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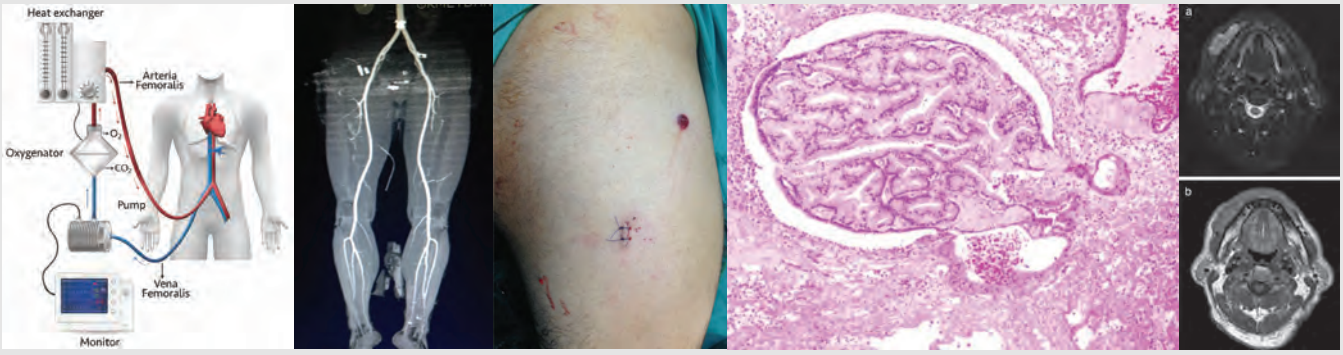

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2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
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- Grant information and detailed information on the other sources of support,
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- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables.

Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	40	6	7 or total of 15 images
Review Article	5000	250	80	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city

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and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Stephane A. Management of Congenital Cholesteatoma with Otoendoscopic Surgery: Case Report. Turkiye Klinikleri J Med Sci 2010;30:803-7.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press;2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme;2003.

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

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dçent Res. 1974. Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5):1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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CONTENTS

REVIEW

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Extracorporeal Membrane Oxygenation for Pulmonary Embolism During Pregnancy and Postpartum

Sevilay Sema Ünver[1], Asım Kalkan[1], Ahmet Demirel[1], Neşe Kaya[1], Özlem Uzun[2]

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Abstract

The maternal and fetal mortality rate in unstable pulmonary embolisms accompanied by obstructive cardiac shock is approximately 30%. An intervention aimed at the pulmonary clot is essential under these conditions. There are various ways of removing this clot from the pulmonary arteries, including thrombolytic administration, percutaneous catheter-based thrombectomy, and direct surgical clot removal. These procedures all have advantages and disadvantages. Increasing use is being made of extracorporeal membrane oxygenation (ECMO) as a means of reducing these risks to a minimum. There are studies recommending ECMO together with thrombolysis or surgical thrombectomy. However, which study is superior to another is unclear. The purpose of the present study was, therefore, to assess the benefits and risks of ECMO use in pregnant patients with pulmonary embolism and to endeavor to produce a new algorithm.

Keywords: Extracorporeal membrane oxygenation, ECMO, pulmonary embolism, pregnancy, peripartum, postpartum

INTRODUCTION

Although pulmonary embolism is seen in between 1/1000 and 1/3000 pregnancies, it is responsible for 5% of all mother and baby deaths. The maternal and fetal mortality rate in unstable pulmonary embolisms accompanied by obstructive cardiac shock is approximately 30%. An intervention aimed at the pulmonary clot is essential under these conditions (1-3). There are various ways of removing this clot from the pulmonary arteries, including thrombolytic administration, percutaneous catheter-based thrombectomy, and direct surgical clot removal. These procedures all have advantages and disadvantages. Separate advice exists for each procedure in pregnant women. Studies have reported that thrombolytic administration increases the risk of bleeding. The peripartum and postpartum risks of bleeding differ. Case reports have shown an increased risk of bleeding following administration of thrombolysis to patients scheduled for cesarean delivery in particular (4-6). Catheter-based thrombectomy of surgical thrombectomy can be performed in patients in whom thrombolysis is thought to be impossible or high-risk. Increasing use is being made of extracorporeal membrane oxygenation (ECMO) as a means of reducing these risks to a minimum. There are studies recommending ECMO together with thrombolysis or surgical thrombectomy. However, which study is superior to another is unclear. Considering maternal and fetal complications, there exists no specific algorithm concerning whether thrombolysis or thrombectomy should be performed before or during ECMO. At the same time, the literature consists solely of case reports, and there are no clinical studies involving large numbers of patients. Although there is one systematic review study of the management of pulmonary embolism in pregnant women, no studies have investigated ECMO use by itself (7). The purpose of the present study was, therefore, to assess the benefits and risks of ECMO use in pregnant patients with pulmonary embolism and to endeavor to produce a new algorithm.

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ECMO

ECMO use has increased markedly in recent years. Despite being an invasive method, frequent reports of clinical success have encouraged interest in its use. Mechanical ventilation and conservative fluid therapy are available to protect the lung in the traditional treatment of Acute Respiratory Distress syndrome (ARDS). ECMO is used to protect against the deleterious effects of the ventilator in refractory cases incapable of treatment. It provides temporary respiratory support until the lung damage resolves (by providing a period of "lung rest") (8). When the patient receives ECMO support, the clinician can lower both tidal volume and high oxygen concentrations fraction of inspired oxygen. The important thing is that the underlying disease in the patient scheduled for ECMO should be reversible (9). Two main methods are currently employed in clinical practice, and these are briefly discussed below.

Veno-Venous (VV) ECMO

The decision concerning when a patient should receive ECMO is complex. VV-ECMO should not be used in every patient with ARDS, and the fact it delays 'rescue therapies' in the course of the disease may limit its benefits. Patients indicated for VV-ECMO are shown in Table 1, but none of these represent absolute criteria. Experience clinicians must individualize patient selection (10).

In the application of ECMO, the majority of modern units employ a dual lumen cannula inserted inside the right jugular vein. One distal and one proximal lumen (both constituting a "drainage lumen") drain blood into the extracorporeal circuit from the inferior and superior vena cava. Oxygenated blood is subsequently returned from a second lumen (in the same cannula, in the middle of the catheter), through which the blood flows into the right atrium and then into the right ventricle (facing the tricuspid valve). The location and position of the cannula must be confirmed using echocardiography in order to avoid malpositioning. Blood flows in the circuit through an oxygenator and a temperature regulator that warms the blood before returning to the body. Oxygenation is set with a blood flow rate in the circuit (generally between 3 and 4 L/min) and an oxygen fraction generally set at 1.0 (100%). Clean air and oxygen are mixed through a semi-porous membrane in a mixer before the gas is exposed to blood. Carbon dioxide (CO_2) removal is independent of blood flow (11). Since both inflammatory and clotting systems are activated by contact with the ECMO circuit, fractionated heparin anticoagulation is generally required to prevent clotting (12). At the same time, other interventions, such as aggressive diuresis and antibiotics (in case of sepsis), must be provided in order to optimize pulmonary functions. ECMO can easily be stopped once lung functions improve. When this happens, blood flows easily from the circuit, but no gas exchange takes place. If sufficient oxygenation and ventilation are achieved after a few hours' observation, the cannula can then be removed. Unsurprisingly, therapeutic evidence in the pregnant population is very limited. The use of VV-ECMO in the treatment of severe ARDS during pregnancy and postnatally first appeared in the H1N1 epidemic of 2009. Observational data showed that ECMO might be beneficial in pregnant patients with ARDS secondary to H1N1 infection. One recent meta-analysis concluded that there is a 75% survival rate in pregnant patients receiving VV-ECMO for ARDS secondary to H1N1. However, there are no data comparing ECMO with respiration preserving mechanical ventilation in the same patient group. To summarize, there are no data supporting the usefulness of VV-ECMO for severe ARDS in any sub-population (13-16).

Veno-Arterial (VA) ECMO

VA-ECMO can provide support in patients with both respiratory distress and severe cardiac problems. These indications may be listed as cardiac arrest due to reversible causes (such as drug intoxications), refractory cardiogenic shock (such as peripartum cardiomyopathy and myocardial infarction), cardiopulmonary bypass failure, or pulmonary embolism (17). The precipitating factor should be reversible in deciding on whether pregnant patients are suitable for VA-ECMO (Table 2).

In clinical practice, peripheral cannulation is more widely employed for VA-ECMO. Venous blood is generally drained via a cannula inserted in the femoral vein, and the flow is diverted to the EC<O circuit. Similarly to VV-ECMO, CO_2 removal depends on the sweep gas flow and oxygenatıon pump flow set by the operator. Oxygenated blood obtained from the venous system is most commonly transferred to the arterial system through a catheter installed in the femoral artery. This permits blood oxygenation (Figure 1) (18,19).

Table 1. Probable indications for gestational and postpartum VV-ECMO support
Severe (but potentially reversible) respiratory failure
Severe respiratory acidosis and hypercapnia despite respiratory rate increasing to 35/minute with mechanical ventilation
$FiO_2 \geq 0.9$ and PEEP ≥10 cm H_2O and a PaO_2/FiO_2 ration less than 100 despite ventilator support and the use of normal support techniques
VV: Veno-venous, ECMO: Extracorporeal membrane oxygenation, FiO_2: Fraction of inspired oxygen PEEP: Positive end expiratory pressure, PaO_2: Partial oxygen pressure

Appropriate keywords were scanned up to 31 December 2019, in English on PubMed, Clinical Key/Elsevier, EBSCO Discovery Service, MD Consult Science Direct, Scopus, EMBASE, Medscape, and Google Scholar electronic search engines for data collection. The search criteria involved the keywords "pregnancy", "pregnancy and pulmonary embolism", "ECMO", and "pregnancy-pulmonary embolism and ECMO". Publications in languages other than English were not included in this study. We detected 2819 studies using the keywords pregnancy and pulmonary embolism published between 1947 and 2020. These consisted of 575 review studies, four book chapters, 34 clinical studies, 14 meta-analysis, and 11 randomized controlled studies. The remainders were other types of publications, particularly case reports. When we added ECMO to the keywords pregnancy and pulmonary embolism, the number of studies identified declined to 21. One, a case report, described a 27-year-old woman with uterine arteriovenous malformation, and since the patient was not pregnant, the publication was not included in this study (20). Another publication concerned a patient initially thought to have pulmonary embolism but subsequently diagnosed with pre-eclampsia and undergoing ECMO. That report was also excluded from the present study (21). Another case report involving peripartum heart failure and ECMO application was also excluded (22). One of the publications we identified concerned a case report of respiratory insufficiency developing after influence, and another concerned ECMO us in a pregnant patient developing acute lung damage. Another case report concerned a pregnant woman with amniotic fluid embolism. There were also four review studies. All these concerned the use of ECMO in respiratory insufficiency in pregnant women, and one also concerned pulmonary embolism and ECMO use in pregnancy (7,23,24).

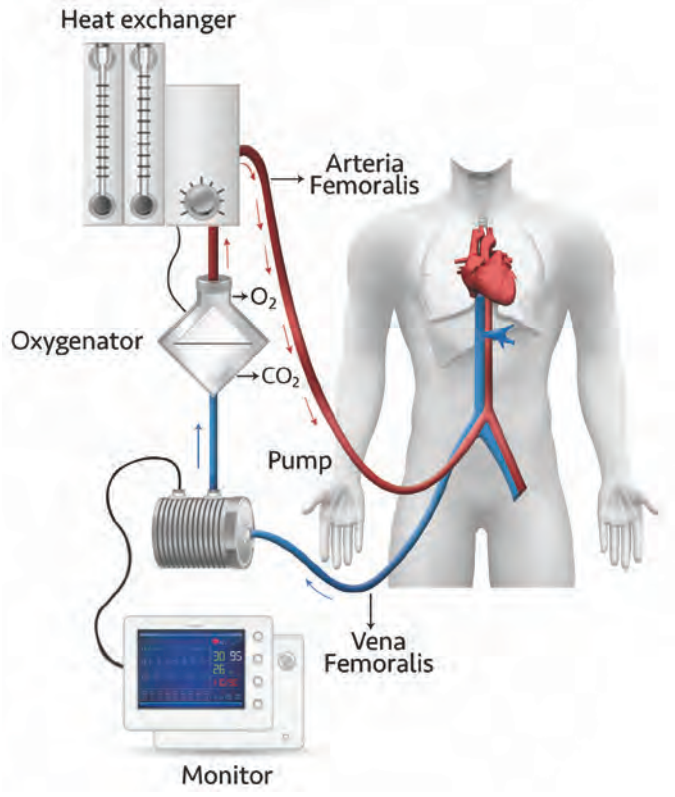

Figure 1. Demonstration of extracorporeal membrane oxygenation

Once all these publications had been excluded, we identified nine case reports compatible with the scope of our review. These case reports involved ten patients. The number of cases was very small, and we, therefore, deepened our research to examine the content of cases of pulmonary embolism and pregnancy in greater detail. The reviews were examined in terms of content. Three pulmonary embolisms were identified in patients undergoing ECMO due to respiratory insufficiency. Examination of the references to these pulmonary embolism cases showed that they were the same as the cases included in our study. The references of the case reports included in our study were then examined, and no different cases were encountered.

