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Contents

Review

Case report

ULAKBİM Dergi Sistemleri (//dergipark.org.tr/en/)

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Research article
Araştırma makalesi

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Is Pitanguy's ligament a true ligament? A prospective cohort study

Pitanguy ligamenti gerçek bir ligament midir? Bir prospektif kohort çalışma

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Abstract

Aim: Facial region anatomically differs from other parts of the body by various structures it contains, for example, the superficial musculoaponeurotic system (SMAS). Among these structures, the most discussed is the dermocartilaginous ligament (DCL). There are some researchers who claim that this ligament is the continuity of the SMAS as well as those who consider it to be a separate ligament. Our aim is to determine whether the DCL, known as Pitanguy's ligament, is a true ligament based on histopathologic findings.

Methods: Open technique rhinoplasty was performed to all 52 patients with nasal obstruction and deformity complaints. During the operation, specimens were excised from the tissues thought to be the DCL in all patients for histopathological examination, which was performed by pathologists.

Results: Gross findings during the operation revealed that in most of the 52 patients, white dense fibrotic tissue, considered the DCL, was observed in the middle part of the nose. During histopathological examination, vascularized fibromuscular tissue fragments were observed in one patient and edematous connective tissue components were seen in the others.

Conclusion: Based on our results and literature research, the presence of fibrous tissue components in the intermedial crural area demonstrates that the DCL is a true ligament, but the absence of regular dense fibrous tissue components in our histopathologic findings requires further histological studies. In addition, we believe that DCL should be preserved to obtain natural and functional noses in open technic rhinoplasties.

Keywords: Dermocartilaginous ligament, Pitanguy's ligament, M. depresor septi nasi, Superficial musculoaponeurotic system, Histopathology

Öz

Amaç: Fasiyal bölgede yüzeysel musküloaponörotik sistem (SMAS) adı verilen bir yapı olması nedeniyle, fasiyal bölgenin anatomik yapısında diğer vücut bölgelerinden farklılıkları vardır. Bu yapılar arasında en çok tartışılanı dermokartilajinöz ligamenttir (DCL). Bu ligamentin farklı bir ligament olduğunu düşünenlerin yanı sıra SMAS'ın devamlılığı olduğunu iddia eden bazı araştırmacılar da vardır. Bu çalışmadaki amacımız, Pitanguy'un ligamenti olarak bilinen DCL'nin histopatolojik bulgulardan sonra gerçek bir ligament olup olmadığını ortaya koymaktır.

Yöntemler: Burun tıkanıklığı ve deformite şikâyeti olan 52 hastanın hepsine açık teknik rinoplasti operasyonu uygulandı. Tüm hastalarda operasyon sırasında DCL olduğu düşünülen dokulardan histopatolojik inceleme için örnekler alındı. Histopatolojik incelemeler patologlar tarafından yapıldı.

Bulgular: Operasyon sırasında izlenen gross bulgularda 52 hastanın çoğunda bunun orta kesiminde DCL olduğu düşünülen beyaz dens fibrozis görüldü. Bir hastanın histopatolojik sonucunda vaskülarize fibromusküler doku fragmanları tespit edilmiş olup diğer hastaların spesmenlerinde ödemli bağ doku elemanları görülmüştür.

Sonuç: Elde ettiğimiz sonuçlara göre ve literatür ile karşılaştırıldığında gross bulgularda intermediyal krural alanda fibröz doku komponentlerinin varlığı DCL'nin gerçek bir ligament olduğunu gösterse de histopatolojik sonuçlarımızda düzenli sıkı bağ dokusu elemanlarının olmaması daha ileri histolojik çalışmaların yapılması gerektiğini ortaya koymaktadır. Ayrıca açık teknik rinoplastilerde doğal ve fonksiyonel burunlar elde edebilmek için DCL'in korunması gerektiğine inanmaktayız.

Anahtar kelimeler: Dermokartilajinöz ligament, Pitanguy'un ligamenti, M. depresor septi nasi, Yüzeysel musküloaponörotik sistem, Histopatoloji

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Ethics Committee Approval: The study was approved by Yeni Yuzyil University Ethical Committee (12/24/2018-042). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Introduction

The facial region differs from other areas of the body. The soft tissue between the skin and osseocartilaginous skeleton in the face consists of four layers: Superficial fatty layer, superficial musculoaponeurotic system (SMAS), deep fatty layer and perichondrium or periosteum layer [1]. The SMAS contains a superficial fatty layer, a fibromuscular layer, a deep fatty layer, a longitudinal fibrous sheet and an intercrural ligament [1, 2]. The deep fatty layer, composed of loose areolar fat tissue, separates the fibromuscular layer from the pericondrium-periostium, allows SMAS mobility and contributes to facial expressions [1]. There are no fibrous reticulated structures in this tissue layer which form a surgical dissection plan [2]. The SMAS allows the distribution of forces resulting from contractions of multiple muscles. The fibrous component of the SMAS is usually in two layers, consisting of superficial and deep fascia for each nasal muscle. Thus, the nasal muscles and their facia function as a single unit. Each nasal muscle and their fascia are interconnected by a nasal SMAS component and their movements are balanced by the SMAS. This complex structure with nasal muscles and ligaments formed by the SMAS aids in phonation, respiration and formation and control of the facial mimic movements [3]. The SMAS extends superiorly to the galea aponeurotica at the rhinion level, inferiorly joins the M. procerus fascia and caudally connects with interdomal cross fibers at the nasal dorsum. It also forms the dermocartilaginous ligament (DCL) described by Pitanguy in the supratip region, passes through the intermedial crural area, combining with the M. depresor septi nasi [4]. This structure described by Pitanguy has been presented by some researchers as an extension of the SMAS rather than a true ligament [5,6]. The aim of this study is to investigate whether the DCL is a true ligament by revealing the histological features of this structure.

Materials and methods

This prospective cohort study was conducted between 2018 and 2019 at the Otorhinolaryngology Department of Istanbul Yeni Yuzyil University and Bahat Hospital. Fifty-two patients who underwent open technique rhinoplasty by a single surgeon for nasal obstruction and deformity were included. Approval of Yeni Yuzyil University Ethical Committee (24.12.2018/042) and written informed consents were obtained from the patients after full explanation of the procedure. The principles of the Declaration of Helsinki and Guidelines for Good Clinical Practices were adhered to during the study.

Open technique rhinoplasty operation was conducted under general anesthesia, beginning with a transcolumellar V incision, which was extended by staying in the subcutaneous tissue until the medial crura was reached. Care was taken not to damage the tissues filling the space between the medial crura and to preserve the soft tissue in the columellar flap. The perichondrium of the middle crura was cut with sharp tip scissors. Elevation was continued through the subperichondrial plane with the help of septal mucosal elevator. The dissection was extended into the interdomal region, keeping the perichondrium of the two middle crura in the flap. The perichondrium was then cut at the caudal edge of the lower lateral cartilage and included in the skin flap. After the dissection of the lateral crura was completed, the central fibromuscular tissue stretching under the skin flap was reached. The tissue considered to be the dermocartilaginous ligament was marked and identified as Pitanguy's ligament. After the DCL was elevated from the intercrural region, a tissue of approximately 4x3 mm in size was removed, placed into solution, and sent to histopathological analysis.

Histopathological analysis of 52 specimens excised from the DCL was performed by pathologists. The tissues were immediately fixed in 10% formalin for 24 hours. After decalcification in 5% hydrochloric acid, the specimens were embedded in paraffin, serially sectioned, and stained with Masson trichrome and Hematoxylin & Eosin stains. Then, microsections were observed under light microscopy.

Statistical analysis

The analysis was performed using SPSS Statistics 20 software. The data were reported as mean (standard deviation) (SD).

Results

Gross findings

In most patients, following the dissection of the lateral crura, as central fibromuscular tissue was reached, a group of dense fibrotic bands passing through the intermedial crural region were visualized in the middle part of the nose, and recognized as the DCL, also known as Pitanguy's ligament. The ligament was surrounded by subcutaneous tissue (Figure 1).

Histopathologic findings

Histopathological analysis of the specimens of 52 patients (38 males, 14 females, with an overall mean age of 26.8 (4.23) years) was conducted. We herein present two samples: In Specimen 1, the tissue was excised from the junction of the ligament and muscle. All other specimens were excised from the region anatomically compatible with DCL. The findings of specimen 1 (2%) was the most interesting in terms of revealing the ligament histology. In the specimens of the other 51 (98%) patients, the histopathological findings were similar to those of Specimen 2, as explained below:

Specimen 1

Macroscopic findings: The specimen consists of cream-colored soft tissue that measures 0.6x0.4x0.2 cm in aggregate.

Microscopic findings: Fibromuscular tissues rich in stromal vascular fractions were observed during the examination of microsections (Figure 2).

Pathological diagnosis: Vascularized fibromuscular tissue fragment

Specimen 2

Macroscopic findings: The specimen consists of cream-colored soft tissue which measures 0.7x0.6x0.5 cm in aggregate.

Microscopic findings: Fibrosis, mature adipocytes, sparse inflammatory cell infiltration, dilated vascular structures were observed in the edematous stroma during the examination of microsections (Figure 3).

Pathological diagnosis: Edematous connective tissue

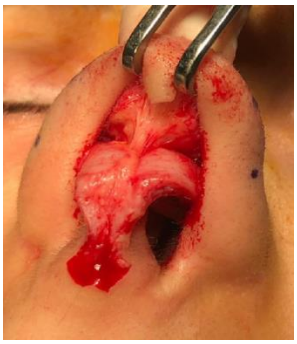

Figure 1: Dermocartilaginous ligament (Pitanguy's ligament)

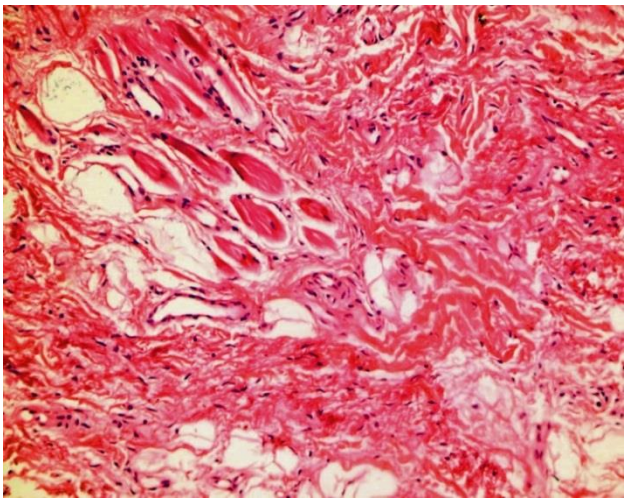

Figure 2: Microscopic image of Specimen 1 (Hematoxylin and eosin staining X40)

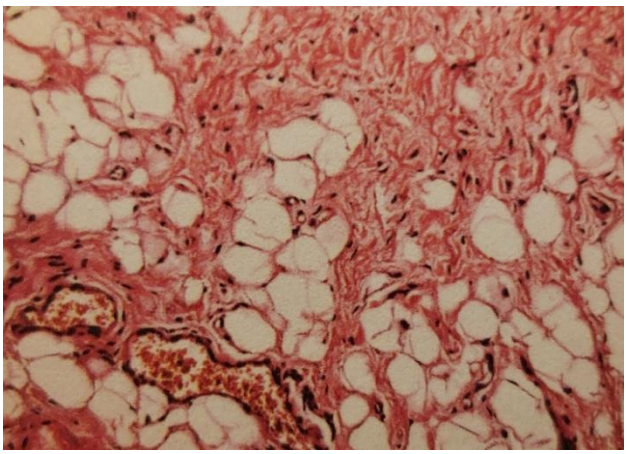

Figure 3: Microscopic image of Specimen 2 (Hematoxylin and eosin staining X40)

Discussion

Recently, septorhinoplasty operations have increased considerably. In addition to the aesthetic appearance, it has become important to consider the ligaments and soft tissues of the nose in terms of functional results. If these structures are not given the necessary attention, the appearance, and functions of the nose (breathing, participation in facial expressions and speech) will be insufficient. One of the most important structures in the nose is the nasal dermocartilaginous ligament described by Pitanguy [7-12], functions of which include:

- Contributing to depressing nasal tip,
- Contributing to elevating the middle part of the upper lip during laughing,
- Contributing to lowering the dorsal border of columella, nasal type and nostril,
- Contributing to the mobilization of the nasal type during speech and laughing
- Contributing to the expansion of the nostril stretching the membranous septum of the nose at the beginning of the inspiration.

In 1965, the presence of DCL in blacks and bulbous noses was revealed by Pitanguy in his article with the following statement: "Subperichondrial exposure made possible the observation of the presence of a ligament, uniting the derma of the upper third of the nose to the junction of the crux medialis, penetrating anteroposteriorly to help the formation of the fibrous septum." [4]. By 1995, Pitanguy et al. [13] had emphasized the effect of this ligament on the balance of the dorsal tip structures, and even proposed the classification of the ligament by thickness. In 2001, Pitanguy [14] also stressed the role of DCL and proposed the transection of the ligament to increase tip rotation, eliminating tip dependency and preventing bulbosity.

Some researchers claim that this structure, rather than a complete ligament, is the extension of the medial layer of the SMAS, extending from the nasal dermis of supratip to M. depressor septi nasi in the subcolumellar region [5-7].

The results of an anatomical and clinical study, performed by Hwang et al. [15] on adult cadavers and 123 patients, reported that the DCL was the ligament of M. depressor septi nasi based on histological examination. It was also stated that nasal tips were elevated after the resection of the DCL and nasolabial angles increased in 123 patients, thus revealing that depressor septi nasi muscle depressed the nasal tip by DCL.

There are two classes of connective tissue proper: loose and dense. Loose connective tissue is the most common type of connective tissue that fills the muscle cells, supports epithelial tissue, and forms layers of lymphatic and vessels. Fibroblasts, macrophages, collagen, elastic, and reticular fibers can be observed in this connective tissue. Dense connective tissue takes on the role of resistance and protection. It contains the same cells as loose connective tissue but there are fewer cells and more collagen fibers. Dense connective tissue is also divided into regular dense connective tissue and irregular dense connective tissue. In dense regular connective tissue, collagen fibers are arranged in bundles without a definite orientation, as in the dermis. In regular dense connective tissue, fibroblasts are arranged in a straight orientation to resist forces from the same direction. They show great resistance to traction forces [16]. The most prominent example of regular dense connective tissue is the ligaments, which consist of dense fibrous bundles of collagenous fibers, spindle-shaped cells known as fibrocytes and various connective tissue components. Ligaments are also divided into two groups, as those rich in collagenous fibers and those rich in elastic fibrils [17]. The results of the cadaver studies by Han et al. [18] revealed that the DCL is composed of thin, intertwined collagenous fibers which do not show a regular orientation. According to them, although the ligament comprises mostly collagen fibers, few elastic fibers are also visible. Even if several amorphous connective tissue elements were seen, muscle fibrils and chondrocytes were absent. Park et al. [19] also reported similar results with Han et al. In the findings of Pitanguy, muscle fibers and chondrocytes were shown at the region of the DCL. This may be due to the presence of M. depressor septi or M. nasalis transversa in the sections, or the insertion of the muscle cells to the tendon. Besides, Pitanguy defined the DCL as the

connective tissue in the deep layers of the skin. Letourneau and Daniel argue that the DCL is formed by condensation of the parallel collagen fibers in the SMAS layer [20]. In the studies conducted by Saban et al. [5] and Cakir et al. [6], no fibrous structure was found between the middle crurae in histological examination. In our results, the presence of fibrous structures in the specimens excised from the intermedial crural area considered as the DCL and the gross findings showing the presence of the DCL demonstrate that the DCL is a true ligament as explained by Pitanguy. However, regular dense connective tissue and its components are not seen in our histological examinations and many studies in the literature do not define this structure as a ligament. Therefore, further anatomical and histological studies are needed to determine whether the DCL is a true ligament.

Limitations

The main limitation of the study was the absence of regular dense fibrous tissue components in our histopathologic findings, which reveals the need for further histological studies. Other shortcomings included the fact that biopsy was not obtained from multiple parts of DCL and the small number of patients. In future studies, we plan to increase the number of patients, investigate patients who underwent open rhinoplasty, and to add electromyographic Evaluation of M. depressor septi nasi examination to the research protocol.

Conclusion

We believe that the Pitanguy's ligament is the ligament of the M. depressor septi nasi. Preservation of this ligament in open rhinoplasty will contribute to the functions of M. depressor septi nasi and allow the nasal tip to participate in facial mimic movements.

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Research article
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Destroyed thyroid by acidic blood during subarachnoid hemorrhage: Experimental study

Subaraknoid kanama sırasında asidotik kanla oluşan tiroid harabiyeti: Deneysel çalışma

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Abstract

Aim: Metabolic acidosis can negatively affect thyroid functions. The aim of this study is to show the damage in the thyroid gland caused by acidosis following subarachnoid hemorrhage (SAH).

Methods: Twenty rabbits were chosen from our recent SAH studies. Five healthy rabbits were included in the control group, five were included in the SHAM group, which received 1 ml of saline, and ten rabbits, chosen from SAH-induced animals with decreased blood pH, constituted the study group. TSH, T3, T4 and blood pH values were recorded before, during and after the experimental procedures. Densities of the normal and degenerated epithelial cell of thyroid glands were estimated using stereological methods. The relationship between blood pH and thyroid hormone values, and degenerated epithelial cell densities were analyzed statistically.

Results: pH values of blood were measured as 7.35 (0.037), 7.32 (0.05), and 7.21 (0.012) in the control, SHAM and SAH groups, respectively. The estimation of normal and degenerated epithelial cells per square millimeter of follicles was calculated as wall surface/cell surface. The mean normal epithelial cell count was 5,000 (750) in normal thyroid follicles. Mean degenerated epithelial cells counts were 50 (9) in the normal group, 154 (30) in the SHAM group and 460 (80) in the study group. For all results there was statistically significant difference between the control, SHAM and SAH groups (P<0.001).

Conclusions: Acidosis, one of the most fatal complications of SAH, may damage the thyroid gland with neurovascular network degeneration.

Keywords: Subarachnoid hemorrhage, Acidosis, Destroyed thyroid gland

Öz

Amaç: Metabolik asidoz tiroid fonksiyonlarını olumsuz etkileyebilir. Bu çalışmanın amacı subaraknoid kanama (SAK) sonrası oluşan asidozun tiroid bezinde yaptığı harabiyeti göstermektir.

Yöntemler: Çalışma, son SAK deneylerinden seçilen yirmi tavşan verilerinden seçildi. Tiroid bezlerini analiz etmek için kontrol grubu olarak beş tavşan (n=5) seçildi; 1 cc salin enjekte edilen SHAM grubu (n=5) ve SAK sonrası asidoz oluşan tavşanlardan seçilen on tavşandan oluşan çalışma grubu (n=10) saptadı. Deney prosedürleri öncesinde, deney sırasında ve sonrasında TSH, T3, T4 ve düşük pH değerleri kaydedildi. Tiroid bezlerinin normal ve dejenere epitel hücresinin yoğunlukları stereolojik yöntemler kullanılarak hesaplandı. pH ve tiroid hormon değerleri, dejenere epitel hücre yoğunlukları arasındaki ilişki istatistiksel olarak analiz edildi.

Bulgular: Kanın pH değerleri kontrolde 7,35 (0,037), SHAM'da 7,32 (0,05), SAK grubunda 7,21 (0,012) SAH grubunda tespit edildi. Duvar yüzeyi/hücre yüzeyi olarak hesaplanan foliküllerin milimetre kare başına normal/dejenere epitel hücre sayısı hesaplandı. Normal tiroid foliküllerinde normal epitel hücre sayısı 5.000 (750) idi. Dejenere epitel hücre sayısı normal grupta 50 (9) idi; SHAM grubunda 154 (30) ve çalışma grubunda 460 (80) olarak hesaplandı. Tüm sonuçlar için kontrol grubu ile SHAM ve SAH grupları arasında istatistiksel olarak anlamlı fark bulundu (P<0,001).

Sonuç: SAK'ın en ölümcül komplikasyonlarında biri olan asidoz nörovasküler ağ dejenerasyonuyla tiroid bezinde hasar oluşturabilir.

Anahtar kelimeler: Subaraknoid kanama, Asidoz, Tiroid bezi harabiyeti

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Introduction

Current literature has not mentioned that hypothyroidism is the most dangerous complication of acidosis during subarachnoid hemorrhage (SAH). The acidotic injury was first sampled with choroid plexus in acidotic cerebrospinal fluid of brain ventricles by Ozmen et al. [1]. All body fluid pH is mainly regulated by the Carotid body network [2]. Carotid body network injury is the most accountable factor for acidosis following SAH [3]. Binuclear neuronal denervation injury of the carotid body can result in decreased pH in all compartments. In this study, we showed that acidic blood could destroy the thyroid gland, which may lead to untreatable hypothyroidism during or following SAH. Acidosis could cause multiple endocrinopathies [4]. It is known to decrease thyroid hormone levels in newborns , result in encephalopathy complicated with myxedema [5-7]. Thyrotoxicosis is also frequently seen during acidosis [8]. Treatment of metabolic acidosis reportedly improves thyroid function [9]. Hypothyroidism resulting from thyroid gland injury induced by acidic blood was firstly described by that study.

Materials and methods

Twenty rabbits were used in this study. Animal care and the study design followed the guidelines of the Guide for the Care and Use of Laboratory Animals. The study design was approved by the Committee of Animal Research in Ataturk University.

Five rabbits were used to analyze the normal structure of CN_{IX}-Carotid body. Five rabbits were included in the SHAM group, and received injection of 1 ml saline into cisterna magna. The remaining ten rabbits received 1 ml of autologous arterial blood injection into the cisterna magna to create subarachnoid hemorrhage. Blood pH values were recorded by using a pH meter (Mettler Toledo MP 220 pH Meter, Schwarzenbach, Switzerland) before the experiment, three times a week, for two weeks and just before sacrification. Then, they were sacrificed under general anesthesia after all thyroid glands were excised and fixed in 10% formalin solution. Fixed brain tissues were embedded in paraffin blocks, and twenty consecutive sections of 5 µm were obtained for stereological examinations. Thyroid gland preparates were stained with hematoxylene&eosin (H&E) and TUNEL methods as well as Aldehyde Fuchsin. All sections were examined under the light microscope, and the stereological method was used for the determination of epithelial cell density of the thyroid follicles: Cytoplasmic darkening, nuclear narrowing, angulated cells, and peri-cytoplasmic halo development were considered neuronal degeneration criteria. Follicular cell density was estimated by dividing the follicle's inner surface area into the cell sectional surface area.

Statistical analysis

Statistical analysis was performed with SPSS Statistics version 22.0 (IBM, Armonk, NY, USA). Blood pH, thyroid hormone levels, thyroidal follicles cell density were analyzed with the statistical method. Normal distribution of data was assessed with the Kolmogorov–Smirnov or Histogram test. Continuous variables were expressed as mean (standard deviation) (SD). The groups were compared using the One-Way ANOVA test for independent variables. Kruskal Wallis test was used for the non-normally distributed data. *P*-value of less than 0.05 was considered statistically significant.

Results

Clinical and electrophysiological results

In physical examination, consciousness, meningeal irritation, heart rhythm, and respiration disorders returned to normal after one week. Ischemic autonomic network findings were recorded as heart rhythm disorders with depressed ST, bi/trigeminal pulses, separated QRS, and atrioventricular fibrillations in electrocardiograms of animals with SAH. Acidotic respiratory parameters were detected as frequent respiration with decreased respiration amplitude, shortened inspiration/prolonged expiration, apnea-tachypnea intervals, diaphragmatic respiration, and respiratory arrest in animals with fatal SAH. Mean heart rates were 252 (23) beats/min in control, 224 (14) beats/min in SHAM, and 182 (15) beats/min in SAH groups. Heart rhythm was 143 (12) /min in animals with respiratory acidosis. Acidotic respiration patterns increased with decreasing pH values.

Histological findings in the thyroid gland

Figure 1 shows the histological appearance of the thyroid gland with follicles of a normal rabbit and hyperplastic lymph node, decreased thyroid follicles along with degenerated thyroid follicles of a rabbit with acidosis. Figure 2 presents the histological appearance of the thyroid gland with destructed-collapsed follicles, condensed amorphous acellular colloid materials, and apoptotic follicular cells of an acidotic rabbit. Follicular cell counts and thyroid follicle surface estimation method is seen in a normal rabbit. Each follicle is considered to be in ellipsoid form. Follicular surface, total follicle surface, each follicular cell surface and total follicular cell count are calculated by formulas I, II, III, and IV, respectively, as shown in Figure 3.

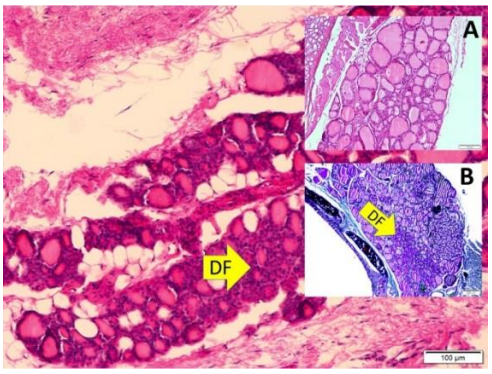

Figure 1: Histological appearance of the normal thyroid gland with follicles (LM, H&E, x10/A) in a healthy rabbit, hyperplastic lymph node and decreased thyroid follicles (DF) (LM, Aldehyde Fuchsine, x4/B) and degenerated thyroid follicles (LM, H&E, x10/Base) in an acidotic rabbit

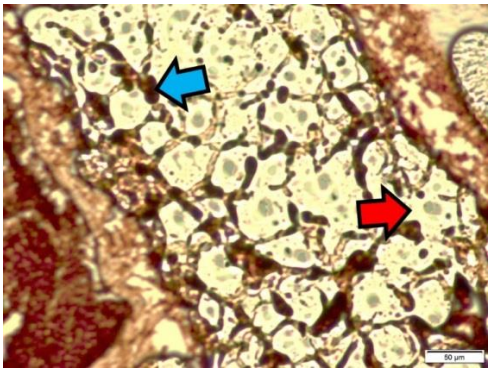

Figure 2: Histological appearance of the thyroid gland with destructed-collapsed follicles, condensed amorphous acellular colloid materials (red arrow), and apoptotic follicular cells (blue arrow) (LM, H&E, x20) of an acidotic rabbit

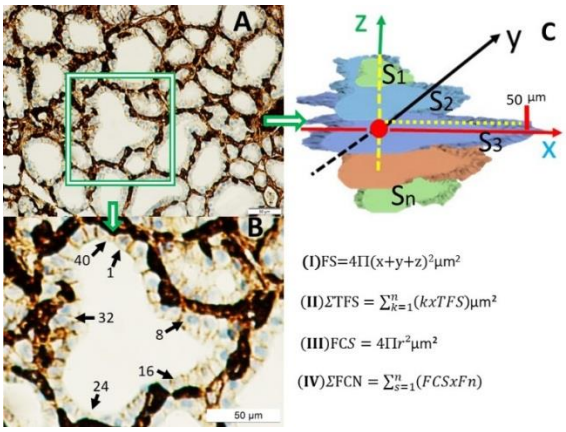

Figure 3: Follicular cell counts and thyroid follicle volume estimation method is demonstrated in a normal rabbit. Each follicle is considered as an ellipsoid form (LM, GFAP, x20/A-B). Cell count estimation method in a slice (S1-n), and both cell and follicle volume estimation method is formulated in C. Follicular volumes (FV), total follicular volumes (TFV), each follicular cell volume (FCV) and total follicular cell counts (FCC) were calculated with Formulas I, II, III and IV, respectively (C)

Numerical results of study

Mean blood pH, T3, T4, TSH values and degenerated epithelial cell counts per follicle are 7.353 (0.037), 108 (10) µg/dl, 1.40 (0.29) µg/dl, <0.5 ng/dl, 50 (9), respectively in the control group, 7.32 (0.05), 94 (9) µg/dl, 1,16 (0.76) µg/dl, >0.5 ng/dl, 154 (30), respectively, in the SHAM group, and 7.21 (0.012), 53 (5) µg/dl, 1.01 (0.12) µg/dl, >0.5 ng/dl, 460 (80), respectively, in the study group. For all results, statistically significant differences were detected between the control group versus SHAM and SAH groups (P<0.001). Numerical and statistical results are summarized in Table 1.

Table 1: Numerical statistical values of study

	Study	Control	SHAM	*P*-value for study vs. control	*P*-value for study vs. SHAM
Blood pH	7.21 (0.012)	7.353 (0.037)	7.32 (0.05)	<0.001	<0.001
T3 level (µg/dl)	53 (5)	108 (10)	94 (9)	<0.001	<0.001
T4 level (µg/dl)	1.01 (0.12)	1.40 (0.29)	1.16 (0.76)	<0.001	<0.001
TSH level (ng/dl)	>0.5	<0.5	>0.5	<0.001	<0.001
DECC	460 (80)	50 (9)	154 (30)	<0.001	<0.001

All values presented as mean (standart deviation). DECC: Degenerated epithelial cell count per follicles

Discussion

Acidosis has been considered a biochemical problem and treatment modalities aim to correct biochemical abnormalities. We believe that acidosis should be accepted as the most troubling complication in intensive care units. In contrast to current explanations, all of our authors think that acidosis should be accused of destroying neuroendocrinological circuitry and related metabolic disorders. Thyroid hormones affect other hormones and regulate the energy metabolism of the body [10]. Thyroid hormone release is influenced by ketoacidosis [11]: Diabetic ketoacidosis disrupts thyroid hormone synthesis and hormone metabolism [12]. Although the article of Valimaki et al. [4] discusses the cause or effect of metabolic disorders in patients with acidosis, we have drawn the conclusion that most of the endocrinological disorders may be secondary to acidosis. Ketoacidosis has a direct effect on thyroid hormone catabolism [13]. Some authors declared that dangerous effects of diabetes mellitus arise from pituitary-thyroid-peripheral tissue axis injury [14]. However, our study showed that acidotic thyroid gland destruction was just as responsible as the explained central mechanism.

Enhanced glucose metabolism in high-grade non-Hodgkin's lymphoma cause lactic acidosis [15] related to multiple endocrine deficiencies in intensive care units. Metabolic acidosis could also destruct the parathyroid gland [16]. In chronic acidosis, the parathyroid gland comes into play and releases bicarbonate from bone to correct acidosis [17]. Also, tachycardia may arise from increased thyroid hormone levels in blood secondary to released hormones by destroyed thyroid gland [8]. Acidosis-based hypothyroidism [12] inducing myxedema [7] may also contribute to edema and coma of the patient. In contrast to common belief some authors indicated that increased thyroid functions could result in renal tubular necrosis [18]. However, this mechanism, which seems to be contrary to the basic philosophy of the paper, can be a negative feedback reaction to protect the organism from the crisis of hyperthyroidism. Encephalopathy associated with Hashimoto thyroiditis [6] should also be attributed to acidosis. Intracellular acidosis may promote atherosclerosis [19]. Maternal hypothyroidism due to acidosis also affects the fetus [5]. Pediatricians should not forget that acidosis-induced maternal hypothyroidism affects the child in the same way.

Acidosis could cause multiple endocrinopathies [4], such as decreased thyroid hormone levels in newborns [5] and encephalopathy [6]. Chronic metabolic acidosis forces the parathyroid glands to obtain bicarbonate from bones to maintain blood pH homeostasis [17]. Especially metabolic acidosis has a provocative role in bone resorption [16]. Metabolism of thyroid hormones is influenced by diabetic ketoacidosis, which results in "low T3 syndrome" [11] and is usually complicated with myxedema [7]. Thyrotoxicosis is frequently seen following stored thyroid hormone release from destructed thyroid gland during acidosis [8]. Correction of metabolic acidosis results in improved thyroid function [9]. Decreased blood pH could be the undetermined cause of hypothyroidism in intensive care units. Parasympathetic denervation and/or decreased blood pH induces hypothyroidism. If the fluid in the thyroid follicles is acidic, it can burn thyroid follicular cells from the inside. The thyroid hormones stored in the follicles can also be denatured in acidic pH in both stored or circulating thyroid hormones. Although thyroid gland destruction occurs, lymphocytes are resistant to pH changes, which may lead to lymphoid hyperplasia in the thyroid. The destruction of follicles in diabetic ketoacidosis may explain the thyrotoxicosis clinic, independent of thyroid hormone levels. We advise urgent correction of metabolic acidosis to improve thyroid functions, prevent local/generalized complications of acidosis in adults, children and most importantly, in both pregnant women and fetuses. Physicians should not forget that body fluids could be hell for organs, and acidosis could write an invitation letter to the angel of the death in intensive care units.

Limitations

This study has been devoid of biochemical, radiological, and electrophysiological data and will not be extended to human studies.

Conclusion

Acidosis should be considered as the most troubling complication and the cause of thyroid gland destruction in SAH.

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The effect of iron carboxymaltose treatment on quality of life in women with iron deficiency

Demir eksikliği olan kadınlarda demir karboksimaltoz tedavisinin hayat kalitesine etkisi

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Ethics Committee Approval: The study was approved by the Ethics and Research Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (REF: 2016/04/10). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Etik ve Araştırma Komitesi (REF: 2016/04/10) tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aim: Iron deficiency is the most common cause of anemia in over the world and affects 20% of women, even in developed countries. In this study, our aim is to calculate the change in the quality of life of patients treated with parenteral ferric carboxymaltose.

Methods: In this retrospective cohort study, quality of life scores were evaluated before and after 6 weeks of treatment using the Short Form 36 scale. Fifty patients receiving parenteral ferric carboxymaltose treatment in Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Gynecology and Obstetrics were included.

Results: Pretreatment ad posttreatment hemoglobin values were 8.22 g/dl and 12.02 g/dl, respectively. Pretreatment physical role functioning score was 34.7 (39) and it was calculated as 54.2 (39.8) after the treatment (P=0.006). There were no significant differences between pre- and post-treatment emotional strength, (P=0.330), energy vitality, (P=0.210), mental health (P=0.910) scores and sub-dimensions. Minor side effects were observed in 3 patients.

Conclusion: Parenteral ferric carboxymaltose therapy significantly improves quality of life, especially physical role strength. Iron deficiency should be replaced effectively.

Keywords: Iron, Anemia, Quality of life, Gynecology

Öz

Amaç: Demir eksikliği anemisi; en sık tespit edilen anemi nedeni olup, gelişmiş ülkelerde bile kadınların %20'sini etkilemektedir. Bu çalışmada parenteral ferrik karboksimaltoz tedavisinin hastaların yaşam kalitesine olan etkisi değerlendirilmiştir.

Yöntemler: Bu retrospektif kohort çalışma SBÜ Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde yapılmıştır. Parenteral ferrik karboksimaltoz tedavisi verilen 50 hastada, tedavi öncesi ve sonrası 6. hafta arasında yaşam kalitesi açısından değişim; Kısa Form 36 ölçeği kullanılarak değerlendirilmiştir.

Bulgular: Tedavi öncesi hemoglobin düzeyi 8,22 gr/dl iken tedavi sonrası 6. Haftada 12,02 gr/dl düzeyine yükselmiştir. Tedavi öncesi 34,7 (39) olan fiziksel rol güçlüğü, tedavi sonrasında 54,2 (39,8)'e yükselmiştir (P=0,006). Emosyonel rol güçlüğü, (P=0,330), enerji canlılık (P=0,210) ve ruh sağlığı (P=0,910) alt boyutlarında anlamlı farklılık olmadığı saptanmıştır. 3 hastada minör yan etki gözlenmiştir.

Sonuç: Parenteral demir karboksimaltoz tedavisi özellikle fiziksel rol güçlüğü kategorisinde olmak üzere yaşam kalitesini belirgin şekilde artırmıştır. Bu yüzden demir eksikliği etkili bir şekilde replase edilmelidir.

Anahtar kelimeler: Demir, Anemi, Yaşam kalitesi, Jinekoloji

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Introduction

When negative iron balance occurs in the body (due to chronic blood loss, increased need for iron, absorption deficiency), hemoglobin (Hb) synthesis is maintained by the mobilization of iron from the stores, and if the iron stores do not provide the iron necessary for Hb synthesis, iron deficiency anemia (IDA) develops [1].

It is known that more than 30% of the patients in developed countries who are admitted to the hospital have anemia and this rate is higher in developing countries [2]. In the world and in Turkey, the most common factor that may cause anemia is iron deficiency. In developed countries, 3% of adult men, 20% of women and 50% of pregnant women have iron deficiency [3,4].

The prevalence of etiologic factors in IDA varies according to age groups. The most prominent factors are type of feeding in 0-2-year-old children, menstrual loss in fertile women and gastrointestinal system disorders in elderly people. Nutritional disorders and parasitic diseases gain importance in the etiology especially in developing countries [5].

The actual control of IDA has two stages: Treatment of the underlying disease and correcting iron deficiency. The aim of treatment is to gradually increase the iron levels and Hb to normal values [6].

The most common treatment method in IDA is oral iron replacement therapy [7]. The main advantage of oral replacement is that it is an inexpensive method. However, it has some disadvantages such as the need for long-term use, adverse effects on gastrointestinal system (GIS) and difficulties in patient compliance. We observed that the oral iron therapy is not used optimally in majority of our patients. Intravenous (IV) iron replacement is a relatively expensive form of treatment, and less patient compliance problems and lack of adverse effects on GIS make it a better treatment option.

Short Form 36 (SF-36) has been developed and presented to use by Rand Corporation to assess the quality of life [8]. SF-36 is a multi-purpose, short health survey form consisting of 36 questions. It has been successfully adapted to general population in many countries, particularly in the United States of America. SF-36 has been translated into Turkish by Bilir Kaya et al. [9] and its reliability and validity have been assessed in patients with rheumatoid arthritis.

The aim of this study was to determine the effects of IV ferric carboxymaltose treatment on quality of life in female patients presenting with anemia symptoms and diagnosed with iron deficiency anemia.

Materials and methods

This retrospective cohort study included 50 women treated with IV ferric carboxymaltose for iron deficiency anemia in Bakirkoy Dr. Sadi Konuk Hospital, Department of Gynecology and Obstetrics. Iron deficiency anemia of the patients was due to gynecological conditions and the patients with chronic kidney disease or gastrointestinal disorders were excluded from the study.

Ferric carboxymaltose (Ferinject®) is a novel non-dextran-containing complex of iron that allows for administration of a large replenishment dose (≤1.000 mg of iron) over a short infusion period (15 minutes). Patients those require higher doses were not included in the study.

Ethics committee approval was obtained from the Ethics and Research Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (REF: 2016/04/10). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments. After obtaining oral and written informed consent from the patients who accepted to join the study, patients were asked to complete the SF-36 questionnaire before and at 6 weeks after the treatment. Nine patients were excluded from the study as they did not attend follow-ups.

