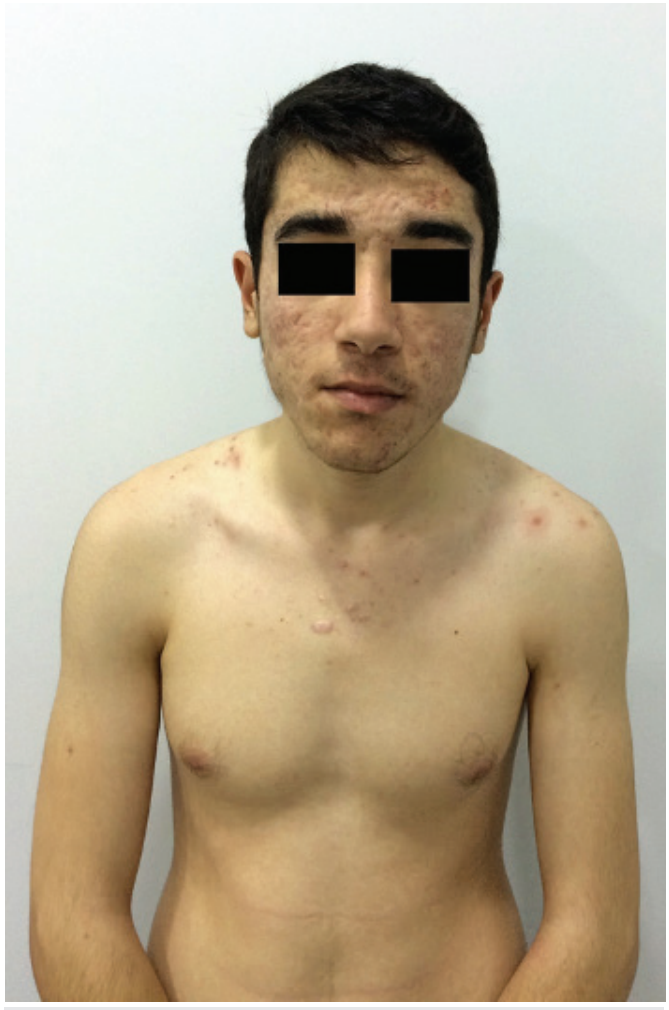

Figure 2. Active nodular cystic lesions dramatically regressed at the 6th month of treatment and atrophic scars developed

Dapsone treatment via per-oral route was planned as the patient could not tolerate isotretionin and was negatively affected from nodular cystic AV. Glucose-6-phosphate dehydrogenase enzyme level was normal. Lesions were detected to regress after using dapsone in the dose of 50 mg daily so the dose was increased to 100 mg daily. Lesions were dramatically regressed after using dapsone 100 mg daily for 4 months and 50 mg daily for 2 months. Whole blood count and routine biochemistry tests were found to be normal during the treatment. Active nodular cystic lesions dramatically regressed at the 6th month of the treatment and atrophic scars developed (Figure 2). Informed consent was obtained from the patient and his mother for the publication of this case report and images.

DISCUSSION

AV is a chronic inflammatory disorder of the pilo-sebaceous unit which affects approximately 80% of adolescents and young adults (3). While topical treatment is sufficient in mild forms of AV, systemic treatment is required in moderate and severe forms. Isotretionin used via per-oral route is the most effective therapeutic agent used for the treatment of moderate/severe acne for longer than 30 years and it influences all factors in the pathogenesis of acne and provides long term remission (4). Isotretionin used via per-oral route which has tolerable muco-cutaneous and systemic side effects keeps its place in the treatment of acne due to its effectiveness and safety (5).

No consensus is available about an effective treatment option when isotretionin cannot be used due to toxicity. In literature, Didona et al. (6) have reported the use of dapsone in a 14-year-old patient whose acne progressed under isotreatinine treatment, and Wakabayashi et al. (7) reported a dramatic response with dapsone treatment in 5 Japanese patients. We planned to use dapsone in our patient who could not use systemic isotretionine due to elevated liver enzymes.

The mechanism of action of dapsone is obscure in inflammatory diseases; however, it is suggested to inhibit neutrophil chemotaxis and lysosomal enzymes (8). Dapsone is among the treatment options in diseases like bullous pemphigoid, eosinophilic folliculitis, Sweet syndrome, erythema elevatum diutinum, leukocytoclastic vasculitis, pyoderma gangrenosum, bullous form

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of lupus erythematosus, relapsing poly-chondritis and rheumatic fever besides dermatitis herpetiformis, sub-corneal pustular dermatosis, erythema elevatum dutinum in which it is used as the first choice of treatment (8). Dapsone was suggested to be able to be effective in the treatment of acne due to having anti-bacterial and anti-inflammatory effect (9).

Studies have been reported about the effectiveness of topical dapsone treatment in AV (9). The use of per-oral dapsone was reported in acne fulminans (10). However, limited data are available about systemic dapsone use in AV. Didona et al. (6) have reported a case report about the effectiveness of dapsone in nodular cystic acne. Wakabayashi et al. (7) have also reported good outcomes about the use of per-oral dapsone in persistent acne. We could obtain satisfactory response with per-oral dapsone treatment.

CONCLUSION

We consider that per-oral dapsone treatment may be a well-tolerated and effective treatment option in patients with moderate/severe, frequently recurring AV which is irresponsive to conventional therapies and dapson can be used for AV in patients who improve severe side effects.

We believe that further prospective clinical studies that will be conducted with more patients and will investigate the effectiveness of dapsone in AV are required.

Informed Consent: Informed consent was obtained from the patient and his mother for the publication of this case report and images.

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