The case reports included in our study were examined, and patients' ages, time of ECMO application (peripartum or postpartum), gestational weeks, anticoagulation applied before ECMO, and thrombolytic conditions or thrombectomy were recorded. Mother and baby survival was also recorded.

Table 2. Probable indications for gestational and postpartum VA-ECMO support
Peripartum cardiomyopathy-related refractory left ventricular failure, myocardial infarction, myocarditis
Drug intoxication requiring prolonged cardiopulmonary resuscitation
Refractory right or left ventricular failure in cases of suspected amniotic fluid embolism
Cardiopulmonary bypass failure following heart surgery
Massive pulmonary embolism with refractory failure in the right ventricle
Prolonged cardiopulmonary resuscitation due to a potentially reversible cause
VA: Veno-arterial, ECMO: Extracorporeal membrane oxygenation

Only nine of the 2891 publications identified could be included in our study. These nine case reports involved a total of 10 patients. The pregnant women in the nine case reports were aged between 21 and 37 years. Six were in the third trimester of pregnancy, three in the second, and one in the first. A cardiopulmonary arrest occurred in the emergency department in seven pregnant women, and acute right heart failure-related shock in three. VA-ECMO was applied in all patients, except for one. However, due to the development of Compartment syndrome associated with bleeding in the upper extremity, VV-ECMO had to be performed subsequently on two patients. Four patients underwent thrombectomy, and four received thrombolytic. Cather-directed thrombolysis was administered to one of the patients. Only one patient received ECMO together with unfractionated heparin. Anticoagulant therapy was only not administered to one of the patients. That patient received thrombolysis with tenecteplase, and ECMO was performed. Five patients received heparin for anticoagulation, and four received low molecular weight heparin. Almost all patients underwent an emergency cesarean section. Abortion was performed on one patient in the first trimester and another in the second (Table 3).

Vaginal, tracheal, and intra-abdominal bleeding occurred in three patients receiving thrombolysis before the cesarean section. Compartment syndrome associated with bleeding in the radial artery subjected to catheterization also occurred in one of these patients. Acute kidney failure associated with intra-abdominal bleeding occurred in one of the two patients receiving thrombolysis immediately after cesarean section, while thrombosis in the femoral vein subjected to catheterization and Compartment syndrome associated with bleeding in the radial artery developed in the other (Table 4).

Vaginal bleeding, tracheal bleeding, uterine artery hemorrhage, and acute kidney failure developed as complications in three of the four patients undergoing thrombectomy following a cesarean. However, three of these had also previously undergone thrombolysis. One patient underwent thrombectomy only, and no complication developed. ECMO was applied for at least 60 hours and a maximum of seven days (Table 4). All patients were discharged. Only two patients were discharged with neurological sequelae, while the others were all discharged in a healthy condition. (25-32)

DISCUSSION

Our detailed examination of the literature revealed nine cases of pulmonary embolism undergoing ECMO. No maternal death was reported in these cases. Two baby deaths occurred in pregnancy. The fact that all patients receiving ECMO, irrespective of thrombolysis or thrombectomy, appears to show that ECMO is a good method in pregnant patients with pulmonary embolism. The presence of postpartum hemorrhages in our patients receiving thrombolysis may encourage ECMO to be used together with percutaneous or surgical thrombectomy. This technique may be suitable for avoiding massive postpartum bleeding associated with

Table 3. Characteristics and outcomes, stratified by treatment modalities

	VA	VV	Thrombectomy	Thrombolysis	Anticoagulant	C/S	Arrest/ Shock
Arlt et al. (25)	+	-	+	Tenecteplase (1000 IU)	-	+	Shock after Arrest
Weinberg et al. (26)	+	-	+	Catheter-directed thrombolysis (urokinase 300,000 IU)	Enoxaparin	+	Shock
Leeper et al. (27)	-	+	-	Alteplase (tPA)	Heparin	+	Arrest
Ho et al. (28)	+	-	+	-	Heparin	+	Shock
Fernandes et al. (29)	+	-	-	Tenecteplase (1000 IU)	Heparin	+	Arrest
Chung et al. (17)	+	-	+	-	Heparin	+	Arrest
Bataillard et al. (30)	+ +	- -	- -	- -	Unfractionated heparin Tinzaparin	+ -	Shock Arrest
McDonald et al. (31)	+	-	-	Tenecteplase (50 mg)	Heparin	+	Arrest
Takacs et al. (32)	+	-	-	-	Enoxaparin	-	Arrest

VA: Veno-arterial, VV: Veno-venous

thrombolysis, particularly after delivery. No complications occurred in the three patients not receiving thrombolysis in this review. ECMO was applied in one of these patients following catheter-directed thrombectomy. Chung et al. (17) applied ECMO after thrombectomy in their case reports, and subsequently administered heparin infusion. They suggested that major complications such as hemorrhage could be avoided with this method. Martilotti et al. (7) made a similar suggestion in their systematic review. Those authors determined a survival rate of 93.8% in 36 pregnant patients undergoing surgical thrombectomy due to pulmonary embolism. They detected major bleeding in only seven of these patients and reported that this was a thrombectomy complication. Although our data are very limited, the use of ECMO together with thrombectomy can improve survival in pregnant patients. All patients receiving thrombolysis were individuals with cardiopulmonary arrest. Tenecteplase was given to all these patients. According to the 2015 cardiopulmonary resuscitation algorithm, thrombolysis should be administered if pulmonary embolism is suspected in pregnant women with cardiopulmonary arrest (33). This may be the main reason for thrombolysis being given to these patients. Despite the limited number of patients, our findings also show that thrombolytic therapy should be administered if cardiopulmonary arrest associated with pulmonary embolism occurs in a pregnant woman. If there is no arrest, but findings of acute right heart failure are present, then percutaneous or surgical thrombectomy represents a good option.

VV-ECMO is more used in respiratory failure in pregnant patients. Moore et al. (11) investigated ECMO use in pregnant patients and found that VA-ECMO was applied to only four out of 45 patients. They determined general maternal and fetal survival rates of 77.8% with VV-ECMO and 65% with VA-ECMO. Based on these data, they suggested that VV-ECMO was superior. That study contains no definitive information concerning pulmonary embolism-related ECMO use. In the present review, VV-ECMO was applied to only one patient. This was then switched to VA-ECMO to increase cardiac support once spontaneous circulation had been established. Our findings directly contradict Moore et al. (11) suggestion. This is because Moore et al. (11) study contained no pulmonary embolism patients, while the present review considered only pregnant patients with pulmonary embolism. Based on our existing data, we may conclude that VA-ECMO is more beneficial in pregnant patients with pulmonary embolism. Bleeding and associated Compartment syndrome occurred around the radial artery in two patients undergoing VA-ECMO. Artery selection was modified to the subclavian artery in these patients. This bleeding may be due to thrombolysis or anticoagulant use. Care must be taken in terms of Compartment syndrome development during ECMO with peripheral vein and artery cannulation. Such complications have been seen less frequently in recent years since the biocompatibility of ECMO has been enhanced (34).

There are several strengths to this review. In particular, we investigated several databases and examined all the review studies we encountered. We then investigated pregnant women

Table 4. Baseline characteristics of the 10 cases

	Age	Time of thrombolysis	Time of thrombectomy	Number of days of application	Complication	Did the baby survive	Trimester
Arlt et al. (25)	27	Before cesarean	After cesarean	4 days	Vaginal and tracheal bleeding	Yes	3
Weinberg et al. (26)	27	After cesarean	After cesarean	4 days	Acute renal failure	Yes	2
Leeper et al. (27)	30	Before cesarean	-	60 h	Vaginal bleeding	Yes	3
Ho et al. (28)	37	-	After cesarean	6 days	Uterine artery bleeding	Yes	3
Fernandes et al. (29)	30	Before cesarean	-	4 days	Intra-abdominal bleeding and Compartment syndrome in the arm	Yes	3
Chung et al. (17)	29	-	After cesarean	2 days	-	Yes	3
Bataillard et al. (30)	35 26	- -	- -	4 days 4 days	- -	Yes No	2 1
McDonald et al. (31)	22	After cesarean	-	5 days	Deep vein thrombosis, Compartment syndrome in the arm	Yes	3
Takacs et al. (32)	21	-	-	7 days	Disseminated intravascular coagulation	No	2

with pulmonary embolism from these reviews. We also checked the references of all the texts we were able to access.

Based on our findings, all patients survived, and no mortality occurred in any case. This also suggested that the case reports might have been biased. The absence of mortality among pregnant women with pulmonary embolism undergoing ECMO may derive from the author thinking that the report would not be capable of publication in any journal. This may be due to false high survival rates. Studies involving large case numbers in a clinic where the procedure is performed will be instructive for the future.

CONCLUSION

In conclusion, although we were unable to produce a definite algorithm with the very low patient number involved, we can list the procedures performed. When pulmonary embolism is suspected in pregnant patients, the presence or absence of cardiopulmonary arrest or acute right heart failure must be investigated. Thrombolysis appears beneficial during cardiopulmonary resuscitation in arrest patients. Emergency cesarean surgery must also be performed to avoid fetal mortality. ECMO must be performed once these procedures have been carried out. VA-ECMO appears to be a preferable option. Care must also be taken over the side effects of thrombolytic drugs in these patients. The duration of ECMO ranges between 60 hour and seven days, the essential factor being the complete disappearance of findings of right heart failure. Surgical or percutaneous thrombectomy may be beneficial in all patients. The best means of reducing bleeding complications appears to be ECMO together with thrombectomy. The best way of supporting all our conclusions will be through future studies involving more patients in this group undergoing ECMO.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.K., S.S.Ü., Design: A.K., N.K., A.D., Data Collection or Processing: A.D., Ö.U., A.K., S.S.Ü., N.K., Analysis or Interpretation: A.D., A.K., N.K., Literature Search: S.U., Ö.U., N.K., A.D., Writing: A.K., S.S.Ü.

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ORIGINAL ARTICLE

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Comparison of Bipolar TURP and Monopolar TURP Patients Who Underwent Surgery Due to Benign Prostatic Hyperplasia

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Abstract

Objective: Benign prostatic hyperplasia (BPH) is the one of the most common disease in the world. Transurethral resection of prostate (TURP) is the gold standard procedure in BPH surgery. So TURP methods are important. The aim of our study is to compare bipolar (B) TURP and monopolar (M) TURP methods.

Methods: In our study is included 120 patients who underwent TURP due to BPH. The patients were examined in two groups of 60 people. M-TURP was applied to one group while B-TURP was applied to the other group. Patients International Prostate Symptom score (IPSS), uroflowmetry (Qmax), hemoglobin loss, postoperative catheterization time, hospital stay, TUR syndrome and 6th month postoperative urethral stricture parameters were investigated. In the statistical analysis, chi-square, Student's t-test and Wilcoxon test were performed.

Results: Two groups were analyzed separately and compared. In IPSS, Qmax, hospital stay, hemoglobin loss parameters there was no significantly difference between two groups. The duration of postoperative catheterization and development of urethral stricture at postoperative 6th months found statistically significant; in the M-TURP group, more stricture development and longer catheterization time were observed ($p<0.05$). At the same time TURP syndrome was observed in 2 patients in M-TURP group and TUR syndrome was not observed in B-TURP group ($p<0,05$).

Conclusion: B-TURP and M-TURP groups were compared. The results of both groups were similar. Only in the B-TURP group, in terms of the probability of stricture and the development of the TUR syndrome was more advantageous than M-TURP. In conclusion, B-TURP is more reliable method than M-TURP and both methods can be reliably applied in BPH surgery.

Keywords: Bipolar TURP, BPH, monopolar TURP, TURP

INTRODUCTION

Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) due to BPH are among the most common diseases in the world. It is estimated that 1.1 billion people were affected by symptoms associated with BPH in 2018 (1). In the US, BPH is seen in 80% of men above 70 years of age and 15-60% of men over 40 years of age. Surgical treatment is performed to 25% of all men (2,3).