Statistical analysis

Statistical analysis was performed using SPSS 23 package program (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: USA). The normal distribution of the data was evaluated by Shapiro-Wilk test. Mean standard deviation and median values were given for descriptive statistics. T test and Wilcoxon signed-rank tests were used to compare normally and non-normally distributed data, respectively. Cronbach Alpha coefficient was calculated for internal consistency of data set. The lowest reliability level was accepted as 0.50. G*Power 3.1.9.2 was used to calculate the power of the tests.

Results

This study included 41 volunteers who completed the baseline SF-36 questionnaire. The mean age of the patients was 43.8 (4.9) years, mean height was 1.61 (0.5) (cm), mean weight was 71.4 (9.2) kg and body mass index (BMI) was 27.6 (3.5) kg/m^2 (Table 1).

Before treatment physical role functioning score was 34.7 (39) and after treatment it increased to 54.2 (39.8) (P=0.006). The median value of physical role difficulty was higher after treatment (Table 2) Post-hoc power, which was statistically significant, was 91% for this variable.

Physical functions score was 58.1 (24.3) before and 64.6 (23.1) after treatment (P=0.059). The pre- and posttreatment pain scores were 46.6 (29.8) and 51.7 (23.89), respectively (P=0.33). General health score increased to 40.6 (20.2) from 38.7 (19.6) after treatment (P=0.49) (Table 2). Improvement in these subscales were numerical, but not statistically significant.

Emotional role functions score was 52.4 (43.2) before treatment, decreasing to 45.1 (44.4) after treatment (P=0.33). Energy and vitality scores were 40.2 (18.8) before and 43.7 (19.9) after treatment (P=0.21). Pre- and post-treatment mental health scores were 56.9 (17.3) and 56.6 (20.5), respectively (P=0.91). The treatment did not significantly affect these quality of life subcategories (Table 3).

While the mean hemoglobin level of the participants was 8.29 gr/dl before the treatment, it increased to 12.2 gr/dl at 6^{th} week following treatment (Table 4). According to these data, there was a 3.8 g/dl difference between pre-treatment and post-treatment hemoglobin levels.

We observed minor side-effects in three participants which were temporary felling of sickness in one patient and

rashes around the infusion site in two patients. There were no major side-effects requiring hospitalization and additional treatments.

Table 1: Descriptive statistics for the mean age, weight, height, and BMI of the study group

(n=41)	Mean (SD)
Age (years)	43.8 (4.9)
Height (m)	1.61 (0.05)
Weight (Kg)	71.4 (9.2)
BMI	27.6 (3.5)

SD: Standard deviation, BMI: Body mass index

Table 2: The comparison between the levels of physical functions, physical role difficulty, pain, general health quality of life before and after treatment

	Before treatment Mean (SD)	After treatment Mean (SD)	*P*-value
Physical functions	58.1 (24.3)	64.6 (23.1)	0.059
Physical role functioning	34.7 (39)	54.2 (39.8)	0.006
Pain	46.6 (29.8)	51.7 (23.8)	0.330
General health	38.7 (19.6)	40.6 (20.2)	0.490

SD: Standard deviation, Wilcoxon Signed Ranks Test

Table 3: The comparison between the levels of emotional role difficulty, energy and vitality, and mental health quality of life before and after treatment

	Before treatment Mean (SD)	After treatment Mean (SD)	*P*-value
Emotional role functioning	52.4 (43.2)	45.1 (44.4)	0.330
Energy and vitality	40.2 (18.8)	43.7 (19.9)	0.210
Mental health	56.9 (17.3)	56.6 (20.5)	0.910

SD: Standard deviation, Wilcoxon Signed Ranks Test, Dependent Sample T Test

Table 4: Before and after treatment hemoglobin levels

	Before treatment Mean (SD)	After treatment Mean (SD)	*P*-value
Hemoglobin levels (gr/dl)	8.2 (1)	12.02(1.2)	0.001

SD: Standard deviation, Dependent Sample T Test

Discussion

Iron is a quite crucial element in oxygen transport. It is found in the structure of hemoglobin in the erythrocytes, myoglobulin, and skeletal muscles, and plays important roles in oxygen diffusion and oxygen storage. In addition, it functions in oxidative reactions in the mitochondria and respiratory chain [10].

The most common cause of anemia in patients who were admitted to the gynecology outpatient clinic is iron deficiency. Iron deficiency anemia is a major health problem in both developed and developing countries. The most common cause of iron deficiency in adult patients is iron loss. According to a study by Davas et al. [11], 74.1% of pregnant women in Turkey have IDA. It is known that when menstrual losses cannot be met by iron intake in women of reproductive age, iron deficiency anemia can easily develop [12].

Viethen et al. [13] have shown that parenteral ferric carboxymaltose balances iron levels in the body and improves the quality of life and physical capacity in patients with pulmonary arterial hypertension and IDA. They have reported that the treatment is well tolerated, and they have not observed any major side-effects.

In an effective oral iron treatment, the increase in hemoglobin concentration levels should be 2 gr/dl in 3-4 weeks [14]. Regular use, good tolerability and low side-effects are prerequisites for an efficient oral iron treatment. We observed that the majority of patients do not regularly adhere to oral iron therapy in our clinic.

We showed that the hemoglobin levels have increased from 8.22 gr/dl to 12.02 gr/dl at 6 weeks after treatment. Khalafallah et al. [15] have reported an increase in hemoglobin levels similar to the results of our study. In the same study, it has been shown that ferric carboxymaltose increases hemoglobin levels in a shorter time compared to oral iron preparations. Unlike oral iron replacement, the most important advantage of parenteral iron therapy is that it does not require long-term patient compliance.

Parenteral iron therapy has the risk of anaphylaxis. Moore et al. [16] have performed a meta-analysis and have shown that the risk of anaphylaxis is quite low in ferric carboxymaltose molecule. Nevertheless, the parenteral carboxymaltose treatment is generally well-tolerated by the patients. We experienced minor side-effects in three participants. One patient had a temporary feeling of sickness and two patients suffered from rashes around the infusion site.

We assessed the effect of ferric carboxymaltose on quality of life by using SF-36 scale. According to our data, there was significant difference in physical role difficulty levels in patients who were treated with ferric carboxymaltose. Emotional role difficulty, energy/vitality and mental health subcategories did not reveal any significant differences. The treatment has not made a difference in these quality of life subcategories.

The improvement in physical role functions may be due to the significant role of iron in oxygen transport. Even though the hemoglobin levels increased after treatment, we did not find any significant relationship between emotional role difficulty, mental health, pain and general health levels. The treatment did not improve the mental quality of life of the patients. The underlying reasons may be the patient psychology, ongoing abnormal uterine bleeding, and other causes.

Previous studies have demonstrated that ferric carboxymaltose has a low risk of immunogenicity and a lower incidence of adverse events compared to oral iron or parenteral iron sucrose [17]. Ferric carboxymaltose has a lower pH and osmolarity than the other parenteral iron molecules which may lead to the increased safety of administration as well as a shorter duration of administration [18]. Ferric carboxymaltose does not require multiple doses so it can affect hemoglobin levels faster. This provides an advantage in especially its preoperative use [19].

We think that completing the SF-36 at the 6th week after treatment may be early in terms of showing the effect of the treatment on quality of life. Having said that, as anemia becomes chronic, treatment may not have improved the quality of life sufficiently due to adaptations in the body. We suggest that ferric carboxymaltose treatment can have more significant effects on quality of life in newly developed anemia cases.

Limitations

The most important limitations of our study were that it was a single-center study and the number of participants was low. In addition, six weeks for assessing the improvements in quality of life can be considered a brief period. Another limitation of our study was that the transferrin, ferritin, iron and serum iron binding capacity values were not compared. Future long-term studies may benefit from these parameters.

Conclusion

IDA is common in patients admitted to gynecology and obstetrics clinics. Iron deficiency must be effectively replaced, and the underlying reasons must be removed. Oral iron treatment requires regular use and patient compliance. Parenteral ferric carboxymaltose treatment improves hemoglobin levels in a brief time. Ferric carboxymaltose treatment positively improves

quality of life in suitable patients and it is a safe preparation in terms of side-effects.

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A comparison of peri-articular injection and femoral block for pain management after total knee arthroplasty: A prospective cohort study

Total diz artroplastisi sonrası periartiküler enjeksiyon ile femoral bloğun ağrı üzerindeki etkinliğinin karşılaştırılması: Prospektif kohort çalışma

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Ethics Committee Approval: The study was approved by the Bursa Yüksek İhtisas Training and Research Hospital, Clinical Research Ethics Committee (no: 2016/02-14). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma, Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Klinik Araştırmalar Etik Kurulu (no: 2016/02-14) tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aim: Though Total knee arthroplasty (TKA) is an effective treatment method for osteoarthritis, insufficient postoperative pain control negatively affects patients' satisfaction and functional results. The aim of this study is to compare the effects of intraoperative peri-articular injection and postoperative single-dose femoral nerve block on functional results, the need for analgesia, and pain in the short-term following total knee arthroplasty (TKA).

Methods: Thirty-one patients who received peri-articular injection (PAI) during TKA and 38 who were administered a single dose of femoral nerve block (FNB) postoperatively were evaluated. In both groups, an intravenous patient-controlled analgesia (PCA) device was utilized for postoperative analgesia. Analgesia demand and the amount administered from the PCA in the first 24 hours were recorded. For the evaluation of the level of postoperative pain, a visual analog scale (VAS) was used at rest at 2nd, 4th, 8th, 12th, and 24th hours, and dynamic VAS was used at the 24th hour to assess pain with mobilization. Range of movement (ROM) was recorded with the measurements of active flexion and extension angles at the first, second and third postoperative days.

Results: The resting VAS scores at the 2nd, 4th, 8th, and 24th hours were significantly lower in the PAI group than in the FNB group (P=0.032, P=0.037, P=0.014, P=0.004, respectively). The number of patients' demands on the PCA for pain relief and the number of doses administered were higher in the FNB group. The ROM values measured on postoperative days 1, 2, and 3 were insignificantly greater in the PAI patients (P=0.956, P=0.103, P=0.162, respectively).

Conclusion: The peri-articular injection technique, when used appropriately, is easy to apply with a low-side effect profile. Therefore, it can be considered a safe and effective analgesia method providing a higher level of patient comfort and greater range of movement.

Keywords: Peri-articular injection, Femoral nerve block, Total knee arthroplasty, Pain management

Öz

Amaç: Total diz artroplastisi (TDA) diz osteoartriti için etkili bir tedavi yöntemi olmasına rağmen, postoperatif yetersiz ağrı kontrolünün uygulanması hastaların memnuniyetini ve fonksiyonel sonuçları etkiler. Bu çalışmanın amacı intraoperatif periartiküler enjeksiyon ile postoperatif tek doz femoral sinir bloğunun total diz artroplastisi sonrası erken dönemde ağrı, analjezik gereksinimi ve fonksiyonel sonuçlar üzerine olan etkilerini karşılaştırmaktır.

Yöntemler: Total diz artoplastisi sırasında intraoperatif periartiküler enjeksiyon uygulanan (PAG) 31 hasta ve postoperatif tek doz femoral sinir bloğu uygulanan (FBG) 38 hasta çalışmada değerlendirildi. Postoperatif iki gruba da analjezi için intravenöz hasta kontrollü analjezi (PCA) cihazı takıldı. 24 saatlik analjezik talebi ve PCA'dan verilen miktar kaydedildi. Postoperatif ağrı düzeyini değerlendirmek için istirahatte vizüel analog skala (VAS) skoru 2., 4., 8., 12. ve 24. saatlerde, mobilizasyon ile değerlendirmeye başlanan dinamik VAS (DVAS) ise 24. saatte değerlendirildi. 1. gün, 2. gün ve 3. günde aktif fleksiyon ve ekstansiyon dereceleri ölçülerek eklem hareket açıklıkları (EHA) kaydedildi.

Bulgular: Postoperatif sırasıyla 2., 4., 8. ve 24. saatteki istirahat VAS skorları PAG'ta FBG'na göre anlamlı şekilde daha düşük bulundu (sırasıyla P-değerleri: P=0,032, P=0,037, P=0,014, P=0,004). Ağrı kontrolü için kullanılan PCA'ya basma miktarı ve PCA tarafından verilen doz sayısı PAG'ndaki hastalarda FBG'undaki hastalara göre daha az olduğu görüldü. PAG'ndaki hastaların eklem hareket açıklıklarının 1., 2. ve 3. günlerde daha fazla ölçülmesine rağmen iki grup arasındaki bu fark anlamlı bulunmadı (sırasıyla P-değerleri: P=0,956, P=0,103, P=0,162).

Sonuç: Periartiküler enjeksiyon tekniğine uygun olarak uygulandığı zaman kolay uygulanabilir, düşük yan etki profili ile ameliyat sonrası daha yüksek düzeyde hasta konforu ve daha fazla hareket açıklığı sağlayan etkili ve güvenilir bir analjezi yöntemidir.

Anahtar kelimeler: Periartiküler enjeksiyon, Femoral sinir bloğu, Total diz artroplastisi, Ağrı yönetimi

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Introduction

With appropriate pain control following total knee arthroplasty (TKA), early functional healing can be provided, and patient satisfaction can be increased. Therefore, multimodal analgesia methods, such as intravenous opioids, peripheral nerve blocks, epidural analgesia, intra-articular injections, infiltration catheter, pre-incisional injections, and oral analgesics [1-3] can be used after TKA. The aim of multimodal analgesia is to reduce narcotic consumption to a minimum while providing pain control through different clinical pathways, thereby avoiding side-effects such as nausea, vomiting, respiratory depression, and urinary retention [4,5].

Although there is no consensus on a gold standard for postoperative pain management, to reduce opioid consumption and avoid opioid-related side-effects, there is now a trend towards multimodal approaches with regional anesthesia for more effective postoperative pain management [6].

The aim of this study was to compare the effects of intraoperative peri-articular injection and postoperative femoral nerve block on functional results, the need for analgesia, and pain in the short-term following TKA.

Materials and methods

This prospective cohort study included patients who underwent TKA surgery for moderate-advanced osteoarthritis in Bartın State Hospital between 2018 and 2019. The study was performed in accordance with the principles of Declaration of Helsinki and approved by the local Ethics committee (no: 2016/02-14). Patients who received spino-epidural or general anesthesia during the surgery, those who underwent bilateral knee surgery in the same session, and those to which multimodal analgesia methods other than peri-articular injection or femoral nerve block had been applied were excluded. A total of 69 patients who underwent TKA under spinal anesthesia were included in the study, comprising 31 patients who received peri-articular injection (PAI group), and 38 who received postoperative single-dose femoral nerve block (FNB group) (Table 1).

Premedication of 0.03 mg/kg intravenous (iv) midazolam (Zolamid®, Defarma, Ankara, Turkey) was administered to all patients in the operating room. Preoperative hydration was provided by 15-20 ml/kg saline administered intravenously in 30 minutes. With the patient in a sitting position, the appropriate area was cleaned, and the subarachnoid space was entered with a 25 G Quinke spinal needle (Egemen ®, Izmir, Turkey) from the midline between L3-4 or L4-5 vertebrae. After the visualization of cerebral spinal fluid (CSF), 10-15 mg 0.5% bupivacaine HCl was administered (Buvasin® 0.5% spinal heavy, VEM, Tekirdağ, Turkey). Following the application of spinal anesthesia, the sensory level was determined with pinprick test and the motor block level with Bromage score: 0: no paralysis, 1: only the knee and foot can be moved, 2: the knee cannot be flexed and only the foot can be moved, 3: the foot and big toe cannot be moved, total paralysis. The surgical procedure began when sensory block reached T10 level and the Bromage score was 2.

All the operations were performed under pneumatic tourniquet. The tourniquet pressure was adjusted to be 150 mmHg higher than the systolic blood pressure of the patient. All patients were approached with an anterior incision and the joint was reached with medial parapatellar arthrotomy. The same prosthesis was used in all cases. A patellar implant was not used in any of the patients. All patients received drains.

For the PAI group, a 100ml solution was prepared in two 50ml syringes, comprising 20ml 0.5% bupivacaine (Bustesin®, Vem, Ankara, Turkey), 0.6ml of 1 mg/ml adrenalin (Adrenalin®, Oesel, Istanbul, Turkey), 1ml of 100 mcg/ml of dexmedetomidine(Precedex®, Meditera, Izmir, Turkey), 4 ml of 8.4% magnesium sulphate (Magnezyum Sulfat®, Biofarma, Istanbul, Türkiye), 4 ml of 10 mg/ml methylprednisolone (Prednol-L®, Mustafa Nevzat, Istanbul, Turkey), 5 ml of 10 mg/ml morphine (MorphineHCl®, Galen, Istanbul, Turkey) and 65.4 ml saline. When administering the injections, attention was paid to areas with increased neurosensorial and mechanoreceptors, as defined in the study by Dye et al [7].

The injections were administered using the technique described by Guild et al [8]. Sixty milliliters of the prepared mixture was injected to the tibial and femoral incisions, then to the medial retinaculum, medial collateral ligament, the medial meniscocapsular junction, the attachment site of the posterior cruciate ligament to the tibia, the attachment site of the anterior cruciate ligament to the femur, the lateral retinaculum, the lateral collateral ligament and the lateral meniscocapsular junction (Figure 1a). Care was taken not inject more than 2-3 ml of active substance at once into each point to avoid overflow to soft tissue. Following placement of the tibial and femoral components, the remaining 40cc of the mixture was administered to the suprapatellar pouch, quadriceps tendon, patellar tendon, and patellar fat pad (Figure 1b).

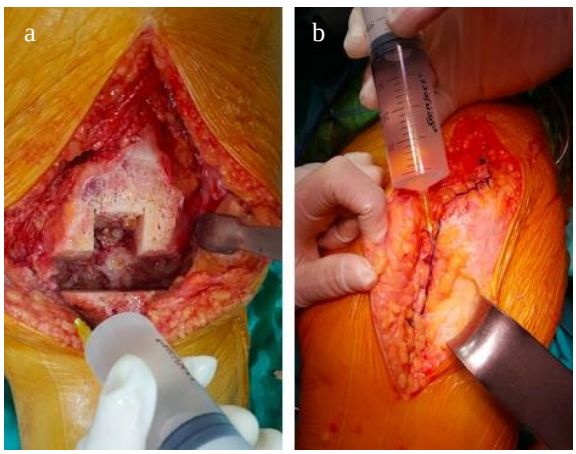

Figure 1a-b: Periarticular injection to the tibial - femoral incisions, and after closure of the joint

The patients in the femoral nerve block (FNB) group were transferred to the recovery room postoperatively. With the patient in a supine position, under ultrasound guidance (SonoSite S-Nerve, Bothell, WA, USA) using a linear probe, the femoral artery was identified immediately below the inguinal ligament (Figure 2a). With visualization of the femoral nerve, and following negative aspiration, 10 mL 0.5% bupivacaine (Bustesin ®, Vem, Ankara, Turkey) was administered along the nerve sheath using a 50mm stimulation needle (Stimuplex, Kanule A, B Braun, Germany) (Figure 2b, 2c).

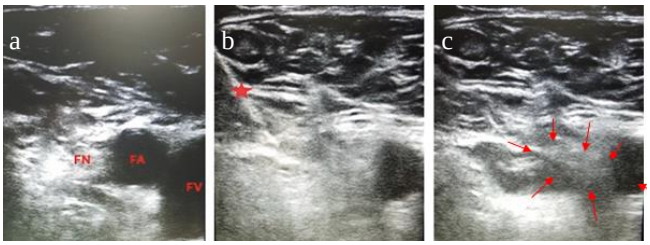

Figure 2: a: Identification of the femoral artery, vein, and nerve. b: The stimulation needle reaching the nerve sheath c: application of anesthesia, Star: Stimulation needle

For postoperative analgesia, both groups received an intravenous patient-controlled analgesia (PCA) device (CADD-Legacy® PCA, Smiths Medical, St Paul, USA). A tramadol solution at a concentration of 4mg/mL was prepared by adding 400mg tramadol to 100mL 0.9% NaCl. The PCA was adjusted to administer 10 mg infusion, with a 10ml bolus at a dose-locked period of 20 mins.

For the evaluation of the level of postoperative pain, a visual analog scale (VAS) was used at rest at the 2nd, 4th, 8th, 12th and 24th postoperative hours. Pain with mobilization was evaluated with dynamic VAS (DVAS) at the 24th hour. The PCA was used for 24 hours and 24-hour analgesia demand and amount administered by PCA were recorded. If postoperative analgesia control was not sufficient, 50 mg dexketoprofene trometamol (Ketavel ®, DEVA, Kocaeli, Turkey) was administered intravenously for rescue analgesia.

Joint range of movement (ROM) was assessed by the active flexion and extension angles measured on postoperative days 1, 2, and 3.

Statistical analysis

Data obtained in the study were analyzed using SPSS for Windows v11.5 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation and as median (minimum-maximum) for normally and non-normally distributed values, respectively. Nominal variables were shown as number (n) and percentage (%). As there were two groups, the significance of the difference between the groups was evaluated with the Student's t-test or the Mann Whitney U-test. Categorical variables were evaluated with the Pearson Chi-square test or the Fisher Exact test. A value of $P<0.05$ was considered statistically significant.

Results

No significant differences were determined between the groups with respect to age, gender, height, weight, and comorbid diseases such as hypertension, coronary artery disease, chronic obstructive pulmonary disease, diabetes, or asthma. All patients had varus alignment. The deformities of the patients were similar (Table 1).

The resting VAS scores at the 2nd, 4th, 8th and 24th postoperative hours were significantly lower in the PAI group than in the FNB group. DVAS results assessed after mobilization at the 24th postoperative hour were similar between the two groups (Table 2).

The number of patients' demands on the PCA was lower in the PAI group. The doses delivered by the PCA within 24 hours were alike. Insignificantly fewer patients in the PAI group required rescue analgesia (Table 3).

The joint ROM values measured on postoperative days 1, 2, and 3 were insignificantly greater in PAI patients (Table 4).

Table 1: Demographic data of the patients

	PAI (n=31)	FNB (n=38)	*P*-value
Age (years) #	66.29(7.39)	67.02(7.81)	0.691
Gender (F) α	26(83.9%)	27(71.1%)	0.209
(M) α	5(16.1%)	11(28.9%)	
Weight (kg) #	76.90(12.54)	76.18(11.46)	0.805
Height (cm) #	163.39(5.73)	162.95(6.62)	0.772
Presence of comorbid diseases α	28(90.3%)	33(86.8%)	0.722
ASA α			
I	7(22.6%)	7(18.4%)	
II	20(64.5%)	27(71.1%)	0.810
III	4(12.9%)	4(10.5%)	
Preoperative Deformity # (Degree)	8.54(5.23)	8.65(4.36)	0.925

ASA: American Society of Anesthesiology, # mean (standard deviation), α n(%)

Table 2: Postoperative resting and dynamic pain scores

	VAS			DVAS		
	PAI	FNB	*P*-value	PAI	FNB	*P*-value
2 hours post-op€	1 (0-5)	2 (0-5)	0.032*	-	-	-
4 hours post-op €	1 (0-6)	2.5 (0-6)	0.037*	-	-	-
8 hours post-op €	1 (0-6)	4 (0-6)	0.014*	-	-	-
12 hours post-op €	2 (0-6)	4 (0-6)	0.064	-	-	-
24 hours post-op €	4 (2-6)	6 (2-8)	0.004*	4 (2-6)	6 (2-8)	0.064

*p<0.05, € median (minimum-maximum)

Table 3: Requirement for analgesia in the postoperative period

	PAI	FNB	*P*-value
Number of demands on PCA in 24 hours €	17 (11-83)	24,5 (13-57)	0.002*
Number of analgesia doses administered by PCA in 24 hours €	16 (8-23)	17 (10-23)	0.126
Number of patients requiring rescue analgesia α	2(6.5%)	9(23.7%)	0.095

*p<0.05, € median (minimum-maximum), α n (%)

Table 4: Postoperative ROM values (degrees)

	PAI	FNB	*P*-value
ROM 1#	99.51(13.80)	98.68(12.61)	0.956
ROM 2#	104.35(12.95)	99.73(10.58)	0.103
ROM 3#	107.58(10.07)	103.94(9.09)	0.162

mean (standard deviation)

Discussion

In this study, the effects of intraoperative peri-articular injection and postoperative single-dose femoral nerve block on postoperative pain were compared. The results showed that the VAS scores at the 2nd, 4th, 8th and 24th postoperative hours, along with the number of demands on the PCA device, were significantly lower in the PAI group. The mean DVAS values, examined with mobilization, were insignificantly higher in the FNB group.

TKA is a routinely performed orthopedic procedure and severe postoperative pain reduces patient satisfaction, limits joint ROM, and delays healing and rehabilitation [9]. Although systemic opioids administered after TKA are still an effective and easy-to-apply pain control method, there are several side-effects on the respiratory, circulatory, urinary, gastrointestinal, and nervous systems [10,11]. Therefore, various methods such as pre-emptive analgesia, preventative analgesia and multimodal analgesia have been developed for improvement of postoperative pain control and management. Although there is no consensus on a gold standard for postoperative pain management, to reduce opioid consumption and avoid opioid-related side-effects, there is now a trend towards multimodal approaches with regional anesthesia for more effective postoperative pain management [6].

In a previous study conducted to avoid the potential side effects of epidural analgesia and compare its efficacy with that of peri-articular injection, peri-articular injection was reportedly more effective than epidural analgesia in reducing postoperative pain and regaining knee flexion, and the incidence of side-effects such as nausea was lower [12].

In the current study, periarticular injection and single-dose femoral nerve block were selected to minimize the systemic effects of opioids and to prioritize the efficacy of multimodal

analgesia. Kovalak et al. [13] compared the effects of continuous femoral nerve block and peri-articular injection, and reported that patients who received continuous femoral nerve block experienced less postoperative resting and dynamic pain than the patients who received peri-articular injection, had lower PCA requirement and reached greater ROM. The difference from our study was that infiltration anesthesia was administered to the posterior capsule of the knee joint continuously for 24 hours.

It has been reported that although nerve blocks are effective for pain relief following TKA, there is an increased risk of quadriceps weakness and postoperative falls because of the motor and sensorial block caused by femoral nerve block [5-14]. In addition, despite more frequent application of continuous femoral blocks, there are studies which show that the application of single dose femoral nerve block is a simpler and cheaper method [15].

In our study, while benefit was obtained from the regional analgesic efficacy of femoral nerve block, single-dose application was preferred to avoid possible adverse effects. In a similar study, Youm et al. [15] administered single-dose FNB, PAI and FNB+PAI, and reported that in the early postoperative period (0-8 hours), PAI was more effective on pain, but at 24 hours, rebound pain was determined in the PAI group. It was concluded that the combination of FNB+PAI could avoid this and provide better pain management.

The VAS and DVAS scores evaluated at the 24th postoperative hour were lower in the PAI group in this study. No 24-hour rebound pain was observed, as mentioned in the previous study. This was attributed to the use of bupivacaine in both our groups, with an effect lasting 30 hours, in contrast to the 24-hour-long effect of ropivacaine, which was used in the other studies [16].

Examining the number of PCA demands allowed the quantitative evaluation of the pain level and the values were consistent with the VAS values in the first 24 hours. The number of PCA demands, in other words, the need for pain relief, of the patients in the PAI group with lower mean VAS values were also lower. Similarly, fewer patients in the PAI group required rescue analgesia. In accordance with these data, PAI can be considered to provide better analgesia.

In this study, the ROM values obtained on the 1st, 2nd and 3rd postoperative days were better in the PAI group compared to the FNB group. In the literature, different multimodal analgesia methods were reported to have conflicting effects on ROM and functional results [1,3,12,13,17]. Evaluating the results of our study and the others, it can be said that sufficient analgesia in the early postoperative period has a direct effect on ROM. A reduction in pain after exercise increases patient comfort and encourages patients to exercise [18].

Limitations

There were some limitations to this study. First, patients could not be randomized and there was no preoperative ROM measurement. It should not be forgotten that studies with a greater number of subjects could obtain different results. Moreover, postoperative functional status could be better evaluated using scoring systems such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Knee Society Score (KSS) in addition to joint ROM measurements.

Conclusion

Peri-articular injection can be recommended as a safe and effective analgesia method. It can be easily applied to the knee joint with appropriate technique, and it provides greater postoperative patient comfort.

To date, there is no consensus on the best practices for pain management following TKA. Further research would be needed to determine the best procedure regarding the use of multimodal analgesia in clinical practice. We will continue to see the development of clinical practice to optimize better postoperative algorithms in pain control.

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Effectiveness and initial outcomes of transvesicoscopic bipolar sealing of vesicovaginal fistula

Vezikovajinal fistülün transvezikoskopik olarak bipolar mühürlenmesinin etkinliği ve ilk sonuçları

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Abstract

Aim: Vesicovaginal fistula (VVF) is a social and psychological problem for the female population, causing urinary incontinence and foul-smelling urine. Open, laparoscopic, robotic, and various minimally invasive techniques have been described for the treatment of VVF. In this study, we presented the effectiveness and initial outcomes of transvesicoscopic bipolar sealing of vesicovaginal fistula (TBSF), a novel, minimally invasive technique which we had previously described.

Methods: This surgical case series included 9 patients with VVF of <1 cm located away from ureteral orifices who underwent TBSF from July 2015 to December 2019. The fistula tract was sealed transvesicoscopically with a bipolar vessel sealer. All patients were informed about the modified surgical procedure prior to the operation.

Results: The mean age of the patients was 47.2 (4.6) years. The mean fistula diameter was 6.6 (1.2) mm. The mean operation time was 41 (9.7) minutes. The hospital stay was 1 day in all cases. After catheter removal at 3 weeks, 8 (89%) patients remained dry while one (11%) patient experienced continuous incontinence.

Conclusion: Transvesicoscopic bipolar sealing of vesicovaginal fistula is a simple and safe procedure to perform for small VVF, has a short learning curve and operative time, and results in reduced blood loss and morbidity, brief hospital stay and improved cosmesis.

Keywords: Vesicovaginal fistula, Sealing, Bipolar, Transvesicoscopic, Laparoscopic

Öz

Amaç: Vezikovajinal fistül (VVF), idrar kaçırma ve idrar kokusu nedeniyle, kadınlar için sosyal ve psikolojik bir problemdir. VVF tedavisi için açık, laparoskopik, robotik ve çeşitli minimal invaziv tedavi seçenekleri tanımlanmıştır. Bu çalışmada, daha önce tarif ettiğimiz yeni bir minimal invaziv teknik olan vezikovajinal fistülün transvesikoskopik yolla bipolar mühürlenmesinin etkinliğini ve ilk sonuçlarını sunduk.

Yöntemler: Cerrahi olgu serisi olarak planlanan bu çalışmada, Temmuz 2015-Aralık 2019 tarihleri arasında, üreter orifislerinden uzak yerleşimli ve çapı 1 cm'den küçük vezikovajinal fistülü olan, 9 hastaya transvezikoskopik olarak bipolar damar mühürleme cihazı kullanılarak vezikovajinal fistül mühürleme işlemi gerçekleştirildi. Tüm hastalar ameliyat öncesi modifiye cerrahi prosedür hakkında bilgilendirildi.

Bulgular: Hastaların ortalama yaşı 47,2 (4,6) yıldı. Ortalama fistül çapı 6,6 (1,2) milimetre, ortalama ameliyat süresi 41 (9,7) dakikaydı. Tüm hastalarda hastanede kalış süresi 1 gündü. 3. haftada kateter çıkarıldıktan sonra 8 (%89) hasta kontinan olup, bir (%11) hastada nüks izlendi.

Sonuç: Vezikovajinal fistülün transvesicoskopik yolla bipolar mühürlenmesi; kısa öğrenme eğrisi ve ameliyat süresi, azalmış kan kaybı ve morbidite oranı, kısa hastanede kalış süresi ve iyi kozmetik sonuçları ile küçük fistüller için uygulaması kolay ve güvenli bir prosedürdür.

Anahtar kelimeler: Vezikovajinal fistül, Mühürleme, Bipolar, Transvezikoskopik, Laparoskopik

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Introduction

Vesicovaginal fistula (VVF), a social and surgical problem for centuries, is a debilitating, devastating and stressful condition among the female population. Due to continuous urinary incontinence and foul-smelling urine, women are exposed to social casting out. The incidence of VVF varies between 0.3% and 2%. While most of them are iatrogenic, other etiologies include pelvic trauma, radiation necrosis, illegal abortion, and radical pelvic surgery [1,2]. In developed countries, it is most caused by gynecological operations, particularly abdominal hysterectomy. In developing countries, however, inadequate obstetric care is the leading cause of VVF [3,4]. VVF generally occurs within 1–6 weeks after gynecological or obstetric surgery [5].

The purpose of treatment in VVF is stopping urine leakage with return of normal urogenital function. VVF can be treated conservatively by bladder drainage in particularly small fistulas. When conservative treatment fails, surgical repair remains the only option. Controversies still exist regarding the surgical approach of VVF repair. The most performed surgical repairs include transvaginal, transabdominal, laparoscopic and robot assisted laparoscopic approaches. Although there is no consensus on which approach is best, laparoscopic repair is the currently preferred method. [6].

We herein present the effectiveness and initial outcomes of "transvesicoscopic bipolar sealing of vesicovaginal fistula (TBSF)", a novel, minimally invasive technique which we have previously reported [6].

Materials and methods

Between July 2015 and December 2019, nine patients with failed catheterization treatments underwent TBSF. All patients had continuous urine leakage from the vagina. Our inclusion criteria consisted of fistulas less than 1 cm in diameter and away from ureteral orifices. Complete blood count, routine biochemistry parameters, urinalysis, urine culture as well as urinary system ultrasonography were obtained from all patients. Imaging studies included cystograms, intravenous urogram, and magnetic resonance imaging when necessary and appropriate. In all cases, we identified the fistula orifice with flexible cystoscopy at the outpatient clinic prior to surgery. The patients were undertaken for surgery at least 3 months after their primary gynecological surgery to allow the inflammation to subside. All patients were informed about the modified surgical procedure, and an informed consent was obtained from all patients. Approval was received from the ethics committee of Health Sciences University, Diyarbakır Gazi Yaşargil Education and Research Hospital (No. 2019/10-03, Date: 15/10/2019).

Surgical technique

All patients placed a povidone-iodine vaginal suppository into the vagina 12 hours before surgery. All procedures were conducted with the patients in lithotomy position under spinal anesthesia. A second-generation cephalosporin was administered as a prophylactic antibiotic half an hour before induction. VVF was identified with a cystoscope using insufflation of gas and fistula tract was verified by a guide wire or ureter catheter (Figure 1). The vagina was packed with Vaseline soaked gauze to block leakage during bladder filling and escape of CO_2 during the operation. A 5 mm laparoscopic port was inserted into the bladder under cystoscopic guidance lateral to the midline, halfway between the umbilicus and symphysis pubis. The second 5 mm port was inserted into the bladder lateral to the midline and inferior to the first port (Figure 2). The cystoscope was used as the transurethral camera for vesicoscopy. Bladder mucosa and muscular layer were gripped with a forceps and raised up for a multilayer closure. If needed, the fistula was manipulated upwards with the help of a finger through vagina. The fistula tract was grasped and sealed by a bipolar vessel sealing device (LigaSure™ 5 mm blunt tip 37 cm sealer, Medtronic, Inc., Dublin, Ireland) (Figure 3). An 18 Fr Ryle's tube was placed into the bladder as a cystostomy through one of the existent ports. In addition, an 18F foley catheter was placed in the bladder.

Patients were discharged after removal of the cystostomy on the first postoperative day. The foley catheter was kept in place for three weeks. Oral anticholinergics were administered until removal of foley catheter. Patients were instructed to return to our office 3 weeks after surgery for urethral foley catheter removal and subsequent cystoscopic and vaginal inspection to confirm VVF repair (Figure 4).

Statistical analysis

Data were entered into Excel version 2013 and then converted into SPSS version 15 for analysis. Continuous variables were presented as mean (standard deviation) (SD) and categorical data, as number and percentages.

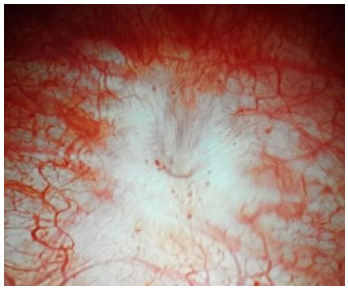

Figure 1: Cystoscopic confirmation of the vesicovaginal fistula

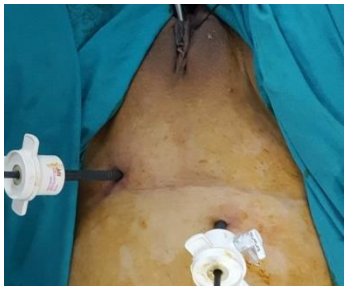

Figure 2: Port configurations of transvesicoscopic bipolar sealing of vesicovaginal fistula

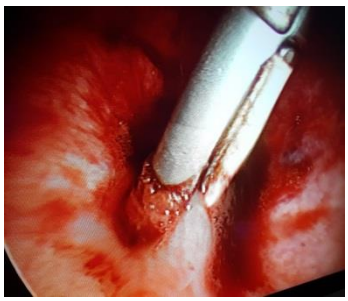

Figure 3: Sealing of the fistula tract using a bipolar vessel sealer

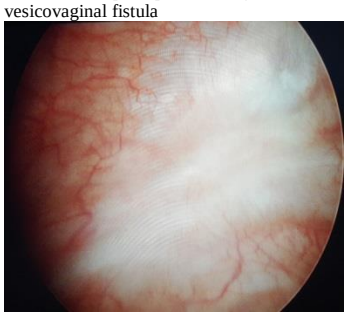

Figure 4: Cystoscopic appearance of a repaired vesicovaginal fistula three weeks after surgery

Results

The mean age of the patients included in the study was 47.2 (4.6) years (range: 40-53 years). All patients had a prior hysterectomy. The mean fistula diameter was 6.6 (1.2) mm (range: 5-9 mm). The mean operation time was 41 (9.7) minutes (range: 30-65 minutes). The first case lasted the longest. Blood loss was minimal in all cases and could not be measured. There were no serious intraoperative or postoperative complications including conversion to laparotomy, aborted operative procedure,

bowel or ureteral injury, blood transfusion, blood clots, pulmonary embolisms, cardiac events, or strokes. All patients began oral feeding within 2-6 hours. Patients were allowed to move within 12 hours. The hospital stay duration was 1 day in all cases. After catheter removal at 3 weeks, 8 patients (89%) remained dry while one patient (11%), who had a fistula diameter of 9 mm, experienced continuous incontinence. That patient underwent open transvesical VVF repair and is followed with no recurrence 6 months after the first operation. No recurrence was observed in other patients during the 6-month follow-up.

Discussion

Many surgical methods, such as transabdominal, transvaginal, suprapubic transvesical, laparoscopic and robot assisted laparoscopic approach, have been described for the repair of VVF. There is currently no consensus on the best surgical approach or timing of the repair. Laparoscopic repair of vesicovaginal fistula was first reported by Nezhat et al. [7] in 1994. At present, laparoscopic procedures tend to replace open surgery with comparable results [8,9]. Laparoscopic VVF repair is beneficial over open surgery as the patient has less postoperative pain and analgesic requirement, shorter recovery time and shorter hospital stay [10,11]. Although laparoscopic repair has excellent success, the major disadvantages with this technique are difficult intracorporeal suturing, prolonged operation time and steep learning curve. For small sized VVF, various conservative treatments have become increasingly popular, reducing the invasiveness of treatment, and shortening convalescence period. Several minimally invasive techniques such as curettage and fulguration have been described for repair of VVF. Endoscopic treatment of VVFs by fulguration of the fistulous tract is the most common minimally invasive technique for small sized fistulas on day-care basis. O'Conor, who popularized the transabdominal approach, applied electrocoagulation for highly situated small fistulae of 3.5 mm or less [12]. Curettage of fistula track with a screw followed by prolonged catheterization has been reported as successful in a small series of patients by Aycinena [13].

Advanced bipolar energy devices such as LigaSure™ are used to seal veins, arteries, lymphatics, and tissue bundles in a number of specialty fields such as gynecologic, colorectal, cardio-thoracic and urologic surgeries [14]. They are particularly advantageous for sealing vessels up to 7 mm in diameter through uniform compression and efficient energy delivery [15]. In addition, they have greatly reduced the need for laparoscopic suturing, which is technically demanding and time consuming [14]. These systems provide precise energy delivery and electrode pressure to tissues for a controlled time to achieve a complete and permanent fusion of tissues and vessel lumens. They have been designed to produce minimal sticking, charring or thermal spread to adjacent tissue.

In most cases, laparoscopic management of VVFs takes a relatively long time. The mean operative time in the literature ranges from 70 to 280 minutes in laparoscopic repairs and from 110 to 330 minutes in robot-assisted laparoscopic repairs [16-18]. The mean operative time in our study is 41 minutes. The first case lasted the longest (65 min). Intraoperative difficulties were noted in the first case in grasping the fistula and adjusting the pressure of insufflation to maintain pneumovesicum during port insertion. These difficulties subsided in the other cases as we were able to overcome these initial discomforts.

Generally, there is no major bleeding in VVF repair operations. There are some studies comparing bleeding rates in VVF repair in the literature. It was reported that blood loss in robotic surgery was significantly less compared to open surgery (88 vs. 170 mL) [17,19]. In addition, it was reported that blood loss ranges from 50 mL to 125 mL in various laparoscopic repair cases [18]. There was no notable blood loss in our cases.

Increased number of ports and the internal dissections are the main causes of postoperative pain following laparoscopic repair. Four ports have been used in many studies about repair of VVF while more ports have been used in others [18]. In the present study, all cases were done using 2 ports only.

The success rate in transabdominal and transvaginal approaches ranges from 65% to 100% [20]. The reported overall success rate in the literature is 86 to 100% for laparoscopic VVF repair [18,21]. Stovsky and colleagues [22] reported success in 11 of 15 patients by electrocoagulation of small fistula of <3.5 mm. Falk and Orkin [23] reported that they applied electrocoagulation to 10 cases with a fistula diameter of 3 to 6 millimeters and were successful in 8 patients. Shah [24] reported success in 4 of 5 patients who underwent endoscopic fulguration of VVF <7 mm. Our success rate is 80%. Recurrence of the VVF occurred in the patient with the largest fistula diameter (9 mm). Bipolar vessel sealing devices are designed for sealing vessels as large as 7 mm in diameter [25]. We think that this diameter cut-off is valid for fistulae as well. The success of this technique will increase with the number of cases and experience. However, this approach is probably not applicable for large, complicated fistulae or those located near the ureteral orifices.

No matter which approach performed, surgeons believe that the most prominent issue of VVF repair remains a "watertight seal", and adequate bladder drainage after surgery to allow for tissue healing, as suggested by the literature. We believe that a watertight seal is achieved in TBSV operations.

Limitations

Small number of patients is the most important limitation of the study, but it should be noted that VVF is already a rare condition. The other limitation is the lack of comparison with other VVF repair techniques. However, this is the initial study on the treatment of VVF by transvesicoscopic bipolar sealing, which is its strength.

Conclusion

Transvesicoscopic bipolar sealing of vesicovaginal fistula appears to be a simple, safe, and effective procedure for small sized VVF with some advantages such as short learning curve and operative time, reduced blood loss and morbidity, brief hospital stay and improved cosmesis. However, a larger number of patients are needed to thoroughly evaluate this approach.

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Research article
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Can red blood cell distribution width (RDW) predict clinical and endoscopic activity in ulcerative colitis patients?

Kırmızı kan hücresi dağılım genişliği (RDW) ülseratif kolit hastalarında klinik ve endoskopik aktiviteyi tahmin edebilir mi?

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Abstract

Aim: Classification of ulcerative colitis (UC) according to disease activity and severity is important in clinical practice for it determines the management of the patient. In this study, we aimed to investigate the relationship between red blood cell distribution width (RDW) and clinical activity index (CAI) in UC patients as well as endoscopic activity indexes (EIA) that determine disease severity relative to mucosal disease.

Methods: This research was planned as a case-control study. Ninety-nine patients diagnosed with UC were divided an active disease group and a remission group according to their clinical and endoscopic findings. Age and gender-matched control groups were formed from 56 individuals with normal colonoscopic findings.

Results: Serum RDW levels were significantly higher in the UC group (P<0.001). In post-hoc comparisons, a statistically significant difference was observed between the control group and active disease groups (P<0.001). However, RDW values did not significantly predict clinical and endoscopic activity in either the active disease or the remission groups (P=0.05 and P=0.09, respectively). In predicting clinical and endoscopic activity indices, the cut-off values of RDW were 14.25 (66% sensitivity and 72% specificity) and 13.75 (64% sensitivity and 62% specificity), respectively.

Conclusion: This study showed that RDW can be used as a marker for disease activity in ulcerative colitis, but it did not show the same efficacy in remission and active disease distinction.

Keywords: Ulcerative colitis, RDW, Endoscopic activity index, Clinical activity index

Öz

Amaç: Ülseratif kolitin (ÜK) hastalık aktivitesi ve şiddetine göre sınıflandırılması klinik uygulamada önemlidir, çünkü hastanın yönetimini belirler. Bu çalışmada, ÜK hastalarında kırmızı kan hücresi dağılım genişliği (RDW) ile klinik aktivite indeksi (KAİ) ve mukozal hastalığa göre hastalık şiddetini belirleyen endoskopik aktivite indeksleri (EAİ) arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Araştırma bir vaka kontrol çalışması olarak planlandı. ÜK tanısı alan 99 hasta klinik ve endoskopik aktivitelerine göre aktif hastalık grubu ve remisyon grubu olmak üzere iki gruba ayrıldı. Kolonoskopi yapılan ve normal bulunan 56 kişiden yaş ve cinsiyet uyumlu kontrol grupları oluşturuldu.

Bulgular: Serum RDW düzeyleri ÜK grubunda anlamlı olarak yüksekti (P<0,001). RDW ile yapılan post-hoc karşılaştırmalarda, kontrol grubu ile aktif hastalık grupları arasında istatistiksel olarak anlamlı farklılıklar gözlenmiştir (P<0,001). Bununla birlikte, RDW değerleri klinik ve endoskopik aktivitenin belirlenmesinde, aktif hastalık ve remisyon grupları arasında anlamlı değildi (sırasıyla P=0,05 ve P=0,09). Klinik ve endoskopik aktivite indekslerini tahmin ederken, RDW'nin cut-off değerleri sırasıyla 14,25 (%66 duyarlılık ve %72 özgüllük) ve 13,75 (%64 duyarlılık ve %62 özgüllük) idi.

Sonuç: Bu çalışma, RDW'nin ülseratif kolitte hastalık aktivitesi için bir belirteç olarak kullanılabileceğini gösterdi, ancak remisyon ve aktif hastalık ayrımında aynı etkinliği göstermedi.

Anahtar kelimeler: Ülseratif kolit, RDW, Endoskopik aktivite indeksi, Klinik aktivite indeksi

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Introduction

Ulcerative colitis (UC) is a chronic, idiopathic, and recurring and remitting inflammatory bowel disease characterized by a limited, diffuse, nonspecific inflammation of the colon's mucosa, often beginning from the rectum, and extending continuously to the end of the ileum. One or more relapses may develop after the first attack in up to 90%, and early relapse or active disease occurring in the first 2 years is associated with a worse disease course [1].

Classification of UC according to disease activity and severity is especially important in clinical practice as it will determine the management of the patient. Early detection of disease activity reduces the rate of surgery and mortality in serious UC cases [2]. In clinical practice, various combinations of endoscopic parameters, including clinical and laboratory studies, imaging tests and histopathology are used to determine the activity of the disease. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBC), fecal calprotectin are widely used to reflect disease activity in UC [3,4]. However, none of them have been identified as an ideal marker. An ideal marker should be fast, easy, inexpensive, be able to identify individuals prone to a disease along with disease activity and indicate the effectiveness of treatment. Unfortunately, such an ideal marker is not yet available [5].

Red blood cell distribution width (RDW), which reflects the variation in the size of circulating red blood cells, is routinely reported by automated lab equipment used to perform complete blood counts [6,7]. The value of RDW in evaluating the severity and clinical outcome of the disease in various diseases has been proven (e.g. sepsis, renal dysfunction, cardiovascular and lung diseases, and malignancies) [7-10]. In addition, some studies suggest that RDW may be an inflammatory marker for UC [11,12]. However, the sensitivity of these and similar inflammatory markers in the identification of endoscopic active disease and their correlation with mucosal sores are low. In this study, we aimed to investigate the relationship between RDW, which is a marker of inflammation, and clinical activity index (CAI) in patients with UC, as well as endoscopic activity indices (EAI), which determine disease severity according to mucosal disease.

Materials and methods

Patient selection

Adult patients with newly diagnosed UC who presented to the territorial hospital's Gastroenterology outpatient clinics between October 2017 and March 2020 were included in this case-control study. The diagnosis of UC was made by gastroenterology specialists based on clinical, laboratory, colonoscopic and pathological examinations. 99 patients diagnosed with UC were divided into two groups as an active disease group and remission group according to their clinical and endoscopic findings.

Within the same age and gender range, 56 healthy individuals from the healthy population who had colonoscopy due to various indications and whose colonoscopy reports were normal were included as the control group. Those with a history of malignancy, those who had undergone surgery in the last 6 months, patients and / or healthy individuals with active infections, which were detected by chest x-ray, urine sample analysis and stool test, were excluded from the study.

Endoscopic procedure

Endoscopic procedures were performed in the endoscopy unit of our Gastroenterology Department with experienced gastroenterology specialists. Following optimal bowel preparation with sodium phosphate solution, accompanied by the appropriate diet, one colonoscope (EVIS LUCERA ELITE CLV-290SL; Olympus Medical Systems, Tokyo, Japan) was used for each colonoscopic procedure. Colonoscopy reports of each patient at the time of admission were taken as a basis.

Montreal classification was used to determine the anatomical prevalence of UC patients who were evaluated [13]. In this classification, disease prevalence was categorized as E1: proctitis, E2: left colon involvement, E3: extensive colitis.

According to the endoscopic findings of patients with UC, activity indices were routinely evaluated with Modified Baron EAI in our unit [14]. There are four classes in this endoscopy-based scoring system: normal mucosa (0), abnormal vascular pattern granular mucosa (1), brittle mucosa (2), microulceration with spontaneous bleeding (3), and gross ulceration (4). Class 0 and 1 were evaluated as remission, and 2, 3 and 4 were evaluated as active diseases.

Clinic and laboratory

Disease activity in UC patients was evaluated with the criteria of Truelove and Witts [15]. These criteria enable the patients with UC to be classified simply and quickly. Using this classification, patients with UC were classified as mild, moderate, or severe depending on their daily bloody stool count, heart rate, hemoglobin, ESR, and body temperature. Moderate and severe disease classes were evaluated as active disease.

Laboratory findings, including complete blood count, obtained on the day of the colonoscopic examination were gathered from the medical records of the patients.

Statistical analysis

Statistical analysis was performed using the SPSS 22.0 statistics package (SPSS, Inc., Chicago, IL, USA). The data were expressed as mean (SD). Mann Whitney U test was used to evaluate the differences in demographic parameters, and Kruskal Wallis test was used to compare laboratory parameters between groups. Statistical difference was analyzed with the Dunnett's T3 test. Spearman correlation was used to analyze the correlation between parameters. All P values were two-way, and $P<0.05$ was considered statistically significant. Sensitivity, specificity, and cut-off points were evaluated using a receiver operating characteristic curve analysis (ROC).

Ethical approval

Written informed consent was obtained from each subject before endoscopic examination. This study was approved by the Mersin City Training and Research Hospital Ethical Committee and conducted in accordance with the Helsinki Declaration.

Results

A study group was established with 99 patients with UC, and a control group was formed with 56 individuals. The general features of the groups are presented in Table 1. The mean

age of the study and control groups was 42.52 (15.82) years and 46.25 (14.50) years, respectively. There were 60 males (60.6%) and 39 females (39.6%) in the study group, and 32 males (57.1%) and 24 females (42.9%) in the control group. There was no statistically significant difference between the groups in terms of age and gender distribution (P=0.09 and P=0.67, respectively).

Considering the anatomical distribution of patients with UC, E1: 34 cases (33.66%), E2: 28 cases (27.72%), E3: 37 cases (36.63%) were identified. According to their EAI, 27 cases (27.3%) were in remission and 72 patients (72.7%) had active disease. The distribution of patients according to their CAI was as follows: 36 patients (36.4%) were in remission, 63 cases (63.6%) had active disease.

Comparison of inflammatory markers between groups of disease clinical activity is presented in Table 2. The mean WBC, CRP and ESR values of the active disease group were significantly higher than that of the remission and control groups (P<0.001). The mean RDW values of the control, UC remission and active UC patient groups were 13.70 (1.00), 14.36 (1.56), and 15.25 (2.07), respectively. The mean RDW value of active patients was significantly higher than that of the inactive UC and control groups (P<0.001). In post-hoc multiple comparisons of WBC, CRP, ESR and RDW (Table 3), statistically significant differences were observed between the control and active disease groups (P<0.001). Only the CRP and ESR variables were significantly different between the remission and control groups (P=0.03 and P<0.001, respectively). Only CRP displayed a significant difference in remission and active disease groups (P<0.001).

Positive correlations were found between CAI and RDW (r_s=0.37; P<0.001), WBC count (r_s=0.39; P<0.001), CRP (r_s=0.62; P<0.001), and ESR (r_s=0.65; P<0.001), as yielded by correlation analyses.

ROC analysis was applied to WBC, ESR, CRP and RDW values to predict the CAI (Figure 1). Variables with the highest AUC values were ESR 0.84 (0.05) (P<0.001), CRP 0.82 (0.06) (P<0.001), WBC 0.74 (0.06) (P=0.01) and RDW 0.71 (0.06) (P=0.01), respectively. The cut-off value of 14.25 for RDW had 66% sensitivity and 72% specificity.

Comparison of inflammatory markers between patient groups according to their EAIs is given in Table 4. The mean WBC, CRP and ESR values of the active disease group were significantly higher than that of the remission and the control groups (P<0.001). The mean RDW values of control, remission and active UC patients were 13.70 (1.00), 14.14 (1.33) and 15.22 (2.05) respectively. The mean serum RDW value of active disease patients was significantly higher than that of inactive UC and control groups (P<0.001). Post-hoc multiple comparisons were made with WBC, CRP, ESR and RDW (Table 5): Statistically significant differences were observed between the control and active disease groups and the remission and active disease groups in terms of CRP (P<0.001, P=0.04, respectively), but no statistically significant difference was observed between the control group and the remission group (P=0.16). In terms of WBC, statistically significant differences were observed between the control and active disease groups (P<0.001), while there was no statistically significant difference between the control and the remission groups (P=0.29) or the remission and active disease groups (P=0.08). In terms of ESR, there was a significant difference between the control group and both the remission and active disease groups (P<0.001). There was no statistically significant difference between remission and active disease groups (P=0.20). In terms of RDW, a statistically significant difference was determined between the control and active disease groups (P<0.001), while no statistically significant difference was observed between the control and the remission group (P=0.35) or the remission and active disease groups (P=0.09).

Table 1: General characteristics of the groups

Variables	Control group	Study group	*P*-value
Age	46.25 (14.50)	42.52 (15.82)	0.09
Gender (%)	32 male (57.1%)	60 male (60.6%)	0.67
	24 female (42.9%)	39 female (39.6%)	
Anatomical distribution (%)		E1:34 (33.66%)	
		E2:28 (27.72%)	
		E3:37 (36.63%)	
EAI n, (%)	Normal	Active disease 72 (72.7%)	
		Remission 27 (27.3%)	
CAI n, (%)	Normal	Active disease 63 (63.6%)	
		Remission 36 (36.4%)	
n	56	99	

EAI: Endoscopic activity index, CAI: Clinical activity index

Table 2: Comparison of inflammatory markers between groups according to CAI

Variables	Control group	Remission group	Active disease group	*P*-value
WBC	7277.86 (1717.22)	8320 (2267.13)	9664.76 (3544.65)	<0.001
ESR	4.89 (2.27)	20.20 (14.88)	27.89 (18.21)	<0.001
CRP	4.47 (2.48)	9.91 (8.12)	42.93 (42.77)	<0.001
RDW	13.70 (1)	14.36 (1.56)	15.25 (2.07)	<0.001

WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width

Table 3: Post-hoc test results after one-way analysis of variance (ANOVA) to determine between which groups the variables differ

Dependent variable	(I) CAI group	(J) CAI group	*P*-value*	95% Confidence Interval	
				Lower Bound	Upper Bound
CRP	Control	Remission	0.03	-10.58	-0.30
		Active	<0.001	-57.53	-19.39
	Remission	Control	0.04	0.30	10.58
		Active	<0.001	-52.53	-13.49
WBC	Control	Remission	0.06	-2126.65	42.36
		Active	<0.001	-3607.20	-1166.61
	Remission	Control	0.06	-42.36	2126.65
		Active	0.07	-2765.52	76.00
ESR	Control	Remission	<0.001	-21.65	-8.97
		Active	<0.001	-28.71	-17.28
	Remission	Control	<0.001	8.97	21.65
		Active	0.09	-16.01	0.64
RDW	Control	Remission	0.08	-1.31	0.06
		Active	<0.001	-2.26	-0.83
	Remission	Control	0.08	-0.06	1.38
		Active	0.05	-1.78	0.01

* Dunnett T3, CAI: Clinical activity index, WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width

Table 4: Comparison of inflammatory markers between groups according to EAI

Variabels	Control group	Remission group	Active disease group	*P*-value
WBC	7277.86 (1717.22)	8164.44 (2553.33)	9555 (3341.69)	<0.001
ESR	4.89 (2.27)	20.62 (13.08)	26.76 (18.56)	<0.001
CRP	4.47 (2.48)	15.21 (19.47)	37.20 (41.60)	<0.001
RDW	13.70 (1.00)	14.14 (1.33)	15.22 (2.05)	<0.001

WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width

Table 5: Post-hoc test results after one-way analysis of variance (ANOVA) to determine between which groups the variables differ

Dependent variable	(I) EAİ group	(J) EAI group	*P*-value*	95% Confidence Interval	
				Lower Bound	Upper Bound
CRP	Control	Remission	0.16	-24.90	3.42
		Active	<0.001	-50.12	-15.34
	Remission	Control	0.16	-3.42	24.90
		Active	0.04	-43.43	-0.54
WBC	Control	Remission	0.29	-2239.06	465.89
		Active	<0.001	-3381.55	-1172.73
	Remission	Control	0.29	-465.89	2239.06
		Active	0.08	-2935.01	153.90
ESR	Control	Remission	<0.001	-22.30	-9.14
		Active	<0.001	-27.30	-16.44
	Remission	Control	<0.001	9.14	22.30
		Active	0.20	-14.43	2.14
RDW	Control	Remission	0.35	-1.15	0.28
		Active	<0.001	-2.19	-0.84
	Remission	Control	0.35	-0.28	1.15
		Active	0.09	-1.94	-0.22

* Dunnett T3, EAI: Endoscopic activity index, WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width

Correlation analysis revealed that CAI positively correlated with RDW (r_s=0.37; *P*<0.001), WBC count (r_s=0.41; *P*<0.001), CRP (r_s=0.55; *P*<0.001), and ESR (r_s=0.65; *P*<0.001).

ROC analysis was applied to WBC, ESR, CRP and RDW values to predict the EAI (Figure 2). Valuables with the highest AUC values were ESR 0.82 (0.05) (*P*<0.001), WBC 0.81 (0.05) (*P*<0.001), CRP 0.74 (0.06) (*P*<0.001), and RDW 0.69 (0.06) (*P*=0.01). The cut-off value for RDW was 13.75 with 64% sensitivity and 62% specificity.

Inflammatory markers were not associated with anatomical distribution in UC patients. P values for WBC, CRP, ESR and RDW were *P*=0.32, *P*=0.22, *P*=0.26, and *P*=0.10, respectively.

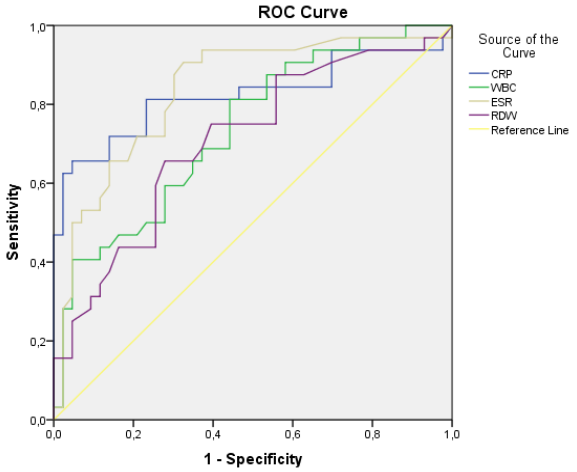

Figure 1: Comparison of inflammatory markers in terms of predicting disease clinical activity (WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width)

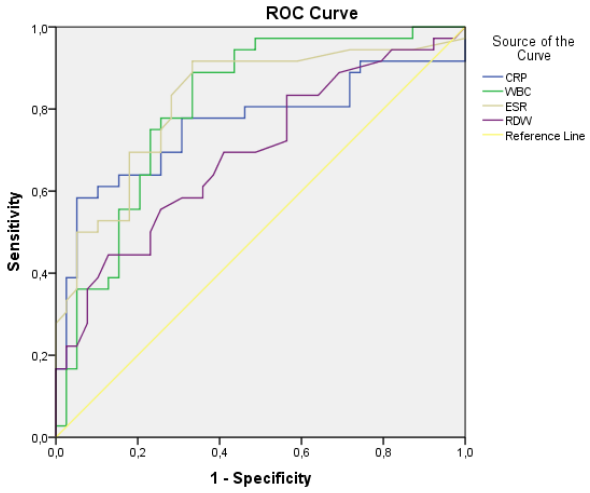

Figure 2: Comparison of inflammatory markers in terms of predicting disease endoscopic activity (WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width)

Discussion

UC is a chronic inflammatory disease that progresses with periods of remission and exacerbation. Classification of UC according to disease activity and severity is important in clinical practice because the patient's management is determined accordingly. For this purpose, a large number of clinical and endoscopic activity indices have been developed [16-18]. Our study revealed that RDW values were associated with both clinical activation and endoscopic activation indices in UC patients, but could not distinguish between remission and active patient groups.

Although an ideal serum marker to predict the severity of the disease is not available, WBC, CRP and ESR are often used in clinical applications to determine UC activity. These markers do not adequately reflect disease activity due to their low sensitivity and specificity for intestinal inflammation [18,19]. Previous studies have shown that CRP and ESR are more significant parameters than WBC in determining disease activity [18-20]. Osada et al. [18] reported that CRP, ESR and WBC counts correlated with the sum of endoscopic and histological scores, and that CRP and ESR were not compatible with distal colon involvement but correlated well with the activity of proximal colon involvement. In our study, it was revealed that the three above-mentioned markers strongly correlated with both CAI and EAI index in accordance with the literature, and this was independent of localization. In terms of predicting EAI, variables with the highest AUC values were ESR (82%), followed by WBC (81%) and CRP (74%). The use of these markers in conjunction with clinical observation, other laboratory parameters and colonoscopy will increase their importance in determining UC activity.

Under normal conditions, the erythrocyte cycle in the body is under strict control. It is observed that there is a change in erythrocyte cycle in pathological conditions. As a result, both the increase in the permanence of old cells in the circulation and the increase due to inflammation may disrupt erythrocyte maturation due to secretion of cytokines and cause early release of larger cells from the bone marrow. Thus, RDW can increase in many diseases [7,21,22].

Several studies have been published in the literature investigating the relationship between RDW and inflammatory bowel diseases. In the study conducted by Song et al. [12], which included 120 UC patients and 101 patients with Crohn's disease, it was found that RDW levels increased in parallel with the severity of the disease activity. They concluded that RDW is a good independent factor in predicting disease activity in patients with UC. Cakal et al. [11], reported high RDW levels in 88.4% of patients with active UC, 29% of patients with UC in remission, and 10% of the control group, and these differences were statistically significant. When fibrinogen, ESR, CRP, PLT and RDW were evaluated together, the most significant indicator for active UC was determined as RDW. The sensitivity and specificity of RDW for the detection of active UC were determined to be 86% and 75%, respectively.

In another study conducted by Yeşil et al. [23], the specificity and sensitivity of RDW in demonstrating active disease in UC were 84% and 17%, respectively, so they concluded that RDW could not be a significant indicator of active disease. Oustamanolakis et al. [24] reported that RDW levels were significantly higher in patients with UC than healthy control group patients. However, the study did not find a significant difference in RDW levels between patients with active disease and those in remission. In addition, they could not find a correlation between RDW and CRP levels. İpek et al. [25] determined that WBC, PLT, CRP, ESR and RDW levels increased significantly in patients with active UC compared to patients in remission. In the non-anemic subgroup, WBC, PLT, CRP and ESR levels increased significantly in patients with active UC compared to patients in remission; however, there was

no significant difference between RDW levels. They concluded that RDW increase developed due to anemia among patients with active disease and in remission.

In this study, it was shown that RDW levels were significantly higher in patients with active UC than healthy controls, but this difference was not significant between remission and active disease groups. Among the variables studied, ESR was the strongest variable in predicting disease CAI, while RDW was the weakest variable (84% and 71%, respectively). The strongest variable in predicting EAI was ESR, while the weakest variable was RDW (82% and 69%, respectively). The cut-off value of 14.25 for RDW had a sensitivity of 66% and a specificity of 72% in predicting CAI. The cut-off value of 13.75 for RDW estimated EAI with 64% sensitivity and 62% specificity.

Limitations

Our study contains several limitations, one being its retrospective nature and the other, including results from a single center. It should also be remembered that the parameters studied are not specific to the disease, and that the results may vary depending on many factors (infection, medication, anemia, inflammation, etc.).

Conclusions

Although no significant difference was found between active disease and disease in remission, our study showed that RDW levels in active UC patients increased significantly, which correlated with clinical, endoscopic and laboratory indices. These inflammatory markers can predict disease activity alone or in combination. The data obtained need to be supported by larger and multi-centered studies. As a result of all this, we believe that these non-invasive, inexpensive markers can be a valuable tool for the rapid assessment of disease activity in UC.

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Comparison of component positioning in robot-assisted and conventional total hip arthroplasty

Robot-yardımlı ve konvansiyonel total kalça artroplastisinde komponent yerleşiminin karşılaştırılması

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Abstract

Aim: For primary total hip arthroplasty, many authors reported that inappropriate component positioning may lead to unfavorable results and complications. In the last two decades, robotic systems were developed to improve component positioning in total hip arthroplasty. However, there are few reports in the literature concerning its efficacy. In this study, we aimed to compare the accuracy of component positioning between robot-assisted and conventional total hip arthroplasty.

Methods: In this retrospective cohort study, forty-four patients were operated using robot-assisted surgery (RAS), and 60 patients were operated using primary conventional manual arthroplasty (CMA). Measurements were done in standing orthogonal antero-posterior x-ray (AP) views to evaluate acetabular inclination, anteversion, and leg length discrepancy. Results were compared between RAS and CMA groups.

Results: The average deviation from desired acetabular inclination was 8^o in the CMA group, 4.7^o in the RAS group, between which the difference was statistically significant (P=0.023). Concerning acetabular inclination, 72% of the patients in the CMA group remained in the safe zone described by Lewinnek while 94% of the patients in the RAS group remained in the same safe zone. The mean deviation from desired anteversion was 6.7^o in the CMA group and 5.6^o in the RAS group. The difference between two groups was not significant (P=0.209). The two groups were similar in terms of leg length discrepancy (P=0.238).

Conclusion: We achieved more consistent acetabular component positioning with robot-assisted total hip arthroplasty compared with conventional total hip arthroplasty. Thus, more patients remained within Lewinnek's safe zone in the robot-assisted surgery group.

Keywords: Total hip arthroplasty, Robot-assisted, Component positioning

Öz

Amaç: Total kalça artroplastisinde protez komponentlerinin uygun olarak yerleştirilmemesi istenmeyen sonuçlara ve komplikasyonlara yol açabilmektedir. Son 20 yılda protez komponentlerinin daha doğru yerleştirilebilmesi için robotik sistemler total kalça artroplastisinde kullanılmaya başlanmıştır. Buna rağmen literatürde robotik sistemlerin uygun protez komponent yerleşimine sebep olduğuna dair kısıtlı sayıda yayın bulunmaktadır. Bu sebeple mevcut çalışmada robot-yardımlı ve konvansiyonel total kalça artroplastisinde komponent yerleşiminin doğruluğu karşılaştırılmaya çalışılmıştır.

Yöntemler: Mevcut retrospektif kohort çalışmasında, 44 hastaya robot-yardımlı total kalça artroplastisi (RYA), 60 hastaya ise konvansiyonel total kalça artroplastisi (KTKA) uygulandı. Tüm vakalar primer artroplasti vakasıydı. Ameliyat sonrası kontrollerde ayakta basarak çekilen bacak uzunluk grafilerinde asetabuler inklinasyon, anteversiyon ve bacak uzunluk farkı ölçümleri yapıldı. Bu sonuçlar her iki grup arasında karşılaştırıldı.

Bulgular: Amaçlanan inklinasyondan ortalama sapma KTKA grubunda 8^o, RYA grubunda 4,7^o idi ve aradaki fark istatistiksel olarak anlamlıydı (P=0,023). Asetabuler inklinasyon parametresinde KTKA grubundaki hastaların %72'si Lewinnek tarafından tanımlanan güvenli aralıkta bulunurken RYA grubundaki hastaların %94'ü aynı güvenli aralıkta yer aldı. Amaçlanan anteversiyondan ortalama sapma KTKA grubunda 6,7^o iken, bu değer RYA grubunda 5,6^o idi. İki grup arasındaki fark istatistiksel açıdan anlamlı değildi (P=0,209). Ortalama bacak uzunluk farkı KTKA grubunda 8 mm iken bu değer RYA grubunda 6mm idi. Bacak uzunluk parametresi bakımından iki grup arasında istatiksel açıdan anlamlı fark bulunamadı (P=0,238).

Sonuç: Çalışmamızda konservatif kalça artroplastisi ile karşılaştırıldığında robot-yardımlı total kalça artroplastisi ile daha tutarlı asetabuler komponent yerleşimi elde edildi. Buna ek olarak robotik cerrahi grubunda daha fazla oranda hasta Lewinnek tarafından tarif edilen güvenli aralıkta yer aldı.

Anahtar kelimeler: Total kalça artroplastisi, Robot-yardımlı, Komponent pozisyonu

Introduction

Regarding stability, function and survival time of the prosthesis, component positioning is crucial in any type of arthroplasty. For total hip arthroplasty, many authors have reported that inappropriate component positioning and improperly adjusted femoral offset increased the risk for dislocation, abductor limping and early polyethylene wear [1–4]. In 1978 Lewinnek and his colleagues defined a safe zone for the acetabular component position. They concluded that there is four times higher risk of dislocation with acetabular component positioning out of 40 ± 10 degrees of inclination and 15 ± 10 degrees of anteversion [5].

Many techniques have been used to improve component positioning, some of which include preoperative templating, rigid patient positioning, external alignment rods, reference pins, compasses, and intraoperative fluoroscopy. However, many authors have reported that prosthetic components might be placed improperly despite using all of these techniques [6–10]. In 2011, a retrospective study at a tertiary hospital demonstrated that among 1823 hips, 63% of the acetabular cups were within the abduction safe zone, 79% of the acetabular cups were within the version safe zone and only 50% of the acetabular cups were within both safe zones [11].

In the last two decades, many Orthopedics clinics started to employ robotic systems in joint replacement surgery to prevent component malpositioning [12]. However, early systems showed similar radiological and clinical results with high technical complications compared with conventional hip arthroplasty [13]. In 2008, a surgeon research team started to work on a new robotic system named MAKO^{TM} (Stryker Mako Surgical Corporation, Fort Lauderdale, FL), in order to improve results of robot-assisted total hip arthroplasty [14]. This robotic system was based on a navigation system and a robotic surgical arm that gives the surgeon haptic feedback during the operation. Also, the new system allowed surgeon to personalize the procedure for each patient on preoperative computed tomography images of the patient's hip joint using a special software called "RIO^{TM}" (Stryker Mako Surgical Corporation, Fort Lauderdale, FL). This robotic system was introduced in 2011. Preliminary results showed precise component positioning in total hip arthroplasty [15, 16]. Despite early superior results, there is limited information in the literature related to this topic. It is still questionable that robot-assisted systems help the surgeons to place prosthetic components more precisely.

In this study, we aimed to compare component positioning between robot-assisted surgery and conventional total hip arthroplasty.

Materials and methods

We conducted this retrospective cohort study in accordance with the Declaration of Helsinki, and we obtained a written informed consent from all patients before the operation, along with the local ethical research committee approval.

We performed 104 primary total hip arthroplasties between the 2017 and 2018, among which 44 patients underwent robot-assisted surgery (RAS), and 60 patients underwent conventional manual arthroplasty (CMA). Patients with minimum follow-up period of 1-year were included in our study. Patients with shorter follow-ups and bilaterally operated patients were excluded. Overall, we included thirty-four patients treated with RAS and 32 patients treated with CMA.

Robot-assisted total hip arthroplasty surgical technique

In the preoperative period, a 3-dimensional pelvis computed tomography was obtained from the patients treated with RAS (Figure 1). The patient-specific virtual 3-D bone model of the pelvis and the proximal femur were created using the MAKO software. The prosthetic components were positioned on the virtual 3-D pelvis bone model for the pre-operative planning (Figure 2). Depth, the center of rotation, inclination, and version of the acetabular cup were determined as needed. Level of the femoral neck osteotomy and best fitting femoral stem, along with the appropriate femoral head were chosen (Figure 2). At this point combined offset and leg length were checked. Few days after preoperative planning, the patient was transferred to the operating room. All patients were operated in lateral decubitus position fixed with rigid patient positioners**.** An anterolateral approach was employed in all procedures, including the CMA group. After surgical exposure three treaded Steinman pins were introduced into the iliac crest 3 cm posterior from the anterior superior iliac spine to fix the pelvic array**.** Then femoral array and femoral checkpoint were inserted to the proximal femur. Proximal femur was registered to the system with the navigation probe. After femoral registration, femoral neck cut was performed at the preoperatively planned level. Following the head removal, acetabular checkpoint was inserted into the supra-acetabular region and acetabulum was registered with the navigation probe. From this point, the robotic system was able to locate the true acetabulum in the spatial plane. The acetabulum was reamed with preoperatively planned angles via using the robotic arm with the surgeon in haptic guidance (Figure 3). The acetabular component was positioned and impacted with the robotic arm with the same angles. As the result of consistent reaming, the acetabular cup was nearly always press-fit, and there was no need for acetabular screws in half of the patients. The femoral canal was prepared manually, and preoperative planned sized trial stem and femoral head were placed. After the hip was reduced with the trial components, the position of the prosthetic components, combined offset, combined anteversion and leg length were checked with the help of the software. At this point, the surgeon had the chance to revise the femoral stem or head. If the components were in the desired position, original components were placed, and hip stability was checked**.** Traditional hemostasis and closure were obtained. The patients were allowed for partial weight bearing with a walker one day after the surgery and full weight bearing at six weeks postoperatively.

Data evaluation

Standard antero-posterior (AP) and lateral x-rays were taken one day after the surgery and a standing orthogonal AP image was obtained to evaluate leg length discrepancy (Figure 4). On the AP standing pelvis view, acetabular cup inclination was measured. The acetabular version was measured as described by Lewinnek [5]. Leg length discrepancy was measured as the distance between the level of the most

prominent point of the trochanter minors. Results were compared between RAS and CMA groups.

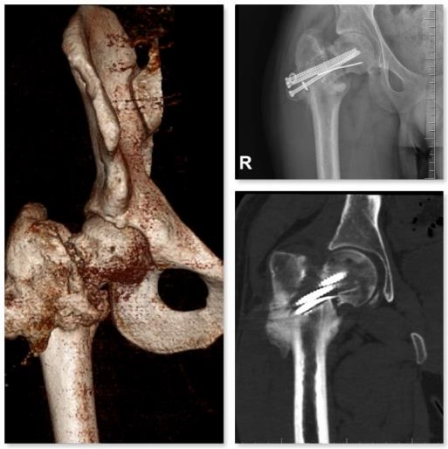

Figure 1: 44 year-old patient with right hip femoral neck fracture non-union. Pre-operative x-rays and 3-D computed tomography views of the patient are illustrated

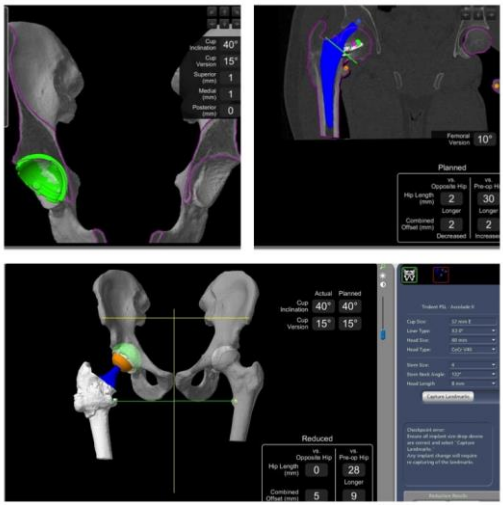

Figure 2: Preoperative planning of the same patient in Figure 1

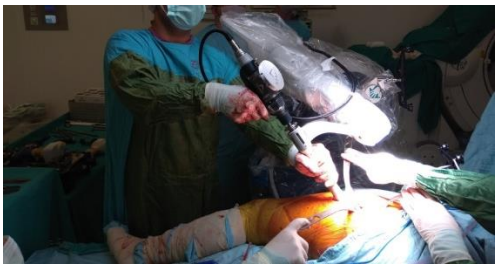

Figure 3: Reaming of the acetabulum by the surgeon with preoperative defined angles under haptic guidance of the robotic arm

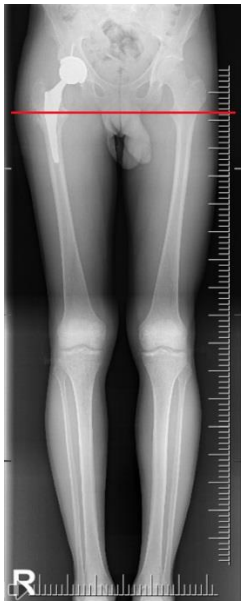

Figure 4: Postoperative orthogonal A-P standing x-ray of the patient demonstrated in Figure 1

Statistical analysis

SPSS 20.0 software was used for statistical analysis, and Kolmogorov-Smirnov test was used for normality analysis. Mean values were compared using Mann Whitney U test. *P*-value under 0.05 was considered statistically significant for all statistical analyses.