Amid the high prevalence of BPH in population, both medical and surgical treatments of BPH are widely used. In the last 20 years, more technologically advanced and minimally invasive methods with fewer complications than the transurethral resection of prostate (TURP) like high intensity focused ultrasound, laser vaporization, and laser enucleation were described. Although these methods have lower complication rates than TURP, their efficiencies have not surpassed that of TURP, and they have higher rates of reoperation. Therefore, TURP is still the gold-standard treatment for BPH lower than 80 cc in volume (4,5).

TURP also has considerable complications. Monopolar (M) TURP, which was the first method used in previous studies, had severe complications such as postoperative early and late bleeding, postoperative urinary retention, TUR syndrome, urethral stricture

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in the late period, and erectile dysfunction (5). Therefore, new methods have been developed for TURP, and bipolar methods were started to be used nearly as commonly as unipolar TURP. It is seen as a candidate to replace M-TURP in the future (6). Therefore, many previous trials have compared M and bipolar (B) TURP methods.

The aim of this study was to compare operation room efficiencies and complication rates of unipolar and B-TURP methods. The results of this study may help to choose the method to be used for patients in the future.

METHODS

This study was performed after approval by Okmeydani Training and Research Hospital Ethics Committee (approval date: 17.11.2015; No: 358). This trial included 120 patients who had prostatic surgery due to BPH at Beylikduzu State Hospital between September 2016 and June 2018. Patients with acute prostatitis, patients using 5 alpha reductase inhibitors due to their effects on prostate specific antigen (PSA), patients with urethral strictures, patients who previously undergone prostate biopsies, patients with neurogenic bladders, and patients with previous lower urinary tractus operations were excluded. In this trial, the patients were classified into two equal groups and M-TURP and B-TURP, which are two different methods of gold-standard TURP for BPH treatment. Before the operation, digital rectal examination, urinary and transrectal ultrasonography, PSA, uroflowmetry, postvoiding residual volume measurement, and prostate measurement were performed routinely to investigate LUTS. Urine biochemistry and culture were also routinely performed to exclude infection. International Prostate Symptom score (IPSS) was used to measure symptom score of the patients. According to this scale, the patients were divided into three groups as no-mild (0-7), moderate (8-19), and severe (20-35).

Storz resectoscope (Karl Storz GmbH, Tuttlingen, Germany) with 26 French (F) device was used in the M-TURP group and storz bipolar resectoscope (Karl Storz GmbH, Tuttlingen, Germany) with 26 F device was used in the B-TURP group. BOWA ARC 400 device was used as cautery for both of the groups. For the M-TURP group, 120-watt cautery force was used for cutting mode, and 80-watt cautery force was used for coagulation mode. The same values were used for B-TURP to achieve standardization. These two groups were compared according to the development of postoperative urethral stricture, postoperative hemoglobin loss, postoperative catheterization; development of TUR syndrome, and postoperative Qmax and IPSS.

Statistical Analysis

SPSS 15.0 package program (SPSS for Windows, 15.0, SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses. To evaluate quantitative data, paired-sample Student's t-test was used for comparisons that meet normal distribution criteria, and the Wilcoxon test was used for those that don't meet criteria. The chi-square test was used to evaluate qualitative data. A p value lower than 0.05 was accepted as significant.

RESULTS

This study included 120 patients. These patients were divided into two 60-patient groups. The demographic data of the patients were similar. Mean ages and preoperative IPSS, PSA, uroflowmetry, and hemoglobin values of the patients are shown in Table 1.

Postoperative IPSS, Qmax, hemoglobin loss, postoperative catheterization time, hospital stay duration, TUR syndrome, and stricture at postoperative 6th month were evaluated separately in the M-TURP and the B-TURP groups. Statistical analysis revealed no significant difference in IPSS, uroflowmetry, duration of hospital stay, and hemoglobin loss parameters ($p>0.05$). Postoperative catheterization duration and urethral stricture development at postoperative 6th month were statistically significant. In the M-TURP group, the duration of catheterization was longer, and stricture development at postoperative 6th month was more frequent ($p<0.05$). Two patients in the M-TURP group developed TUR syndrome, while no TUR syndrome was observed in the B-TURP group ($p<0.05$). Isotonic irrigation fluid was used in the B-TURP group while irrigation fluid with mannitol, which is known to increase TUR syndrome, was used in the M-TURP group. Detailed data for all parameters are shown in Table 2.

DISCUSSION

Surgeries for BPH are among the most frequently performed surgeries in the world. Treatment guidelines define recurrent urinary infections, resistant hematuria, and impairment of

Table 1. Demographic data of the patients

Parameters n=120	M-TURP	B-TURP
Age (mean ± SD)	63.95±7.7	64.82 ±8.1
Prostate volume	70.3±13.2	68.4±14.8
PSA	3.3±0.4	3.2±0.3
IPSS	22.8±4.7	22.6±4.9
Uroflowmetry (Qmax)	7.3±3.2	7.8±3.4
Hemoglobin	13.8±1.2	13.4±1.3

SD: Standard deviation, PSA: Prostate specific antigen, IPSS: International Prostate Symptom score, M-TURP: Monopolar transurethral resection of prostate, B-TURP: Bipolar transurethral resection of prostate

renal functions as the absolute indications for surgery. In other patients, symptoms of the patients should be assessed, and treatment should be chosen according to the severity of symptoms (7). TURP is the most commonly applied surgical method for BPH. According to the European Urology Association guidelines complications of TURP include incontinence (1.8%), bladder neck contraction (4.7%), urethral stricture (3.8%), TUR syndrome (1.1%), blood transfusion requirement (8.4%), retrograde ejaculation (65.4%), and erectile dysfunction (6.5%) (8).

Many trials have compared monopolar and bipolar surgeries in terms of functional results, complications, and irrigation fluids. In a meta-analysis by Cornu et al. (9), which included 69 of these trials, no difference could be found in 1-year results for IPSS, life quality parameters, Qmax in uroflowmeter, postvoiding residual volume, and prostate volume. In the same study, no difference could also be detected for operation lengths and the rate of infection after operations. In this meta-analysis, there was no TUR syndrome in patients operated with B-TURP (9). Also, B-TURP groups were better in terms of duration of hospitalization and catheterization, the number of transfusions, retention secondary to clots, and postoperative retention (9). Similar to this meta-analysis, Ahyai et al. (10) and Mamoulakis et al. (11) found similar functional results and postoperative complications at 12th month in their meta-analysis.

In contrast to these meta-analysis, in their case series including 1000 patients, Puppo et al. (12) found that urethral stricture is more frequent with M-TURP (2-10%) compared with B-TURP compared with M-TURP (1%) which is consistent with the working mechanisms of these two methods. Several other studies which compared M and B-TURP yielded conflicting results (12-14).

Erectile dysfunction is also a frequently investigated parameter in trials comparing B-TURP and M-TURP. No significant difference could be found between the two methods (15).

Table 2. Comparisons of several posoperative parameters

Parameters n=120	M-TURP (60)	B-TURP (60)	p value
IPSS	6.4±1.3	6.3±1.6	0.62
Postop Uroflowmetry (Qmax)	19.8±3.6	20.3±3.9	0.38
Postop duration of catheterization	3.5 ± 0.9	3.1±0.8	0.008
Hemoglobin loss	2.2 ±0.6	2.0±0.7	0.15
Duration of hospital stay	4.4 ±0.8	4.2 ±0.9	0.098
Urethral stricture	7	3	0.006
TUR syndrome	2	0	0.009

IPSS: International Prostate Symptom score, TUR: Transurethral resection, M-TURP: Monopolar transurethral resection of prostate, B-TURP: Bipolar transurethral resection of prostate

Hemoglobin values, postoperative electrolyte values, and TUR syndrome were also evaluated in several trials comparing M-TURP and B-TURP. Karadeniz et al. (16) couldn't find a statistically significant difference between the two methods for hemoglobin values but detected significant differences in postoperative 1st-hour and 24th-hour sodium levels. Also, Michielsen et al. (17) detected significant differences in postoperative sodium levels. In both of these studies, postoperative TUR syndrome wasn't detected in any cases treated with B-TURP. In our study, Qmax and IPSS parameters were similar between B and M-TURP. Urethral stricture rate was better in the B-TURP group than the M-TURP group, similar to the meta-analysis findings. No difference was detected in length of hospital stay, or hemoglobin value. The duration of catheterization was longer in the M-TURP group. No TUR syndrome was detected in the B-TURP group, while 2 cases of TUR syndrome were detected in the M-TURP group. Small sample size was a limitation of our study.

CONCLUSION

In conclusion, the results of B and M-TURP are generally similar. B-TURP was better only in TUR syndrome and stricture development and duration of catheterization. The complication rate was low. Both methods can be used safely in BPH surgery.

Ethics

Ethics Committee Approval: Okmeydani Training and Research Hospital Ethics Committee (approval date: 17.08.2016; No: 458). This trial included 120 patients who had prostatic surgery due to BPH at Beylikdüzü State Hospital between September 2016 and June 2018.

Informed Consent: Form was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.E., Concept: M.E., Design: M.E., Analysis or Interpretation: H.B., M.E., Literature Search: H.B., Writing: H.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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The Correlation of Carbon Monoxide Level, Lactate, Creatine Kinase Myocardial Band, Troponin T, Magnetic Resonance Imaging and Clinical Results in Acute Carbon Monoxide Poisoning

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Abstract

Objective: In this study, it was aimed to investigate the correlation between arrival-carboxyl hemoglobin (COHb) levels, lactate, creatine kinase-myocardial band (CK-MB), troponin T and radiological findings in patients who were admitted to emergency service with a pre-diagnosis of carbon monoxide (CO) poisoning between the years 2014-2016.

Methods: The patients who were admitted to emergency service with a pre-diagnosis of CO poisoning between the years 2014-2016 were screened retrospectively. Demographic data, arrival-COHb levels, lactate, CK-MB, troponin T, and if available, computed tomography or magnetic resonance (MR) imaging of the patients, their clinical treatment, and results were compared.

Results: While COHb values of the patients at emergency department arrival were 14.536±13.047%, they were found as 4.536±3.698% at discharge from the hospital. A correlation was not observed statistically between arrival-COHb, lactate, troponin T, and CK-MB. Arrival-lactate level was found as >2.1 mmol/L in 47 patients (36.90%). Cranial MR findings that suggest CO poisoning were determined in four cases who underwent hyperbaric oxygen treatment; millimetric signal enhancements being concordant with chronic microangiopathic ischemic gliotic foci in white matter were determined in the level of the periventricular field, bilateral corona radiata and centrum semiovale in MRI.

Conclusion: There is no correlation between arrival-COHb levels of the patients and lactate, CK-MB and troponin T in CO poisoning. Radiological evaluation should be used for excluding the reasons for a neurological disorder, not for diagnostic reasons.

Keywords: Carbon monoxide poisoning, lactate, troponin, creatine kinase

INTRODUCTION

Carbon monoxide (CO) is a gas that is produced through incomplete combustion of fuels that contain "carbon" and it is regarded as highly "toxic". CO poisoning is the most frequently encountered poisoning in Turkey (1).

In case of breathing, CO causes tissue hypoxia by two important effects: First, the binding capacity of CO to hemoglobin is 200-300 times more than that of oxygen, and second, the part dissolved in plasma causes decrease in 2,3-diphosphoglyceride production thus leading to left shift in oxyhemoglobin dissociation curve, and the oxygen that is bound to hemoglobin cannot be released. Because of the first effect, oxygen content of blood decreases, and because of "carboxyhemoglobin (COHb)" produced by the second effect, oxygen offer to tissues decreases. Therefore hypoxia develops in tissues, and then anaerobic glycolysis increases, thus leading to lactic acidosis;

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the formation of free oxygen radicals, hypotension, and loss of consciousness are followed by lipid peroxidation and apoptosis (2). Multi-variance analyses suggested that arrival-lactate level, old age, leucocyte, and mental condition are independent factors related to critical complications and need of intensive medical treatment in order to determine the patient prognosis after CO poisoning (3). Nevertheless, the medical records on CO poisoning cases in our country are considered to be inadequate. Also, the number of patients applied to health institutions because of CO poisoning and how many of them were diagnosed with CO poisoning are unknown; moreover, the diagnoses are considered to be recorded with different codes in ICD-10 coding system (4).

In this study, it was aimed to investigate the correlation between arrival-COHb levels and lactate, creatine kinase-myocardial band (CK-MB), troponin T, and radiological findings of the patients who were admitted to emergency service with a pre-diagnosis of CO poisoning between the years 2014 and 2016.