Results

The mean age was 64.1 years (min=36, max=87) and 51.7 years (min=32, max=78) in CMA and RAS groups, respectively. The average acetabular inclination was 47.2^o (min=32^o, max=57^o) in the CMA group and 43.7^o (min=36^o, max=58^o) in the RAS group. The difference between average acetabular inclination angle was statistically significant (*P*=0.029). The average deviation from desired acetabular inclination was 8^o (min=0^o, max=17^o) in the CMA group, 4.7^o (min=0^o, max=18^o) in the RAS group, the difference between which was significant (*P*=0.023). Concerning acetabular inclination, 72% of the patients in the CMA group and 94% of the patients in the RAS group remained in the safe zone described by Lewinnek (Figure 5). The average acetabular anteversion was 9.5^o (min=0^o, max=20^o) and 11.2^o (min=3^o, max=20^o) in the CMA and RAS groups, respectively. The difference between acetabular anteversions was not statistically significant (*P*=0.209). The mean deviation from the desired anteversion was 6.7^o (min=0^o, max=15^o) in the CMA group and 5.6^o (min=0^o, max=12^o) in the RAS group (*P*=0.235). While 75% of the patients in the CMA group remained in the Lewinnek's safe zone for acetabular anteversion, the rate was 95% in the RAS group. The mean leg length discrepancy was 8 mm (min=2, max=18) in the CMA group and 6 mm (min=0, max=16) in the RAS group (*P*=0.238). The average surgical time was 70 and 80 minutes in the CMA and RAS groups, respectively (*P*=0.326) (Table 1).

One deep and one superficial infections, two periprosthetic fractures, and one dislocation occurred in the CMA group. Two deep, one superficial infections, one periprosthetic fracture, and one pulmonary embolism occurred in the RAS group.

Table 1: Parameters in both groups

	Group	n	Mean	SD	*P*-value
Acetabular Inclination	CMA	32	47.2	6.7	0.029
	RAS	34	43.7	5.2	
Acetabular anteversion	CMA	32	9.5	5.8	0.209
	RAS	34	11.2	5.3	
Deviation from desired acetabular inclination	CMA	32	8.0	5.7	0.023
	RAS	34	4.7	4.2	
Deviation from desired acetabular anteversion	CMA	32	6.7	4.4	0.235
	RAS	34	5.6	3.1	
Leg length discrepancy	CMA	32	8.0	5.7	0.238
	RAS	34	6.3	5.2	
Surgical time	CMA	32	70	6.3	0.326
	RAS	34	80	7.8	

SD: Standard deviation, CMA: Conventional manual arthroplasty, RAS: Robot-assisted surgery, AP: Antero-posterior

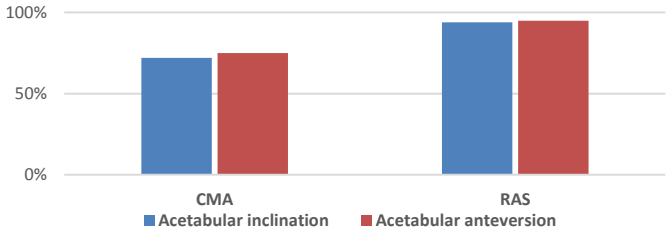

Figure 5: The percentage of the patients that remained in the safe zones described by Lewinnek in both groups (CMA: Conventional manual arthroplasty, RAS: Robot-assisted surgery)

Discussion

Total hip arthroplasty is one of the most frequently performed orthopedic procedures. Every year, the demand for primary total hip arthroplasty is increasing and is estimated to grow by 174% by 2030. Furthermore, the number of revision arthroplasty procedures performed is expected to double by the year 2026 in the United States [17]. For this reason, the survival of the prosthesis became more important nowadays. It is well established that appropriate component positioning and restoration of the femoral offset is crucial concerning the joint stability and early wear [18–22]. Many techniques have been employed to improve component positioning in hip arthroplasty. It is not always possible to achieve appropriate component positioning despite these methods. After the 20th century, robotic systems have been employed in arthroplasty to improve component positioning. However, preliminary results didn't show better functional results compared with conventional techniques [23].

Different robotic systems have been utilized in arthroplasty. A relatively newer technology called "MAKO" is a robotic system used in clinical practice for unicompartmental - total knee and total hip arthroplasty. MAKO is an image-based robotic system that uses preoperative CT in surgical planning to help determine component sizing, positioning, and bone resection. These parameters are confirmed and adjusted intra-operatively based on the patient's specific kinematics before any surgical resection. This system provides haptic feedback during surgery and prevents resection outside of the surgeon's plan [24]. In 2012 Domb and colleagues reported preliminary results of the MAKO system in total hip arthroplasty. They reported that 100% of the patients operated with the MAKO system remained in Lewinnek's safe zone, while this rate was only 82% in patients operated with conventional arthroplasty [25].

For 2 years, we have been utilizing MAKO^{TM} robotic system in arthroplasty surgery. In our study, the mean age was 64.1 and 51.7 years in CMA and RAS groups, respectively. Based on this fact, we believe that younger patients with higher demands are more interested in novel techniques promising higher functional results and longer survival of the arthroplasty.

In the CMA group, we used preoperative templating, rigid patient positioning, external guides, and intraoperative fluoroscopy to improve component positioning. However, there is an 8^{o} deviation of desired acetabular cup inclination in the CMA group, compared with 4.7^{o} in the RAS group. Although this seems like a minor difference, it was statistically significant. Thus, only 72% of the patients in the CMA group were within Lewinnek's safe zone compared with 94% in the RAS group. In terms of acetabular anteversion, there was mean 6.7^{o} and 5.6^{o} of deviation from desired values in the CMA and RAS groups, respectively, which was not significantly different. The rate of staying within Lewinnek's safe zone was 75% in the CMA group and 95% in the RAS group. For leg length discrepancy, there was an average of 8 mm difference between the most prominent level of trochanter minors in the CMA group. This value was 6mm in the RAS group, which was similar.

In our study, there was a significant difference between both groups in acetabular inclination values but anteversion angles were alike**.** This may be due to mean values being used for statistical analysis. When we projected the results to safe zones described by Lewinnek we realized an apparent difference between two groups**.** This is probably because there were more extreme cup positions in terms of inclination and anteversion in the CMA group. On the other hand, it is questionable that the robotic system might be inferior in measuring cup version. However, Redmond et al. reported that correlation between the robotic system and postoperative radiographs was within 10° for 95.9% of cases for inclination and 99.3% for anteversion [26]. Our study revealed similar results with Domb et al. [27]. They reported that patients operated with the MAKO system via posterior hip approach remained 97.7% within Lewinnek's safe zone. There is limited information in the literature comparing intra-operative accuracy and post-operative implant position of the MAKO hip system. Nodzo et al. [28] demonstrated that there was a significant correlation between intra-operative and post-operative cup angles. They showed 1.6^{o} error in inclination and 0.8^{o} error in anteversion respectively for intra-operative and post-operative acetabular cup angles.

In 2012, Nawabi and colleagues [16] compared manual and robot-assisted total hip arthroplasty implantation in a cadaveric model. They found that error for manual implantation compared to robotic assistance was five times higher for cup inclination and 3.4 times higher for cup anteversion. Error for the robot-assisted system was within 3° for cup placement and within 1 mm for leg length equalization. In our study, deviation from the desired acetabular inclination and anteversion were higher than the Nawabi and colleagues' study. We thought that this is the result of the long learning curve of the technique. Several authors reported that robotic systems provide more accuracy compared with standard hip arthroplasty [29–31].

Published data regarding limb length discrepancy after MAKO robot-assisted total hip replacement is limited. In a study, the radiographic discrepancy was 5 mm or less in 89.6% of robot-assisted posterior total hip replacements, with none greater than 1 cm. Results were similar in the conventional arthroplasty group, and the difference was not significant compared with the robot-assisted group [32]. Similarly, in our study, both CMA and RAS group demonstrated less than 1 cm leg length discrepancy.

Although the MAKO robotic system seems to be accurate for component positioning, there are limited data regarding the clinical and functional outcomes of this system. Bukowski and Colleagues reported that robot-assisted cohort demonstrated significantly higher mean postoperative UCLA scores, higher mean postoperative modified Harris Hip Scores (mHHS), and a more significant percentage of patients with mHHS of 90 to 100 points compared with the conventional group at a minimum one-year follow-up [33]. However, Banchetti and colleagues [34] were unable to demonstrate improved patient-reported outcomes with robot-assisted surgery. More studies are needed to show clinical benefits and improvement of the patient reported outcomes after robot-assisted surgery.

Complications are another issue regarding robot-assisted hip arthroplasty. A recent meta-analysis demonstrated that compared with conventional THA, robot-assisted THA was associated with longer surgical time (not significant), lower

intraoperative complication rates, better cup placement, stem placement and global offset, and a higher rate of heterotopic ossifications. Functional scores, limb length discrepancy, rates of revision, and stress shielding were similar in the two groups. The relative amount of blood loss was unclear [29]. Similarly, we could not demonstrate a difference in complications between CMA and RAS groups.

In our study, the robot-assisted system showed better results in terms of prosthetic component positioning and leg-length discrepancy. However, results were not statistically significant, despite acetabular inclination.

Limitations

There were some limitations in our study. Patient numbers were relatively small and follow-up time was short. We did not measure hip offset and true clinical leg length discrepancy. In addition, we did not compare patient-reported outcomes. This study was mainly based on radiographic measurements.

Conclusion

Our study demonstrated more accurate component positioning with robot-assisted hip arthroplasty without increased complication rates. We thought that robot-assisted surgery is a valuable tool to achieve preoperatively planned component positioning. However, long-standing studies are required to prove this technique's patient reported and long-term outcomes, and effects on prosthetic survival.

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An investigation of platelet parameters in smoking patients with coronary slow flow detected during coronary angiography

Koroner anjiyografi sırasında saptanan koroner yavaş akım olan sigara içen hastalarda trombosit parametrelerinin araştırılması

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Abstract

Aim: Coronary slow flow (CSF), which is linked to increased morbidity and mortality, is associated with atherosclerosis, and considered a variant of coronary artery disease (CAD). CSF is more common in smoking patients. We aimed to evaluate laboratory parameters, especially platelet indices, in smoking patients with CSF.

Methods: Patients were selected from those who underwent coronary angiography (CAG) between January 2017 and October 2019. CAG records of 7287 patients were screened retrospectively for our case-control study. Procedures were carried out to identify ischemic heart disease based on clinical indications. CAG was performed in patients with positive non-invasive stress tests and/or high clinical suspicion for atherosclerotic CAD. Smoking patients with CSF (n=226) constituted the study group and matched number (n=226) of smoking patients with NCA were included in the control group. The demographic characteristics of all patients were recorded. Hematologic and biochemical parameters of all subjects were recorded and evaluated.

Results: LDL cholesterol, triglyceride, total cholesterol, ALT, CRP, MCV, RDW, platelet count, PDW, MPV, PCT, and PLR levels were higher in smoking patients with CSF (study group) than normal coronary artery patients (control group) (P=0.034, P=0.015, P=0.033, P=0.006, P<0.001, P=0.033, P=0.021, P=0.039, P=0.006, P=0.010, P=0.021 and P=0.008, respectively). HDL cholesterol was found lower in smoking patients with CSF compared to controls (P=0.007).

Conclusion: According to our results, high platelet parameters may play a role in coronary flow pathogenesis. The height of platelet parameters may indicate the presence of CSF. Our findings support the evidence for inflammation and platelet dysfunction in smoking patients with CSF. Extensive studies at a randomized molecular level are needed to demonstrate this relationship.

Keywords: Coronary slow flow, Mean platelet volume, Plateletcrit, Platelet distribution width, Smoking

Öz

Amaç: Artmış morbidite ve mortalite ile ilişkili olan koroner yavaş akış (KYA), ateroskleroz ile ilişkilidir ve koroner arter hastalığının (KAH) bir varyantı olarak kabul edilir. KYA sigara içen hastalarda daha yaygındır. KYA'lı sigara içen hastalarda laboratuvar parametrelerini (özellikle trombosit indeksleri) değerlendirmeyi amaçladık.

Yöntemler: Hastalar Ocak 2017 ile Ekim 2019 arasında koroner anjiyografi (KAG) uygulanan hastalardan seçildi. 7287 hastanın KAG kayıtları retrospektif olarak tarandı. Çalışmamız bir vaka kontrol çalışması olarak tasarlandı. Bu prosedürler, klinik endikasyonlara dayanarak iskemik kalp hastalığını tanımlamak için gerçekleştirildi. KAG pozitif invaziv olmayan stres testleri ve/veya aterosklerotik KAH için yüksek klinik şüphesi olan hastalara uygulandı. KYA'lı sigara içen hastalar (n=226) çalışma grubunu oluşturdu ve NKA'lı eşleşen sayıda sigara içen hastalar (n=226) kontrol grubuna dahil edildi. Tüm hastaların demografik özellikleri kaydedildi. Tüm deneklerin hematolojik ve biyokimyasal parametreleri kaydedildi ve değerlendirildi.

Bulgular: KYA'lı sigara içen hastalarda (çalışma grubu) LDL kolesterol, trigliserit, total kolesterol, ALT, CRP, MCV, RDW, Trombosit sayısı, PDW, MPV, PCT ve PLR düzeyleri normal koroner arter hastalarına (kontrol grubu) göre daha yüksek bulundu (sırasıyla P=0,034, P=0,015, P=0,033, P=0,006, P<0,001, P=0,033, P=0,021, P=0,039, P=0,006, P=0,010, P=0,021 ve P=0,008). HDL kolesterol KYA'lı sigara içen hastalarda kontrol grubuna göre daha düşük bulundu. (P=0,007).

Sonuç: Sonuçlarımıza göre, yüksek trombosit parametreleri koroner akım patogenezinde rol oynayabilir. Trombosit parametrelerinin yüksekliği KYA varlığını gösterebilir. Bulgularımız sigara içen KYA hastalarında inflamasyon ve trombosit fonksiyon bozukluğu kanıtlarını desteklemektedir. Bu ilişkiyi göstermek için randomize moleküler düzeyde kapsamlı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Koroner yavaş akım, Ortalama trombosit hacmi, Plateletkrit, Trombosit dağılım genişliği, Sigara kullanımı

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Introduction

The delayed progression of opaque material in epicardial coronary arteries without stenosis is known as coronary slow flow (CSF) [1]. The pathophysiology of CSF is not fully understood, and its prevalence varies between 1-7% [2]. CSF is considered a variant of coronary artery disease (CAD) [3]. Clinical presentation of CSF patients can range from atypical chest pain to ST-elevated myocardial infarction [4]. Endothelial dysfunction is considered the foundation of CSF pathogenesis [1,5]. Other proposed pathophysiological mechanisms are platelet dysfunction, diffuse atherosclerosis, imbalance of vasoconstrictor and vasodilator functions, small vessel disease, and inflammation [6-10]. Inflammation plays a vital role in atherosclerosis [11], and platelet function disorders are thought to play a role in the development of CSF [12]. Hence, inflammation and platelet dysfunction are shown to be effective in CSF formation [13]. The treatment strategy in CSF patients is also unclear, as the pathophysiology is not fully known [14].

Platelets significantly trigger the formation and progression of atherosclerotic CAD, and play a significant role in fatal thrombosis [15]. In patients with acute coronary syndrome, they were shown to be more active than in healthy controls [16]. The mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) derived from a complete blood count are indices specific to platelet morphology and proliferation kinetics [17].

In this study, we aimed to evaluate laboratory parameters, especially platelet indices, in smoking patients with CSF.

Materials and methods

Patient selection

Patients were selected from those who underwent coronary angiography (CAG) between January 2017 and October 2019. CAG records of 7287 patients were screened for this case-control study. Flow diagram with exclusion criteria is summarized in Figure 1.

A Siemens Axiom Artis diagnostic device (Siemens Healthcare GmbH, Forchheim, Germany) was used to perform CAG in patients with positive non-invasive stress tests and/or high clinical suspicion for atherosclerotic CAD. These procedures were conducted to identify ischemic heart disease based on clinical indications.

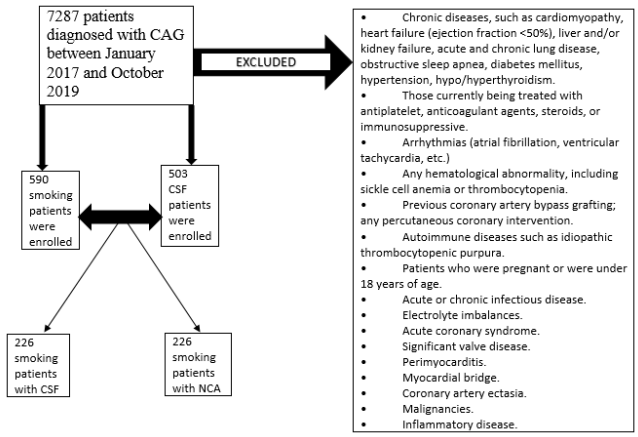

Figure 1: Flow diagram of the study (CAG: Coronary angiography, CSF: Coronary slow flow, NCA: Normal coronary artery)

Various risk factors related to CSF, such as hypertension, obesity, diabetes, smoking status, dyslipidemia, previous history of coronary artery disease, and family history (presence of disease in first-degree relatives) were recorded. Body mass index was calculated by dividing weight in kilograms by the height in meters squared (kg/m^2). Hematologic and biochemical parameters of all subjects were recorded and evaluated. Smoking patients with CSF (n=226) constituted the study group and matched number (n=226) of smoking patients with NCA were included in the control group.

Bolu Abant Izzet Baysal University Ethics Committee approved the study (Decision date: 21/11/2019, decision number: 2019/284), which was conducted in accordance with the principles of the Helsinki Declaration.

Statistical analysis

SPSS 20.0 Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois) was used in all statistical analyses. Kolmogorov-Smirnov test was used to evaluate the distribution model. Normally distributed numerical variables were presented as mean (standard deviation) and non-normally distributed ones were presented as median and range. The significance of the difference between the mean values of the groups were evaluated with Student's t-test. Mann-Whitney U test was used to assess the significance of the difference between continuous numerical variables. Categorical variables were compared with the Chi-square test. Confidence interval was accepted as 95%. A *P*-value <0.05 was considered statistically significant.

Results

The demographic characteristics of smoking patients with CSF (study group) and smoking patients with NCA (control group) are presented in Table 1.

LDL cholesterol, triglyceride, total cholesterol, ALT, CRP, MCV, RDW, platelet count, PDW, MPV, PCT, and PLR levels were higher in smoking patients with CSF (study group) than normal coronary artery patients (control group) (P=0.034, P=0.015, P=0.033, P=0.006, P<0.001, P=0.033, P=0.021, P=0.039, P=0.006, P=0.010, P=0.021, and P=0.008 respectively). HDL cholesterol was found lower in smoking patients with CSF compared to the controls (P=0.007) (Table 2).

Table 1: General characteristics of the patients

Baseline characteristics	Study group Smoking patients with CSF (n=226)	Control group Smoking Patients with NCA (n=226)	*P*-value
Age (years)	52.9 (10.2)	53.5 (10.8)	0.534
Male/Female	194/32	182/44	0.132
LVEF (%)	60.6 (3.5)	61.0 (3.5)	0.197
Heart rate	75 (54-98)	74 (53-105)	0.809
SBP (mmHg)	120 (90-140)	120 (90-156)	0.154
DBP (mmHg)	70 (50-92)	70 (58-90)	0.200
BMI	28.3 (4.8)	28.3 (5.5)	0.957

CSF: Coronary slow flow, NCA: Normal coronary artery, LVEF: Left ventricular ejection fraction, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index.

Table 2: Laboratory data of study groups

	Study group Smoking patients with CSF (n=226) Median (Min-Max)	Control group Smoking Patients with NCA (n=226) Median (Min-Max)	*P*-value
LDL-cholesterol (mg/dL)	109.2 (36.8-221)	111.5 (36.8-174.4)	0.034
Triglyceride (mg/dL)	164 (39-634)	137 (39-634)	0.015
Total cholesterol (mg/dL)	192 (101-287)	186 (101-264)	0.033
HDL-cholesterol (mg/dL)	41.6 (22.8-63.1)	42.3 (22.8-92.8)	0.007
Glomerular Filtration Rate (GFR) (%)	97.5 (71.6-125.4)	97.5 (71.6-125.4)	0.812
Sodium (Na) (mmol/L)	139 (134-146)	139 (134-146)	0.075
Potassium (K) (mmol/L)	4.3 (3.3-5.5)	4.4 (3.7-5.7)	0.159
Alanine aminotransferase (ALT) (u/l)	20 (8-64)	19 (8-61)	0.006
Aspartate aminotransferase (AST) (u/l)	22 (12-50)	20 (12-48)	0.157
Thyroid-stimulating hormone (TSH) (μIU/mL)	1.3 (0.2-3.7)	1.3 (0.4-3.7)	0.611
C-reactive protein (CRP) (mg/L)	0.4 (0.01-15)	0.4 (0.01-4.9)	<0.001
White blood cell (WBC) (u/mm^3)	8.1 (4.0-12.4)	7.9 (4.0-11.8)	0.930
Hemoglobin (gr/dL)	14.9 (11.1-19.3)	14.6 (10.5-19.4)	0.592
Mean corpuscular volume (MCV) (fL)	89 (64.8-99.1)	88.6 (74.7 -100)	0.033
Red cell distribution width (RDW) (%)	15.4 (12.8-20)	15.2 (12.3-17.8)	0.021
Neutrophil, (u/mm^3)	4.6 (2.2-9.4)	4.6 (2.1-7.7)	0.809
Lymphocyte, (u/mm^3)	2.3 (0.8-5.9)	2.3 (1.3-5.9)	0.281
Monocyte, (u/mm^3)	0.6 (0.006-1.4)	0,5 (0.063-1.4)	0.050
Basophils, (u/mm^3)	0.07 (0.001-0.400)	0.07 (0.001-0.142)	0.604
Eosinophil, (u/mm^3)	0.16 (0.016-0.664)	0.16 (0.002-0.891)	0.966
Platelet counts (Plt) (k/mm^3)	239 (145-442)	234 (115-340)	0.039
Platelet distribution width (PDW) (%)	17.6 (14.8-20.9)	17.5 (12.3-19.8)	0.006
Mean platelet volume (MPV) (fL)	8.0 (5.7-14.0)	7.8 (5.7-9.8)	0.008
Plateletcrit (PCT) (%)	0.19 (0.10-0.41)	0.19 (0.07-0.27)	0.010
Neutrophil Lymphocyte Ratio (NLR)	1.9 (0.2-9.7)	1.9 (0.7-5.3)	0.096
Platelet Lymphocyte Rate (PLR)	99.6 (24.7-528.6)	99.1 (27.7-211.4)	0.008

CSF: Coronary slow flow, NCA: Normal coronary artery

Discussion

This study showed that low-density lipoprotein (LDL) cholesterol, triglyceride, total cholesterol, alanine aminotransferase (ALT), C-reactive protein (CRP), mean corpuscular volume (MCV), red cell distribution width (RDW), platelet count, platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT), and platelet lymphocyte rate (PLR) levels were higher in smoking patients with CSF than normal coronary artery patients. HDL cholesterol was found lower in smoking patients with CSF compared to the control group. To the best of our knowledge, this is the first study to investigate platelet indices in smoking patients with CSF. In our study, we detected CSF among 6.9% of patients when we retrospectively assessed CAGs. This rate was 3.1% in smoking patients.

CSF is associated with life-threatening arrhythmia, acute coronary syndrome, and significant cardiac vascular events, including sudden cardiac death [18], along with increased cardiovascular mortality [19]. CSF risk factors are found to vary among studies. Beltrame et al. [20] have shown that male gender and smoking are independent risk factors for CSF. In a Chinese study, hyperuricemia, high hsCRP levels, thrombocytosis, and hyperglycemia were reported as independent risk factors [21]. In our study, CRP levels were high in smoking patients with CSF.

Cardiovascular diseases were associated with increased RDW [22]. A strong correlation was observed between RDW, which was reportedly linked with decreased coronary blood flow and inflammatory markers [23]. RDW levels were high in our study.

Platelets play an essential role in atherosclerotic coronary artery disease, atherothrombosis, coagulation, and inflammation processes [24]. MPV represents platelet volume. PDW shows the difference in platelet size. PCT reflects the volume occupied by platelets in a whole blood sample. These parameters are indicators of platelet activation. An increase in MPV is related with the risk of thrombosis [25]. PDW is an indicator of platelet activation in patients with CAD [26]. Gokce et al. [12] reported that the platelet aggregation rate increased significantly in patients with CSF compared to control groups. Işık et al. [27] found the MPV levels high in patients with CSF. On the contrary, Altun et al. [28] reported that MPV and PDW levels were not significantly higher in patients with CSF compared to the controls. PLR is reported to increase in patients with CSF [29]. Platelet count and increased PLR are essential markers of inflammation, and PLR was associated with mortality in ST-elevated myocardial infarction [30]. A study conducted by Çetin et al. [31] in 2016 found that neutrophil lymphocyte ratio (NLR) was high in CSF patients. On the contrary, in our study, compared to the control group, NLR was not higher in smokers with CSF, but platelet count, PDW, MPV, PCT, and PLR levels were.

Limitations

Visual evaluation of angiography images for CSF diagnosis and the inability to use intravascular ultrasound are essential limitations of the study. The presence of large atherosclerotic plaques, demonstrated by intravascular ultrasound, were shown with autopsy studies in CSF patients.

Conclusions

This study showed that LDL cholesterol, triglyceride, total cholesterol, ALT, CRP, MCV, RDW, platelet count, PDW, MPV, PCT, and PLR levels were higher in smoking patients with CSF than NCA patients, while HDL cholesterol was lower.

According to our results, high platelet parameters may play a role in coronary flow pathogenesis. Increased platelet parameters may indicate the presence of CSF. Our findings support the evidence for inflammation and platelet dysfunction in smoking patients with CSF. Extensive, randomized studies at a molecular level are needed to further demonstrate this relationship.

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A case-control study of two polymorphisms of HIF1A in children with cleft lip/palate and in their mother

Yarık damak ve dudaklı çocuklar ve annlerinde HIF1A'nın iki polimorfizminin vaka kontrol çalışması

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Abstract

Aim: Palatogenesis is a metabolic event that occurs in the initial stages of fetal life. Reports indicate that hypoxia is a critical condition in the formation and elevation of the palate and fusion of the lips. It is known that both environmental and genetic factors play important roles in hypoxia. The ability of the cells to respond to changes in the oxygen pressure that lead to hypoxia depends on the activation of a transcription factor family known as hypoxia-inducible factors (HIFs). This study was conducted to determine the distribution of two polymorphisms of hypoxia-inducible factor 1, alpha subunit (HIF1A) in children with cleft lip/palate and their mothers.

Methods: Two polymorphic structures of HIF1A (Pro582Ser and Ala588Thr) were studied in children with cleft lip/palate and their mothers along with control group children and mothers using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. DNA fragments were monitored by agarose gel electrophoresis after cleavage.

Results: In Ala588Thr comparison, no difference was observed between mothers, children, and their controls. Regarding Pro582Ser, there were differences in the comparison of maternal and children genotypes with control groups (P=0.034 and P=0.023, respectively). In allelic comparisons, there was a difference between mothers of children with cleft lip/palates and the control group (P=0.001). Although this was different in children, it was not as high as in mothers (P=0.026).

Conclusion: HIF1A polymorphisms that change the proline residues may affect the activity or lifespan of HIF1A protein and play a role in the formation of cleft lip/palate.

Keywords: Hypoxia-inducible factor 1, Cleft lip, Cleft palate

Öz

Amaç: Palatogenez, fetal yaşamın erken evrelerinde ortaya çıkan metabolik bir olaydır. Raporlar, hipoksinin damak oluşumunda ve yükselmesinde ve ayrıca dudakların füzyonunda kritik bir durum olduğunu göstermektedir. Çevresel faktörlerin yanı sıra, genetik faktörlerin hipokside önemli rol oynadığı bilinmektedir. Hücrelerin hipoksiye yol açan oksijen basıncındaki değişikliklere cevap verebilme yeteneği, hipoksi ile indüklenebilir faktörler (HIF'ler) olarak bilinen bir transkripsiyon faktörü ailesinin aktivasyonuna bağlıdır. Bu çalışma, yarık dudak/damaklı çocuklar ve bu çocukların annelerinde hipoksi ile indüklenebilir faktör 1, alfa alt birimi (HIF1A)'nin iki polimorfizminin dağılımını belirlemek için yapılmıştır.

Yöntemler: HIF1A'nın (Pro582Ser ve Ala588Thr) iki polimorfik yapısı, çalışma grubu olan yarık dudak/damaklı çocuklar ve annelerinde ve kontrol grubu çocuklar ve annelerinde polimeraz zincir reaksiyonu fragment uzunluğu polimorfizmi (PCR-RFLP) yöntemi kullanılarak incelendi. DNA fragmentleri, kesim işleminden sonar agaroz jelde görüntülendi.

Bulgular: Polimorfik yapılardan Ala588Thr karşılaştırmasında, yarık dudak/damaklı çocuklar ve anneler ile kontrol grubu çocuklar ve anneleri arasında fark gözlenmemiştir. Pro582Ser karşılaştırmasında ise; anne ve çocuk genotiplerinin kontrol gruplarıyla karşılaştırılmasında farklılıklar görülmüştür (P=0.034 ve P=0.023, sırasıyla). Alell karşılaştırmalarında, yarık dudak/damaklı çocukların anneleri ile kontrol grubu anneleri arasında fark gözlenmiştir (P=0.001). Çocuklardaki allel karşılaştırmalarında da, annelerdeki kadar yüksek olmasa da fark görülmüştür (P=0.026).

Sonuç: HIF1A proteinindeki Prolin aminoasitlerinin değişimine neden polimorfizmler, HIF1A proteininin aktivitesini veya ömrünü etkiliyor ve yarık dudak/damak oluşunda rol alıyor olabilir.

Anahtar kelimeler: Hipoksi ile indüklenebilir faktör 1, Yarık dudak, Yarık damak

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Introduction

Cleft lip and palate, the most common craniofacial deformities seen in 700 to 1000 newborns, can be examined in two groups: Syndromic and non-syndromic [1]. Non-syndromic type is more frequent. Cleft lip is more common in males and mostly seen on the left side, while cleft palate is more commonly observed among females [2]. Environmental factors play a significant role in the genetic background of this deformity [3]. It has been determined that folate intake by pregnant women reduced the incidence of cleft lip and palate [1]. After this finding, studies focused on the genes involved in folate metabolism and some candidate genes were identified, which include transforming growth factor-alpha (TGFA), transforming growth factor-beta 2 (TGFB2), transforming growth factor-beta 3 (TGFB3), Msh homeobox 1 (MSX1), Methylenetetrahydrofolate Reductase (MTHFR) and protooncogene B-cell leukemia protein 3 (Bcl3) [1]. Results are controversial. While researchers found a relationship between cleft lip/palate and these genes in some studies, various other studies reported the contrary [1,4-6]. The major risk factors for cleft lip and palate formation have not been clearly elucidated, and it is unclear which of the mutant genes are causing this disease. The reason behind this is the complexity and diversity of the relevant mechanisms at the molecular level during embryogenesis [7].

When the development of the palate in the embryo is examined, the secondary palate elevation and tissue fusion of lips are seen to play important roles in this process. In the development of the second palate, glucosamine and hyaluronan-hydration are needed, and collagen fibers direct the elevator force [8,9]. Interestingly, the pathways of these three components intersect in the hypoxic event. There is a complex relationship between glucosamine, hyaluronan, collagen, and hypoxia. Hypoxia up-regulates hyaluronan, reduces collagen synthesis and enhances the effect of D-glucosamine to down-regulate HIF1A [10-12]. HIF1A, a component of HIF1 and a significant mediator of hypoxia, functions as a key regulator of cellular and systemic homeostatic response to hypoxia by coordinating the genes involved in energy metabolism, angiogenesis, apoptosis, and other genes whose protein products increase oxygen delivery or facilitate the metabolic adaptation to hypoxia [13,14]. HIF1A is rapidly degraded in cells under normoxic conditions by the von Hippel-Lindau tumor suppressor protein (pVHL), which targets the minimal N-terminal transactivation domain (N-TAD) (within the oxygen-dependent degradation domain (ODD)) of HIF1 [13,14]. Two substations of the HIF1A may change the lifespan of HIF1A: One encodes serine at codon 582 (Pro582Ser) and the other encodes threonine at 588 (Ala588Thr) position that is within or near the N-TAD domain.

In this study, we aimed to determine the distribution of these two polymorphisms in children with cleft lip and palate and their mothers to assess the role of these two polymorphisms in cleft lip/palate development and learn about the role of hypoxia in this pathology.

Materials and methods

A total of 76 children with non-syndromic cleft lip/palate and their mothers were included in the study group. This study was approved by the Ethics Committee of the Dicle University Medical Faculty, Diyarbakır, Turkey (No 69-18/03/2011). All parents provided informed consent before blood tests were performed. Control group consisted of 78 healthy children and mothers with no family history of clefting or other congenital disorders.

All subjects underwent peripheral blood sampling for genotype analyses. Genomic deoxyribonucleic acid (DNA) was isolated from peripheral blood by DNA isolation kit (Bio Basic Inc., EZ-10 Spin Column Genomic DNA Kit for Blood Samples; Ontario, Canada). Genotyping was performed by the PCR-RFLP method. The oligonucleotide primers for single-nucleotide polymorphisms (SNPs) were selected from a previous study and optimized for appropriate PCR conditions in our laboratory [15]. *Bsl1* and *Aci1* restriction enzymes were used for the digestion of amplicons according to protocols provided by the supplier of the enzymes. SNPs, oligonucleotide primers, and restriction enzymes are given in Table 1. Restriction enzyme-digested fragments were monitored by agarose gel electrophoresis.

Table 1: SNPs, primer pairs and restriction enzymes [15]

SNPs	Primers	Restriction Enzymes
rs11549465	12A F: 5'-TGTGGCCATTGTAAAAACTCA-3'	Bsl1
(Pro582Ser)	12 PR:5'-CTTGCGGAACTGCcTTCTAA-3'	
rs11549467	12A F: 5'-TGTGGCCATTGTAAAAACTCA-3'	Aci1
(Ala588Thr)	12A R: 5'-TTTAATTCATCAGTGGTGGCA-3'	

SNPs: single-nucleotide polymorphism

Statistical analysis

Descriptive statistics were expressed as count and percentage. Chi-square test was used to evaluate the significance of the distribution of polymorphisms between the study group and healthy controls. *P*-value <0.05 was considered statistically significant and SPSS (version-21) statistical program was used for all statistical computations.

Results

Associations of two known polymorphisms of HIF1A in cleft lip/palate were investigated. For this purpose, allele frequencies obtained from study group and mothers were compared with control individuals and mothers. Interestingly, we did not find any polymorphisms in Ala588Thr (rs11549467; G1790A) in any of the participants. All showed homozygous GG genotype. This result was confirmed by the DNA sequencing of randomly selected samples.

For Pro582Ser (rs11549465; C1772T), we found differences in the genotypes between children and between mothers of the study and control groups. Genotyping results and allele distribution of children (study and control groups) are given in Table 2. Results of the mothers are presented in Table 3.

CC and CT genotype frequencies of the control group children were higher than the study group children and TT genotype frequency of the study group was higher than that of the control group (*P*=0.034). Also, differences were seen in allele frequencies of the children: The C allele was seen more in the control group than the study group (*P*=0.026). Similar to the results of children, a difference was detected between the genotype frequencies of mothers (*P*=0.023). The C allele was seen higher in the control group than the study group (*P*=0.001).

Table 2: Genotype and allele frequencies of children for rs11549465 with cleft lip/palate and healthy controls

Genotypes	Case n=76	Controls n=78	Genotype frequencies of cases %	Genotype frequencies of control %	χ2	*P*-value
CC	48	64	63.2	82.1	8.75	0.034
CT	28	13	36.8	16.7		
TT	0	1	0	1.2		
Alleles	n=152	n=156	Odds ratio (95% CI)		χ2	*P*-value
C allele	124	141	2.1226 (1.084-4.1562)		4.97	0.026
T allele	28	15				

CI: Confidence Interval

Table 3: Genotype and allele frequencies of mothers of children with cleft lip/palate and mothers of healthy controls

Genotypes	Case (mother) n=76	Controls (mother) n=78	Genotype frequencies of cases %	Genotype frequencies of control %	χ2	*P*-value
CC	46	64	60.5	82.1	9.763	0.023
CT	24	13	31.6	16.7		
TT	6	1	7.9	1.2		
Alleles	n=152	n=156	Odds ratio (95% CI)		χ2	*P*-value
C allele	116	141	2.9172 (1.5221-5.591)		11.029	<0.001
T allele	36	15				

CI: Confidence Interval

Discussion

Cleft lip and palate are orofacial defects that occur during pregnancy. These individuals cannot breathe normally from the nose due to the inadequate mouth pressure, and pronunciation is also affected [16]. In addition, there is facial asymmetry. It is difficult to eat solid foods. There are deformities in the shape of the teeth and in their placement, and maintaining oral hygiene is a challenge [17]. Surgical treatment is the main solution.

The mechanism of the formation of cleft lip and palate is not entirely clear. After studies have shown that the use of folic acid reduces the incidence of cleft lip and palate, researchers focused on genes involved in folic acid metabolism and transport. Some of the candidate genes are folate receptor alpha (FR), reduced folate carrier (RFC), 5,10-methylenetetrahydrofolate reductase (MTHFR), cystathionine β-synthase (CBS), methionine synthase (MTR), and methionine synthase reductase dehydrogenase (MTHFD) [18-20]. HIF1, another one of the candidate genes, a heterodimer composed of an alpha and a beta subunit, plays an essential role in embryonic vascularization and pathophysiology of ischemic diseases [21]. HIF1 regulates the transcription of genes involved in apoptosis, angiogenesis, energy metabolism and those whose protein products increase oxygen delivery or facilitate metabolic adaptation to hypoxia [21]. Hypoxia is an important instrument in embryogenesis and HIF-1 is the master regulator of hypoxia. Homozygous inactivation of HIF-1 is lethal due to the lack of vascular formation in the embryo [22].

Under normoxic conditions, HIF1A protein degrades rapidly with the binding of von Hippel Lindau tumor suppressor protein (pVHL). pVHL targets the N-terminal transactivation domain (N-TAD) of HIF1A which is a part of the oxygen-dependent degradation domain (ODD) [13,14]. This blocks the subsequent activity of HIF1A, preventing HIF1A from translocating to the nucleus, and merging with HIF1 beta to form the transcription factor HIF1 [13]. N-terminal transactivation domain (N-TAD) is important in the degradation of HIF1A and affinity of HIF1A to pVHL is determined by proline residues within the N-TAD domain [13]. One of the polymorphisms we studied is the substitution of proline to serine within N-TAD domain, which may affect the lifespan of HIF1A protein. In this study, we found significant differences between children with cleft lip/palate, healthy control groups and their mothers.

HIF1, an important mediator of hypoxia, functions as a key regulator of cellular and systemic homeostatic response to hypoxia by regulating genes whose protein products increase oxygen delivery or facilitate metabolic adaptation [1,13]. During embryogenesis, hypoxia plays a key role in the development of palate in the embryo [23]. As mentioned above, hypoxia is an intersection point for the formation and elevation of the palate and the fusion of lips. HIF1 is the orchestra chef of this pathway and if its lifespan is longer than normal, it may downregulate collagen and upregulate hyaluronan and D-glucosamine, which may subsequently affect the formation of cleft lip/palate.

The strength of this study is that it involves mothers to investigate the intrauterine effects of these two polymorphisms of HIF1A on cleft lip/palate formation. One of the limitations is the relatively small number of patients and controls. It would be better to study in a larger population. Another limitation is the lack of research at protein and mRNA levels.

Conclusion

We studied two substitutions of HIF1A near the binding place of pVHL. We have not found any polymorphisms in Ala588Thr. The other substitution was the conversion of proline to serine amino acid at the 582nd position. pVHL binds to proline residues, and if proline residues change, this may affect the lifespan of HIF1A protein. This finding needs to be confirmed by messenger RNA (mRNA) and protein expression levels.

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The effect on conception rates of bladder fullness during intrauterine insemination: A retrospective cohort study

İntrauterin inseminasyon esnasında mesane doluluğunun gebelik oranlarına etkisi: Retrospektif kohort çalışma

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Ethics Committee Approval: Approval for the study was granted by the Clinical Research Ethics Committee of Kahramanmaraş Sütçü Imam University (decision no: 14, session: 2019/11). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: Embryo transfer in in-vitro fertilization (IVF) cycles is performed with a full bladder, being careful to avoid surgical instrumentation to the cervix as much as possible, so that uterine contractions are not stimulated. The aim of this study was to investigate whether a full bladder during the application of intrauterine insemination increased pregnancy rates by correcting the cervico-uterine axis, thereby enabling easier access of sperm to the uterine cavity.

Methods: This study included 61 patients undergoing IUI procedures, which were performed on patients with infertility since at least one year and those with at least one open oviduct as seen on hysterosalpingography (HSG). Patients' demographic data, folliculometry measurements, spermiogram parameters, bladder fullness status on abdominal ultrasonography during the application, and beta hGC levels on the 14th day following the application were recorded from the patient files.

Results: No statistically significant differences were determined between the two groups in terms of demographic data and folliculometry measurements. The conception rate was 20% in the full bladder group, and 12% in the empty bladder group. Tenaculum application was at a statistically significantly higher rate in the empty bladder group than in the full bladder group (P<0.001). The conception rate was insignificantly higher in the full bladder group (P=0.342).

Conclusion: A full bladder facilitates sperm access to the uterine cavity and may increase conception rates. There is a need for further prospective randomized studies with a larger series to obtain better results.

Keywords: Bladder fullness, Conception rate, Intrauterine insemination

Öz

Amaç: In vitro fertilizasyon (IVF) sikluslarında embriyo transferleri uterus kontraksiyonlarını uyarmamak için mümkün mertebe servikse cerrahi alet enstrümentasyonundan kaçınmaya dikkat edilerek ve dolu mesane ile yapılır. Çalışmamızda da intrauterin inseminasyon uygulaması esnasında da mesane doluluğunun serviko-uterin aksı düzeltip spermlerin uterin kaviteye erişimini kolaylaştırarak gebelik oranlarını artırıp artırmadığını araştırmayı amaçladık.

Yöntemler: Bu çalışmaya histerosalpingografisinde en az bir tüpünün açık olduğu tespit edilip en az bir yıllık infertilitesi olan ve intrauterin inseminasyon tedavisi yapılan 61 hasta dahil edilmiştir. Hastaların demografik özellikleri, folikülometri ölçümleri, spermiogram parametreleri, uygulama esnasındaki abdominal ultrasonografide mesane doluluk durumu ve uygulama sonrası 14. günde beta hGC kaydedildi.

Bulgular: İki grup arasında demografik özellikler, folikülometri ölçümleri açısından istatistiksel olarak anlamlı fark yoktu. Gebelik oranı mesane grubunda %20, boş mesane grubunda %12 olarak bulundu. Tenakulum uygulama oranı boş mesane grubunda dolu mesane grubundan anlamlı düzeyde yüksek bulundu (P<0,001). Gebelik oranı dolu mesane grubunda daha yüksek olmasına rağmen, fark anlamlı bir seviyeye ulaşmadı (P=0,342).

Sonuç: Dolu mesane, spermlerin uterin boşluğuna erişimini kolaylaştırıp gebe kalma oranını artırabilir. Daha iyi sonuçlar elde etmek için daha geniş serilerle yapılacak prospektif randomize çalışmaların gerekli olduğuna inanıyoruz.

Anahtar kelimeler: İntrauterin inseminasyon, Mesane doluluğu, Gebelik oranı

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Introduction

Intrauterine insemination (IUI) is used in infertility treatment in many cases when there is open tubal access. The most common indications are cervical factor-associated infertility, sexual dysfunction, mild male infertility, and unexplained infertility. Sperms prepared in a laboratory environment are administered via a catheter to the uterine cavity of the patient in lithotomy position at the appropriate time in a natural or stimulated cycle [1]. There are many studies in the literature which have investigated the factors that can affect IUI success, which include sperm parameters (number, motility, morphology), the duration of infertility, methods used for ovulation induction and their monitorization, the number of cycles in which they were applied and the application technique [2].

Of the factors affecting pregnancy success in in-vitro fertilization (IVF) cycles, studies related to embryo transfer have focused on triggering uterine contractility in particular [3]. Increasing uterine contractions with intrauterine manipulation and instrument application to the cervix was found to decrease the pregnancy rate in IVF cycles [4]. Similarly, flattening the uterus by filling the bladder during embryo transfer in IVF cycles was found to increase pregnancy rates [5]. However, there are insufficient studies which have investigated the effects of the methods of tenaculum application or increasing the cervico-uterine angle on pregnancy success. The aim of this study was to retrospectively investigate whether there was an increase in pregnancy rates by facilitating sperm access to the uterine cavity during the IUI procedure with fullness of the bladder, which is effective in correcting the cervico-uterine axis.

Materials and methods

Approval for the study was granted by the Clinical Research Ethics Committee of Kahramanmaraş Sütçü Imam University (decision no: 14, session: 2019/11). The study was conducted in accordance with the principles of Helsinki Declaration. We included all 61 patients with accessible hospital records from January 2016 to June 2018, who had at least one tube open on hysterosalpingography (HSG), were followed with at least one year of infertility and treated in our clinic with IUI. During investigation of the infertility etiology, transvaginal ultrasonography was performed on the 2nd or 3rd day of the cycle and FSH, LH and E2 levels were measured. IUI was not performed on patients with spermiogram results of <10 million/cc mobile sperm. Ovulation induction was applied to patients with unexplained infertility and polycystic ovary syndrome-related infertility with the routinely used Clomiphene Citrate (Klomen, Koçak Farma İlaç ve Kimya Sanayi A.Ş., Üsküdar, Istanbul), or recombinant FSH (Gonal-F, Merck Serono SA, Geneva, Switzerland).

When the dominant follicle size reached 18-20 mm in those who received clomiphene citrate and 17-18mm in those who received recombinant FSH, 6500 units of human chorionic gonadotropin (Ovitrelle, Merck Serono SA, Geneva, Switzerland) was administered. The standard Swim Up method was used in the sperm preparation. IUI was performed to all patients after 36 hours by the same doctor (ZB). Using an insemination catheter (Gynemed Medical GmbH, Lensahn, Germany), 0.3-0.5 ml of the prepared insemination material was administered slowly to the uterine cavity. During the IUI procedure, whether there was any dominant follicle rupture and the amount of fullness of the bladder were recorded with transabdominal ultrasonography. For calculation of the bladder volume, the longest oblique diameter on sagittal slices, the sagittal anterior-posterior diameter, and the width on the transverse slice were multiplied by 0.7 [6].

Patients with >200cc urine in the bladder were included in the full bladder group. During the procedure, difficulty in tenaculum application to the cervix for correction of the cervico-uterine axis was recorded. At 2 weeks after IUI, β-HCG levels were measured and noted. The patients were separated into 2 groups according to the fullness of the bladder, as the full bladder group and the empty bladder group. The results were analyzed and compared between these two groups.

Statistical analysis

Data obtained in the study were statistically analyzed using IBM SPSS for Windows v. 22.0 software (IBM Corporation, Armonk, NY, USA). Results were stated as mean (standard deviation (SD)). In the variance analysis for repeated measures, the Repeated Measures ANOVA with Bonferroni correction test was utilized. Tukey HSD was used for the comparison of paired groups. *P*-value <0.05 was considered statistically significant.

Results

The full bladder group included 30 patients and the empty bladder group, 31 patients. No statistically significant differences were determined between the two groups with respect to patient age, BMI, FSH, LH, and E2 levels on the 3rd day of the cycle, duration of infertility, the total drug dose in those using recombinant FSH, endometrium thickness on Hcg day, dominant follicle number and size, and the total number of mobile sperm inseminated. Pregnancy rate was 20% in the full bladder group and 12.9% in the empty bladder group.

There was a significantly lower need for tenaculum application for correction of the cervico-uterine axis in the full bladder group (n=1, 3.33%) compared to the empty bladder group (n=12, 38.7%) (*P*<0.001). The pregnancy rate was insignificantly higher in the full bladder group (*P*=0.342) (Table 1).

Table 1: Patient demographic data, laboratory values, cycle findings and pregnancy outcomes

	Full bladder (n=30)	Empty bladder (n=31)	*P*-value
Age (years)	26.83 (3.51)	26.54 (3.51)	0.753
Duration of infertility(years)	3.43 (1.56)	3.32 (1.57)	0.784
BMI (kg/m^2)	25.56 (2.56)	25.90 (2.53)	0.608
HCG day endometrium thickness (mm)	7.96 (1.95)	7.93 (1.89)	0.950
D3 FSH	5.36 (1.95)	5.12 (1.96)	0.645
D3 LH	11.66 (5.14)	11.51 (5.20)	0.910
D3 E2	43.86 (14.05)	44.80 (14.84)	0.801
Dominant follicle count	1.22 (0.51)	1.18 (0.16)	0.886
Dominant follicle size (mm)	19.1 (0.96)	18.84 (1.02)	0.842
Total number of inseminated mobile sperm (million)	33.2 (5.67)	35.91 (4.47)	0.718
Requirement for tenaculum use (n)	1 (3.33 %)	12 (38.7 %)	<0.001
Pregnancy Yes	6 (20%)	4 (12.9%)	0.342
No	24 (80%)	27 (87.1%)	

Values are presented as Mean (SD), LH: luteinizing hormone, FSH: follicle-stimulating hormone, E2: Estradiol

Sub-group analysis of the pregnancy rates of the two groups according to the use of clomiphene citrate and recombinant FSH revealed that pregnancy rates reached with IUI performed with a full bladder were insignificantly higher in both drug groups compared to those with an empty bladder (21.4% vs. 13.3%, and 18.75% vs. 12.5%) (Table 2).

Table 2: Subgroup analysis of the agents used in ovulation induction

	Full bladder		Empty bladder		
	Gonadotropin (n = 14)	Clomiphene (n = 16)	Gonadotropin (n = 15)	Clomiphene (n = 16)	*P*-value
Age (years)	26.71 (3.87)	26.93 (3.29)	26.26 (3.30)	26.06 (3.64)	0.903
Duration of infertility (years)	3.57 (1.69)	3.50 (1.50)	3.23 (1.53)	3.37 (1.62)	0.972
BMI (kg/m^2)	25.14 (2.47)	25.93 (2.67)	25.64 (2.73)	25.93 (2.40)	0.819
HCG day endometrium thickness (mm)	8.92 (1.73)	7.12 (1.78)	8.35 (1.65)	7.50 (1.96)	0.031
D3 FSH	5.78 (1.88)	5.00 (2.16)	5.70 (1.79)	4.75 (2.17)	0.391
D3 LH	12.85 (5.08)	10.62 (5.13)	13.23 (5.39)	10.50 (5.40	0.317
D3 E2	45.92 (15.86)	42.06 (12.51)	42.70 (15.56)	45.37 (14.50)	0.850
Pregnancy Yes	3 (21.4%)	3 (18.75%)	2 (13.3%)	2 (12.5%)	0.896
No	11 (78.6%)	13 (81.25%)	13 (86.7%)	14 (87.5%)	

Values are presented as Mean (SD), LH: luteinizing hormone, FSH: follicle-stimulating hormone, E2: Estradiol

Discussion

The main hypothesis of this study was that just as in embryo transfer in IVF cycles, the IUI procedure would be easier with passive uterine flattening, in other words, with a full bladder. As it would be easier to advance the catheter from the cervical canal, there would be less requirement for cervico-uterine flattening with tenaculum application to the cervix, which would not trigger uterine contractions, consequently resulting in increased pregnancy success. Consistent with this hypothesis, a full bladder was found to reduce the need for tenaculum application to flatten the uterus. However, although the rate of tenaculum application in the full bladder group was low, as was expected, and the pregnancy rate was higher than in the empty bladder group (20% vs. 12.9%), the difference was not statistically significant.

Passive uterine flattening in this study, and the comfortable and easy placement of the catheter in the uterus is related more to IVF studies in the literature than IUI. Two well-designed studies published in Human Reproduction in 1998 [4] and 1999 [3] showed that pregnancy success reduces by increased uterine contractions due to manipulation of the cervix with surgical instruments during embryo transfer in IVF cycles. Supporting the findings of those studies, a 2002 study by Thomas C et al. [7] compared the pregnancy rates of 3 groups of embryo transfer classified as easy, moderate, and difficult. The pregnancy rates were reported as 21.2% in the difficult group and 30.3% in the easy and moderate group, revealing the importance of the degree of ease of embryo transfer as a factor affecting IVF success independent of other factors, and it was therefore recommended to avoid difficult transfers as much as possible. In another study, Dorn et al. [8] determined that uterine contractions stimulated by tenaculum application caused an increase in serum oxytocin levels. Lesny et al. [9] also reported that contact of the catheter with the uterine fundus during embryo transfer in IVF cycles triggered uterine contractions.

Studies related to uterine flattening methods in IUI cycles and the effect of these on pregnancy outcomes were published in the literature approximately 10 years after IVF studies. In a study by Park et al. [10], 233 IUI cycles of 143 couples diagnosed with unexplained infertility were retrospectively examined. It was reported that tenaculum application to the cervix for correction of the cervico-uterine axis did not change pregnancy outcomes and a pregnancy rate of 14.6% was obtained. This was an acceptable rate when compared with the success rate of 12.6% in the ESHRE study, which examined 120,613 IUI cycles [11]. In a prospective randomized study of 468 IUI cases by Balci et al. [12], the effects of tenaculum application to the cervix on uterine contractions were examined with transabdominal ultrasound. It was determined that tenaculum application increased uterine contractions and this increase both decreased and increased pregnancy outcomes. This was reportedly because the uterine contractions could have increased the sperm transport to the uterine tube.

Another study in literature by Ayas et al. [13], which was similar in design to the current study, is the only prospective, randomized study to have investigated the effect of passive uterine flattening with a full bladder on pregnancy outcomes. Although it was stated that a full bladder increased pregnancy rates by facilitating the IUI procedure, there were several biases in that study related to patient selection and randomization.

Despite the retrospective design and small number of cases in the current study, it can be considered of value as there are few well-designed studies on this subject in literature. That the increased pregnancy rate in the full bladder group did not reach a statistically significant level could be attributed to the number of cases in the study and it can be considered that with a sufficient number of cases this increase would reach a level of statistical significance.

Limitations

Limitations of this study were primarily the retrospective design and the relatively low number of cases. However, when the legal difficulties of conducting prospective human studies using drugs are considered in Turkey, the findings of this study can be considered to make a valuable contribution to the literature on this subject.

Conclusion

A full bladder during IUI can affect pregnancy outcomes by reducing the need for cervical manipulation. To objectively demonstrate the effects of uterus flattening methods on uterine contractions, there is a need for electrophysiological studies and prospective, randomized, well-designed studies with a sufficient number of patients.

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Transaxillary mini thoracotomy as an alternative to thoracoscopy in the treatment of primary spontaneous pneumothorax: A prospective cohort study

Primer spontan pnömotoraks tedavisinde torakoskopinin alternatifi olarak transaksiller mini torakotomi: Prospektif kohort çalışma

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Abstract

Aim: Arguments comparing the outcomes of traditional open surgery and endoscopic approach performed for the treatment of primary spontaneous pneumothorax persist. This study aims to reveal the efficiency of transaxillary mini thoracotomy which is considered an alternative to thoracoscopy.

Methods: This study was conducted with 40 patients who underwent 3-port thoracoscopy and 40 patients who were treated with transaxillary mini thoracotomy for pneumothorax between 2012 and 2018. Two different types of surgery were compared in terms of age, gender, side of operation, duration of hospital stay, complications, recurrence and total cost.

Results: The whole group included 68 (85%) males and 12 (15%) females. Mean age was 25 (3.96) (range 18-35) years. Pneumothorax was right sided in 42 (52.5%) patients. Mean hospital stay was 2.86 (0.56) (range 2-4) days. Average cost was 3263.75 (563.71) TL per patient. Complications occurred in 11 (13.75%) patients whereas 4 (5%) cases developed recurrence. Groups of different surgeries had no statistically significant difference in terms of age, gender, side of operation, duration of hospital stay, rates of complication and recurrence while the average of cost was significantly lower for thoracotomy group.

Conclusion: Regarding the identical surgical outcomes and lower cost, transaxillary mini thoracotomy can be safely preferred as an alternative to thoracoscopy for the treatment of spontaneous pneumothorax.

Keywords: Video-assisted thoracic surgery, Transaxillary mini thoracotomy, Spontaneous pneumothorax, Cost

Öz

Amaç: Primer spontan pnömotoraks tedavisinde uygulanan geleneksel açık cerrahi ve endoskopik yaklaşımların sonuçları karşılaştırılmaya devam etmektedir. Bu çalışma torakoskopinin alternatifi olarak kabul edilen transaksiller mini torakotominin etkinliğini belirlemeyi hedeflemektedir.

Yöntemler: 2012 ile 2018 tarihleri arasında pnömotoraks nedeniyle 3-port torakoskopi ve transaksiller mini torakotomi uygulanmış olan 40'ar hastayı içeren bir çalışma yürütüldü. İki farklı cerrahi tipi yaş, cinsiyet, ameliyat tarafı, hastanede kalış süresi, komplikasyonlar, nüks ve toplam maliyet açısından karşılaştırıldı.

Bulgular: Tüm grupta 68 (%85) erkek ve 12 (%15) kadın hasta vardı. Ortalama yaş 25 (3,96) (aralık 18-35) yıl idi. Pnömotoraks 42 (%52.5) hastada sağ tarafta saptandı. Ortalama hastanede kalış süresi 2,86 (0,56) (aralık 2-4) gün olarak hesaplandı. Hasta başına ortalama 3263,75 (563,71) TL masraf yapıldı. Toplam 11 (%13,75) hastada komplikasyon gelişirken 4 (%5) hastada nüks saptandı. Farklı cerrahi yapılan grupları arasında yaş, cinsiyet, ameliyat tarafı, hastanede kalış süresi ile komplikasyon ve nüks oranları açısından istatistiksel olarak anlamlı fark yokken maliyet torakotomi grubunda belirgin olarak düşüktü.

Sonuç: Spontan pnömotoraks tedavisinde benzer cerrahi sonuçları ve daha düşük maliyeti göz önüne alındığında transaksiller mini torakotomi torakoskopiye alternatif olarak güvenle tercih edilebilir.

Anahtar kelimeler: Video yardımlı göğüs cerrahisi, Transaksiller mini torakotomi, Spontan pnömotoraks, Maliyet

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Introduction

Primary spontaneous pneumothorax (PSP) occurs in patients without any underlying pulmonary diseases and is frequently induced by the rupture of subpleural blebs and bullae. Conservative treatment or tube thoracostomy is usually adequate in the first episode of pneumothorax whereas recurrent pneumothorax, persistent air leakage or expansion defect of the lung parenchyma following chest tube insertion and bilateral pneumothorax are considered as principal indications for surgery [1].

Surgical approaches are represented by conventional thoracotomy and video-assisted

thoracoscopic surgery (VATS) where both techniques depend on the idea of removing the deformed tissue and preventing deflation of the lungs [2].

Current literature consists of numerous studies comparing these two approaches with regards to surgical outcomes. Aim of this study was to compare VATS and transaxillary mini thoracotomy (TMT) in terms of complications, recurrence, and cost effectiveness.

Materials and methods

Following the approval of Namik Kemal University's Ethics Committee (form number: 2019.20.02.04 on 28 March 2019), the patients with second-episode PSP who had undergone VATS and TMT in Thoracic Surgery Departments of Istanbul and Namik Kemal University between 2012 and 2018 were analyzed. Exclusion criteria included diagnosis of secondary spontaneous pneumothorax, recurrent pneumothorax, and incompatibility with the scheduled postoperative follow-ups whereas patients who had chest tubes at the first or second episodes were included in the study.

The same two surgeons performed operations regardless of who performed VATS or TMT. The patients were surgically treated via wedge resections and bullectomy in addition to partial parietal pleurectomy through a 3-port thoracoscopy or a transaxillary thoracotomy. TMT was performed through a standardized 10 cm incision also sparing the serratus anterior muscle. Pleurodesis was not performed in any of the cases. At the end of the operations, a single 24-French chest tube was placed into the thoracic cavity. Radiological screening was conducted beginning at postoperative day one and ending the day after the chest tube was pulled out. Patients were invited to follow-up examinations during the first and third weeks after being discharged. Recurrence was considered when it was confirmed radiologically during the follow-ups in the first three weeks on the same side of initial operation.

Forty patients included in each of VATS and TMT groups were comparatively examined in terms of age, gender, side of the affected hemithorax, duration of hospital stay, complications, status of recurrence and cost. Total cost was calculated by reviewing records for each patient including the expenditures of hospital stay and surgical instruments.

Statistical analysis

SPSS (IBM SPSS for Windows, ver.24) statistical package program was used for calculations. Descriptive statistics for continuous variables in the study were expressed as mean, standard deviation, minimum and maximum; categorical variables were expressed as number (n) and percentage (%). The data were confirmed to be normally distributed via Shapiro-Wilk and Skewness-Kurtosis tests. Independent T-test was used to compare the average of measurements for patient groups and Chi-square test was employed to reveal the relation between categorical variables. *P*-value <0.05 was considered statistically significant.

In the power analysis based on recent studies and the prevalence of recurrent pneumothorax, the minimum number of patients required for the study was calculated as 70 with 80% power (1-β err prob=0.80) and 5% error margin (α err prob=0.05). Therefore, a total of 80 cases, 40 for each of two groups, were included in the workup.

Results

A total of 80 patients included 68 (85%) males and 12 (15%) females. Mean age was 25 (3.96) (range 18-35) years. Pneumothorax was right-sided in 42 (52.5%) and left-sided in 38 (47.5%) patients. Average of hospital stay was 2.86(0.56) (range 2-4) days. Mean cost was 3263.75(563.71) TL. Complications occurred in 11 (13.75%) patients whereas a total of 4 (5%) cases developed recurrence. Related data are summarized in Tables 1 and 2.

Table 1: Demographic and clinical features of the patients

Parameters		n	%
Gender	Male	68	85
	Female	12	15
Side of surgery	Right	42	52.50
	Left	38	47.50
Complication	Present	11	13.75
	Absent	69	86.25
Recurrence	Present	4	5
	Absent	76	95
Total		80	100

Table 2: Evaluation of the general data

Parameters	Mean	SD	Min.	Max.
Age (years)	25	3.96	18	35
Length of hospital stay (days)	2.86	0.56	2	4
Cost (TL)	3263.75	563.71	2310	4340

SD: Standard deviation

Thirty-three (82.5%) males were included in VATS group while TMT group had 35 (87.5%) males. Mean age was calculated as 25.3 years for VATS and 24.7 years for TMT. Right-sided operations were performed for VATS and TMT in 24 (60%) and 18 (45%) patients, respectively. Mean hospital stay was 2.87 days for VATS and 2.85 days for TMT. An average of 3780 and 2747.5 TL were spent for VATS and TMT, respectively. Six (15%) patients who had undergone VATS developed complications whereas recurrence occurred in 2 (5%) patients included in both groups. The difference between cohorts of patients in terms of age, gender, side of pneumothorax, length of hospital stay and rates of complications or recurrence were not statistically significant while cost of hospital stay was demonstrably higher for cases who had undergone VATS (Table 3 and 4).

None of the surgical interventions resulted in mortality. Complications were similar, 3 wound discharges and 2 atelectasis for both groups except arrhythmia in one additional patient who had undergone VATS. Two patients from both groups developed recurrence which necessitated re-operation.

Table 3: Comparison of VATS and TMT groups

Parameters		VATS		TMT		*P*-value
		n	%	n	%	
Gender	Male	33	82.5	35	87.5	0.531
	Female	7	17.5	5	12.5	
Side of surgery	Right	24	60	18	45	0.369
	Left	16	40	22	55	
Complication	Present	6	15	5	12.5	0.745
	Absent	34	85	25	87.5	
Recurrence	Present	2	5	2	5	1
	Absent	38	95	38	95	
Total		40	100	40	100	----

Chi-square test, VATS: Video-assisted thoracic surgery, TMT: Transaxillary mini thoracotomy

Table 4: Assessment of quantitative variables

Parameters	VATS				TMT				*P*- value
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	
Age (years)	25.30	3.88	18	34	24.70	4.01	18	35	0.475
Length of hospital stay (days)	2.87	0.55	2	4	3.85	0.57	2	4	0.840
Cost (TL)	3780	249.9	2660	4340	2747.5	200.3	2310	3290	0.0007

Independent T-test, SD: Standard deviation, VATS: Video-assisted thoracic surgery, TMT: Transaxillary mini thoracotomy

Discussion

The findings of this study clearly indicate that mini axillary thoracotomy is a dependable alternative to thoracoscopy in the surgical treatment of pneumothorax regarding its similar outcomes at lower costs.

Since 1937 when thoracoscopy was first used to identify a bulla, technological advances in medical devices have contributed to the development of VATS which is currently considered the most convenient approach for the treatment of pneumothorax by most thoracic surgeons [3]. On the other hand, disadvantages of a thoracotomy have been commonly emphasized as deterioration of pulmonary function, evident postoperative pain, and longer hospitalization [4].

Regarding the outcomes of pneumothorax surgeries, current studies report the rate of recurrence ranging between 2% and 14% for VATS and up to 5% for thoracotomy [5,6]. Joshi et al. announced that recurrence rate did not significantly differ between patients who had undergone VATS and thoracotomy [7]. Compatible with this statement, both groups in this study developed recurrence at the same rate of 5%. Patients undergoing thoracoscopy suffer peroperative complications including bleeding or conversion to thoracotomy at rates between 3% and %8 whereas less threatening events such as wound infections or prolonged air leakage may occur for VATS and open surgery at identical frequencies [8,9]. The patients in this series developed no peroperative complications whereas 6 (15%) cases in VATS and 5 (12%) in TMT group encountered postoperative problems that resolved successfully. Mean hospital stay has been reported as between 2.8 and 6.9 days for VATS and 4.3 and 9.4 days for thoracotomy denoting a significant difference for two procedures [10-12]. Our patients who had undergone VATS and thoracotomy were discharged after an average of 2.87 and 3.85 days, respectively. Recent studies revealed no cost advantage of VATS considering the use of mostly disposable and more expensive instruments for surgery [13-15]. In our experience, the costs were significantly lower in the thoracotomy group.

Thoracotomy is the basic surgical intervention to approach the pleural cavity and the first stage of education in thoracic surgery whereas thoracoscopy indicates a learning curve of experience numbered between 30 and 100 cases reported by previous studies [16-18]. Therefore, thoracotomy, which is an easily applicable procedure not requiring an advanced level of experience and elaborative surgical equipment appears to hold its place as the first choice of surgical treatment for pneumothorax as well as some other thoracic pathologies.

Limitations

The principal limitation of this study was the design in two centers focusing on a limited number of cases. To obtain more heterogeneous cohorts, future studies may contain secondary pneumothorax patients and data obtained from a larger group of surgeons.

Conclusion

Considering the cost effectiveness in addition to identical surgical outcomes and recurrence rates of thoracoscopy, transaxillary mini thoracotomy may be confidently preferred as the treatment choice of pneumothorax.

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Evaluation of knowledge and behavior of nurses working in intensive care units for endotracheal aspiration application

Yoğun bakım ünitelerinde çalışan hemşirelerin endotrakeal aspirasyon uygulamasına yönelik bilgi ve davranışlarının değerlendirilmesi

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Abstract

Aim: Endotracheal aspiration is one of the most common invasive procedures administered by intensive care nurses in patients receiving mechanical ventilation to provide and maintain adequate oxygenation, alveolar ventilation, and gas exchange, prevent pulmonary consolidation and atelectasis, and reduce the risk of ventilator-associated pneumonia. When the endotracheal aspiration procedure is not administered correctly, the patient may have serious complications such as arterial and venous desaturation, cardiac arrhythmia, cardiac arrest, atelectasis, bronchospasm, lower respiratory tract contamination, ventilator-induced pneumonia, anxiety, and dyspnea. The study aims to evaluate the knowledge and behaviors of nurses working in intensive care units for endotracheal aspiration applications.

Methods: This study used a cross-sectional and descriptive design including a questionnaire-based nurse survey. It was conducted between 17 March 2015-30 June 2015 with 54 nurses working in intensive care units in a public hospital. In the study, the data were collected with a questionnaire, endotracheal aspiration information form, and nurse observation form for endotracheal aspiration. The evaluation of the data was conducted using numbers and percentages. The ethics committee approval, institutional permission, and participant consent were obtained before starting the research.

Results: It was determined that the nurses participating in the study were incompetent before, during, and after the endotracheal aspiration procedure and that they did not have sufficient information about endotracheal aspiration.

Conclusion: In line with the results of the study, it was suggested that the nurses should be trained on endotracheal aspiration, the effect of education on practice should be evaluated, and that standardization studies should be carried out to minimize deficient and erroneous practices in endotracheal aspiration.

Keywords: Intensive care, Nurse, Endotracheal aspiration, Knowledge, Behavior

Öz

Amaç: Mekanik ventilasyondaki hastalarda yeterli oksijenasyon, alveoler ventilasyon, gaz değişimini sağlamak ve sürdürmek, pulmoner konsolidasyon ve atelektaziyi önlemek, ventilatör ilişkili pnömoni riskini azaltmak amacı ile yoğun bakım hemşirelerinin en sık uyguladığı invaziv işlemlerden biri endotrakeal aspirasyon uygulamasıdır. Endotrakeal aspirasyon işlemi doğru yapılmadığında hastada arteriyel ve venöz desatürasyon, kardiyak aritmi, kardiyak arrest, atelektazi, bronkospazm, alt solunum yolları kontaminasyonu, ventilatöre bağlı pnömoni, anksiyete ve dispne gibi ciddi komplikasyonlara yol açabilir. Araştırma yoğun bakım ünitelerinde çalışan hemşirelerin endotrakeal aspirasyon uygulamasına yönelik bilgi ve davranışlarının değerlendirilmesini amaçlamaktadır.

Yöntemler: Tanımlayıcı türde olan kesitsel, anket tabanlı hemşirelik araştırması bir devlet hastanesindeki yoğun bakım ünitelerinde çalışan 54 hemşireyle, 17 Mart 2015 - 30 Haziran 2015 tarihleri arasında yapıldı. Araştırmada veriler kişisel bilgi formu, endotrakeal aspirasyon bilgi formu ve endotrakeal aspirasyona ilişkin hemşire gözlem formu ile toplandı. Verilerin değerlendirilmesi sayı ve yüzdelik ile yapıldı. Araştırmaya başlamadan önce etik kurul, kurum izni ve katılımcı onamları alındı.

Bulgular: Araştırmaya katılan hemşirelerin endotrakeal aspirasyon işlemi öncesi, sırası ve sonrası uygulamalarının yetersiz olduğu, endotrakeal aspirasyon konusunda yeterli bilgiye sahip olmadıkları belirlendi.

Sonuçlar: Araştırmanın sonuçları doğrultusunda, hemşirelere endotrakeal aspirasyon konusunda eğitimin verilmesi ve eğitimin uygulamaya etkisinin değerlendirilmesi, endotrakeal aspirasyonda yapılan hataları, eksik uygulamaları en aza indirmek amacıyla uygulamaya yönelik standardizasyon çalışmalarının yapılması önerildi.

Anahtar kelimeler: Yoğun bakım, Hemşire, Endotrakeal aspirasyon, Bilgi, Davranış

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Introduction

Although the need for mechanical ventilation support is the most common reason for hospitalization, it is one of the most frequently used and indispensable technologies in intensive care [1]. Endotracheal aspiration is one of the most common invasive procedures administered by intensive care nurses in patients receiving mechanical ventilation to provide and maintain adequate oxygenation, alveolar ventilation, and gas exchange, to prevent pulmonary consolidation and atelectasis, and to reduce the risk of ventilator-associated pneumonia [2]. When endotracheal aspiration procedure is not administered correctly, the patient may have serious complications such as arterial and venous desaturation, cardiac arrhythmia, cardiac arrest, atelectasis, bronchospasm, lower respiratory tract contamination, ventilator-induced pneumonia, anxiety, and dyspnea [3,4].

Studies have shown that intensive care nurses generally act following their personal experience, rather than in accordance with evidence-based practices in endotracheal aspiration [4-8]. This shows that there is an inconsistency between theory and practice in endotracheal aspiration practices. According to the results of the limited number of studies conducted on the topic in Turkey, the application of endotracheal aspiration procedure varies among intensive care unit nurses [8-10]. The lack of standardization in endotracheal aspiration may also affect the quality of nursing care negatively. Conducting studies in different sample groups on the subject is of significance in strengthening the existing data and revealing various aspects. As a result of the present study, knowledge, and practices of intensive care unit nurses for endotracheal aspiration will be evaluated. We think that this evaluation can increase the awareness of the intensive care unit nurses and help shape the programs planned to improve their endotracheal aspiration practices.

Materials and methods

The study used a cross-sectional and descriptive design including a questionnaire-based nurse survey to determine the knowledge and behaviors of intensive care unit nurses regarding endotracheal aspiration.

Universe and sample of the study

The study was conducted between 17 March 2015 and 30 June 2015 in the secondary and tertiary level intensive care units in a public hospital. Nurses in intensive care units worked between 08:00 and 16:00, and 16:00 and 08:00 on weekdays, and between 08: 00 and 08: 00 on weekends with shifts. In-service training programs were provided in the hospital; however, no training on endotracheal aspiration had been provided yet, and there was no endotracheal aspiration procedure.

The universe of the study consisted of 54 nurses working in the secondary and tertiary level intensive care units of the public hospital, for they were already performing endotracheal aspiration in the mentioned units. No sampling procedure was used in the study; instead, all the nurses were included as they had already agreed to participate in the study.

Data collection tools

The study data were collected using a personal information form, an endotracheal aspiration knowledge form, and endotracheal aspiration-related nurse observation form [11], which were designed in line with the literature.

The questionnaire form

The questionnaire form consisted of 10 items aiming to collect information about nurses' age, gender, educational background, professional seniority, seniority in the intensive care clinic, and education status regarding endotracheal aspiration application.

The endotracheal aspiration knowledge form

The endotracheal aspiration knowledge form consisted of a total of 35 propositions to determine the endotracheal aspiration-related knowledge [11,12].

The endotracheal aspiration-related nurse observation form

The endotracheal aspiration-related nurse observation form consisted of a total of 57 steps regarding pre-(1-27), during-(28-49), and post-(50-57) application to determine whether the nurses follow endotracheal aspiration standards [11].

Implementation of the study

To ensure the intelligibility of the data collection tools, the personal information form, the endotracheal aspiration-related nurse observation form, and the endotracheal aspiration knowledge form were piloted to 10 nurses working in the intensive care unit. After the pilot study, no corrections were made in the personal information form, endotracheal aspiration knowledge form, and endotracheal aspiration-related nurse observation form. For this reason, the pilot study data were included in the study.

To avoid pre-observation contamination in nurses, firstly, the endotracheal aspiration-related nurse observation form was filled out. After completing the observations, the personal information form and endotracheal aspiration knowledge form were administered. Each of the application steps in the endotracheal aspiration-related nurse observation form was evaluated according to whether they were done correctly. The researcher made three observations at different times to ensure the reliability of the observation. Nurses were told that their behaviors regarding aspiration application could be observed, but no information was given about when and by whom the observation would be performed. Observation forms were not filled out near nurses to avoid behavioral changes. The researcher who made the observation also took notes. The researcher took care not to let the nurses know that they were observed.

Each observation took about 15-20 minutes. Nurses were given the personal information and the endotracheal aspiration propositions forms, and they were asked to fill them out right away. While the nurses were filling out the forms, the researcher accompanied them to prevent interactions. It took nurses 15-20 minutes to complete the forms.

Statistical analysis

The coding and statistical analyses of the data were conducted on the SPSS 20 statistical software package. Numbers, percentages, mean and standard deviation values were used in the analyses. “No” response to items 1, 3, 7, 9, 11, 12, 14, 16, 18, 19, 22, 24, 26, 29, 30, 31, and 34 and “yes” response to items 2, 4, 5, 6, 8, 10, 13, 15, 17, 20, 21, 23, 25, 27, 28, 32, 33, and 35 were accepted as correct [11,12]. Each correct answer was

assigned 1 point. The total knowledge score of each nurse was calculated by summing the points obtained from each correct response given to items in the endotracheal aspiration knowledge form. The highest knowledge score to be obtained was 35.