METHODS

Subjects and Study Protocol

Following the approval of the Ethics Committee of Ministry of Health Okmeydanı Training and Research Hospital (approval date: 14/06/2016, decision no: 495), the patients admitted to emergency service with a pre-diagnosis of CO poisoning between the years 2014 and 2016 were screened retrospectively.

Measurements and Calculations

Demographic data, arrival-COHb levels, lactate, CK, troponin T, and, if available, brain computed tomography (CT) scans or magnetic resonance imaging (MRI) of the patients, their clinical treatment and results were compared.

Statistical Analysis

Statistical analysis of the data was performed by SPSS 21.0 (SPSS, Chicago, IL). The correlation between arrival-COHb and lactate, troponin T, CK-MB was analyzed by the Pearson correlation test. P values of <0.05 were considered significant.

RESULTS

While COHb values of the patients at emergency department arrival were 14.536±13.047%, they were found as 4.536±3.698% at discharge from the hospital (Table 1). A correlation was not observed statistically between arrival-COHb, lactate, troponin T and CK-MB (Table 2, Figure 1, p>0.05). Arrival-lactate level was found as >2.1 mmol/L in 47 patients (36.90%). Cranial MRI findings that suggest CO positioning were determined in four cases who underwent hyperbaric oxygen (HBO) treatment; millimetric signal enhancements being concordant with chronic microangiopathic ischemic gliotic foci in white matter were determined in the level of the periventricular field, bilateral corona radiata and centrum semiovale in MRI (Figure 2).

DISCUSSION

The first symptoms of CO intoxication are nonspecific; history is the most valuable finding. Physical examination has been used to a limited extent in diagnosis. Blood COHb levels should be measured as soon as possible; nevertheless, COHb levels frequently may not be useful in diagnosis and treatment (half-life is 4-6 hours at room air) (5). The relationship between the severity of poisoning and blood CO level is not drastic, but it can be used as an indicator to follow-up on the treatment. On

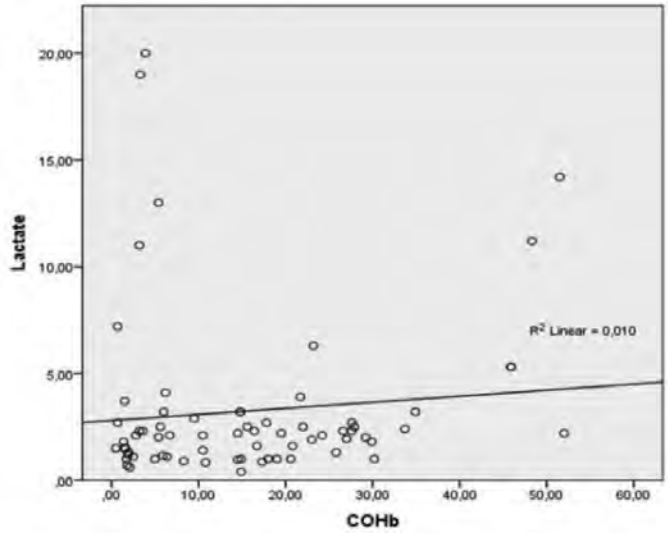

Figure 1. Correlation between arrival-COHb and lactate
COHb: Carboxyl hemoglobin

Table 1. Carboxyl hemoglobin, lactate, troponin T, creatine kinase-myocardial band levels of the cases on admission to the emergency department

	Mean ± SD	n=132				
Arrival COHb (%)	**Discharge COHb (%)**		**Lactate (mmol/L)**	**Troponin T**	**CK-MB**	**Length of hospital stay**
14.536±13.047	4.536±3.698		3.172±3.670	0.086±0.478	3.226±6.849	1.410±1.668
COHb: Carboxyl hemoglobin, CK-MB: Creatine kinase-myocardial band, SD: Standard deviation						

the other hand, if a long time passed after CO exposure or if supportive oxygen treatment was administered, blood CO level can erroneously be detected as low. Detection of high-level CO in the blood is important for diagnosis, but low CO level in blood does not detract from diagnosis (6). In the early period or weeks after the exposition, various symptoms occur in organs because of hypoxia. In addition to major symptoms affecting the neuropsychiatric and cardiovascular systems, other systems and organs are also affected (7-9). Especially when the children with acute CO poisoning were compared with those who were healthy, the heart seems to be the most critical organ and subclinical systolic and diastolic left ventricle dysfunction, and ventricular repolarization failure were observed (10). Similar findings ranging from simple arrhythmia to myocardial infarction are also seen in the poisoning of adults (11). Thus, a correlation is expected between blood COHb and cardiac troponin T. In their retrospective study in 141 patients, Huysal et al. (1) found a weak correlation for this, although the COHb level greater than 25% was described as severe acute CO intoxication and, they found no correlation with CK-MB. Also, in our study, a correlation was not found between arrival-COHb (14.536±13.047) and troponin T and CK-MB. In another study on correlation from the point of arrival-blood lactate, COHb, and electrocardiography (ECG) findings (COHb values on average 21.5±13.9%), normobaric oxygen treatment was applied to 67.6% of the patients while HBO treatment was administered to 32.4% of the patients. Blood lactate levels of HBO treated patients were found greater when admitted to emergency service (2.3 mmol/L vs 1.0 mmol/L, $p<0.001$), and a positive correlation was determined between lactate level and clinical findings of poisoning and COHb values. Nevertheless, this study was criticized on the basis of its results, such that HBO treatment is a therapy method rather than a measure of clinical outcome, and more than one factor is required for the decision regarding HBO therapy, and it does not indicate more severe poisoning (12). Also, in our study, although arrival-lactate values of the patients were above 3, no correlation was found between arrival-COHb and arrival-lactate values. Arrival-COHb values above 30%, low lactate, troponin T, and Glasgow Coma scale (GCS) show that more than one factor was considered in the decision-making process for four patients whose HBO treatments were planned. In another study, HBO treatment was planned for 37 of 57 patients who admitted to the emergency department for CO poisoning (COHb levels 10.1±5.7% (range=3-25%) (13). HBO treatment was administered to four patients in our study. The first patient had a GCS score of 4 in the neurologic examination, was hypotensive, had metabolic acidosis in arterial blood gas, COHb level was 30%, and lactate was 2.2 mmol/L, ECG showed dysrhythmia, ST-T variances and had pulmonary edema. The second patient had a COHb level of 52%, lactate was 2.2 mmol/L. The third patient had a COHb level of 51% and lactate was 14.2 mmol/L. The fourth patient

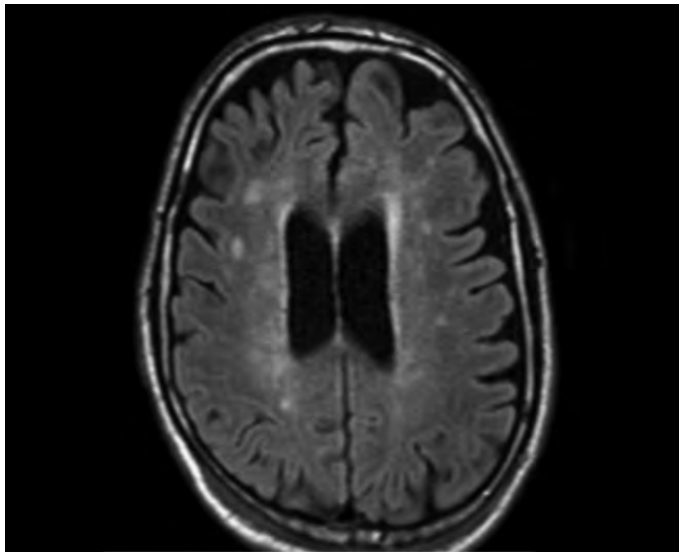

Figure 2. Cranial MRI; millimetric signal enhancements being concordant with chronic microangiopathic ischemic gliotic foci in white matter were determined in the level of the periventricular field, bilateral corona radiata and centrum semiovale in MRI
MRI: Magnetic resonance imaging

Table 2. Correlation of arrival- carboxyl hemoglobin, lactate, troponin T, creatine kinase-myocardial band

	Arrival COHb	Lactate (mmol/L)	Troponin T	CK-MB	
Arrival COHb	1	0.098	0.059	-0.003	Pearson correlation
		0.421	0.662	0.983	Sig. (2-tailed)
Lactate	0.098		-0.082	-0.017	Pearson correlation
	0.421		0.556	0.906	Sig. (2-tailed)
Troponin T	0.059	-0.082		0.138	Pearson correlation
	0.662	0.556		0.269	Sig. (2-tailed)
CK-MB	-0.003	-0.017			Pearson correlation
	0.983	0.906			Sig. (2-tailed)

p<0.05, COHb: Carboxyl hemoglobin, CK-MB: Creatine kinase-myocardial band, Sig: Strikethrough

had a COHb level of 45.9% and lactate was 5.3 mmol/L. The normal level of COHb is 0.5-3%, and it is 3-7% in neonatal and 4-12% in smokers. Poisoning begins when the concentration is 15%. The toxic level is 20-50% and the lethal level is above 50-60%. COHb level was found 50% in people staying several hours in an environment with CO, and it was found as 25% in a person staying in such an environment for 34 minutes (14). Mild poisoning can have subtle symptoms such as headache, fatigue, weakness, gasping, nausea, and vertigo (COHb=15-30%). When the level of COHb exceeds 20%, the heart and brain are affected severely, and if it is above 30-70%, it leads to dizziness, vomiting, loss of muscular coordination, unconsciousness and death (15).

The first treatment option in CO poisoning is 100% O_2 (normobaric oxygen) treatment at least for six hours until reaching the normal values of COHb. The aim is to decrease COHb. Continuous oxygen treatment should be carried on until the patient becomes asymptomatic, or the level of COHb is below 10%. It should be decreased to 2% in those with cardiovascular or pulmonary symptoms (16).

HBO modulates the inflammatory processes that cannot be maintained with normobaric oxygen, enhances mitochondrial function, and temporarily inhibits lipid peroxidation. It also repairs leukocyte adhesion to damaged microvasculature and promotes myelin formation in the brain. Therefore, HBO treatment is recommended in acute symptomatic CO poisoning and, in the same way, in poisoning due to CO inhalation for patients with unconsciousness and those with the permanent neurological deficit; nevertheless, it remains somehow unclear (17,18). Brain CT or MRI should be used for excluding the reasons for a neurological disorder, not for diagnostic reasons. Hypoxic brain damage is primarily observed in the cerebral cortex, cerebral white matter, and basal ganglions, especially in Globus pallidus (19). In our study, cranial MRI findings that suggest CO positioning were determined in four cases; millimetric signal enhancements being concordant with chronic microangiopathic ischemic gliotic foci in white matter were determined in the level of the periventricular field, bilateral corona radiata, and centrum semiovale.

A standard HBO treatment protocol for CO poisoning includes 100% oxygen for 90 minutes. Cases with moderate symptoms can benefit from the initial treatment. However, for the patients whose symptoms do not regress, second or third treatment sessions could be planned. Temporary unconsciousness, coma or seizure, ischemic ECG changes, focal neurological deficit, pregnant women with COHb levels >15%, COHb levels exceeding 40% together with headache and nausea are the indications for HBO treatment. The only absolute contraindication for HBO treatment is untreated pneumothorax (20). In a study involving 68 centers from 23 countries, temporary or prolonged unconsciousness was accepted as an indication for HBO treatment in 95% of the centers; also, positive neurologic findings, acute cardiac ischemia and, pregnancy were of priority for HBO treatment (21). Our priorities were formed by these data in our four cases; for our first case, the symptoms regressed after the first session, and therefore, the treatment program was terminated, nevertheless for our second case, there was no regression even after three sessions. In their ten years of study, Chan et al. (22) administered HBO treatment for 24 of 93 patients, and none of these patients were found to have neurological sequelae in the follow-up. Neurological sequelae were found in seven patients who were not treated with HBO. The degree of the patient's consciousness on admission to the hospital, GCS score, increased troponin levels, creatine kinase, and intubation requirement were defined as prognostic factors for the development of neurological sequelae (21,23,24).

CONCLUSION

There was no correlation between arrival-COHb levels of the patients and lactate, CK-MB and troponin T in CO poisoning. Radiological evaluation should be used for excluding the reasons for a neurological disorder, not for diagnostic reasons. The first treatment option is 100% oxygen treatment for at least six hours. HBO treatment plan to reduce the half-live of COHb should be prepared considering prognostic factors; national protocols are required for the issue.