Nurses' behaviors were evaluated over three observations. Doing the procedure correctly in at least two of the three observations was accepted as "correct" while doing it incorrectly in two out of three observations was evaluated as "incorrect".

Ethics of the study

At the outset, the ethics committee approval of Nevşehir Hacı Bektaş Veli University Ethics Committee (issue: 84902927-25-462) was obtained, in addition to the written permission of the General Secretariat of the Public Hospitals Association (issue: 45003370-2888) of the province where the study was conducted and the written consent of the nurses who participated in the study.

Results

Of the nurses participating in the study, 90.7% were women, 37.1% belonged to the 24-28 age group, 37.0% were graduates of health vocational high schools, 61.1% had been working for 1 to 5 years, and 59.3% had been serving in the intensive care unit for 1 to 5 years. Also, 66.7% of the nurses stated that they had received aspiration training.

All of the nurses participating in the study were observed to apply the following procedures incorrectly: The patient is informed before the procedure (100.0%), while the patient is oxygenated, gloves are worn following the principles of surgical asepsis (100.0%), and the aspiration pressure is adjusted to 80-120 mmHg (100.0%) (Table 1).

On the other hand, the nurses participating in the study were determined to apply the following procedures incorrectly compared to the other steps: During endotracheal aspiration, the procedure is terminated when the heart rate of the patient decreases 20 beats/min or more or increases 40 beats/min or more, or cardiac arrhythmias are observed (98.1%); the patient's respiratory rate is evaluated from the monitor (96.3%); the patient's pulse rate is evaluated from the monitor (92.6%) (Table 2).

Of the nurses participating in the study, 83.3% were determined to record the endotracheal aspiration procedure. The nurses were observed to never apply the following steps: The pulse rate of the patient is evaluated from the monitor and compared to the pre-aspiration pulse value (100.0%); the blood pressure of the patient is evaluated from the monitor and compared to the pre-aspiration blood pressure value (100.0%); the respiratory rate of the patient is evaluated from the monitor and compared to the pre-aspiration respiratory rate (100.0%) (Table 3).

The mean knowledge score of the nurses regarding endotracheal aspiration was determined as 22.98 (3.21) [mean (SD)].

Table 1: Distribution of nurses by their practices in preparation steps before the endotracheal aspiration (n=54)

Preparation steps before endotracheal aspiration procedure	Correct		Incorrect	
	n	%	n	%
1. Hands are washed before the procedure.	5	9.3	49	90.7
2. Materials are prepared for open system endotracheal aspiration procedure.	53	98.1	1	1.9
3. Materials are brought near the patient.	54	100	0	0
4. Aspiration requirement of the patient is evaluated.	31	57.4	23	42.6
5. Patient's pulse rate is evaluated from the monitor.	5	9.3	49	90.7
6. Blood pressure of the patient is evaluated from the monitor.	7	13.0	47	87.0
7. Respiratory rate of the patient is evaluated from the monitor.	4	7.4	50	92.6
8. The patient is informed before the procedure.	0	0.0	54	100
9. The curtain hanging around the patient bed is pulled to ensure patient privacy.	3	5.6	51	94.4
10. Before the procedure, the patient's head is raised by 20-30 ° to set the correct position.	25	46.3	29	53.7
11. The lid of sterile saline solution is opened.	2	3.7	52	96.3
12. The aspirator is checked if it operates.	15	27.8	39	72.2
13. Sterile connector tube is attached to the tip of the aspirator.	1	1.9	53	98.1
14. The cap is attached to the connector tube of the aspirator.	1	1.9	53	98.1
15. The tip of the sterile aspiration catheter package is opened.	53	98.1	1	1.9
16. The catheter package is located in an accessible area.	48	88.9	6	11.1
17. Oxygen rate on the ventilator is set to100%.	13	24.1	41	75.9
18. The patient is given100% O_2 for 1 minute with a ventilator.	8	14.8	46	85.2
19. While the patient is oxygenated, gloves are worn under the principles of surgical asepsis.	0	0.0	54	100
20. The package of aspiration catheter is grasped with the non-dominant hand.	20	37.0	34	63.0
21. The catheter inside the sheath is wrapped around the dominant hand, without harming sterility.	23	42.6	31	54.7
22. The lid of the connector located at the tip of the aspirator is removed by the non-dominant hand.	3	5.6	51	94.4
23. The connection of the aspiration catheter is set with the aspirator tube in the non-dominant hand.	23	42.6	31	57.4
24. Aspirator is turned on with the non-dominant hand.	17	31.5	37	68.5
25. Aspiration pressure is adjusted to 80-120 mm Hg.	0	0	54	100
26. The catheter tip is dipped into sterile saline and then removed.	1	1.9	53	98.1
27. With the non-dominant hand, the ventilator is removed from the patient.	26	48.1	28	51.9

Table 2: Distribution of nurses by their practices in preparation steps during the endotracheal aspiration (n=54)

Preparation steps during the endotracheal aspiration procedure	Correct		Incorrect	
	n	%	n	%
28. The catheter is advanced straight, quickly but gently, without aspiration (pressure closed) in the endotracheal tube.	38	70.4	16	29.6
29. The catheter is advanced to the trachea (until resistance is felt) and retracted 1 cm.	28	51.9	26	48.1
30. While the catheter is being removed from the endotracheal tube, it is removed by rotating it with intermittent aspiration.	38	70.4	16	29.6
31. Aspiration process takes no more than 10 seconds.	21	38.9	33	61.1
32. The connection of the endotracheal tube with the ventilator is done with the non-dominant hand.	48	88.9	6	11.1
33. The patient's pulse rate is evaluated from the monitor.	4	7.4	50	92.6
34. Blood pressure of the patient is evaluated from the monitor.	6	11.1	48	88.9
35. Respiratory rate of the patient is evaluated from the monitor.	2	3.7	52	96.3
36. During the aspiration, the procedure is terminated when the heart rate of the patient decreases 20 beats/min or more or increases 40 beats/min or more, or cardiac arrhythmias are observed.	1	1.9	53	98.1
37. After the aspiration procedure, the endotracheal tube and ventilator are connected with the dominant hand.	50	92.6	4	7.4
38.100% O_2 is given with the ventilator for 1 minute.	10	18.5	44	81.5
39. Ventilator setting is brought to the pre-aspiration position.	11	20.4	43	79.6
40. After the endotracheal aspiration procedure, the catheter is washed in saline.	38	70.4	16	29.6
41. Intraoral and oropharyngeal areas are aspirated.	43	79.6	11	20.4
42. The catheter and the aspirator tube are washed with remaining saline.	44	81.5	10	18.5
43. The aspirator is switched off.	49	90.7	5	9.3
44. The catheter is detached from the aspirator pipe.	54	100	0	0
45. End of the aspirator pipe is closed.	5	9.3	49	90.7
46. The catheter is wrapped around the dominant hand.	5	9.3	49	90.7
47. The catheter is removed to remain in the glove.	6	11.1	48	88.9
48. Gloves and other materials are thrown into the medical waste bin.	53	98.1	1	1.9
49. Hands are washed.	48	88.9	6	11.1

Table 3: Distribution of nurses by their practices in preparation steps after the endotracheal aspiration (n=54)

Steps after the aspiration process	Correct		Incorrect	
	n	%	n	%
50. The pulse rate of the patient is evaluated from the monitor and compared with the pre-aspiration pulse rate value.	0	0	54	100
51. The blood pressure of the patient is evaluated from the monitor and compared with the pre-aspiration blood pressure value.	0	0	54	100
52. The respiratory rate of the patient is evaluated from the monitor and compared to the pre-aspiration respiratory rate.	0	0	54	100
The effectiveness of the aspiration process is evaluated.				
53. a) There will be no wheezing sounds when the patient's lung sounds are listened.	1	1.9	53	98.1
54. b) O_2 saturation should be 98 or above in pulse oximeter when the oxygen level is evaluated.	38	70.4	16	29.6
55. c) The ventilator should show no alarm regarding the presence of secretion.	24	44.4	30	55.6
56. The patient is given a comfortable and confident position.	35	64.8	19	35.2
57. Aspiration procedure is recorded.	45	83.3	9	16.7

Discussion

The examination of the nurses' practices in the preparation steps before endotracheal aspiration indicated that almost all of the nurses prepared sterile aspiration catheters (98.1%), but they were observed to aspire without wearing surgical gloves following the principles of surgical asepsis (100.0%) and without attaching a sterile connector tube to the tip of the aspirator (98.1%) (Table 1). Özden [11] observed that more than half of the nurses (66.7%) prepared non-sterile disposable gloves, but that some of them (4.2%) prepared sterile gloves. On the other hand, some of the nurses (12.5%) who did not prepare gloves administered endotracheal aspiration with bare hands, while others (16.6%) administered the aspiration with the same gloves that they used for previous care. Elbokhary et al. [13] observed that all the nurses performed the aspiration procedure without wearing sterile gloves. In the study of Çelik and Elbaş [9], none of the nurses were found to use sterile connector tubes, and 97.6% were determined to not wear sterile gloves. Using a sterile connector tube before each aspiration procedure is important in maintaining the sterility of the aspiration catheter and gloves and preventing infection development in the patient. These findings were highly important in terms of showing that nurses knew that sterile aspiration catheters should be used but that their knowledge and practice regarding wearing gloves and attaching a sterile connector tube to the tip of the aspirator under the principles of surgical asepsis were inadequate. Also, these findings showed that the endotracheal aspiration procedure was not performed with the appropriate technique. Therefore, the findings also indicated that the risk of developing complications related to endotracheal aspiration might also be high. Determining why nurses do not wear sterile gloves during the administration of endotracheal aspiration and gaining the ability to wear sterile gloves is important. Wearing gloves is a basic requirement for protecting the person who administers the aspiration, the patient who is aspirated, and other patients from the risk of infection. It is also clear that nurses need information about the use of sterile connector tubes.

Patients have the right to receive information about the procedures to be performed. On the other hand, one of the principal functions of the nurse is to educate and inform the individuals they serve. In this context, the nurse has to inform patients who will be aspirated. Due to the perception of aspiration "as an unpleasant and fearful experience" by patients and feelings such as fear and anxiety it causes in the patient, giving information to the patient both increases the effectiveness of the aspiration application and reduces the anxiety, as well as providing patients with collaboration. The procedure should be explained to the patient, even if the patient is unconscious [11]. In our study, all the nurses (100.0%) were observed to not explain the procedure to the patients (Table 1). The rate of nurses informing the patient about the procedure was found to be 26.7% in Elbokhary et al. [13], 2.8% in BülbülMaraş et al. [10], and 2.4% in Çelik and Elbaş [9]. The result of our study suggested that nurses neglected the patients in intensive care because they were generally unconscious.

Aspiration procedure affects the pulse and respiratory rate; therefore, it should be evaluated by nurses. Elbokhary et al. [13] reported that all the nurses monitored the heart rate before the procedure, they recorded blood pressure and that 70% monitored oxygen saturation. BülbülMaraş et al. [10] found that only 6% of nurses monitored vital signs following the procedure. In our study, very few of the nurses were observed to evaluate pulse (7.4%) and respiratory rate (3.7%) (Table 2). This finding of our study suggested that nurses did not have adequate information about the complications of the aspiration procedure. The nurse should correctly evaluate the patient before, during, and after aspiration and prevent possible complications [14]. One of the most positive indicators of nursing care is to prevent the emergence of diseases and complications. By providing proper care, nurses can help reduce patients' hospitalization time and labor loss and cost due to hospitalization, and increase patient satisfaction [15, 16]. Therefore, the role of nurses is especially important in knowing and preventing the causes of complications. For this reason, nurses should do their practices according to current research recommendations and guidelines.

In our study, more than half of the nurses (83.3%) were observed to correctly perform the "aspiration procedure is recorded" step, which is one of the post-aspiration steps (Table 3). In the study of Sevinç [17], 70.83% of the nurses were determined to keep records at the end of the aspiration process. On the other hand, Elbokhary et al. [13] found that none of the nurses (100%) recorded the aspiration procedure. Recording the aspiration procedure is important in determining how often the patient needs aspiration. Besides, it creates a legal basis for nurses and provides communication between team members. According to this result of our study, intensive care nurses can be said to have behaviors of recording data of the procedure.

In our study, the mean score of the nurses regarding endotracheal aspiration was 22.98 (3.21) [mean (SD)] out of 35 points. In the study of Sevinç [17], the knowledge and practices of the nurses for tracheal aspiration were evaluated over 100 points, and the rate of the nurses who received a knowledge score of more than 50 points was 50%, while the rate of nurses who received an application score of 50 points or more was determined as 20.83%. The results of the study showed that the nurses participating in the study did not have sufficient knowledge about endotracheal aspiration.

Limitations

The sample of the study consisted of 54 nurses working only in the secondary and tertiary level intensive care units of a public hospital. Therefore, the results of the study are valid only for the nurses participating in the study.

Conclusion

The present study found that the nurses participating in the study did not have sufficient knowledge about endotracheal aspiration according to the evaluation with the endotracheal aspiration information form. In light of these findings, we recommend that nurses should be provided training on endotracheal aspiration and that the effect of the training on practice should be evaluated. Also, standardization studies should be carried out so that mistakes and deficient practices in endotracheal aspiration can be minimized.

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Is comorbidity related to the independence of patients with spinal cord injury?

Omurilik yaralanmalı hastalarda komorbidite bağımsızlık ile ilişkili midir?

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Abstract

Aim: Apart from the complications of spinal cord injury, some comorbidities in patients with this injury should be considered in the long term. In this study, we aimed to identify the comorbidities in patients with chronic spinal cord injury and the relationship of these comorbidities with the patients' level of independence.

Methods: This retrospective cohort study involved 40 patients who had spinal cord injury and were admitted to an inpatient rehabilitation program at our hospital between March 2014 and January 2016. The participants were evaluated in terms of age, height, weight, body mass index, place of residence, and marital status. Their type, level, and duration of injury were also assessed. ASIA Impairment Scale (AIS), Functional Independence Scale (FIM), Functional Ambulation Scale (FAS), Spinal Cord Independence Scale (SCIM), and Cumulative Illness Rating Scale (CIRS) were used to evaluate the patients.

Results: The mean age of the 40 patients with chronic spinal cord injury was 41.83 (16.87) years. Their most common comorbidities were genitourinary (62.5%), lower gastrointestinal (50%), and ophthalmological–otolaryngologic problems (42.5%). No correlation was found between the CIRS scores and the SCIM Personal Care, Respiratory and Sphincter Management, Mobility, and the total SCIM scores of the participants. (P=0.949, P=0.469, P=0.452, P=0.521, respectively). By contrast, the FIM scores were correlated with the SCIM scores of the cases (P=0.014).

Conclusion: The most common long-term comorbidities in patients with spinal cord injury were genitourinary, lower gastrointestinal, and ophthalmological–otolaryngologic problems. However, these comorbidities were not directly related to the patients' ambulation and independence levels.

Keywords: Spinal cord injury, Comorbidity, Independence, Ambulation

Öz

Amaç: Omurilik yaralanması ile yaşayan bireyler de gelişebilecek komplikasyonlar dışında birtakım komorbiditelerde uzun vade de göz önünde bulundurulmalıdır. Bu çalışmada kronik omurilik yaralanmalı hastalarda görülebilecek komorbiditelerin tanımlanması ve bunların bağımlılık düzeyi ile ilişkisini incelemeyi amaçladık.

Yöntemler: Mart 2014-Ocak 2016 tarihleri arasında hastanemizde omurilik yaralanması nedeni ile yatarak rehabilitasyon programına alınan 40 olgu ile retrospektif kohort çalışma yapıldı. Katılımcılar; yaş, boy, kilo, vücut kitle indeksi, yaşadığı yer, medeni hal vb. demografik yönden değerlendirildi. Yaralanma şekli, yaralanma seviyesi, yaralanma süresi ile ASIA Bozukluk Skalası (AIS), Fonksiyonel Bağımsızlık Ölçeği (FBÖ), Fonksiyonel Ambulasyon Skalası (FAS), Spinal Kord Bağımsızlık Ölçeği (SBÖ) ve Kümülatif Hastalık Değerlendirme Ölçeği (CIRS) ölçekleri ile de değerlendirildi.

Bulgular: Yaş ortalamaları 41,83 (16,87) olan toplam 40 kronik omurilik yaralanmalı hasta çalışmaya dahil edildi. En sık görülen komorbiditeler; genitoüriner sistem problemleri (%62,5), alt gastrointestinal sistem problemleri (%50), oftalmolojik-otolaringolojik problemler (%42,5) olarak görüldü. Çalışmaya katılan olguların CIRS skorları ile FBÖ skorları ve SCIM skorları ile arasında istatistiksel olarak anlamlı ilişki saptanmamıştır (sırasıyla P=0,949, P=0,469, P=0,452, P=0,521). Olguların FBÖ skorları ile SCIM skorları arasında pozitif yönlü ilişki istatistiksel olarak anlamlı bulunmuştur (P=0,014).

Sonuç: Omurilik yaralanmalı hastalarda uzun dönemde en sık görülen komorbiditeler; genitoüriner sistem problemleri, alt gastrointestinal sistem problemleri, oftalmolojik-otolaringolojik problemlerdir. Komorbiditelerin, ambulasyon düzeyi ve bağımsızlık düzeyi ile doğrudan ilişkisi bulunmamıştır.

Anahtar kelimeler: Omurilik yaralanması, Komorbidite, Bağımsızlık, Ambulasyon

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Introduction

The vast majority of individuals who have had a spinal cord injury (SCI) face disability-related challenges. Such patients are strictly followed for care, complications, and social and psychological wellbeing after having had an SCI [1]. These patients may have had existing illnesses before getting an SCI. Moreover, being in such a chronic condition, in the long term, they may face numerous health problems that may develop due to the injury, addiction, or aging [2,3]. SCI is associated with numerous factors, such as current risk factors, genetic predisposition, daily life activities, and predisposing factors associated linked with the injury. However, the already existent comorbidities or those developing with time in these individuals are ignored.

Although many studies have examined the complications of SCI, we could not find in the literature a study examining the comorbidities associated with SCI and their effect on patients' independence [4]. Thus, this study aimed to identify the comorbidities in patients with SCI and examine their relationship with the patients' independence.

Materials and methods

This study involved 40 patients who have had SCIs and were admitted for the inpatient rehabilitation program in Erenkoy Physical Therapy and Rehabilitation Hospital between March 2014 and January 2016. The participants were analyzed in terms of age, height, weight, body mass index, place of residence, and marital status, and assessed using the ASIA Impairment Scale (AIS), Functional Ambulation Scale (FAS), Functional Independence Measurement (FIM), Spinal Cord Independence Measurement (SCIM), and Cumulative Illness Rating Scale (CIRS). AIS is a standard neurological evaluation method used to assess patients with SCI, which classifies SCI into five categories from A to E. AIS A indicates full motor (complete) motion and sensory loss, AIS B indicates incomplete sensory loss, AIS C and D indicate an incomplete motor loss and AIS E indicates normal motor motion and sensation [5]. The FAS evaluates a patient's sit-up activity, lower limb strength, and dynamic balance. It involves a scale of 0 to 5, 0 indicating the patient's inability to walk and 5, the patient's ability of walking independently [6]. The FIM is an 18-item measurement tool that evaluates the physical, psychological, and social functions of an individual. Also, it evaluates a patient's disability level and the progress in the patient's response to rehabilitation or medical intervention [7]. The SCIM was developed to address three specific functional areas in patients with spinal cord injuries: self-care (nutrition, care, bathing, and dressing), respiratory and sphincter management, and mobility (bed and transfers and indoor/outdoor). Scores range from 0 to 100, wherein 0 indicates total dependency, and 100 indicates complete independence. Each subscale score was evaluated on a 100-point scale (self-care: 0–20; respiratory and sphincter management: 0–40; and mobility: 0–40) [8]. The CIRS is a short, comprehensive, and reliable scale used to assess physical impairment. This scale divides the body systems into 13 subsections [9].

Inclusion criteria were determined as being over 18 years, having had SCI at least six months ago, having signed the consent form to give permission for the use of her/his data at the time of hospitalization or treatment, and not having had other injuries concurrent with the SCI. Exclusion criteria included patients with syringomyelia, ischemic cardiac pathology, osteoporotic fracture, dependence on a mechanical ventilator, acute cancer process, or recently emerging pressure ulcers.

Written permission was obtained from our hospital, and approval was obtained from Erenkoy Mental and Neurological Diseases Training and Research Hospital Ethics Committee (2019/62). Written informed consent was obtained from all participants, and all procedures regarding the study were performed in accordance with the principles of the Helsinki Declaration of the World Medical Association.

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used when evaluating the study data. The suitability of quantitative data for normal distribution was tested by the Shapiro-Wilk test and graphical examinations. Independent groups t-test was used for comparison of two groups of quantitative variables with a normal distribution, and Mann-Whitney U test was used for comparisons between two non-normally distributed groups of quantitative variables. Kruskal-Wallis and Dunn-Bonferroni tests were used for comparison of more than two groups of quantitative variables that did not show normal distribution. Pearson correlation analysis and Spearman correlation analysis were used to evaluate the relationships between quantitative variables. Statistical significance was considered as $P < 0.05$.

Results

This study included a total of 40 cases aged 15–75 years (average age: 41.83 (16.87) years). Table 1 shows the distribution of the demographic and clinical characteristics of the patients, whereas Table 2 shows the distribution of the CIRS.

The relationship between the FIM scores with the CIRS and SCIM scores were shown in Table 3. No correlation was observed between the FIM scores with CIRS scores (P=0.931), and a significant difference was observed between the FIM scores and the total SCIM scores (r=0.384; P=0.014). The FIM scores were positively correlated with the SCIM Respiratory and Sphincter Management subscale scores (r=0.333; P=0.036). Similarly, the FIM scores were positively correlated with the SCIM Mobility subscale scores (r=0.507; P=0.001). No correlation was found between the FIM scores and the SCIM Personal Care subscale scores (P=0.322).

The relationship between the CIRS scores and the SCIM scores were shown in Table 4. No correlation was found between the CIRS scores and the SCIM Personal Care, Respiratory and Sphincter Management, Mobility, and total SCIM scores (P=0.949, P=0.469, P=0.452, P=0.521, respectively).

Table 1: Demographic and clinical characteristics

		n (%)
Age (year)	Min-Max(Median)	15-75 (40)
	Mean(SD)	41.83(16.87)
Height(m)	Min-Max(Median)	1.5-1.93 (1.69)
	Mean(SD)	1.67(0.10)
Weight(kg)	Min-Max(Median)	50-116 (74)
	Mean(SD)	73.08(13.36)
BMI (kg/m^2)	Min-Max(Median)	19.03-39.21 (26.00)
	Mean(SD)	26.16(3.77)
Marital status	Married	24 (60.0)
	Single	16 (40.0)
Residence	Home	35 (87.5)
	Institution	5 (12.5)
Level	C5	2 (5.0)
	C6	2 (5.0)
	C7	4 (10.0)
	C8-T1	4 (10.0)
	T2-T10	19(47.5)
	T11-L2	9 (22.5)
Type of injury	Traumatic	33 (82.5)
	Nontraumatic	7 (17.5)
Time from injury	Min-Max(Median)	9-240 (48)
	Mean(SD)	62.48(47.48)
AIS*	A	8 (20.0)
	B	17 (42.5)
	C	13 (32.5)
	D	2 (5.0)
Functional Independence Measurement (FIM)	Min-Max (Median)	52-120 (75)
	Mean (SD)	76.80(15.40)
Functional Ambulation Scale (FAS)	No	4 (10.0)
	Non-Ambulatory	6 (15.0)
	Therapeutic ambulation	16 (40.0)
	House ambulation	10 (25.0)
	Social ambulation	4 (10.0)

AIS:ASIA Impairment Scale

Table 2: Cumulative Illness Rating Scale (CIRS) Scores

	Yes	No
Cardiac	2 (5.0)	38 (95.0)
Vascular	8 (20.0)	32 (80.0)
Hematologic	9 (22.5)	31 (77.5)
Respiratory	6 (15.0)	34 (85.0)
Ophthalmological and otolaryngologic	17 (42.5)	23 (57.5)
Upper gastrointestinal system	13 (32.5)	27 (67.5)
Lower gastrointestinal system	20 (50.0)	20 (50.0)
Hepatic and pancreatic	0 (0.0)	40 (100.0)
Renal	3 (7.5)	37 (92.5)
Genitourinary	25 (62.5)	15 (37.5)
Musculoskeletal and dermatological	11 (27.5)	29 (72.5)
Neurological	8 (20.0)	32 (80.0)
Endocrine - Metabolic	9 (22.5)	31 (77.5)
Psychiatric	12 (30.0)	28 (70.0)

Table 3: The relationship between FIM scores with CIRS and SCIM scores

	FIM Score	
	[a]r	*P*-value
CIRS score	-0.014	0.931
SCIM		
Personal care	0.161	0.322
Respiratory and sphincter management	0.333	0.036
Mobility	0.507	0.001
SCIM total score	0.384	0.014

[a]r: Pearson correlation coefficient

Table 4: The relationship between CIRS scores with SCIM scores

	CIRS Scores	
	[a]r	*P*-value
Personal care	0.011	0.949
Respiratory and sphincter management	0.118	0.469
Mobility	0.122	0.452
SCIM total score	0.105	0.521

[a]r: Pearson correlation coefficient

Discussion

SCI creates experiences that suddenly alters the life of patients, their family and relatives. Many neurological and medical problems arise after the damage, and almost all bodily functions of the patient are affected. The aim of SCI rehabilitation includes maximizing physical independence, increasing the quality of life, and helping the patient assume productive and age-appropriate social roles. Determining the patient's expectations and achievable goals affect follow-up and treatment motivation [10]. In this process, the presence of comorbidities, in addition to the patient's SCI, is an issue that is neglected as a parameter that may affect this target. In this research, by reviewing the comorbidities of SCIs and their effects on independence, a contribution to the quality of life is aimed at the early diagnosis and treatment of comorbidities.

One of the essential problems encountered after an SCI is the loss of gastrointestinal function. Gastrointestinal system problems are among common societal health problems in epidemiological studies. The combination of two simultaneous conditions negatively affects the treatment. Another frequently seen problem is the loss of essential genitourinary function. Comorbidities related to genitourinary function are also common. Having comorbid problems increases morbidity and mortality in complications that may occur [11]. In our study, the most common cause of comorbidity in patients with SCIs was genitourinary problems. It was followed by lower gastrointestinal problems and ophthalmological and otolaryngologic problems. Although a rare loss of vision has been defined in the literature, many comorbid conditions can accompany it [12]. Considering the low prevalence of vision and hearing problems in the literature, the ratio of ophthalmological and otolaryngologic problems in our example was particularly striking [13-15]. We think that the high rate of ophthalmological and otolaryngologic problems seen in our study may be associated with aging (e.g., presbyopia, cataracts, senile hearing loss). There were also additional conditions due to SCIs that can negatively affect this population, such as autonomic dysreflexia or postural hypotension.

In individuals with chronic physical disabilities and ambulation difficulties, addictive social isolation occurs during daily life activities. This problem causes a decrease in life satisfaction and quality of life. In individuals with chronic physical disabilities, there was a relationship between functional independence and quality of life [16-17]. In our study, we obtained results in the direction of confirming this finding

Many studies have shown that comorbidities negatively affect the course of the disease and quality of life in different disease states. Quality of life is affected as comorbid diseases increase in patients with rheumatoid arthritis [18,19]. It has also been stated that quality of life is related to independence and mortality in hemodialysis patients [20-21].

In our study, we did not observe a significant relationship between SCIM and FIM with comorbidity in patients with SCI or with the level of ambulation. It is well-known that comorbid diseases increase with age [22]. Therefore, we think that the results may be related to the limited number of patients and our wide age range.

Limitations

Besides the number of patients and our wide age range, our limitation was that there is no scale for comorbidity in SCIs. CIRS' comorbidity assessment is not a scale that excludes possible complications of SCIs. In our study, we specifically mentioned that comorbidity was the identification of conditions not related to primary SCI that developed before or simultaneously in the course of the disease. However, studies carried out with an SCI-specific comorbidity scale will shed light on this.

Conclusion

SCI is a lifelong chronic disease and can be accompanied by multiple comorbidities. An integrative approach

to patient care is essential; physiatrists should provide not only acute care of SCIs and complications but also the assessment of comorbidities through adequate diagnosis/treatment/prevention and accurate information. We can reach different results by examining the effects of comorbid conditions according to age groups in a broader patient group of SCIs.

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Can rigid ureteroscopic lithotripsy be an alternative to flexible ureteroscopic lithotripsy in the treatment of isolated renal pelvis stones smaller than 2 cm?

İki santimetreden küçük izole böbrek pelvis taşlarının tedavisinde rijit üreteroskopik litotripsi, fleksibl üreteroskopik litotripsiye alternatif olabilir mi?

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Abstract

Aim: Although flexible ureteroscopy (FURS) is preferred over rigid ureteroscopy in the treatment of kidney stones, rigid ureteroscopy (RURS) is also often sufficient for reaching the renal pelvis in many patients. In this study, we aimed to analyze the results of rigid (RURSL) and flexible ureteroscopic lithotripsy (FURSL) for the treatment of isolated renal pelvic stone (IRPS) <2 cm in size by evaluating stone-free rates, operation times, and associated complications.

Methods: This retrospective cohort study included patients who underwent RURSL (group 1, n=24) and FURSL (group 2, n=21) for IRPS <2 cm in size between June 2012 and May 2017. RURS was routinely performed in all patients. The stones reached by rigid ureteroscope were fragmented with holmium laser. When the stones were not reachable by rigid ureteroscope, FURS was performed, and the stone was fragmented with the same laser energy.

Results: In 24 of 45 (53.3%) patients, stones were reached by rigid ureteroscope and fragmented with holmium laser. In the remaining 21 (46.7%) patients, the stones could not be reached by rigid ureteroscope, and they were managed with FURS and fragmented with the same laser energy source. RURS was successful in reaching renal pelvic stones in 15 of 25 (60%) female patients; however, the stones were reached in 9 (45%) of 20 male patients (P=0.173). There was no significant difference between the two groups in terms of age, gender, side of stone, mean stone size, hospital stay, stone-free rates, and associated complications (P=0.298, P=0.396, P=0.775, P=0.266, P=0.742, P=0.428, P=0.186, respectively). The mean operative times were significantly lower in RURSL group than in FURSL group, and they were 66.75 (15.77) minute and 89.54 (17.71) minute, respectively (P<0.001).

Conclusions: FURSL is a more appropriate procedure for the treatment of kidney stones; however, it should be kept in mind that RURSL is an alternative procedure to FURSL with shorter operation time, similar stone-free rates and similar complication rates for IRPS in selected cases.

Keywords: Rigid, Flexible, Ureteroscopic lithotripsy, Renal pelvis stone

Öz

Amaç: Her ne kadar böbrek taşlarının tedavisinde fleksibl üreteroskopi rijit üreteroskopiye tercih edilse de, birçok hastada renal pelvise ulaşmak için rijit üreteroskopi yeterli olmaktadır. Bu çalışmada, 2 cm'den küçük izole böbrek pelvis taşı tedavisinde rijit ve fleksibl üreteroskopik litotripsi sonuçlarını taşsız oranları, operasyon süreleri ve ilişkili komplikasyonları değerlendirerek analiz etmeyi amaçladık.

Yöntemler: Bu retrospektif kohort çalışması, Haziran 2012 ile Mayıs 2017 tarihleri arasında, 2 cm'den küçük izole renal pelvis taşı için RURSL (grup 1, n=24) ve FURSL (grup 2, n=21) uygulanan hastaları kapsamaktadır. Tüm hastalara rutin olarak rijit üreteroskopi uygulandı ve rijit üreteroskop ile ulaşılan taşlar holmiyum lazer ile parçalandı. Rijit üreteroskop ile ulaşılamayan taşlara fleksibl üreteroskopi yapıldı ve aynı lazer kaynağı ile kırıldı.

Bulgular: 45 hastanın 24'ünde (%53,3) rijit üreteroskop ile taşlara ulaşıldı ve holmiyum lazer ile kırıldı. Rijid üreteroskop ile taşlara ulaşılamayan 21 (%46,7) hastada fleksibl üreteroskop ile taşlara ulaşıldı ve aynı lazer kaynağı ile parçalandı. Rijit üreteroskopi 25 kadından 15'sinde (%60) taşlara ulaşmada başarılı olurken; 20 erkek hastanın 9'unda (%45) taşlara ulaşıldı (P=0,173). İki grup arasında yaş, cinsiyet, taşın yönü, ortalama taş boyutu, hastanede kalış süresi, taşsızlık oranları ve ilişkili komplikasyonlar açısından istatistiksel olarak anlamlı bir fark yoktu (sırasıyla P=0,298, P=0,396, P=0,775, P=0,266, P=0,742, P=0,428, P=0,186). Ortalama ameliyat süreleri rijit üreteroskopik litotripsi grubunda fleksibl üreteroskopik litotripsi grubuna göre anlamlı olarak daha düşüktü ve sırasıyla 66,75 (15,77) dakika ve 89,54 (17,71) dakika idi (P<0,001).

Sonuç: Fleksibl üreteroskopik litotripsi böbrek taşlarının tedavisi için daha uygun bir prosedür olmakla beraber, daha kısa operasyon süresi, benzer taşsızlık ve komplikasyon oranları ile rijit üreteroskopik litotripsi 'nin seçilmiş izole böbrek pelvis taşlarında fleksibl üreteroskopik litotripsiye alternatif bir prosedür olduğu unutulmamalıdır.

Anahtar kelimeler: Rijit, Fleksibl, Üreteroskopik litotripsi, Renal pelvis taşı

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Introduction

Today, there are numerous options for the treatment of kidney stones, such as extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), ureteroscopic lithotripsy (URSL), their combinations, laparoscopic techniques, and open surgery [1]. Technological advances and more advanced equipment have increased success rates and decreased morbidity in the treatment of kidney stones. This improvement in technology has extended the indications of ureteroscopic surgery. For isolated renal pelvic stones (IRPS) <1 cm, ESWL or retrograde intrarenal surgery (RIRS) are first-line treatment options whereas for kidney stones >2 cm, PCNL is the first option. For IRPS 1-2 cm, ESWL or endourologic surgeries such as RIRS and PCNL are recommended [2].

Although it is well known that flexible ureteroscopy (FURS) permits a detailed caliceal examination and therapeutic interventions, rigid ureteroscopy (RURS) is also often sufficient for reaching the renal pelvis in many patients [3]. RURS is an applicable option for whole ureteral stones. Although RURS is not recommended in kidney stones due to limited maneuverability and difficulty in reaching the middle and lower calyces, in some patients, it can be used to reach the kidney without any difficulty. The advantages of RURS in these patients are larger working channel, thus larger working equipment and better visualization owing to higher irrigation flow [4]. Even though it can be applied in isolated renal pelvic stones, the reported data is limited.

We analyzed the results of rigid (RURSL) and flexible ureteroscopic lithotripsy (FURSL) for the treatment of IRPS <2 cm by evaluating stone-free rates, operation times, and associated complications.

Materials and methods

We retrospectively reviewed the records of 45 patients who underwent RURSL (group 1, n=24) or FURSL (group 2, n=21) for the treatment of IRPS <2 cm between June 2012 and May 2017. Approval was obtained from the Ethics Committee of Health Sciences University, Diyarbakır Gazi Yaşargil Education and Research Hospital (No. 2019/11-04, Date: 03/12/2019). The same surgeon performed all procedures. Prior to operation, all patients were evaluated by renal function tests, urinalysis, and urinary culture. Preoperative radiologic investigation consisted of kidney-ureter-bladder (KUB) plain film, intravenous pyelogram, and non-contrast spiral computed tomography (CT) in all cases. The stone size was assessed with the maximum diameter of stone shown in the CT. The patients having stones in other areas of the collecting system other than the renal pelvis and those with anatomical kidney abnormalities such as pelvic kidney, horseshoe kidney, ureteropelvic junction obstruction and rotation anomalies were excluded from the study.

Surgical technique

RURS was routinely performed in all patients to dilate the ureter and place a hydrophilic guidewire to the renal pelvis. All of the RURSL were performed with a 8/9.8 F rigid ureteroscope (Karl Storz®, Tuttlingen, Germany). Ureteral balloon dilation was not performed in any of the cases. The stones reached by rigid ureteroscope were fragmented with holmium laser with an energy setting of 0.6 to 0.8 J and a rate of 8 to 10 Hz. When the stones were not reachable, a second 0.035/0.038-inch safety guidewire was placed into the renal pelvis through a rigid ureteroscope. After removing the rigid ureteroscope, a ureteral access sheath (9.5/11.5F) was placed to allow for optimal visualization, maintain low intrarenal pressure, and facilitate the extraction of stone fragments. FURS was performed with a 7.5 F flexible ureteroscope (Karl Storz, Tutlingen, Germany). The stones were fragmented with similar laser energy settings and fibers. After lithotripsy, a 4.8 F double-J stent was routinely placed in all cases and removed 3 weeks after the operation.

All patients were evaluated with plain radiography at 3 weeks after operation. Ultrasonographic examination was performed at 3 months after surgery. CT was conducted when residual stone was detected in ultrasound or plain radiography. Success of the surgery was defined as no evidence of residual stones of >2 mm in diameter.

Statistical analysis

IBM SPSS Statistics 22.0 (IBM Corp. Released 2013, IBM SPSS Statistics for Windows, Version 22.0, IBM Corp.) program was used for statistical analysis. The normality in the distribution of the data was determined using the Kolmogorov-Smirnov test, and the normally distributed variables were presented as mean (standard deviation) (SD). The differences between the groups were analyzed with independent-samples t-tests. The categorical variables were presented as frequencies and percentages, and they were compared with the chi-square test or Fisher exact probability test. A *P*-value of <0.05 was considered statistically significant.

Results

In 24 of 45 (53.3%) patients, IRPS were reached by rigid ureteroscope and fragmented with holmium laser. In the remaining 21 (46.7%) patients, the stones were not reached by rigid ureteroscope. They were managed with FURS and fragmented with the same energy source. Rigid ureteroscopy was successful in reaching renal pelvic stones in 15 of 25 (60%) female patients; however, the stones were reached in 9 (45%) of 20 male patients (P=0.173).

The characteristics of the patients including age, gender, laterality, and size of stones are summarized in Table 1. There was no significant difference between the two groups in terms of the parameters mentioned above (P=0.298, 0.396, 0.775, 0.266, respectively).

The mean operative times were significantly lower in the RURSL group than in the FURSL group, which were 66.75 (15.77) minutes and 89.54 (17.71) minutes, respectively (P<0.001). The stone clearance rates at postoperative week 3 and month 3 were 70.8% and 76.2% in the RURSL group and 83.3% and 85.7% in the FURSL group, respectively (P=0.787 and P=0.428). The mean hospital stay times were 1.5 (1.3) days in the RURSL group and 1.5 (1.5) days in the FURSL group (P=0.742). We found no significant differences between the groups regarding stone clearance rates and hospital lengths of stay. There were no intraoperative complications in either of the groups. At postoperative day 1, three patients (12.5%) in the RURSL group and two patients (9.5%) in the FURSL group had

fever and were treated with appropriate antibiotics (P=0.186). The complication rates were similar in both groups and these complications were classified as grade 1 according to the Clavien-Dindo classification (Table 2). None of the patients required FURS during RURS due to the mobilization of the stone to the lower or other calyces.