Ethics

Ethics Committee Approval: Following the approval of the Ethics Committee of Ministry of Health Okmeydanı Training and Research Hospital (approval date: 14/06/2016, decision no: 495), the patients admitted to emergency service with a pre-diagnosis of CO poisoning between the years 2014 and 2016 were screened retrospectively.

Informed Consent: Retrospective analysis.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.T., B.A., N.A., S.K., S.D.Ö., E.D., H.F., Y.İ., T.M., Concept: N.T., B.A., Design: N.T., B.A., Data Collection or Processing: N.T., B.A., N.A., İ.G., E.D., H.F., Y.İ, Analysis or Interpretation: N.T., B.A., İ.G., Literature Search: N.T., B.A., S.K., T.M., İ.G., Writing: N.T., B.A., T.M.

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Mean Platelet Volume in Myocardial and Neurological Injury Associated with Carbon Monoxide Poisoning

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Abstract

Objective: Carbon monoxide (CO) poisoning is one of the most commonly encountered causes of fatal intoxication worldwide. Mean platelet volume (MPV) elevation has been shown in several diseases associated with tissue hypoxia and inflammation. This study investigated the association between MPV levels and CO poisoning and examined the relations between MPV and myocardial or neurological injury.

Methods: The research was planned as a single-center, prospective, cross-sectional clinical study. Cases with ischemic chest pain, ischemic electrocardiography change, or troponin elevation were classified as CO poisoning-related myocardial injury. Cases with severe neurological findings were classified as CO poisoning-related neurological injury.

Results: Eighty-nine patients with CO poisoning and 20 healthy volunteers were enrolled. Mean MPV levels at the presentation in patients with CO poisoning were 9.26±0.99 femtolitre (fL), and 9.19±0.97 (fL) in patients with myocardial injury and 9.11±1.04 (fL) in those with neurological injury. MPV values at the presentation in patients with CO poisoning were significantly higher than those in healthy volunteers ($p<0.001$).

Conclusion: MPV rises significantly in CO poisoning compared to healthy individuals. However, this is not correlated with the clinical findings that may emerge and does not appear to be a reliable parameter in identifying the potential myocardial or neurological injury.

Keywords: Carbon monoxide poisoning, mean platelet volume, hypoxia, platelet activation

INTRODUCTION

Carbon monoxide (CO) is a colorless, tasteless, scentless, and non-irritating gas resulting from the incomplete burning of carbon-containing fuels (1,2). CO poisoning is one of the most commonly encountered causes of fatal intoxication worldwide. Various clinical outcomes, including such nonspecific symptoms as coma, may occur depending on the degree of poisoning. The early and late injury occurs in several organs, including the brain, heart, skeletal muscle, and kidneys. The most commonly affected systems in CO poisoning are the central nervous system and cardiovascular system, with their high oxygen dependence. Mortality, to a large extent, results from the involvement of these two systems, the most sensitive to the toxic effects of CO (3,4). The most important cause of the development of toxic effects in CO poisoning is tissue hypoxia, which results from the binding affinity to the hemoglobin of CO being higher than that of oxygen (5-7). CO, as in anemia, triggers myocardial damage by reducing oxygen content in the blood presented in the myocardium (8). Also, CO causes direct cellular injury by combining with extravascular proteins and also leads to the formation of free oxygen radicals by affecting oxidative metabolism. Inflammation and oxidation accompanying hypoxia in CO poisoning also contribute to the emergence of toxic effects (9,10).

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While platelets are primarily involved in preventing bleeding, they may also be involved in the release of pro-inflammatory, anti-inflammatory, and angiogenic factors, and in the accumulation of leukocytes and progenitor cells in areas of vascular injury and inflammation (11). Karabacak et al. (12) postulated the involvement of platelet activation in the etiopathogenesis of acute CO poisoning and investigated mean platelet volume (MPV), a marker of platelet activation, in patients presenting with CO intoxication. They determined higher levels than in the control group (12). MPV is one of the parameters routinely tested at complete blood count, and is a widely used indicator of platelet function, showing the mean volume of platelets in the circulation. Increased platelet activation and MPV elevation have been shown in several diseases associated with tissue hypoxia and inflammation (13,14).

This study was planned around the hypothesis of a possible association between MPV levels and clinical symptoms. The purpose of the study was to examine the relation between MPV levels and the development of myocardial or neurological injury.

METHODS

Design and Setting

The research was planned as a single-center, prospective, cross-sectional clinical study. It was performed in the emergency department of a tertiary hospital receiving 200.000 patient presentations annually. Patients presenting to the emergency department due to CO poisoning in the six months following receipt of approval from Kanuni Training and Research Hospital ethical committee (no: 2014/13) were enrolled as the study group. Information concerning the study was given to and signed consent received from all patients volunteering to participate, or from relatives if patients were unable to express consent. Also, 20 healthy volunteers were enrolled in order to determine any variation in MPV between patients with CO poisoning and healthy individuals.

Study Population

All patients with suspected CO poisoning based on their histories and physical examination, with serum carboxyhemoglobin (COHb) levels at the time of presentation above threshold values (>5% for smokers and >2% for non-smokers) and aged over 18 were enrolled as the study group. Patients not meeting these criteria or not being monitored due to needing to be transferred to another center for any reason were excluded from the study.

Clinical and demographic characteristics such as age at the time of presentation, sex, symptoms, physical examination findings, Glasgow Coma scale, electrocardiography (ECG), and laboratory records were recorded. Significant clinical parameters, such as symptoms, findings, and treatment administered throughout the study from the time of presentation, were also recorded. Patients with any one of ischemic chest pain, ischemic ECG changes, or troponin elevation at the end of the study period were classified as the CO poisoning-related myocardial injury group. Differences in terms of COHb and MPV between patients with or without myocardial injury were investigated. Patients with CO poisoning with more serious neurological symptoms and findings, other than mild headache and dizziness, such as lethargy, loss of consciousness, seizure, or coma, were classified as subjects with CO poisoning-related neurological injury. Differences in terms of COHb and MPV between patients with or without neurological injury were investigated.

MPV levels were also measured, after receipt of consent, from 20 healthy volunteers presenting to the emergency department in order to compare MPV between patients with CO poisoning and healthy individuals.

Laboratory Measurements

Patients' COHb and MPV levels were measured twice, at presentation to the emergency department, and at discharge after hyperbaric oxygen (HBO) or normobaric oxygen (NBO) therapy. Only one blood specimen was taken from the healthy control for MPV measurement. Blood specimens collected for MPV measurements were placed into ethylenediaminetetraacetic acid containing tubes. Measurements were performed within 15 min using a Mindray BC-5800 automatic hematology analyzer. COHb measurement was performed from arterial blood specimens using a radiometer Abl80 CO-OX blood gas analysis device.

Statistical Analysis

Collected data were entered into SPSS 13. software for statistical analysis. Compatibility with the normal distribution of numerical data was evaluated using the Kolmogorov-Smirnov test. Categoric data were expressed as frequency and percentage (n, %) and numerical data as mean ± standard deviation. The Student's t-test was used to compare normally distributed numerical data in independent groups and the chi-square test for the comparison of categoric data. Wilcoxon's t-test was used to compare COHb and MPV levels at the time of presentation to the emergency department and discharge. Relations between COHb and MPV were evaluated using Pearson correlation analysis. Significance was set at $p<0.05$.

RESULTS

Clinical and Demographic Characteristics

Eighty-nine patients with CO poisoning and 20 healthy volunteers were included in the study. No patients died during the study, and all intoxications were accidental. Forty-six (51.7%) of the 89 patients with CO poisoning were male, and 43 (48.3%) were female. Ten (50%) of the 20 healthy volunteers constituting the control group were male, and 10 (50%) were women. There was no statistical significance between the groups in terms of gender distribution (p=0.894). The mean age of the patients in the CO poisoning group was 39.3±16.1 years, compared to 38.1±7.4 in the control group. The difference was not statistically significant (p=0.747). Demographic data for the study group are shown in Table 1.

Basic Results

COHb at the time of presentation of patients with CO poisoning was 22.4±8.8 (%), and MPV levels were 9.26±0.99 femtolitre (fL). The mean MPV level in the healthy volunteers constituting the control group was 7.57±0.51 (fL). MPV levels at the time of presentation in patients with CO poisoning were significantly higher than those in the control group (p<0.001). No correlation was determined between COHb and MPV levels in patients with CO poisoning (r=0.142, p=0.186). COHb and MPV levels according to symptoms and findings at the time of presentation in our patients with CO poisoning are shown in Table 2. Based on our findings, COHb levels in patients with ischemic-type chest pain among symptoms at presentation were significantly higher than those in patients without chest pain (p=0.008). No significant correlation was determined between other symptoms and findings and COHb and MPV levels.

Relations Between MPV and Myocardial and Neurological Injury

Nine patients (10.1%) were classified as the CO poisoning-related myocardial injury group. Fifty-four patients (60.7%) were classified as patients with CO poisoning-related neurological injury. COHb and MPV levels measured at the time of presentation and discharge based on CO poisoning-related myocardial or neurological injury based on this classification are shown in Table 3. Receiver-operating characteristic (ROC) curves obtained from ROC analysis performed in order to determine optimal cut-off values for COHb and MPV levels at the time of presentation in the prediction of myocardial and neurological injury are presented in Figures 1a, 1b, and 2a, 2b. Probable and optimal cut-off values based on these curves are shown in Tables 4 and 5.

Based on these findings, COHb levels at the time of presentation were higher in subjects with myocardial injury than in those without. However, MPV levels in subjects with a myocardial injury did not differ from levels in those without. Similarly, neither COHb nor MPV values investigated at the time of presentation emerged as markers of neurological injury.

Table 1. Demographic characteristics of patients with carbon monoxide poisoning

Characteristics	
Sex n, (%)	
M	46 (51.7)
F	43 (48.3)
Age (mean ± SD)	39.3±16.1
M	37.1±14.2
F	41.7±17.9
Cause of exposure to CO n, (%)	
Stove	73 (82%)
Fire/smoke	9 (10%)
Water heater	6 (7%)
Generator	1 (1%)
The month of exposure to CO	
October	9 (10%)
November	6 (7%)
December	12 (14%)
January	23 (25%)
February	11 (13%)
March	23 (25%)
April	5 (6%)
Symptoms and findings at the time of presentation n, (%)	
Headache	64 (71.9%)
Nausea-vomiting	55 (61.8%)
Dizziness	47 (52.8%)
Lethargy	47 (52.8%)
Clouded consciousness	13 (14.6%)
Palpitation	11 (12.4%)
Blurred vision	8 (9%)
Respiratory difficulty	7 (7.9%)
Chest pain	7 (7.9%)
Troponin-I increase	7 (7.9%)
Loss of consciousness	4 (4.5%)
Ischemic ECG change	4 (4.5%)
Muscle pain	1 (1.1%)
Abdominal pain	1 (1.1%)

CO: Carbon monoxide, MPV: Mean platelet volume, SD: Standard deviation, ECG: Electrocardiography, F: Female, M: Male

Table 2. Carboxyhemoglobin and mean platelet volume levels at the time of presentation to the emergency service in patients with carbon monoxide poisoning in terms of symptoms and findings

		Parameter	
		COHb % (Mean ± SD)	MPV fL (Mean ± SD)
Headache (n=64)	+	22.68±9.27	9.33±1.01
	-	21.86±7.70	9.08±0.93
	p values	0.696	0.292
Nausea-vomiting (n=55)	+	22.42±8.60	9.30±0.97
	-	22.50±9.30	9.19±1.04
	p value	0.968	0.626
Dizziness (n=47)	+	22.70±9.18	9.05±1.09
	-	22.18±8.51	9.49±0.82
	p values	0.785	0.041
Lethargy (n=47)	+	24.12±8.64	9.39±0.95
	-	20.59±8.75	9.11±1.03
	p value	0.059	0.185
Clouded consciousness (n=13)	+	24.95±10.35	9.46±1.05
	-	22.08±8.59	9.21±0.98
	p value	0.283	0.398
Palpitation (n=11)	+	25.85±10.93	9.70±0.85
	-	21.97±8.46	9.20±1.00
	p value	0.174	0.113
Blurred vision (n=8)	+	24.15±11.2	9.52±1.05
	-	22.34±8.66	9.22±0.99
	p value	0.585	0.420
Respiratory difficulty (n=7)	+	22.71±11.31	9.55±0.77
	-	22.43±8.66	9.23±1.01
	p value	0.937	0.419
Chest pain (n=7)	+	30.84±11.69	9.80±0.17
	-	21.74±8.24	9.21±0.97
	p values	**0.008**	0.138
Troponin-I increase (n=7)	+	25.02±11.79	9.71±0.89
	-	22.23±8.58	9.22±0.99
	p value	0.425	0.213
Loss of consciousness (n=4)	+	27.40±14.83	9.75±1.25
	-	22.27±8.55	9.22±0.98
	p value	0.261	0.309
Ischemic ECG change (n=4)	+	27.52±14.56	9.80±1.33
	-	22.22±8.52	9.23±0.98
	p value	0.242	0.272
Muscle pain (n=1)	+	22.90±0	9.10±0
	-	22.37±8.84	9.26±1.00
	p value	0.400	0.870
Abdominal pain (n=1)	+	14.70±0	9.70±0
	-	22.54±8.83	9.25±1.00
	p value	0.380	0.661

MPV: Mean platelet volume, COHb: Carboxyhemoglobin, ECG: Electrocardiography, SD: Standard deviation, fL: Femtolitre, p<0.05

The Effect of Normobaric or Hyperbaric Oxygen Therapy on MPV Levels

Eighty (89.9%) of our patients received NBO therapy, and 9 (10.1%) received HBO therapy. Pre-treatment COHb levels of patients presenting to our emergency department with CO poisoning

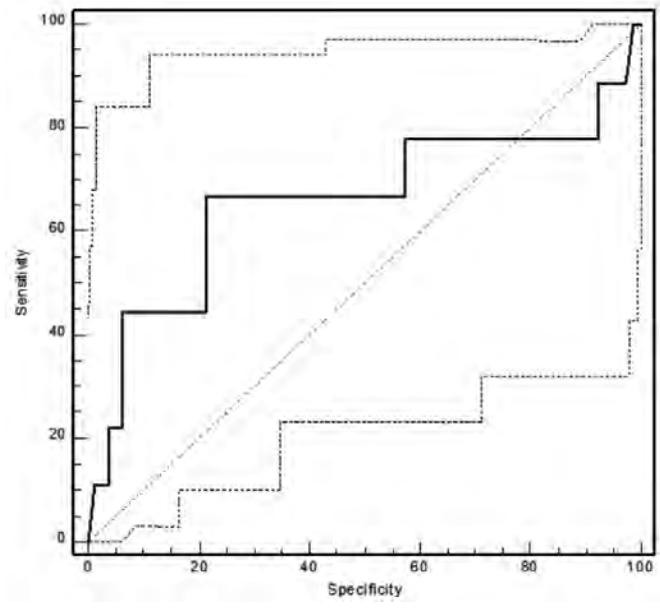

Figure 1a. ROC curves obtained at ROC analysis performed to determine the optimal cut-off of COHb levels for the development of CO poisoning-related myocardial injury

ROC: Receiver-operating characteristic, COHb: Carboxyhemoglobin, CO: Carbon monoxide

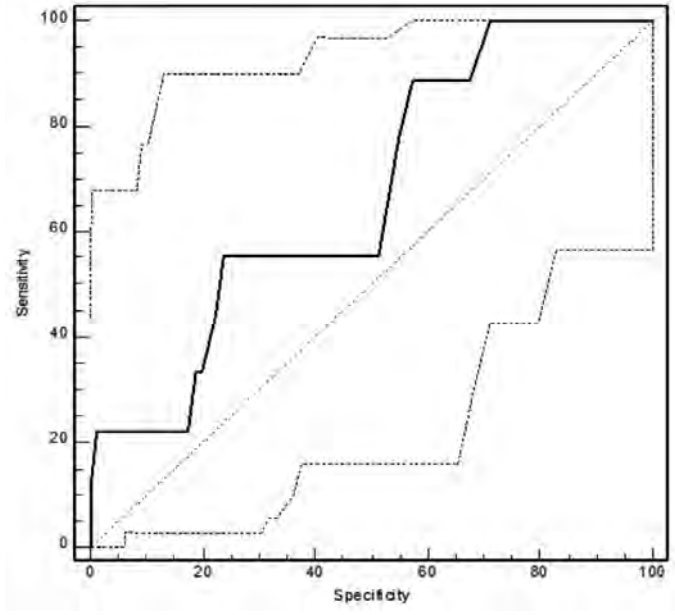

Figure 1b. ROC curves obtained at ROC analysis performed to determine the optimal cut-off of MPV levels for the development of CO poisoning-related myocardial injury

ROC: Receiver-operating characteristic, MPV: Mean platelet volume, CO: Carbon monoxide

were 22.4±8.8 (%), decreasing to 2.71±1.33 (%) after therapy. Pre-treatment MPV levels were 9.26±0.99 (fL), decreasing to 8.86±0.95 (fL) after treatment. These decreases in COHb and MPV levels after NBO or HBO were significant (p<0.001).

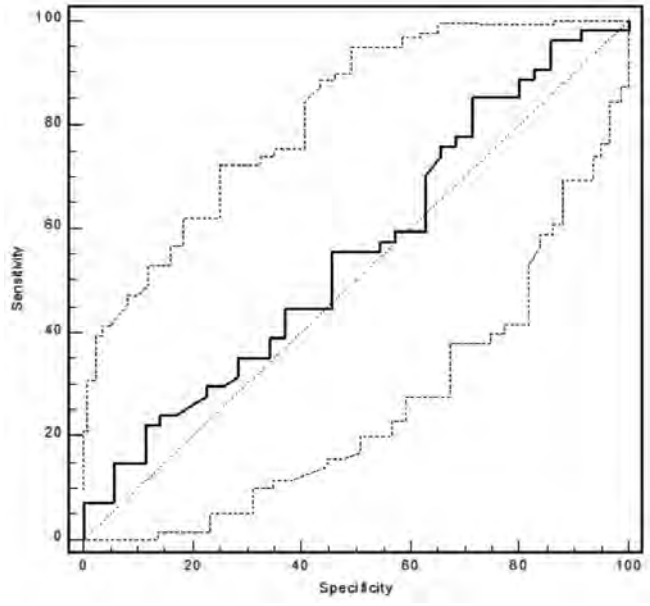

Figure 2a. ROC curves obtained at ROC analysis performed to determine the optimal cut-off of COHb levels for the development of CO poisoning-related neurological injury

ROC: Receiver-operating characteristic, COHb: Carboxyhemoglobin, CO: Carbon monoxide

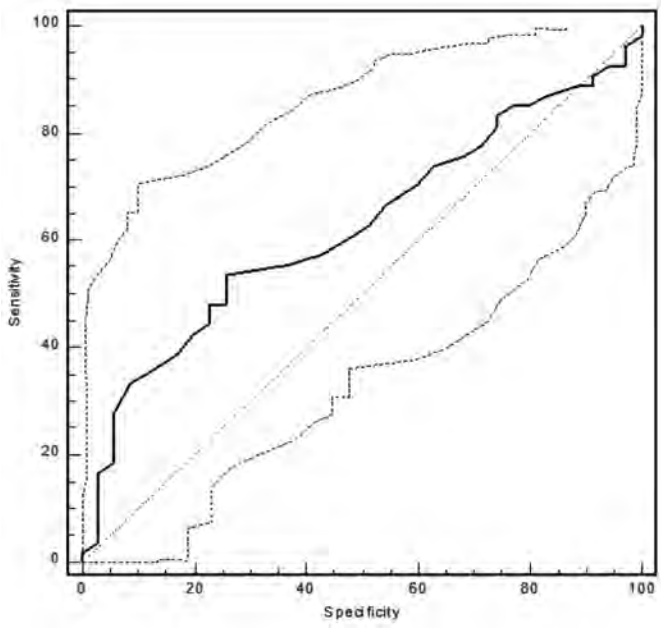

Figure 2b. ROC curves obtained at ROC analysis performed to determine the optimal cut-off of MPV levels for the development of CO poisoning-related neurological injury

ROC: Receiver-operating characteristic, MPV: Mean platelet volume, CO: Carbon monoxide

DISCUSSION

This study was planned on the hypothesis of a potential relation between MPV levels and clinical symptoms in patients with CO poisoning. We investigated the relationship between MPV levels and the development of myocardial or neurological injury. Although significantly higher MPV levels were determined in patients with CO poisoning compared to the healthy controls, that elevation was not associated with clinical symptoms and findings. It does not appear possible for high MPV levels in patients with CO poisoning to be used as a marker or myocardial or neurological injury.

Serum COHb level is still the most crucial test in the diagnosis of CO poisoning. However, several studies in the literature show no correlation between COHb elevation and clinical severity (15). Initially investigated COHb levels are not correlated with symptoms, the severity of intoxication, or late neurological sequelae that may develop. This may be attributed to the time lost until arrival at the emergency department or to a rapid decrease in COHb levels with oxygen therapy administered before arrival at the hospital so that COHb levels measured on arrival at the emergency department are too low to be associated with the clinical condition (15,16). Although high COHb levels are essential in the diagnosis of the disease, predicting the clinical course based on this parameter will not be particularly reliable. In this study, we investigated the association between clinical intoxication and MPV shown to rise in hypoxic conditions in addition to COHb levels. COHb and MPV levels in the determination of myocardial and neurological injury in CO poisoning were evaluated based on symptoms at the time of presentation and clinical markers during observation. Based on our findings, only COHb levels of patients with ischemic-

Table 3. Carboxyhemoglobin and mean platelet volume levels at the time of presentation to the emergency department in terms of carbon monoxide poisoning-related myocardial and neurological injury and carboxyhemoglobin and mean platelet volume levels at the time of discharge

		Presentation	
		COHb % (Mean ± SD)	**MPV fL (Mean ± SD)**
Myocardial injury (n=9)	+	28.28±12.21	9.19±0.97
	-	21.80±8.20	9.83±1.02
	p value	**0.036**	0.070
Neurological injury (n=54)	+	23.14±9.08	9.11±1.04
	-	21.40±8.42	9.49±0.87
	p value	0.365	0.078

MPV: Mean platelet volume, COHb: Carboxyhemoglobin, SD: Standard deviation, p<0.05

type chest pain symptoms at the time of presentation and evaluated as having myocardial injury were significantly higher than those of subjects with no such symptoms. No significant correlation was observed between COHb and MPV levels and other symptoms and findings.

MPV is a marker of platelet function and activation. MPV has been shown to increase in association with an increase in young platelets in the circulation in the presence of a stress factor stimulating platelet production (17). In our study, MPV levels studied at the time of presentation to the emergency department in cases of CO poisoning were significantly higher compared to the MPV levels of healthy individuals. Karabacak et al. (12) also reported significantly higher MPV values in patients with CO poisoning compared to a healthy control group. However, and similarly to Karabacak et al. (12) study, the MPV levels in our study being higher than those in healthy individuals confirming the idea that platelet activation is an essential component of the pathogenesis of CO poisoning. The factor most probably leading to platelet activation in CO poisoning is thought to derive from various mechanisms triggering hypoxia. CO impairs the electron transport chain by binding to cytochrome c oxidase, increases the level of nitric oxide released from thrombocytes, and increases the production of free oxygen radicals (18). Increased free oxygen radicals lead to changes in platelet aggregation and adhesion and blood circulation (12). This entire process can be

Table 4. Probable cut-off values for development of carbon monoxide poisoning-related myocardial injury

	AUC (95% CI)	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	-LR (95% CI)	PPV (95% CI)	NPV (95% CI)
COHb	0.658 (0.550-0.756)	>11.6	88.89 (51.7 98.2)	7.50 (2.815.6)	0.96 (0.42.1)	1.48 (0.29.4)	9.8 (4.318.3)	85.7 (42.297.6)
		>28.2*	66.67 (30.1 92.1)	78.75 (68.287.1)	3.14 (1.95.0)	0.42 (0.21.2)	26.1 (10.348.4)	95.5 (87.399.0)
		>38.7	22.22 (3.5 59.9)	96.25 (89.499.2)	5.93 (1.720.1)	0.81 (0.32.6)	40.0 (6.584.6)	91.7 (83.696.6)
MPV	0.672 (0.565-0.768)	>8.5	88.89 (51.7 98.2)	32.50 (22.443.9)	1.32 (0.91.9)	0.34 (0.052.2)	12.9 (5.724.0)	96.3 (81.099.4)
		>9.8*	55.56 (21.4 86.0)	76.25 (65.485.0)	2.34 (1.34.2)	0.58 (0.31.3)	20.8 (7.242.2)	93.8 (85.098.3)
		>11.1	22.22 (3.5 59.9)	98.75 (93.299.8)	17.78 (5.260.4)	0.79 (0.15.7)	66.7 (11.694.5)	91.9 (83.996.7)

MPV: Mean platelet volume, COHb: Carboxyhemoglobin, +LR: Positive likelihood ratio, -LR: Negative likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under curve, CI: Confidence interval, *: Optimal cut-off values