Table 1: Demographic data of patients

Variables	RURSL group (n=24)	FURSL group (n=21)	*P*-value
Age (years)	44.70±10.80	47.05±11.05	0.298
Gender			0.396
Male	9 (37.5%)	11 (52.4%)	
Female	15 (62.5%)	10 (47.6%)	
Side			0.775
Right	14 (58.3%)	12 (57.1%)	
Left	10 (41.7%)	9 (42.9%)	
Mean stone size (mm)	14.20 (6.50)	12.90 (6.20)	0.266

RURSL: Rigid ureteroscopic lithotripsy, FURSL: Flexible ureteroscopic lithotripsy

Table 2: Operative and postoperative data of patients

Variables	RURSL group (n=24)	FURSL group (n=21)	*P*-value
Mean operative time (minute)	66.75 (15.77)	89.54 (17.71)	0.001
Stone clearance rate			
Postoperative week 3	17 (70.8%)	16 (76.2%)	0.787
Postoperative month 3	20 (83.3%)	18 (85.7%)	0.428
Mean hospital stay (day)	1.5 (1.3)	1.5 (1.5)	0.742
Complication rate	3 (12.5%)	2 (9.5%)	0.186

Discussion

With the development of endourology, in the last 3 decades, the treatment of kidney stones has dramatically changed, and minimally invasive treatments such as ESWL, PCNL, mini and ultramini-PCNL, RIRS or laparoscopic surgery, have replaced open surgery [5]. Although patients with isolated renal pelvic stones <20 mm in size have several treatment options (ESWL, RIRS or PCNL), it is still challenging to decide which treatment should be the first choice. Advancements in the flexible equipment and laser technology have made FURSL for renal calculi more popular. The high stone clearance and low retreatment rates after FURSL seem to establish FURSL as equivalent or superior to ESWL for treating kidney stones <2 cm in size [6,7]. Although FURSL is a safe and effective procedure for the treatment of kidney stones, it has some disadvantages, such as a small caliber working channel that allows only small sized stone extractors and laser fibers to pass through the ureteroscope; prolonged operation time, and impaired vision quality due to reduced irrigation during the operation [8]. Additionally, the other major disadvantages of flexible ureteroscope include less durability of the instruments compared to rigid ureteroscopes and the higher cost of repair [9,10].

It was reported that in approximately half of the patients, the renal pelvic stone was reached with rigid ureteroscope and the patients were treated with RURSL without the need for FURSL [3,4]. In our study, in 53.3% of the patients, IRPS were reached by rigid ureteroscope and fragmented.

In the literature, there are few reported studies on the RURSL for the treatment of kidney stones. Bryniarski et al. [11] analyzed the safety and efficacy of RURSL and PCNL in the treatment of kidney stones of >2 cm in diameter. They reported that, although the rate of stone clearance was superior in the PCNL group than RURSL group, RURSL offers advantages for operating times, blood loss, postoperative pain and the duration of hospital stay.

Zengin et al. [12] compared the efficacy of RURSL and ESWL in the treatment of small sized kidney stones. They reported that, in RURSL and ESWL groups, the overall stone-free rates were 91.7% and 93.9% at the third postoperative months, respectively and the difference was not statistically significant.

Süer et al. [4] performed the study of RURSL and requirement of FURSL after RURSL in kidney stones to report that the kidney stones were fragmented with RURSL in 54.5% of the patients and FURSL was required in 45.5% of the patients. In RURSL and FURSL groups, the overall stone-free rates were 83% and 87%, respectively (P>0.05).

In another study designed similarly to the above-mentioned study, the renal pelvic stones were treated with RURSL only in 25 of 47 (53%) patients and they found no significant differences among groups with regards to stone-free rates [3].

There are various major and minor complications such as ureteral wall injury or avulsion, bleeding, stone migration, fever and urosepsis in ureteroscopic procedures. Breda et al. reported that the overall complication rate for FURSL was 8% and the frequency of major complications was 1.9% [13]. Sabnis et al. [14] reported that in the 35 patients treated with FURSL, Clavien Grade I complication occurred in 11.4% of the patients, and no other Clavien Grade complication was noted. In our study, the complication rates were similar between RURSL and FURSL groups and none of our patients developed major perioperative or postoperative complications.

There are various studies in literature that have reported that prolonged operation time is an independent prognostic risk factor for postoperative fever and infection and in those studies, the operation time was reported as 60-120 minutes [15-18]. In our study, the mean operative times were significantly lower in RURSL group than in FURSL group, and compatible with the literature. The rates of infectious complications including sepsis and fever in the patients undergoing FURSL have been reported to vary from 3% to %5 and from 2% to 28%, respectively [19]. In an international multicenter study in which RURSL and FURSL were performed to patients due to kidney and ureter stones, postoperative infection rates were reported as 2.2%. This rate may be low since patients who undergo RURSL due to ureter stones are included in the study [20]. Başeskioğlu [21] reported the postoperative infection rates as 12.6% in their study, which included 111 FURSL patients. In a study comparing RURSL with FURSL in the treatment of renal pelvic stones, postoperative fever rates were reported as 16% and 9.1%, respectively [3]. In our study, we did not observe any septic complications after both of two type of surgeries. Three patients (12.5%) in the RURSL group and two patients (9.5%) in the FURSL group had fever and were treated with appropriate antibiotics.

The main objective of the present study was not to investigate and advise RURSL as the first option in the treatment of kidney stones, but rather to demonstrate that RURSL could be used in the treatment of IRPS in selected cases. In our operations, we routinely performed RURS in all patients to dilate the ureter and place the hydrophilic guidewire into the collecting system. If the pelvic stones were reachable with RURS, they were fragmented through rigid ureteroscope using a Ho:YAG laser under direct vision. When the stones were not reachable,

FURSL was performed. With this technique, the number of FURSL procedures for the treatment of renal pelvic stones decreased. We think that this practice reduces both the cost of surgery and the need for repair of flexible ureteroscope.

Limitations

Relatively few patients, lack of the other demographic characteristics of the patients such as body mass index, lack of the hydronephrosis grades and not considering the cost-effectiveness are the limitations of our study. However, it is one of the limited number of studies in the literature on the treatment of isolated renal pelvic stones with RURSL, which is its strength.

Conclusion

The results of our study indicate that RURSL has shorter operation time, similar stone-free rates and similar complication rates compared with FURSL in the treatment of isolated pelvic stones. In light of the current literature, FURSL is a more appropriate procedure for the treatment of kidney stones; however, it should be kept in mind RURSL is as an alternative procedure to FURSL for IRPS in selected cases. Further studies are needed to determine the effectiveness of RURSL on the treatment of IRPS.

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Impact of tranexamic acid on bleeding during coronary artery bypass for patients under treatment of low molecular weight heparin

Koroner arter bypass operasyonlarında düşük molekül ağırlıklı heparin tedavisi gören hastalarda traneksamik asidin kanama üzerine etkileri

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Abstract

Aim: Tranexamic acid (TA) is an antifibrinolytic agent that prevents the dissolution of fibrin clot. We investigated the impact of the use of tranexamic acid (TA) on bleeding for patients under treatment of low molecular weight heparin during coronary artery bypass graft (CABG) operations.

Methods: Among 82 patients, 60 patients undergoing CABG with cardiopulmonary bypass (CPB) were enrolled into a case-control study within a six month-period. On the first postoperative day, patients were divided into two groups depending on the intraoperative use of TA. TA was not administered to control group patients (n=30) while those in the study group (n=30) received TA intravenously at a dose of 10 mg/kg. Coagulation variables including complete blood cell count, D-Dimer, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR) values were collected preoperatively and 24 hours after surgery. Estimated blood loss, loss by drainage, total amounts of packed red blood cell and fresh frozen plasma transfusions were recorded. *P*-value <0.05 was considered statistically significant.

Results: Among 60 patients included in the study, there were 39 and 21 males and females, respectively. The mean age of all patients was 61.6 years. The two groups were similar in terms of use of fresh frozen plasma, age, height, and weight (P=0.268, *P*=0.586, *P*=0.787, *P*=0.641, respectively). The amount of postoperatively transfused packed red blood cells in units were lower in the study group (*P*=0.04). Total mediastinal drainage amounts in the 4th, 8th, 12th hours and overall were lower in the study group (*P*=0.016, *P*=0.006, *P*=0.013, *P*=0.04, respectively).

Conclusion: TA is a safe drug that reduces postoperative bleeding without side effects in patients using DMAH undergoing CABG operations.

Keywords: Coronary bypass surgery, Low molecular weight heparin, Tranexamic acid, Bleeding, Blood products

Öz

Amaç: Traneksamik asit (TA), fibrin pıhtısının çözünmesini önleyen antifibrinolitik bir maddedir. Koroner arter bypass greft (KABG) operasyonları sırasında düşük moleküler ağırlıklı heparin tedavisi alan hastalarda TA kullanımının kanama üzerindeki etkisini araştırdık.

Yöntemler: Toplam 82 hastadan, kardiyopulmoner bypass (CPB) ile KABG uygulanan 60 hasta, altı aylık bir dönemde vaka-kontrol bir çalışmaya alındı. Ameliyat sonrası birinci günde, intraoperatif TA kullanımına bağlı olarak hastalar iki gruba ayrıldı. Kontrol grubunda (n=30) TA verilmezken, çalışma grubunda Grup 2'de (n=30) TA intravenöz 10 mg/kg dozda uygulandı. Pıhtılaşma değişkenleri; tam kan hücresi sayımı, D-Dimer, fibrinojen, protrombin zamanı (PT), aktive parsiyel tromboplastin zamanı (aPTT) ve uluslararası normalleştirilmiş oran (INR) değerleri ameliyat öncesi ve ameliyattan 24 saat sonra toplandı. Tahmini kan kaybı, drenaj kaybı, toplam eritrosit süspansiyonu ve taze donmuş plazma hacimleri kaydedildi. *P*-değeri <0.05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışmaya alınan, 60 hastanın 39'si erkek, 21'i kadın, hastaların yaş ortalaması 61,6/ yıl idi. Hastaların yaş, boy, kilo verileri benzerdi (sırası ile; *P*=0,586, *P*=0,787, *P*=0,641). Postoperatif verilen taze donmuş plazna transfüzyonu iki grupta benzer iken (*P*=0,692), postoperatif verilen eritrosit süspansiyonu ünite miktarı çalışma grubunda daha düşüktü (*P*=0,04). Ameliyat sonrası, 4., 8., 12. ve total mediastinal drenaj miktarları çalışma grubunda daha düşüktü (sırasıyla; *P*=0,016, *P*=0,006, *P*=0,013, *P*=0,04).

Sonuç: TA, CABG operasyonları sırasında DMAH tedavisi alan hastalarda yan etki olmaksızın postoperatif kanamayı azaltan güvenli bir ilaçtır.

Anahtar kelimeler: Koroner bypass cerrahisi, Düşük molekül ağırlıklı heparin, Traneksamik asit, Kanama, Kan ürünleri

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Introduction

In cases which the cardiac muscle, also known as myocardium, is not oxygenated due to several reasons (such as an increase in the volume of blood reaching the heart and decrease in heart contractility), ischemic cardiac diseases develop. In this disease, blood flow into cardiac muscle is decreased, which deteriorates the balance of oxygen demand and supply of myocardium. Hypertension, tachycardia, spasm of the coronary arteries or anatomical obstruction, severe hypotension, anemia, aortic stenosis, and regurgitation are among the main causes of myocardial ischemia [1,2].

The first objective of cardiopulmonary bypass (CPB) in open-heart surgery is to ensure systemic homeostasis. This is achieved by establishing systemic perfusion, blood oxygenation, and carbon dioxide elimination. Hemorrhage, which requires immediate reoperation after open-heart surgery, constitutes one of the most severe postoperative complications. Among patients undergoing open-heart surgery, 2-7% require reoperation due to hemorrhage [3-5]. Some of the reasons for not being able to detect a hemorrhagic focus in almost half of the patients who are reoperated include the depletion of hemodilution and coagulation factors, thrombocyte function disorders, decrease in number of thrombocytes, abundance of heparin and protamine, excessive fibrinolysis, complement activation, and common intravascular coagulation. The most frequently seen are thrombocyte function disorders and excessive fibrinolysis [6-8].

The release of plasmin during CPB activates fibrinolysis. The activity of heparin is monitored with activated clotting time (ACT). The normal value of ACT is between 80 and 120 seconds. Antithrombin III is a serine protease inhibitor which inhibits clotting when combined with heparin. The dose of heparin needed for increasing ACT above 480 seconds during CPB is 3.5 mg/kg. 1.3 mg protamine is required to neutralize every 1 mg of heparin administered during CPB. Protamine adheres to heparin, preventing it from forming a complex with antithrombin III, thus retuning thrombin functions and the coagulation cascade to normal [5,8-10].

The hemostatic mechanisms are negatively affected from cardiopulmonary bypass. Increased fibrinolysis, decreased number and function of thrombocytes, dilution of coagulation factors, effect of heparin, residual effects of excessive protamine, and preoperative use of anticoagulant medications such as LMWH, along with the operation, increase the risk of postoperative hemorrhage. Tranexamic acid (TA), a synthetic derivative of the amino acid lysine, is an antifibrinolytic agent. In numerous studies and meta-analyses, this anti-fibrinolytic medication was shown to decrease postoperative hemorrhage [8,11,12].

In the present study, our aim was to investigate whether the use of tranexamic acid (TA) and low molecular weight heparin (DMAH) together may have an impact on bleeding-related parameters in coronary artery bypass graft (CABG) operations.

Materials and methods

From a total of 82 patients, 60 patients undergoing CABG with cardiopulmonary bypass (CPB) were enrolled into a case-control study within a six month-period. Eleven patients refused to participate in the study. Ethics committee approval was received from Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital Ethics Committee (date and number: 2010.4/02). All included patients and their relatives provided written informed consent forms to participate in the study, which was conducted in accordance with the Helsinki Declaration for human rights preservation.

On the first postoperative day, patients were divided into two groups depending on the use of intraoperative TA. TA was not administered to control group patients (n=30) while those in the study group (n=30) received TA intravenously before CPB at a dose of 10 mg/kg.

The eligibility criteria included patients older than 18 and younger than 80 years, those undergoing elective CABG surgery with CPB, with an American Society of Anesthesiology (ASA) physical status of 2 or 3 and those who received DMAH preoperatively. The CABG operation was planned for patients with severe stenosis in left main coronary artery or unstable angina who would have to undergo two or three vessel operations.

Exclusion criteria included those undergoing repeat cardiac surgery, emergency surgery, patients with preoperative coagulation disorders, preoperative use of coumarin anticoagulants, heparin, or acetylsalicylic acid within 5 days before the operation, preoperative congestive heart failure, a history of severe heart failure (ejection fraction below 30 %), preoperative renal dysfunction (serum creatinine > 1.3 mg/dl), chronic oliguria/anuria requiring dialysis, preoperative hepatic dysfunction (serum aspartate/alanine amino transferase > 40U/L), preoperative electrolyte imbalance, history of pancreatitis or current corticosteroid treatment, and a history of allergy to LMWH or TA.

The standard anesthesia, surgical and myocardial protection methods were followed for all patients. Before the operation, patients were administered 10 mg diazepam (Deva, Istanbul, Turkey) intramuscularly as premedication. For induction of anesthesia, 0.05 mg/kg midazolam (Dormicum, Deva, Istanbul, Turkey), 8 microgram/kg fentanyl (Fentanyl, Abbot, North Chicago, USA) and 0.1mg/kg pancuronium (Pavulon, Organon, Istanbul, Turkey) were administered intravenously. Fentanyl citrate infusion was maintained at a dose of 1 microgram/kg/hour. During anesthesia maintenance, intravenous pancuronium and midazolam bolus doses were administered. A thermodilution catheter was placed in the internal jugular vein (7.5 F Opticath, Abbot, North Chicago, IL, USA).

After sternotomy and preparation of the left internal thoracic artery pedicle and the ascending aorta, right atrium was cannulated. During CPB, a roller pump (Stöckert, Munich, Germany) and membrane oxygenator (D 708 Simplex Adult Fiber Oxygenator, Dideco, Mirandola, Italy) were used under normothermia. Due to the risk of hypersensitivity and allergic reactions, a test dose of 1 ml intravenous tranexamic acid was applied, followed by TA administration to the study group at a dose of 10mg/kg 10 minutes before the pump as a slow bolus [9,12,15]. The anticoagulation was ensured using heparin (Nevparin Mustafa Nevzat, Istanbul, Turkey) at 300 unit/kg.

Activated clotting timing was monitored with Hemochron 801 device. Anticoagulation was maintained by keeping ACT longer than 400 seconds and administering additional doses of heparin as needed [7-9]. During CPB, the rate of perfusion was ensured with non-pulsatile flow at 2.4 liters/m^2/minute and higher. After clamping the ascending aorta, cardiac arrest was achieved via antegrade hyperkalemic blood cardioplegia, which was applied every 20 minutes. After completion of the distal anastomoses, the clamp at the aorta was removed and partial bypass was initiated. The proximal anastomoses were performed by placing clamps collaterally on the aorta. After exiting cardiopulmonary bypass, heparin was neutralized with 1:1-1.3 protamine hydrochloride (Protamine ICN, Onko, İstanbul, Turkey) [7-9]. The operations were performed at 33°C and moderate hypothermia (nasopharyngeal temperature). The room temperature was kept at 20-22°C. Before leaving CPB, patients were heated to 37°C. After placing the clamp on the aorta, 1000 cc cold (4-8°C) blood cardioplegia (25mEq/l potassium) was given with administration of additional doses of 500 cc every 15-20 minutes (antegrade at the root of the aorta and venous grafts and retrograde in main coronary artery disease). The hot blood cardioplegia (36-37°C) was administered before removing the aortic clamp. The operation was completed after placing 2 silicone-coated drains to the mediastinum and one latex drain to the thorax, and by implementing standard hemorrhage control. These drains were removed when the amount of drainage was under a total of 100ml/day. Depending on the electrolyte level, electrolyte replacement solutions were administered when needed during bypass.

After the surgery, packed red blood cell (PRBC) transfusion was considered when hemoglobin level was under 8 g/dL, and hematocrit level was under 25%. Fresh frozen plasma (FFP) was transfused in case of excessive bleeding (>400 mL/h) in the presence of an activated partial thromboplastin time >60 seconds. Platelet concentrates were given if bleeding continued (>400 mL/h) despite normal ACT. Fresh frozen plasma and platelet concentrates were administered in cases of documented postoperative coagulation abnormalities. In case of presence of a hemorrhage disorder (international normalized ratio>1.5, active prothrombin time >60 seconds, thrombocyte count < 80,000/mm^3) or in case of suspected postoperative thrombocyte and clotting factor dysfunction, fresh frozen plasma and thrombocyte suspensions were transfused. The decision of re-exploration for hemorrhage was made when 200 ml/h of drainage was documented in two consecutive hours despite measures taken or in case of more than 300 ml/h drainage. Estimated blood loss was defined as the sum of objective losses, e.g., via drainage and swabs plus clinically estimated additional losses. Blood samples were obtained before heparinization, 24 and 48 hours after CPB. Samples for coagulation factor analyses were immediately cooled on ice and plasma was stored at -70°C. The hemoglobin values and platelet count in the whole blood were determined with a Cell-Dyn 610 hematology analyzer (Sequoia-Turner Corp., Mountain View, CA, USA).

Primary and secondary end points

As a primary end point, we analyzed and compared the values of hemoglobin, hematocrit, platelet, prothrombin time, activated prothrombin time, and international normalized ratio (INR) between groups. Also, estimated blood loss, the amount of mediastinal drainage, transfused PRBC in unit value, transfused fresh frozen plasma in unit value and coagulation variables before and 24 hours after surgery were compared between groups. Possible side effects related to TA administration intraoperatively were noted and these include hemodynamical changes such as hypotension or hypertension, bradycardia or tachycardia, allergic skin reactions, anaphylactoid reactions, heart rhythm disturbances, or other possible suspected adverse events [13].

Statistical analysis

Statistical analyses were performed using SPSS software for Windows version 17.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). Continuous variables were expressed as median or mean values (standard deviation (SD)). Categorical variables were expressed as number and percentages. Demographic characteristics and outcomes of the groups were compared using "independent samples *t*-test" for continuous variables, and 'Chi-square test' and 'Fisher's exact test' for categorical variables. *P*-value <0.05 was considered statistically significant. Repeated measures of two groups were compared with analysis of variance and Kruskal Wallis tests. The sample size was estimated depending on previous data showing that 24-hour postoperative blood loss indicated by chest tube drainage was 250 mL. A minimum sample size of 60 patients (30 per group) was sufficient to detect a 250 mL difference between groups with 90% power at 0.05 significance level [13].

Results

TA was administered intraoperatively, and group assignments were made on the first postoperative day based on whether they received TA. There were no differences in terms of demographic features, preoperative and postoperative data between the control and TA groups (Table 1). Durations of cardiopulmonary bypass and aortic cross clamp, extubation time, duration of intensive care unit and hospital stay were similar (*P*=0.121, *P*=0.491, *P*=0.380, *P*=0.106, *P*=0.326), along with estimated blood loss (*P*=0.322). While postoperative FFP transfusion was similar in two groups (*P*=0.692), postoperative erythrocyte suspension transfusion was lower in the study group with 1(0-7) units, compared to 2(0-3) units in the control group (*P*=0.04). The postoperative mediastinal drainage was lower in the study group compared to the control group at the 4^{th}, 8^{th}, 12^{th} $16h^{th}$ hours, and overall (*P*=0.016, *P*=0.006, *P*=0.001, *P*=0.312, *P*=0.004) (Table 2). There was no difference between D-dimer, fibrinogen, INR, hemoglobin and platelet values before and after surgery (*P*=0.728, *P*=0.196, *P*=0.535, *P*=0.632, *P*=0.108, *P*= 0.057, *P*=0.750, *P*=0.293, *P*=0.579, *P*=0.252, respectively) (Table 3). Side effects related to TA administration were not observed intraoperatively. No adverse events related to TA were noted postoperatively.

Table 1: Demographic data and preoperative characteristics of the groups

Parameters	Control group (n=30)	Study group (n=30)	*P*-value
Mean age (SD)	60.8 (9.1)	62.2 (10.2)	0.586
Gender (M/F) (n %)	11/19 (37/63)	10/20 (33/67)	0.787
Height (cm)	164.1 (9.6)	163.2 (9.1)	0.690
Weight (kg)	76 (10.9)	74.7 (11.2)	0.641
BMI	28.2 (3.4)	28.1 (4.2)	0.936
ASAPS of 2	21 (70)	18 (60)	0.417
ASAPS of 3	9 (30)	12 (40)	
EuroSCORE	6 (2.8)	6 (3.2)	0.571
Preoperative EF (%)	55.0 (35-65)	60 (30-65)	0.804
Number of coronary vessels	3.0 (1.0-5.0)	3.0 (1.0-5.0)	0.881
Preoperative risk factors for CAD			
Diabetes mellitus	19 (28.8)	11 (16.7)	0.145
Hypertension	13 (43.3)	12 (40)	0.793
COPD	7 (23)	8 (27)	0.697
Use of smoke	9 (30)	7 (23)	0.459
Obesity	6 (20)	7 (23)	0.663
Hypercholesterolemia	5 (17)	8 (27)	0.347

SD: Standard deviation, M/F: male/female, n %: number percentage, BMI: body mass index, ASAPS: American Society of Anesthesiologists Physical Status, EF: ejection fraction, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease

Table 2: The intraoperative and postoperative parameters and comparisons between the two groups

Parameters	Control group (wo/TA) (n=30)	Study group (TA) (n=30)	*P*-value
CPB* (minute)	90 (45.0-204.0)	87.5 (36.0-193.0)	0.121
ACC* (minute)	54.50(28.0-140.0)	51.50(20.0-151.0)	0.491
Postoperative EF* (%)	50.0(40.0-65.0)	50.0(40.0-65.0)	0.491
Extubation time (hours)	8.0(3.0-17.0)	10(4.0-29.0)	0.380
Intensive care unit stay (day)	2.0(1.0-9.0)	2.0(1.0-12.0)	0.106
Hospital stay (days)	9.13 (3.45)	8.97 (3.65)"	0.326
Estimated blood loss (ml)	1100 (700-1350)	1250 (750-1450)	0.322
Postoperative 24 hour blood transfusion (units)	2(0-6)	1(0-7)	0.040*
Postoperative 24 hour FFP transfusion (units)	2(0-3)	2(0-3)	0.692
0-4h drainage amount (ml)	175 (50-500)	150 (0-500)	0.016*
4-8h drainage amount (ml)	200 (50-1250)	150 (50-1250)	0.006*
8-12h drainage amount (ml)	125 (0-450)	100 (0-500)	0.001*
12-16 h drainage amount (ml)	100(0-350)	100(0-350)	0.312
Total drainage (ml)	725(200-1500)	550(50-1500)	0.040*

*$P<0.05$ statistical significance, n,%: number, percentage; ACC: aortic cross-clamp time; CPB: cardiopulmonary bypass time; EF: ejection fraction; FFP: fresh frozen plasma; NS: not significant

Table 3: The comparison of hemostasis related parameters between groups

Parameters	Control group (wo/TA) (n=30)	Study group (TA) (n=30)	*P*-value
D-dimer (preop) (ng/mL)	0.49(0.20)	0.55(0.26)	0.728
D-dimer (postop. day 1-24h) (ng/mL)	1.87(0.76)	2.43(1,44)	0.196
Fibrinogen (preop) (mg/mL)	343.4(82.3)	330.2(82.5)	0.535
Fibrinogen (postop. day 1-24h) (mg/mL)	394.8(108.1)	387.34(108.0)	0.632
INR (preop)	1.20(1.0-1.7)	1.24(1,0-1.9)	0.108
INR (postop. day 1-24h)	1.26(1.1-1.7)	1.29(1.1-1.90)	0.057
Hemoglobin (mg/dL) (preop)	13.1(10.8-15.5)	12.8(8.0-16.3)	0.750
Hemoglobin (mg/dL) (postop. day 1-24h)	10.3(7.3-12.3)	10.4(7.1-13.2)	0.293
Platelet count (preop) ($x10^9$/L)	269(142-589)	246(132-487)	0.579
Platelet count (postop. day 1-24h) ($x10^9$/L)	150.5(97-325)	168(99-453)	0.252

*$P<0.05$ statistical significance, INR: International normalized ratio, Hgb: Hemoglobin

Discussion

Nowadays, many physiological changes related to cardiopulmonary bypass occur during CABG surgery, which include depletion of hemodilution and coagulation factors, decrease in the number of thrombocytes, thrombocyte dysfunction, and hemorrhage due to severe fibrinolysis. Excessive hemorrhage is observed after CABG operation in 11% of the patients. Within 24 hours after the surgery, 3-5% of the patients experience blood loss more than 2 liters and the incidence of reoperation due to hemorrhage between 4 and 5%. Bleeding depends on the deterioration of physiological mechanisms postoperatively in more than 50% of the patients [14,15]. Mortality increases by 3-4 times together with the re-exploration, the reasons for which include higher incidence of renal failure, higher need for mechanic ventilation support and higher incidence of sepsis, and increase in hospital stay [15,16]. The increase in the postoperative need for blood and blood product transfusion also increases the complication risk and negatively affects the patient's quality of life. Moreover, it prolongs hospitalization and ICU stay durations and increases hospital costs [4-6].

The use of TA in the treatment of common microvascular hemorrhage seen after coronary artery bypass operations is getting gradually more popular [11,12,15]. The anti-fibrinolytic effect of tranexamic acid occurs after the reversible blockage of the lysine-binding zones on the plasminogen molecules. There still is no consensus in the literature on the dose of TA and there are various protocols (50, 100 and 150 mg/kg). The implementation times also vary (before, after and both before and after CPB) [17]. In another study, 32ºC systemic hypothermia instead of 28ºC enabled the increase in effectiveness of tranexamic acid and decrease in doses [18]. In another study, it was determined that TA was administered intravenously at the dose of 50mg/kg following protamine and heparin neutralization after CPB [21]. In our study, 10mg/kg TA was given intravenously before CPB in the TA group and the results were compared to those of controls. We determined that in patients who used LMWH until the day before surgery and had CABG, postoperative hemorrhage and the amount of blood transfusion statistically significantly decreased. In another study, patients to undergo coronary artery bypass surgery and using aspirin (acetylsalicylic acid) until the operation were given 30mg/kg TA [20]. In some of the studies, TA was administered as bolus before the anesthesia induction [21,22]. In this study, TA was administered intravenously in a single dose bolus just before CPB. Despite the differences in TA practices, it was shown that postoperative hemorrhage and the amount of blood erythrocyte suspension transfusion decreased in a comparable manner.

The risk of thromboembolic event development and thrombus formation are significant adverse effects related with the use of TA. While using TA, complications secondary to thrombus formation in coronary arteries, such as ischemic events, pulmonary thromboembolism, cerebrovascular events, myocardial infarction, and deep vein thrombosis may develop [23,24]. No complication related with the thrombus formation and thromboembolism was observed in our study and some of the previous studies [19,25]. This is because complete systemic heparinization during open heart surgery prevents the formation of thrombotic complications of TA. Coagulation returns to the normal only 12 hours after cardiopulmonary bypass, but TA's plasma half-life is 80 minutes [10,17]. It was reported that the postoperative seizures might be seen in recent periods [26]. In this study, it was remarkable that no seizures were observed in any of the 30 patients. This result is similar to those obtained in other studies [19,25]. However, it was also reported that these results were achieved when using TA doses higher than 50 mg/kg [19,26].

In the study performed by Wong et al. [27], heart surgery patients with high transfusion risk were divided into two groups and the effects of aprotinin and TA were examined. No

difference was observed between these patients in terms of the use of blood and blood products and loss of blood. Although it is stated that the aprotinin is an expensive medication, it is now not in use because of its adverse effects [7,8]. In the present study, we observed that fibrinogen was maintained at similar levels with the preoperative values in both groups, and that it remained at the similar levels to the preoperative values in the TA group. Moreover, although D-dimer, one of the breakdown products of fibrin significantly increased on the first postoperative day in both groups, its increase was at a lower level in TA group. In a study conducted by Chauhan et al. [28], TA was compared to aminocaproic acid in cardiac surgery cases. Similar to the results of the present study, the coagulation test results showed that fibrinogen was protected better and the fibrin breakdown products were at lower levels. In numerous studies and meta-analyses, this anti-fibrinolytic medication was shown to reduce postoperative hemorrhage [8,10,17]. In this study, postoperative hemorrhage decreased in patients using TA and the fibrin breakdown products were found to be at low levels.

Limitations

This study was conducted in a small group of patients, and a double-blinded study design was not employed, which may have reduced bias. There is need for randomized controlled studies in larger groups.

Conclusions

In CABG operations with high risk of bleeding due to the preoperative use of low molecular weight heparin (DMAH), a statistically significant decrease in the amount of postoperative bleeding and the amount of transfused blood was detected in a group of patients receiving TA intraoperatively. Side effects related to TA administration were not observed. TA is a safe drug that reduces postoperative bleeding in patients using DMAH undergoing CABG operations.

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Review
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Iron poisoning

Demir zehirlenmesi

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Abstract

Iron, represented by Fe on the periodic table, is the fourth most common element found on Earth. Although it has important tasks in the human body such as oxygen transfer, DNA synthesis, and electron exchange, it may also become toxic and harmful in excess. The toxicity of iron poisoning starts to appear with an intake of 20 mg/kg of elementary iron ions, along with GIS symptoms. In iron poisoning, patients usually present with various clinical findings and symptoms such as nausea, vomiting, palpitation, metabolic acidosis, deteriorated respiration, or mental disorders varying up to coma. Intervention in all patients begins with ABC evaluation, obtaining vascular access, monitoring, and (if necessary) providing oxygen support. Endotracheal intubation can be considered to ensure airway security and avoid aspiration, especially for lethargic patients. After abdominal and intestinal lavage, IV support treatment can begin, considering the liquid-electrolyte deficiency of these patients. In patients with a poor general condition and toxic appearance, hemogram, serum iron levels, kidney function tests, liver function tests, serum electrolytes, coagulation panel, arterial or venous blood gas, lactate, and in women of childbearing age, β-Hcg tests should be obtained. Abdominal radiography can be planned in the early stage. In patients thought to have serious iron poisoning, chelation treatment with deferoxamine is administered without delay.
Keywords: Iron, Poisoning, Toxic

Öz

Demir, Dünya'da en yaygın bulunan dördüncü elementtir. Periyodik tablodaki sembolü Fe'dir. Demirin insan vücudunda oksijen transferi, DNA sentezi ve elektron değişimi gibi önemli görevleri olmasına rağmen, aşırı toksik ve zararlı etkileri vardır. Demir zehirlenmesinin toksisitesi 20 mg/kg elementer demir iyonu alımı ile ortaya çıkmaya başlar. Demir zehirlenmesinde hastalar, bulantı, kusma, çarpıntı, metabolik asidoz, bozulmuş solunum veya komaya kadar değişen bilinç bozuklukları gibi çeşitli klinik bulgular ve semptomlarla karşı karşıya kalabilirler. Tüm hastalarda müdahale, ABC değerlendirmesiyle başlar. Hastanın damaryolu açılır, monitörize edilir ve (gerekirse) oksijen desteği sağlanır. Endotrakeal entübasyon, özellikle bilinç bozukluğu olan hastalar için, hava yolu güvenliğini sağlamak ve aspirasyondan korumak için düşünülebilir. Barsak lavajı nedeniyle oluşabilecek sıvı-elektrolit eksikliği göz önünde bulundurularak IV destek tedavisi başlanabilir. Genel durumu kötü ve toksik görünümü olan hastalardan hemogram, serum demir seviyeleri, böbrek fonksiyon testleri, karaciğer fonksiyon testleri, serum elektrolitleri, pıhtılaşma panelleri, arteriyel veya venöz kan gazı, laktat ve çocuk doğurma çağındaki kadınlar için BetaHcg testi istenebilir. Ayakta direk batın grafisinde erken aşamada planlanabilir. Ciddi demir zehirlenmesi olduğu düşünülen hastalarda demir seviyesi nedeniyle deferoksamin ile şelasyon tedavisi gecikmeden geçilmelidir.
Anahtar kelimeler: Demir, Zehirlenme, Toksik

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Introduction

Iron, represented by Fe on the periodic table, is the fourth most common element found on Earth. Although it has important tasks in the human body such as oxygen transfer, DNA synthesis, and electron exchange, it may also become toxic and harmful in excess [1]. Iron changes from the ferric form to the ferrous form with oxidation, joins the hemoglobin structure, and plays a role in the mitochondria and cytochrome. While anemia may develop in cases of iron deficiency, hemochromatosis may be seen in excess iron accumulation. The human organism keeps iron balance under tight control because of all these important tasks.

While iron can be consumed from meat and meat products as Heme, it can also be consumed as non-Heme iron from plants. Only a small portion of the consumed iron is expelled from the body through feces, urine, and the skin. A vast majority is stored as ferritin or hemosiderin in myoglobin in the liver and bone marrow. Iron follows various routes based on its form after intake. If the consumed iron is Heme-based Ferrous iron (Fe II), it is absorbed from the enterocytes in the small intestines with Heme carrier protein 1. It uses the same route as non-Heme iron when in plasma. Non-Heme iron, a.k.a. Ferric iron (Fe III), must be converted to Fe II first to be absorbed by the enterocytes. Ascorbic acid and stomach acid are necessary in the process. Thanks to the reductase enzyme that performs this transformation, DCytb (duodenal cytochrome b), it is absorbed into the enterocyte as Fe II through the Divalent Metal Transporter 1 (DMT 1). Before transfer to the plasma from the enterocyte, it transforms into Fe III once again. Fe III is removed from the cell with ferroprotein, a substance found in reticuloendothelial macrophages and hepatocytes, especially in the placenta and intestine. Hepcidin, a hormone which is synthesized in the liver, reduces iron secretion into the plasma by affecting ferroprotein. It plays a crucial role in the iron balancing of organisms. Based on these hormonal control and transportation mechanisms, it can be stated that iron, consumed in either Heme or non-Heme form, is managed by binding. Despite these mechanisms of control, the saturation of transferrin, normally at 30% of that of iron, further increases saturation and can accumulate in organs like the liver and heart and create toxic effects by moving freely in the plasma. This tight control mechanism over the absorption, storage, and transportation of iron is particularly important because the human organism itself cannot produce it. A substantial portion of the iron taken orally is absorbed as needed through the duodenum. Iron absorption, which occurs in about 10-35% of enterocytes, can reach 95% in case of iron deficiency. However, controlled absorption from enterocytes in instances of excessive iron intake increase passive iron absorption.

Supportive iron preparations are used as medication in deficiency treatment or multivitamins. Because iron preparations or iron-consolidated multivitamins are taken at extreme doses, a total of 5,910 cases were reported in the United States in 2016, and it was determined that of these, 2,204 were under the age of 5 years, 119 were between the ages of 6 and 12 years, and 475 were between the ages of 13 and 19 years. While five of all cases had major complications, only one case ended in mortality [2]. To the contrary, no organ failure or death was encountered in a cohort study conducted on iron poisoning cases admitted to a hospital in the United Kingdom between 2008 and 2017 [3]. The prevalence of serious toxicity tied to the excessive use of iron for pediatric patients is less than that of adult poisoning with iron preparations. While mortality did not occur in any of the 195,780 patients in the United States within the pediatric age group and among those who incorrectly and excessively used iron preparations between 1983 and 1998, 60 of the 147,079 adult cases of poisoning with iron preparations during the same period were mortal [4]. Cases of iron poisoning are now less frequent, yet still preserve their importance.

Medication doses and forms of preparates were arranged to prevent cases of iron poisoning, which decreased its prevalence of and doctors' related experience. For this reason, there are challenges in early diagnosis and effective treatment. Emergency care physicians must not ignore iron poisoning in cases admitted with clinical symptoms such as metabolic acidosis, mental state degradation, hypotension, and shock.

The iron preparations can be classified in two groups: Ionic and nonionic. The ionic forms of iron are ferrous chloride, ferrous fumarate, ferrous gluconate, ferrous lactate, and ferrous sulfate [5]. The nonionic forms of iron are carbonyl iron and iron polysaccharide. These nonionic forms of iron contain more elementary iron, and their GIS absorption is more limited. Parenteral iron, used in patients with kidney failure and chronic anemia, can have side effects such as anaphylaxis and toxicity.