Table 5. Probable cut-off values for development of carbon monoxide poisoning-related neurological injury

	AUC (95% CI)	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	-LR (95% CI)	PPV (95% CI)	NPV (95% CI)
COHb	0.553 (0.444-0.659)	>11.6	96.30 (87.299.4)	14.29 (4.930.3)	1.12 (0.52.5)	0.26 (0.071.0)	63.4 (52.073.8)	71.4 (29.395.5)
		>13.9*	85.19 (72.993.4)	28.57 (14.746.3)	1.19 (0.72.0)	0.52 (0.31.0)	64.8 (52.575.8)	55.6 (30.878.4)
		>34.3	14.81 (6.627.1)	94.29 (80.899.1)	2.59 (1.44.9)	0.90 (0.23.5)	80.0 (44.496.9)	41.8 (30.853.4)
MPV	0.625 (0.516 -.725)	≤8	16.67 (7.929.3)	97.14 (85.099.5)	5.83 (3.210.6)	0.86 (0.15.9)	90.0 (55.598.3)	43.0 (31.954.7)
		≤9*	53.70 (39.667.4)	74.29 (56.787.5)	2.09 (1.52.9)	0.62 (0.31.2)	76.3 (59.888.5)	51.0 (36.665.2)
		≤10.9	92.59 (82.197.9)	5.71 (0.919.2)	0.98 (0.33.8)	1.30 (0.53.3)	60.2 (48.970.8)	33.3 (5.377.3)

MPV: Mean platelet volume, COHb: Carboxyhemoglobin, +LR: Positive likelihood ratio, -LR: Negative likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under curve, CI: Confidence interval, *: Optimal cut-off values

regarded as the mechanism causing an increase in MPV in CO poisoning. Interleukin-6 has been shown to cause an increase in platelet volume during thrombopoiesis in bone marrow in various other hypoxic conditions other than CO poisoning (19-21). High MPV values are associated with cardiovascular and cerebrovascular pathologies giving rise to significant morbidity and mortality (22-24). Platelets may also play a significant role in the development of cardiovascular and cerebrovascular events in subsequent periods in patients with CO poisoning. In our study, however, we determined no significant elevation in MPV levels in the myocardial injury group established based on the criteria of ischemic chest pain, ischemic ECG changes, or increased troponin levels. Similarly, no significant difference was observed in MPV levels between patients with CO poisoning and suspected neurological injury compared to those with no such injury. However, the fact that NBO or HBO caused a significant decrease in MPV levels, as well as COHb, suggests that MPV levels may be useful in evaluating the effectiveness of treatment. If further, wider-ranging studies support this, then MPV values may be used as a marker for guiding treatment in patients with CO poisoning, and patients with MPV elevation may require closer monitoring or more aggressive treatment.

A few studies have shown that MPV levels decrease with the correction of hypoxia. In a study of patients with obstructive sleep apnea syndrome (OSAS), Varol et al. (25) assessed the effectiveness of continuous positive airway pressure (CPAP) therapy on MPV. They reported that MPV values were significantly higher in patients with severe OSAS compared to the control group and that 6-month CPAP therapy led to a significant decrease in MPV values in patients with severe disease (25). Similarly, in our study, oxygen therapy administered to cases of CO poisoning significantly reduced MPV.

The basis of the treatment in CO poisoning is the elimination of CO and the minimization of injury, together with the reversal of cellular metabolic dysfunction. The most critical step in the treatment of CO poisoning is the administration of 100% oxygen. Patients with a high suspicion of CO poisoning must be started on NBO therapy without waiting for the COHb results. HBO therapy is required for patients with confusion, altered consciousness, a history of loss of consciousness (presyncope or syncope), convulsion, coma, focal neurological deficit or findings of acute myocardial ischemia, pregnant subjects with COHb levels above 15%, or with symptoms (headache or neurological symptoms) persisting despite 4-6 h 100% NBO therapy (26). The HBO option is not available in most centers. Treatment is, therefore, usually restricted to NBO. Although the option of HBO is available in the center in which the study was performed, very few patients have received this due to the lack of an underwater and hyperbaric physician able to provide the service. Problems regarding the means for providing HBO or inaccessibility of a physician capable of performing it are a significant problem frequently encountered in the management of patients with CO poisoning.

When CO binds to myoglobin in heart muscle, it impairs oxygen transport in the mitochondria and causes myocardial dysfunction. Myocardial ischemia results from an imbalance between blood supply and oxygen requirements in the myocardium. One study showed that CO poisoning also elevated cardiac markers in patients with healthy cardiac arteries. That study reported high creatine kinase - myocardial band and Tn-I levels in 30% of patients without obstructive lesions (27). Based on our results, only COHb levels investigated at the time of presentation are higher in patients with myocardial injury compared to patients without myocardial injury and may represent a marker capable of use in predicting myocardial injury. However, MPV levels investigated at the time of presentation do not vary between patients with or without myocardial injury. Since rising MPV in patients with CO poisoning plays a vital role in the development and progression of intracoronary thrombus, MPV may be a risk factor for myocardial infarction in the chronic period. MPV may, therefore, be a marker capable of use in predicting myocardial injury that occurs in later stages in patients with CO intoxication. Wider-ranging studies are now needed to determine this.

We determined no significant elevation in either COHb or MPV levels at the time of presentation in patients we classified as having CO poisoning-related neurological injury. The decrease in COHb and MPV levels and improvement in some symptoms may be due, as already described, to the time lost before patients' arrival at the emergency department or to oxygen therapy administered by the 112 emergency service.

Limitations

This study has several limitations. First, our study population was small, and the number of cases with severe CO poisoning was very low. Therefore, in post hoc power analysis, the power of our study was determined as 62%. Our findings may be affected by the low number of severe CO poisoning patients and the low number of CO poisoning patients, especially cardiac damage. The difference between MPV levels in patients with neurologic or myocardial damage and non-CO poisoning may have caused this situation to be meaningless. Second, the oxygen therapy administered by the 112 emergency service during transportation may have caused changes in COHb, MPV, and symptoms and thus have prevented us from obtaining reliable findings. Although the center where

this study was performed does have the equipment with which to provide HBO, very few patients receive it due to the lack of an underwater and hyperbaric physician therapeutic option.

CONCLUSIONS

Based on our study findings, MPV in CO poisoning increases significantly compared to that in healthy individuals and decreases after oxygen therapy. However, this elevation does not appear to be a parameter correlated with which symptoms or findings will be seen in which patient, nor to be an effective predictor of myocardial or neurological injury.

Ethics

Ethics Committee Approval: Kanuni Training and Research Hospital (No: 2014/13)

Informed Consent: Informed consent was given from all patients volunteering to participate, or from relatives if patients were unable to express consent

Peer-review: Externally and internally peer-reviewed

Authorship Contributions

Surgical and Medical Practices: A.A.T., G.A., Ş.A., Ö.T., Concept: S.T., Design: Ş.A., A.A.T., Data Collection or Processing: A.A.T., G.A., Analysis or Interpretation: S.T., A.Ş., Literature Search: A.A.T., G.A., Writing: A.A.T., A.A.

Conflict of Interest: The authors state no conflict of interest.

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ORIGINAL ARTICLE

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Evaluation of Preoperative and Postoperative Findings in Hysterectomy Cases for Benign Conditions

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Abstract

Objective: To evaluate the demographic patient characteristics, indications, operative findings, preoperative and postoperative histopathology reports in hysterectomies for benign conditions in our clinic.

Methods: One thousand four hundred seventeen patients who underwent hysterectomy for benign conditions were included in the study. Patient files and records from the Hospital Information Management system were reviewed. IBM SPSS Statistics 22 program was used for statistical analysis. Shapiro Wilks, One-way ANOVA, Tamhane's, Kruskal-Wallis, Mann-Whitney U, chi-square and Fisher's Exact test and Continuity (Yates) Correction were used as statistical tests. Statistical significance was defined as $p<0.05$.

Results: Mean age of the patients was 50.78±9.24, mean gravidity and parity were 4.09±2.56 and 3.06±1.96, respectively. History of gynecological surgery, cesarean section and non-gynecological abdominal surgery were 26.7%, 17.1%, and 11.2%, respectively. The most common indication was uterine myoma with 43%, 78.3% of the patients had abdominal, 14.3% had vaginal, 6.5% had laparoscopic hysterectomy. Complications occurred in 5.4% of the cases; major in 3.2% and minor in 2.2%. Patient age, gravidity and parity in vaginal hysterectomy cases were higher. The rate of cesarean section history (28.9%) in the group with subtotal hysterectomy was significantly higher than the rate of cesarean section history (16.3%) in the group with total hysterectomy. Postoperative histopathology results were reported as leiomyoma in 53.6% and adenomyosis in 23.1%.

Conclusion: Hysterectomy is the most commonly performed gynecological operation. It may be done abdominally, vaginally or laparoscopically. The most common indication for hysterectomy is symptomatic uterine myomas. The preferred route of operation should be based on the charecteristics and findings of the patient. If there is no contraindication, vaginal hysterectomy should be the preferred operation type.

Keywords: Hysterectomy, indications, histopathology, complications

INTRODUCTION

Removal of all or part of the uterus from the abdominal or vaginal way is called hysterectomy. Hysterectomy is the most commonly applied major gynecologic surgical operation (1).

Hysterectomy rates, indications, and mean ages show great differences among countries and even different regions of the same country. Up to sixfold differences can be seen between the United States, which has the highest rate of hysterectomy and Norway, Sweden and the UK with the lowest rate of hysterectomy (2,3).

Hysterectomies due to benign reasons are commonly performed with abdominal, vaginal, laparoscopic, and robotic methods. Vaginal hysterectomy has advantages because the surgical trauma rate is low, and healing is rapid. But only 25% of all hysterectomies can be performed vaginally (4).

The aim of this study is to retrospectively evaluate demographic features, indications, operation types, pathology results, and postoperative complications of cases who had hysterectomy between 1 January 2014 and 30 November 2017.

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METHODS

This study was initiated after approval was obtained from Okmeydanı Training and Research Hospital Ethics Committee with a date of 21.11.2017 and a number of 764. The study included 1417 patients who admitted to Gynecology and Obstetrics Clinic and had a hysterectomy for benign reasons. Patient files and the records obtained from the Hospital Data Management system were assessed. Operation date, age at operation date, menopausal status, gravity and parity, history of previous operations, Existing Medical diseases, preoperative indication for hysterectomy, operation technique, the performance of salpingo-oopherectomy, operative complications, and postoperative histopathology results were evaluated.

Patients who were operated due to gynecologic malignancies, who were diagnosed as malignant during operation, whose results came to be malignant although the operation was for a benign reason, and who had hysterectomy due to an urgent obstetric reason were excluded.

The indications for the operation were adnexal mass, the descent of uterus, myoma uteri, endometrial hyperplasia, treatment-resistant abnormal uterus bleeding, peristent postmenopausal bleeding, cervical intraepithelial neoplasia, chronic pelvic pain, tuboovarian abscess, and breast cancer.

The operation techniques were grouped as abdominal hysterectomy, vaginal hysterectomy, laparoscopic hysterectomy, and laparoscopic assisted vaginal hysterectomy. In addition, subtotal hysterectomies were determined. Patients who had bilateral and unilateral salpingo-oopherectomy were grouped.

The operative complications were grouped into two: major and minor complications. Complications such as wound infection treated with antibiotics, cuff hematoma, which was followed and treated without surgical intervention, and subileus were called as minor complications. Urinary system injuries, gastrointestinal system injuries, peritonitis, fistula, intraabdominal hemorrhage, and abscess requiring relaparatomy, debrided wound infection, dehiscence, and pulmonary embolism were called as major complications.

Statistical Analysis

IBM SPSS 22 package program was used to analyze the data obtained in the study. Normality of the distribution of study parameters was evaluated with Shapiro-Wilks test. Mean, standard deviation, and frequency were used as descriptive statistics. To analyze quantitative data, One-way ANOVA was used to compare the groups for normally distributed parameters, and Tamhane's T2 test was used to detect the group which was responsible for the difference. The Kruskal-Wallis test was used to compare the groups for non-normally distributed parameters, and the Mann-Whitney U test was used to detect the group which was responsible for the difference. The chi-square test, Fisher's Exact test, and Continuity (Yates) Correction, were used to compare qualitative data. The significance level was accepted as $p<0.05$.

RESULTS

This study included 1417 women who had a hysterectomy due to benign causes. The mean age was 50.78±9.24. 27.7% of the women were operated in 2015, 27.2% were operated in 2014, 25.9% were operated in 2016, and 19.2% were operated in 2017.