The toxicity of iron poisoning starts to appear with an intake of 20 mg/kg of elementary iron, and GIS symptoms can appear simultaneously [6]. Iron most accumulates in the stomach, liver, brain, heat, lungs, small intestine, and kidneys. Damage, edema, congestion, and necrosis can may develop in the GIS mucosa and hemorrhaging and lung edema may occur. A study conducted on mice observed that in cases of iron poisoning, myocardial contractility deteriorated and the sensitivity of myosin ATPase and myofibril to calcium reduced [7].

Clinical properties

In iron poisoning, patients may present with various clinical findings and symptoms, such as nausea, vomiting, palpitation, metabolic acidosis, deteriorated respiration, or mental disorders varying up to coma [8]. The clinical status of the patient can be examined in five phases: The gastrointestinal phase that develops between 30 minutes and 6 hours after intake, the latent phase that appears after 6-24 hours, the metabolic acidosis and shock phase that can be seen after 6-72 hours, the hepatotoxic-haptic necrosis phase that can occur after 12-96 hours, and, finally, the intestinal obstruction phase that can develop after 2-8 weeks [5]. In the first phase of iron intoxication, findings of local irritation such as nausea, vomiting, diarrhea, and abdominal pain occur. Nausea is one of the most important findings of iron intoxication. Patients generally appear toxic due to vomiting and diarrhea. Additionally, edema, transmural inflammation, ulcer, hemorrhaging and, in severe cases, infarction and necrosis can appear in the intestinal system due to iron preparations. If no GIS symptoms are observed in the patient six hours after iron intake, the possibility of serious iron poisoning reduces. GIS symptoms regress in the second phase of

iron poisoning, and latent phase, in which systemic effects do not yet emerge, begins. The toxic effect can continue at the cellular level and, as a result, may cause tachycardia, lethargy, and metabolic acidosis in the patient. Patients whose vital findings and condition are stable after the GIS symptoms regress generally have a good prognosis. The shock phase emerges within a few hours after the intake of high doses of iron and can also occur within 12-24 hours in moderate intake. Tissue performance deteriorates, metabolic acidosis occurs due to hypovolemia caused by fluid loss because of vasodilation, decrease in cardiac output, diarrhea, and vomiting. Lethargy, coma, hyperventilation, or seizure can develop due to systemic toxicity. The fourth phase of poisoning begins two or three days later and is characterized by hepatic failure. Hepatotoxicity and, progressively, liver failure may be observed as a result of the oxidative damage is caused by accumulation of excessive iron in the liver. The fifth phase of iron poisoning is characterized by ileus, which is rarely seen and occurs after 2-8 weeks. Ileus may be caused by stenosis during the repair process of the gastrointestinal system and forms due to scar tissue. However, cases of intestinal obstruction have been reported within a week after iron poisoning with iron tablets [9].

Diagnostic tests

Radiography

It could assist in showing the iron preparations because tablets contain high amounts of iron elements. However, the failure to see preparations in the direct radiography does not eliminate iron poisoning or excessive amounts of iron intake.

Laboratory

Different tests can be requested based on the clinical status of the patient or the consumed amount of iron in iron poisoning. In patients with poor prognoses, it is recommended to obtain hemogram and blood gas and monitor lactate levels. To determine fluid-electrolyte imbalances due to vomiting and diarrhea, plasma electrolyte levels are preferably analyzed. Beta-Hcg is obtained from women of childbearing age. Serum iron levels and liver function tests are useful with regards to hepatotoxicity [5]. The level of blood iron concentration reaches a peak level approximately 2-6 hours after the consumption of iron preparations. Previous studies have shown that, when the blood-iron concentration level is between 300 µg/dL and 500 µg/dL, GIS symptoms or a moderate systemic toxic effect develop. Between 500 and 1000 µg/dL, systemic symptoms and shock status occurs, and levels higher than 1000 µg/dL are related to morbidity and mortality. Although serum iron level has much importance in terms of intoxication, a lower serum iron level does not exclude a serious case of intoxication [10]. Elementary iron has 50% mortality with an intake at doses of 200-250 mg/kg, and mortality can occur at doses of 130 mg/kg in the pediatric age group [11].

The total iron binding capacity is no longer used in the diagnosis of iron poisoning.

Initial treatment

Intervention in all patients begins with ABC evaluation, obtaining vascular access, monitoring, and (if necessary) providing oxygen support. Endotracheal intubation can be considered to ensure airway security and prevent aspiration, especially for lethargic patients. With gastric and intestinal lavage, IV support treatment can begin, considering the liquid-electrolyte deficiency of these patients. In patients with a poor general condition and toxic appearance, hemogram, serum iron levels, kidney function tests, liver function tests, serum electrolytes, coagulation panels, arterial or venous blood gas, lactate, and for women of childbearing age, β-Hcg test can be requested. Abdominal radiography can be planned in the early stage. Patients in a generally good condition and who have vomited only once or twice are monitored for vital signs and serum iron levels. After the patient stabilizes, attempts can be made to reduce GIS absorption of excess iron by lavage of the stomach or the entire intestine. Orogastric stomach lavage must be performed in admitted patients in the first 1-2 hours after iron intake [12]. However, lavage may prove difficult due to the hard materials which cover iron tablets. Nonetheless, in cases of iron intake at fatal levels, intestinal irrigation is recommended [13].

Inducing vomiting with ipecac syrup should be discussed in patients with iron poisoning. While some publications claim that patients made to vomit with ipecac syrup can partially remove the iron preparations and that it has no meaningful effect on serum iron levels, there are some who recommend its use during the first 60 minutes in patients admitted to emergency department and who have a high intake history of iron preparations [12].

Endoscopic and surgical methods could be considered if there are iron preparations that adhere to the abdominal mucosa, remain in the gastrointestinal system, or if it cannot be removed through orogastric lavage and full intestinal irrigation.

Deferoxamine treatment

Deferoxamine has a high affinity to iron and is acquired through cultures of bacteria called Streptomyces Pilosus. It is a white-yellow colored substance in a $C_{25}H_{48}N_6O_8$, CH_4O_3S structure, with an atomic mass of 656.8 daltons. It dissolves in water and alcohol, and is used as a chelator in iron poisoning [14]. It forms the ferrioxamine complex by combining with Fe^{+3}. In this regard, it effectively removes both intra- and extracellular iron by binding. But the penetration into the cell due to its hydrophilic structure is low [15]. As much as 100 mg of deferoxamine binds approximately 8.5 mg of Ferric iron. A prospective study conducted with non-transfusion dependent thalassemia patients concluded that the iron load in the liver was reduced with a deferoxamine chelation [16].

In patients thought to have serious iron poisoning, chelation treatment with deferoxamine is administered without delay. If the serum iron level is greater than 350 mcg/dL in patients with toxicity findings but without clinically very serious symptoms or greater than 500 mcg/dL In patients without any symptoms or findings, initiation of chelation treatment is recommended. Intravenous dose of deferoxamine should be titrated to 15 mg/kg/dour. In very serious iron poisoning, it can reach up to a dose of 35 mg/kg/hour in the first 24 hours. Only when the toxic appearance disappears, metabolic acidosis of the patient is corrected, or urine discoloration ends, should the deferoxamine infusion be stopped [10].

In case of serious iron poisoning during pregnancy, deferoxamine should be used without considering the status of the fetus. The treatment of these patients is the same as other

patients. Previous animal studies have not shown that deferoxamine or excessive iron intake has a negative effect on the fetus.

In the pediatric age group, exchange transfusions can be useful in situations where deferoxamine is insufficient [17].

Hemodialysis

Hemodialysis only affects the elimination of freely circulating iron, and its benefit is limited because it has no effect in removing excessive intracellular iron from the body. A decrease in iron levels and clinical improvements were reported when hemodialysis was implemented in addition to deferoxamine for patients with life-threatening findings after receiving excessive doses of iron [18]. Hemodialysis can be considered especially in patients with levels of serum iron higher than 1000 mcg/dL [11].

Discharge

Asymptomatic patients, those who have received less than 40 mg/kg of iron element, whose intake amount is unclear but have a blood-iron level of less than 500 mcg/dL and in those which iron preparations are not observed in the Standing Direct Abdominal Radiography are kept under six hours of observation. These patients can be discharged if their asymptomatic state continues. Mildly symptomatic patients, those who received more than 40 mg/kg of elementary iron, those with an unclear amount of intake but have a blood-iron concentration of less than 500 mcg/dL and in whom iron preparations are not observed in the Standing Direct Abdominal Radiography are monitored for 6-12 hours. Unstable patients, patients with anion gaps, metabolic acidosis, or lethargy, or those who are in shock are should be monitored in the intensive care unit [5].

Conclusion

Iron preparates are common and widely used. Serious negative consequences can occur, either intentionally or because of misuse. Physicians should pay attention to iron poisoning, know the emergency approach to such patients, and keep iron poisoning in mind for differential diagnosis. Early intervention plays a significant role in diagnosing and treating the disease.

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A rare cause of surgical abdomen: Heterotopic pregnancy rupture

Cerrahi batının nadir bir nedeni: Heterotopik gebelik rüptürü

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Abstract

Heterotopic pregnancy is simultaneous extrauterine and intrauterine localization of the fertilized ovum. In this article, we aimed to present the case of a ruptured heterotopic pregnancy patient who had abortion a week ago. A 28-year-old female patient was referred to the Emergency Department due to vaginal bleeding and abdominal pain. Physical examination revealed that the patient, who had an abortion a week ago because of unwanted pregnancy at the 7th gestational week, had widespread sensitivity in the abdomen. Active bleeding was observed in vaginal examination. Her serum β-human chorionic gonadotropin level was 14562 mIU/mL. A fetus surrounded by hematoma with an 8 mm crown-rump length and heartbeat was observed in the right adnexal area during pelvic ultrasonography. The patient was diagnosed with ruptured heterotopic pregnancy and underwent surgery. In female patients who are in reproductive age and who refer to Emergency Department with acute abdominal pain and vaginal bleeding, it must not be ignored that there might be extrauterine pregnancy along with intrauterine pregnancy and/or rupture. Ectopic pregnancy is a disease, which might occur in sexually active women in reproductive period and develops as a result of abnormal implantation of blastocyst. It can be localized in the ovaries, and less commonly, in the fallopian tubes. Ovarian pregnancy is characterized with the blastocyst being implanted in the ovary. It constitutes 0.15-3% of ectopic pregnancies and is observed in approximately one in every 7000 pregnancies. In our case, the blastocyst was localized in the right ovarian area, which is exceedingly rare.

Keywords: Acute abdomen, Abdominal pain, Ectopic pregnancy, Heterotopic pregnancy, Rupture

Öz

Heterotopik gebelik, fertilize ovumun eş zamanlı olarak ekstrauterin ve intrauterin yerleşimidir. Yazımızda bir hafta önce kürtaj olmuş rüptüre heterotopik gebelik olgusunu literatür eşliğinde tartışmayı amaçladık. Yirmi sekiz yaşında kadın hasta vajinal kanama ve karın ağrısı şikayetleri nedeniyle acil servise müracaat etti. Bir hafta önce, 7 haftalık intrauterin istenmeyen gebelik nedeniyle kürtaj olan hastanın fizik muayenede batında yaygın hassasiyeti mevcut idi. Vajinal muayenede aktif kanama izlendi. Kan tetkik sonuçlarında serum β-human koryonik gonadotropin düzeyi 14562 mIU/mL olduğu saptandı. Yapılan ultrasonografide sağ adneksiyal alanda, kalp atımı mevcut crown-rump length 8 mm ve etrafında hematom mevcut fetüs izlendi. Hastaya rüptüre heterotopik gebelik tanısı konularak ameliyata alındı. Ektopik gebelik, üreğen dönemde cinsel yönden aktif olan kadınlarda ortaya çıkabilen çok ciddi hastalıklardan birisidir. Blastokistin anormal implantasyonu sonucu gelişen ektopik gebelik en sık fallop tüplerinde, daha az sıklıkta over yerleşimli olabilir. Ovaryan gebelik, blastokistin over içinde implante olması ile karakterizedir. Ektopik gebeliklerin %0,15-3'ünü oluşturur. Yaklaşık 7000 gebelikte bir görülmektedir. Bizim vakamızda blastokist, nadir görülen bir yerleşim yeri olan sağ over lokasyonundaydı. Akut karın ağrısı ve vaginal kanama şikayetleriyle acil servise gelen üreme dönemdeki bayan hastalarda intrauterin ile beraber ekstrauterin gebelik ve/veya rüptürü de olabileceği göz ardı edilmemelidir.

Anahtar kelimeler: Akut batın, Karın ağrısı, Ektopik gebelik, Heterotopik gebelik, Rüptür

Introduction

Ectopic pregnancy occurs when the fertilized ovum is implanted in any tissue other than endometrial cavity. Heterotopic pregnancy, on the other hand, is simultaneous extrauterine and intrauterine placement of fertilized ova. Ectopic pregnancy occurs in one of 200 pregnancies in reproductive age, from menarche to menopause. It is most detected between the ages of 30 and 40. Heterotopic pregnancy prevalence, on the other hand, is 0.6-2.5 per 10,000 pregnancies. Ectopic pregnancy is an important morbidity and mortality cause in women in reproductive period. It is the most prominent cause of pregnancy-related mortality in the first trimester in developed countries [1,2]. A total of 6% of the pregnancy-related mortality is linked to ectopic pregnancy rupture [3]. The purpose of this study was to discuss a ruptured heterotopic pregnancy together with literature research with a patient who had an abortion a week ago and who was referred to the Emergency Service with complaints of vaginal bleeding and abdominal pain.

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Case presentation

A 28-year-old female patient, from whom verbal consent for this case report was obtained, was referred to the Emergency Department because of vaginal bleeding and abdominal pain. General condition of the patient was well, she was conscious and cooperative at the time of admission. Arterial blood pressure was 90/60 mmHg, her pulse was 114 /min and weak. She was referred to a hospital one week ago with nausea and vomiting complaints, and a 7-week intrauterine pregnancy was determined. She had an abortion because it was an unwanted pregnancy, after which the patient was discharged uneventfully. It was also learned that the patient had frequent pelvic infections and had another abortion one year ago because of unwanted pregnancy.

In physical examination, the patient had widespread sensitivity in the lower right quadrants of the abdomen, and there was no defense or rebound. Active bleeding was observed in vaginal examination. Intravenous (IV) isotonic saline infusion was administered. Laboratory results revealed that Hemoglobin (Hb) was 12.2 g/dL and serum β-human Chorionic Gonadotropin (β-hCG) level was 14562 mIU/mL. A fetus with a Crown-Rump Length (CRL) of 8 mm and a heartbeat, surrounded by hematoma, was observed in the right adnexal area in ultrasonographic (US) examination (Figure 1). In addition, there was widespread free fluid in the abdomen (Figure 2). The patient was diagnosed with ruptured heterotopic pregnancy. After one hour, control Hb value was 10.8 g/dL. The patient underwent emergency surgery for right salpingectomy. On the postoperative fourth day, the patient was discharged healthily without complications.

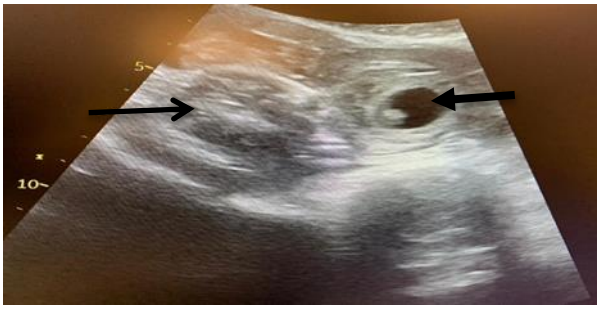

Figure 1: CRL: 8 mm fetus (arrow) with a heartbeat and hematoma in right adnexal area (full arrow)

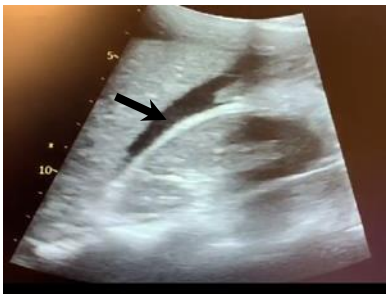

Figure 2: Free fluid in the hepato-renal cavity (arrow)

Discussion

Ectopic pregnancy is one of the most significant diseases that can be detected in women who are sexually active in their reproductive period. Premature implantation, which is caused by factors that delay or prevent fertilized ovum from reaching the endometrial cavity, is more common in women with certain risk factors, such as previous abdominal pelvic surgery and pelvic infections, smoking, past ectopic pregnancy, menstrual reflux, hormonal changes and malignancies affecting tubal motility, Intrauterine Devices (IUD), protection with pills that contain only progesterone, and vaginal shower [4]. The known risk factors of our patient included smoking, frequent pelvic infections, and occasional post-coital vaginal showering.

Ectopic pregnancy, which develops as a result of abnormal implantation of blastocyst, most commonly occurs in one of the fallopian tubes, at a rate of 95-98%. Less frequently, it may also occur in the ovaries, cervix, and abdominal cavity. Since these anatomical regions are not suitable for placenta placement and embryo development, rupture and bleeding potential is high [4-6]. Ovarian pregnancy, a rare form of ectopic pregnancy that is characterized by a blastocyst implanted in ovaries, constitutes 0.15-3% of ectopic pregnancies. It is observed in one of approximately 7000 pregnancies. It is more common especially in women with IUDs [7]. In our case, the blastocyst was implanted in the right ovary, which is rare. However, our patient did not have IUD. The most common complaint in ovarian pregnancy rupture is abdominal pain and vaginal bleeding. Hypovolemic shock may also develop as a result of rupture-related bleeding [8]. The complaints of our patient for referring to the Emergency Service were in line with the literature, and she had rupture and bleeding as a clinical manifestation and was in pre-shock condition.

Ovarian ectopic pregnancy diagnosis is possible with serum β-hCG level measurement and transvaginal USG. The characteristic sonographic findings of ovarian ectopic pregnancy include a wide echogenic ring accompanying an echo-lucent area within an ovary. For definitive diagnosis, a yolk sac or embryo should be observed within the echogenic ring [9]. If ovarian ectopic pregnancy is not diagnosed earlier, life-threatening conditions can be caused by rupture of an ectopic gestational sac and consequent hemoperitoneum resulting from the high vascularity of ovarian tissues [10]. The current complaints of our patient could be attributed to the recent abortion she went through, which was the main factor that made considering the pre-diagnosis of ectopic pregnancy difficult. Our patient was diagnosed with serum β-hCG level measurement and USG. If the hemodynamic findings of the patient in ruptured ectopic pregnancy are unstable, the only treatment option is surgery [11]. Our patient underwent emergency right salpingectomy.

Conclusion

The possibility of extrauterine pregnancy and/or rupture together with intrauterine pregnancy must not be ignored in patients who refer to Emergency Department with acute abdominal pain and vaginal bleeding complaints.

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Case report
Olgu sunumu

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Unusual concomitance during the neonatal period: Tachyarrhythmia and hypothyroidism

Yenidoğan döneminde olağandışı birliktelik: Taşiaritmi ve hipotiroidizm

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Abstract
Congenital hypothyroidism is a significant issue in neonates. A variety of cardiac abnormalities have been described in cases of severe hypothyroidism. It is commonly associated with sinus bradycardia, low QRS complexes, prolonged QT interval and conduction blocks but may rarely cause arrhythmias. Although supraventricular arrhythmias are ordinary features of hyperthyroidism, the aim of this report is to underline the possible etiological link between supraventricular tachycardia and hypothyroidism. Although a few adult cases with hypothyroidism and tachyarrhythmia have been previously reported in the literature, to our knowledge, these are the only neonatal cases reported.
Keywords: Neonate, Hypothyroidism, Tachycardia

Öz
Konjenital hipotiroidizm yenidoğanlarda önemli bir sorundur. Şiddetli hipotiroidizm vakalarında çeşitli kardiyak anormallikler tanımlanmıştır. Hipotiroidizm yaygın olarak sinüs bradikardisi, düşük QRS kompleksleri, uzun QT aralığı ve iletim blokları ile ilişkilidir, ancak nadiren aritmilere neden olabilir. Supraventriküler aritmiler hipertiroidizmin sıradan özellikleri olmasına rağmen; Bu çalışmanın amacı supraventriküler taşikardi ve hipotiroidizm arasındaki olası etyolojik bağın altını çizmektir. Literatürde hipotiroidizm ve taşiaritmi birlikteliği olan birkaç erişkin olgu daha önce bildirilmiş olmasına rağmen, bilgimize göre yenidoğanlarda bildirilen vakalar sadece bunlardır.
Anahtar kelimeler: Yenidoğan, Hipotiroidizm, Taşikardi

Introduction

Thyroid hormones are important for cardiovascular function. In case of decreased thyroid function, neither the heart nor the blood vessels function normally [1].

A variety of cardiac abnormalities, consisting of functional, structural, and electrical conduction problems, have been described in cases of severe hypothyroidism [2]. Electrocardiographic changes are commonly recognized; however, sustained, or life-threatening ventricular ectopy is rarely seen [3].

Although a few adult cases with hypothyroidism and tachyarrhythmia have been previously reported in the literature, to our knowledge, these are the only neonatal cases reported.

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Case presentation

Parents gave written informed consent for their children.

Case 1

A female infant of non-consanguineous parents was born via vaginal delivery at 30 weeks of gestational age. Apgar scores were 7 and 9 at 1st and 5th minutes of life, respectively. She received ventilator support. On admission, she had supraventricular tachycardia. Electrocardiography revealed that the heart rate was 200 beats/min with narrow QRS complexes. Adenosine was effective in inducing a sinus rhythm, however as supraventricular tachycardia recurred (with 220 beats/min), the patient was digitalized. Echocardiography yielded no pathologic findings. On the 4th and 5th day of life she had recurrent supraventricular tachycardia attacks, which were treated with adenosine and digitalization. Propranolol treatment was added to digoxin on the 3rd day of life. As digoxin level was high, it was ceased on the 10th postnatal day.

Hematological parameters, BUN, creatinine, electrolytes were within normal limits. On 5th day of life, thyroid stimulating hormone level was 438.12 mIU/ml and free thyroxine was 0.73 pg/ml. Thyroid ultrasonography was normal. Levothyroxine treatment was started at a dose of 10 µg/kg. The mother was euthyroid and had no autoimmune diseases.

Supraventricular tachycardia attacks did not recur after the 10th postnatal day. She was discharged on the 42nd postnatal day with propranolol treatment. Hyperthyroidism was detected during follow-up, and levothyroxine treatment was stopped at 60 days of life. Supraventricular tachycardia did not continue, and propranolol was stopped at 90 days of life. She is now 17 months old and uneventfully observed in the outpatient clinic without any medication.

Case 2

The male infant of healthy consanguineous parents was born on the 33rd gestational week by caesarean section due to acute fetal distress. Bradycardia and tachyarrhythmia were detected during monitorization in the NICU. On the 7th postnatal day, he was referred to our hospital for arrhythmia. Body weight was 1,800 g (50%), length was 47 cm (75-90%). Echocardiography yielded no pathologic findings. He was monitored on Holter for 24 hours, which revealed atrial tachyarrhythmia with atrioventricular block. On electrocardiography, heart rate was 220-230 beats/min with narrow QRS complexes. Propafenone (10 mg/kg/d) was started on 10th day of life. WBC, BUN, creatinine, blood glucose and electrolytes were within normal limits. On the 8th day of life, thyroid stimulating hormone level was 58.8 mIU/ml and free thyroxine was 0.63 pg/ml. Thyroid ultrasonography was normal. Levothyroxine treatment was started at a dose of 10 µg/kg. The mother was euthyroid and had no autoimmune diseases.

He was discharged with propafenone and levothyroxine treatments on the 23rd postnatal day. At 7 months of age, propafenone was stopped during follow-up. He had no tachyarrhythmia on Holter monitoring. He is now 15 months old and still using levothyroxine.

Case 3

The male infant of non-consanguineous parents was born via C/S at 35 weeks of gestational age. Fetal arrhythmia was diagnosed at the 32nd gestational week. Apgar scores were 4 and 6 at 1st and 5th minutes of life, respectively. He was intubated in the delivery room due to resistant bradycardia. The mother had a cardiac pacemaker due to Brugada Syndrome. Body weight and length were 3,280 g (75-90%) and 49 cm (75-90%), respectively. Auscultatory findings of the lungs were normal. On admission, he had supraventricular tachycardia. On electrocardiography, heart rate was 260 beats/min with narrow QRS complexes. Adenosine was not effective in inducing a sinus rhythm. Atrial flutter was observed, after which amiodarone was administered on the first postnatal day. Propranolol was added on the 4th postnatal day to amiodarone. On the 7th postnatal day, he was extubated. Echocardiography yielded no pathological findings. On the 8th postnatal day, thyroid stimulating hormone level was 62 mIU/ml and free thyroxine level was 0.38 ng/dl. Thyroid ultrasonography was normal. Levothyroxine treatment was started at a dose of 10 µg/kg. The mother was euthyroid and had no autoimmune diseases. Supraventricular tachycardia and atrial flutter attacks did not recur after the 10th postnatal day. He was discharged on the 13th postnatal day with propranolol and levothyroxine.

Case 4

The male infant of non-consanguineous parents was born via C/S at 32 weeks of gestational age. Apgar scores were 5 and 7 at 1st and 5th minutes of life, respectively. He was intubated in the delivery room due to respiratory distress and surfactant was administered. Body weight and length were 2,500 g (75-90%) and 47 cm (75-90%), respectively. On admission, he had supraventricular tachycardia. On electrocardiography, heart rate was 240-260 beats/min with narrow QRS complexes. Adenosine was not effective in induction of a sinus rhythm, and synchronized cardioversion was performed on the first postnatal day. After return to normal sinus rhythm following cardioversion, maintenance digoxin was started. On the 5th postnatal day, he was extubated. Echocardiography yielded no pathologic findings. On the 7th postnatal day, thyroid stimulating hormone level was 89 mIU/ml and free thyroxine level was 0.3 ng/dl. Thyroid ultrasonography was normal. Levothyroxine treatment was started at a dose of 10 µg/kg. The mother was euthyroid and had no autoimmune diseases. Supraventricular tachycardia occurred on the 15th postnatal day and adenosine was ineffective, so esmolol infusion was started. As esmolol was gradually stopped, propranolol was administered at the 16th postnatal day. He was discharged on the 25th postnatal day with propranolol and levothyroxine.

Discussion

Supraventricular tachycardia is the most common arrhythmia in childhood, including the neonatal period. It can manifest as tachycardia antenatally and restlessness, sucking disorder, tachypnea, tachycardia, and heart failure postnatally. Although many newborns tolerate supraventricular tachycardia in the first hours, in cases lasting more than 6-12 hours, heart failure may develop after decreasing heart rate [4]. 15% of patients have a history of sepsis and drug use [5]. Wolf

Parkinson White (WPW) pattern is available on ECG in 10-20% of cases. Some congenital heart anomalies (Ebstein anomaly, single ventricle, large artery transposition) tend to manifest with supraventricular tachycardia [4]. Gilljam et al. [6] reported that the median age of onset in supraventricular tachycardia was 1 day (1-30 days) and mean heart rate was 270±27 beats/min by retrospectively examining the files of 109 newborns hospitalized with the diagnosis of supraventricular tachycardia for 27 years. In 52 (48%) of the patients, they found heart failure during the first referral and reported that 17% were resistant to treatment. In antenatal follow-up of patients with heart failure, hydrops fetalis was found in 10 patients and intrauterine supraventricular tachycardia, in 9 patients. In this study, the electrocardiographic findings of our patients were compatible with supraventricular tachycardia, and there were no WPW pre-excitation findings in the ECG obtained during sinus rhythm. Echocardiographic examinations did not any heart abnormalities. It was stated that the antenatal follow-up of the patients was normal. There was no evidence of sepsis, drug intake history, or placement of any central catheters which could cause pain and supraventricular tachycardia.

These are the first neonates with tachyarrhythmia and hypothyroidism in the literature to our knowledge. There are reported adult patients with this concomitance [7,8].

The heart is a major target organ for thyroid hormone action. Normal thyroid hormone levels are essential for maintaining normal heart structure and function. In hypothyroidism, the muscle of the heart is weakened in contraction and relaxation phases. This means that the heart cannot pump, and the stroke volume is reduced [9].

Changes in thyroid hormone levels also exert influence on electrophysiological function of the heart. The basic reason of alteration in electrophysiological function that is caused by changes in different thyroid hormone levels has not yet been completely explored. To the best of our knowledge, tachyarrhythmia is an unusual finding in hypothyroidism.

In neonates with congenital hypothyroidism, left systolic and diastolic functions were lower [10]. Although our patients had hypothyroidism, all of them had tachyarrhythmia. Thyroid hormone exerts its effect by influencing thyroid hormone regulating gene expression via interactions with the high affinity thyroid hormone receptor located in the nucleus [9]. Thyrotropin-releasing hormone triggers the pituitary gland to release thyroid stimulating hormone. Thyrotropin-releasing hormone-containing fibers innervate autonomic motor and premotor nuclei of the brainstem and spinal cord which regulate functions of cardiovascular system [11]. It is reported that thyrotropin-releasing hormone itself can cause high blood pressure, tachyarrhythmia, palpitations. It can increase the release of noradrenalin; and it also acts like adrenalin [12]. We can speculate that thyrotropin-releasing hormone in our patients may have caused these supraventricular tachycardia attacks, but on the other hand it is not clear why all newborns with hypothyroidism do not have tachyarrhythmia. Measuring of thyrotropin-releasing hormone level is not used in practice.

Thyroid hormone receptor plays a key role in mediating the physiologic actions of thyroid hormone so pre or post receptor effects might play a role in those patients with tachycardia. Case 2 had atrioventricular block that might be detected in hypothyroidism [13]. However, the physiopathological basis of tachyarrhythmia in these patients is not elucidated.

Conclusion

Hypothyroidism should be kept in mind in cases with tachyarrhythmia as well as bradycardia.

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Repair of diaphragmatic biliary pleural fistula in a hydatid cyst with pericardial patch: A case report

Bilioplevral fistüle neden olan bir hidatik kistte perikardiyal yama ile diafragma tamiri: Olgu sunumu

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Abstract
Intrathoracic complications are rare events in postoperative recurrence of hepatic hydatid cysts; however, they are serious causes of mortality. In this report, we aimed to present a case of diaphragmatic defect developing as an intrathoracic complication after recurrence, which we repaired using a pericardial patch. Based on the literature, we encountered no use of pericardial patches in such cases.
Keywords: Hydatid cyst, Recurrence, Biliopleural fistula, Diaphragm repair, Autologous graft

Öz
Karaciğer kist hidatiklerinde operasyon sonrası oluşan nükslerde intratorasik komplikasyonlar nadirdir. Oluşan komplikasyonlar ise ciddi mortalite sebebidir. Biz nüks sonrası intratorasik komplikasyon olan diafragma defektini primer onardıktan sonra perikardiyal yama ile güçlendirdiğimiz bir olguyu sunduk. Yaptığımız litaratür taramalarında bu tür vakalarda daha önce perikardiyal yama kullanıldığına rastlamadık.
Anahtar kelimeler: Kist hidatik, Nüks, Bilioplevral fistül, Diafram tamiri, Otolog greft

Introduction

The spread of liver hydatid cysts to the thorax is rare. However, direct compression of the liver hydatid cyst on the diaphragm disrupting its vascular supply, the chemical effect of bile content and negative intrapleural pressure may all cause this complication [1,2]. In this report, we present a case of a diaphragmatic defect, an intrathoracic complication after recurrence of a liver hydatid cyst, that was strengthened with a pericardial patch following primary repair.

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Case presentation

A 48-year-old female patient was admitted to our clinic with complaints of dyspnea, fever, and cough. The patient had been operated due to hydatid cyst of the liver three years ago, and the cysts which could not be removed with USG-guided surgery were denaturized with hypertonic saline serum. An USG-guided drainage catheter was placed in the patient due to liver abscess approximately two months ago, and she was treated with albendazole for 6 months. Physical examination revealed decreased breathing sounds on the right. White blood cell count (WBC) was 5600 cells/mm^3 and direct bilirubin was 0.25 g/dL. Pneumothorax and air-fluid levels were observed in the right hemithorax on chest radiograph (Figure 1). Thoracic computerized tomography (CT) showed atelectasis around the right main, middle, and lower lobe bronchi, along with increases in soft tissue density which were not clearly differentiable from lung parenchyma. Also, a peripherally located lesion with lobulated contours and air-fluid levels containing thin septations was observed in the right hemithorax, presumably within the pleural space, accompanied by pleural thickening. A catheter was seen to extend into the liver parenchyma, and free air was visualized within the intrahepatic biliary tract (Figure 2). Thoracotomy revealed that the parietal and visceral pleura were highly adherent and thick. Cystic membrane was observed between the pleural leaves. The diaphragm defect was 4x4.5 cm in size, and membranes of the hydatid cyst were seen within the cavitary lesions of the liver (Figure 3).

Following removal, cystic membranes were sent for pathology, and pleural decortication was performed. General surgery consultation was requested peroperatively. Upon witnessing no bile leakage, the defect was closed primarily. Approximately 3x3 cm pericardial patch was removed from the area closest to the diaphragm and used as a support patch (Figure 4). Since the defect on the diaphragm was remarkably close to the pericardium, it was easily placed. The pericardium was uneventfully closed end-to-end primarily to prevent cardiac herniation.

Pathological examination revealed a hydatid cyst with acute suppurative inflammation. During the postoperative follow-up period, due to bile leakage from the drain, a sphincterectomy was performed in the gastroenterology unit, and a 10 cm-long plastic 10Fr stent was placed at the hilar level to extend into the choledoch. The patient was discharged uneventfully on the 12th postoperative day without complications.

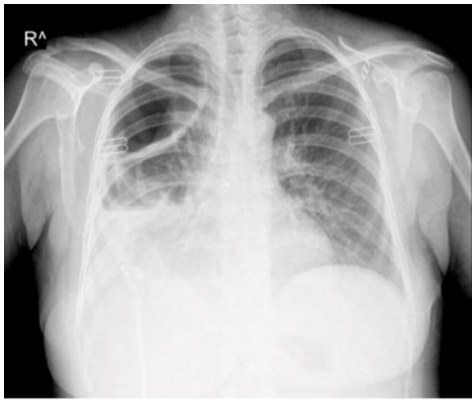

Figure 1: Lung X-ray

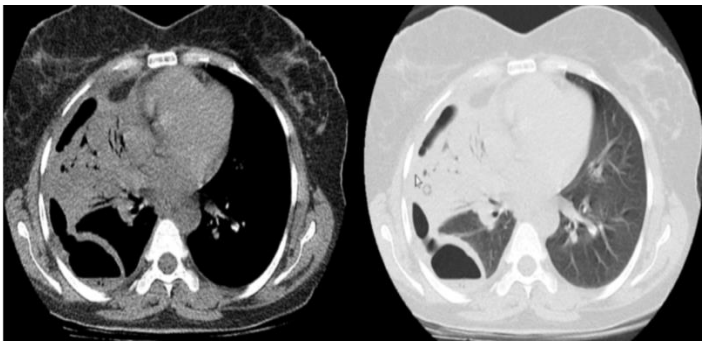

Figure 2: Tomographic section of the mediastinum and lungs

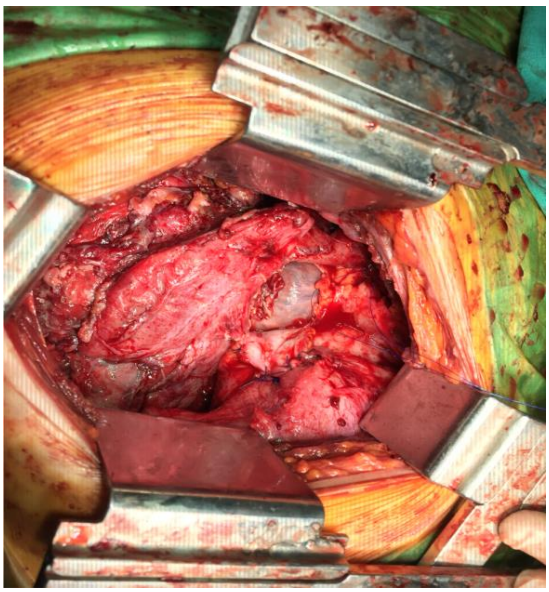

Figure 3: Intraoperative image of diaphragmatic defect and the pericardial patch

Discussion

Intrathoracic complications are rare events in postoperative recurrence of hepatic hydatid cysts; however, they are serious causes of mortality [1].The incidence of spread of liver hydatid cysts to the thoracic area is between 0.6 to 16%, and may be caused by intrapleural negative pressure, disruption in the circulation of the diaphragm due to cyst pressure, and the chemical effect of bile content. Symptoms such as cough, chest pain, shortness of breath, fever may be observed after rupture of liver hydatid cyst into the thoracic cavity [2]. Dyspnea, fever, and cough were observed in our case. Anaphylactic shock may occur if the liver hydatid cyst ruptures into the pleural cavity [3]. In our case, it did not cause anaphylaxis, rather, just a simple itch.

Surgery is the definitive treatment with four main goals: Treatment of the hydatid disease, assurance of free drainage of bile through the common bile duct, cessation of hepatodiaphragmatic communication and ligation of the tracheobronchial fistula [4].

Surgical and percutaneous drainage methods can be utilized in the treatment of the disease. Ultrasonography (USG)-guided percutaneous methods can be used to treat the cysts that cannot be reached during surgery. Recurrence can occur in both surgical and percutaneous methods [5,6]. Percutaneous intervention in hydatid cysts of the liver lowers treatment costs and shortens hospital stay compared to surgical procedures. However, patients treated percutaneously should be well selected. In cases that are not chosen well, serious complications can develop, ranging from abscess and subsequent

bronchobiliary fistula to pneumonia [7]. In our case, the cysts that could not be reached during the operation were treated with percutaneous methods under the guidance of USG. During follow-ups, recurrence and related intrathoracic complications developed. Diaphragmatic defects can be closed primarily [5]. After primary closure of the diaphragmatic defect, we strengthened it with a pericardial patch. During literature review, we saw that strengthening a diaphragmatic defect with a pericardial patch was performed for the first time.

However, the reason we used autologous grafts was that we aimed at strengthening the relatively large defect and the risk of infection is less in autologous grafts, compared with non-autologous grafts. For the patients with postoperative bile leakage, sphincterotomy and biliary catheter placement can be performed endoscopically. This intervention helps reduce and gradually stop the biliary leakage [8]. In our case, sphincterotomy and catheter placement were performed by the gastroenterology department.

Conclusion

Despite being benign disorders, hydatid cysts can cause serious complications. Therefore, we recommend a multidisciplinary approach. Since the risk of infection due to the graft will be lowered, we recommend that the diaphragm be strengthened with an autologous graft, such as a pericardial patch, in relatively large defects of the diaphragm. In addition, even when the diaphragm is sutured primarily, and the patch is placed on, intrathoracic biliary leakage may occur; therefore, endoscopic sphincterotomy should be considered when necessary.

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