Obstetric histories of women revealed that the number of parities was between 0 and 16, and the mean number was 3.06±1.96. Gravidity numbers ranged from 0 to 22, with a mean number of 4.09±2.56.

In 62.1% of the cases, there wasn't a history of previous abdominal surgery. 26.7% had a history of gynecological surgery, and 11.2% had a history of nongynecological abdominal surgery. 17.1% of the women had a history of caesarean section.

In 47% of the cases, there were accompanying medical diseases. 34.9% of all cases were at the postmenopausal period (Table 1).

Preoperative indications of the patients were myoma uteri (43%), adnexal mass (15.9%), descent of uterus (15.3%), treatment-resistant abnormal uterus bleeding (12.8%), endometrial hyperplasia (6.1%), persistent menopausal hemorrhage (2.6%), cervical intraepithelial neoplasia (2.5%), breast cancer (0.7%), tuboovarian abscess (0.6%), and chronic pelvic pain (0.4%) (Table 2).

The comparison of hysterectomy techniques revealed that 78.3% of the patients had abdominal hysterectomy, 14.3% had vaginal hysterectomy, 6.5% had laparoscopic hysterectomy, and 0.8% had laparoscopic assisted vaginal hysterectomy. The operation type was total hysterectomy in 94.1% of the patients and subtotal hysterectomy in 5.9%. Bilateral salpingo-oophorectom (BSO) was performed in 69.5% of the patients in addition to hysterectomy, and unilateral salpingo-oophorectomy (USO) was performed in 6.3% (Table 3).

Perioperative and postoperative complications were detected in 5.4% of the patients. 3.2% of the complications were major, and 2.2% were minor complications (Table 4).

There was a statistically significant difference in the distribution of surgery techniques among study years ($p=0.008$; $p<0.05$).

Binary comparisons to detect the cause of the difference revealed that the rate of patients who were operated with abdominal hysterectomy in 2014 (83.6%) was higher than 2015 (p=0.029; %79.6), 2016 (p=0.001; %74.1), and 2017 (p=0.006; %74.6). There was no statistically significant difference in terms of the distribution of surgical techniques among other years (p>0.05) (Table 5).

There was a significant difference in surgical technique in terms of mean age (p=0.000; p<0.05). Binary comparisons to detect the cause of the difference revealed that the mean age of the patients who had vaginal hysterectomy was higher than the mean ages of the patients who had an abdominal or laparoscopic hysterectomy (p=0.000; p<0.05). No statistically significant difference was found in the mean ages of the patients between abdominal hysterectomy and laparoscopic hysterectomy (p>0.05).

There was a statistically significant difference in surgery technique according to the number of gravidities (p=0.000; p<0.05). Binary comparisons to detect the difference revealed that the number of gravidities was higher in patients who had vaginal hysterectomy compared with abdominal and laparoscopic hysterectomy (p=0.000; p<0.05). There was no statistically significant difference between patient groups who had an abdominal or laparoscopic hysterectomy in terms of gravidity (p>0.05).

There was a statistically significant difference among surgery techniques with regards to numbers of parity (p=0.000; p<0.05). Binary comparisons to establish the group responsible from the difference demonstrated that the number of parity in the vaginal hysterectomy group was statistically significantly higher than the groups who had abdominal and vaginal hysterectomies (p=0.000; p<0.05). There was no statistically significant difference between the patient group who had an abdominal or laparoscopic hysterectomy in terms of parity numbers (p>0.05).

Table 1. General features of the patients

		n	%
Age (Min-Max, Mean ± SD)		34-85	50.78±9.2
Number of operations according to years	**2014**	385	27.2
	2015	393	27.7
	2016	367	25.9
	2017	272	19.2
Gravida (Min-Max, Mean ± SD)		0-22	4.09±2.56
Parity (Min-Max, Mean ± SD)		0-16	3.06±1.96
Previous surgery	**No history of surgery**	880	62.1
	Gynecologic surgery	379	26.7
	Non-gynecologic surgery	158	11.2
Previous cesarean	**No**	1175	82.9
	Yes	242	17.1
Accompanying disease	**Yes**	666	47
	No	751	53

Min: Minimum, Max: Maximum, SD: Standard deviation

Table 2. Hysterectomy technique

		n	%
Operation technique	**Abdominal**	1110	78.3
	Vaginal	203	14.3
	Laparoscopic	92	6.5
	Laparoscopic-assisted vaginal	12	0.8
Total-subtotal hysterectomy	**Total**	1334	94.1
	Subtotal	83	5.9
Removal of ovaries in addition to hysterectomy	**Not removed**	343	24.2
	BSO	985	69.5
	USO	89	6.3

BSO: Bilateral salpingo-oophorectom, USO: Unilateral salpingo-oophorectomy

Table 3. Preoperative indications for surgery

		n	%
Indication for surgery	**Myoma uteri**	609	43
	Adnexal mass	225	15.9
	Descent of uterus	217	15.3
	Treatment-resistant hemorrhage	182	12.8
	Endometrial hyperplasia	87	6.1
	Persistent postmenopausal hemorrhage	37	2.6
	Cervical intraepithelial neoplasia	36	2.5
	Breast cancer	10	0.7
	Tubo-ovarian abscess	9	0.6
	Chronic pelvic pain	5	0.4

Table 4. Distribution of complications

		n	%
Complication	**No**	1341	94.6
	Minor	31	2.2
	Major	45	3.2
Presence of complication	**No**	1341	94.6
	Yes	76	5.4

There was a statistically significant difference in surgery techniques according to the rate of previous abdominal surgery groups (p=0.000; p<0.05). Binary comparisons to detect the group which was responsible from the difference revealed that in the vaginal hysterectomy group the rate of the patients who had a history of gynecological surgery (10.3%) was higher than those who had abdominal hysterectomy (p=0.000; 30.2%), and laparoscopic hysterectomy (p=0.019; 22.1%). No statistically significant difference could be found in abdominal and laparoscopic hysterectomy groups according to the rates of distribution of abdominal surgeries (p>0.05).

No statistically significant difference could be found in complication rates according to surgery techniques (p>0.05) (Table 6).

The evaluation of perioperative and postoperative complications and their management revealed that 34 patients had wound infection. In 25 of these patients, remission was achieved with antibiotics, and in 9 patients, debridement was performed. Laparotomy was performed to 10 patients for intraabdominal hemorrhage. In 4 patients, hematomas were detected at the vaginal cuff. In 9 patients, urinary tract injury (bladder, ureter) was detected. Two of the 8 patients who had bladder injury were detected at the postoperative period, and therefore, the repairment was performed at the postoperative period. In the other 6 patients, intraoperative repair was performed. Four patients were detected to have bowel injury, and primary repair was performed. Five patients had a postoperative pelvic abscess, and peritonitis and laparotomy were performed. One patient had a pulmonary embolus and cardiopulmonary arrest on the 4th postoperative day and died (Table 7).

In patients who had BSO and USO in addition to hysterectomy, a statistically significant difference was detected in mean age (p=0.000; p<0.05). In binary comparisons to detect the group responsible for the difference, the mean age of the group who had BSO was higher than the group who had hysterectomy or USO (p=0.000; p<0.05). No statistically significant difference could be detected in the mean ages of the groups who had only hysterectomy and hysterectomy plus USO (p>0.05). Because generally, oophorectomy is not performed during vaginal

Table 5. Evaluation of the operation technique in years

Operation technique	Year				p
	2014	2015	2016	2017	
	n (%)	n (%)	n (%)	n (%)	
Abdominal hysterectomy	322 (83.6%)	313 (79.6%)	272 (74.1%)	203 (74.6%)	**0.008***
Vaginal hysterectomy	49 (12.7%)	48 (12.2%)	60 (16.3%)	46 (16.9%)	
Laparoscopic hysterectomy	14 (3.6%)	32 (8.1%)	35 (9.5%)	23 (8.5%)	

Laparoscopic-assisted vaginal hysterectomy was analyzed by combining with laparoscopy due to a low number of cases, *p<0.05 chi-square test

Table 6. Evaluation of age, gravidity, parity, history of abdominal surgery, and presence of complications according to the operation technique

	Operation technique			p
	Abdominal	Vaginal	Laparoscopic	
	Mean ± SD	Mean ± SD	Mean ± SD	
Age	49.06±7.91	60.99±10.1	49.19±7.72	[1]**0.000***
Gravidity (median)	3.79±2.41 (3)	5.79±2.76 (5)	3.92±2.44 (3.5)	[2]**0.000***
Parity (median)	2.83±1.75 (2)	4.4±2.38 (4)	2.96±2.12 (3)	[2]**0.000***
History of abdominal surgery n (%)				
No	660 (59.5%)	151 (74.4%)	69 (66.3%)	[3]**0.000***
Gynecological surgery	335 (30.2%)	21 (10.3%)	23 (22.1%)	
Nongynecological surgery	115 (10.4%)	31 (15.3%)	12 (11.5%)	
Presence of a complication n (%)				
No	1043 (94%)	199 (98%)	99 (95.2%)	[3]**0.059**
Yes	67 (6%)	4 (2%)	5 (4.8%)	

[1]One-way ANOVA test, [2]Kruskal-Wallis test, [3]Chi-square test. *p<0.05, Laparoscopic-assisted vaginal hysterectomy was analyzed by combining with laparoscopy due to low number of cases

hysterectomy, the patients who had vaginal hysterectomy were not included in the comparisons (Table 8).

Total hysterectomy and subtotal hysterectomy groups were compared for caesarean history; a caesarean history was present in 16.3% of total hysterectomy group and in 28.9% of subtotal hysterectomy group. In the total hysterectomy group, the caesarean rate was statistically significantly low. In the total hysterectomy group, the rate of caesarean history was statistically significantly lower ($p=0.003$; $p<0.05$) (Table 9).

Pathology results demonstrated that 53.6% had leiomyoma, 23.1% had adenomyosis, 12.9% had ovarian/paraovarian cyst, 9.3% had atrophic endometrium, 6.8% had endometrial polyp, 5.6% had proliferative endometrium, 3.7% had endometriosis/endometriotic cyst, 2.8% had endometrial hyperplasia, 2.3% had cervical intraepithelial neoplasia, and 1.2% had salpingo-oophoritis (Table 10).

DISCUSSION

Hysterectomy is the most commonly performed operation in gynecology, and its indications are very wide. Hysterectomy is used as a treatment option in gynecologic pathologies such as gynecological cancers, leiomyomas, endometriosis, adenomyosis, uterovaginal prolapsus, abnormal uterus bleeding, and pelvic pain (5).

Dinçgez et al. (6) included 949 patients and found the mean age as 50.54. The mean age of the patients who had only vaginal hysterectomies was 60.10.

Seçkin et al. (7) included 828 patients and found the mean age as 48.1.

In our study, similar to the literature, the mean age of the patients was 50.78. The mean age of the vaginal hysterectomy group was 60.99, similar to the previous studies.

Süer et al. (8) included 312 hysterectomy cases and found that in the vaginal hysterectomy group, age, gravidity, and parity were significantly higher than the other groups. Similarly, Sağlam et al. (9) included 245 hysterectomy cases and found that gravidity and parity values of the vaginal hysterectomy group were significantly higher than the abdominal hysterectomy group.

In our study, gravidity (5.79) and parity (4.40) values of vaginal hysterectomies were higher than the abdominal hysterectomy group (3.79, 2.83; respectively). Increased gravidity and parity were associated with uterus descend and vaginal hysterectomy secondary to it.

Lynne et al. (10) retrospectively evaluated 1.7 million hysterectomies and demonstrated that 30% of the cases were due to myoma uteri, 20% were due to endometriosis, 18.2% were due to cancer or endometrial hyperplasia, and 17.5% were due to uterine prolapse.

Vessey et al. (11) included 1885 cases in their study and found that 38.5% of the hysterectomies were due to myoma uteri, 35.3% were due to dysfunctional uterine bleeding, 6.5% were due to uterine prolapse, and 5.6% were due to invasive and preinvasive malignancies.

Table 7. The distribution of operation techniques according to the operation technique

	Minor complication	Number	Major complication	Number
Abdominal Hysterectomy	Wound infection	24	Wound infection (debridement)	9
	Vaginal cuff hematoma	4	Postoperative bleeding (relaparotomy)	8
	Subileus	1	Bowel injury	4
			Abscess, peritonitis	5
			Urinary tract injury (bladder, ureter)	7
			Vesicovaginal fistula	1
			Pulmonary embolus (exitus)	1
			Wound dehiscence	3
Vaginal Hysterectomy	-	0	Postoperative bleeding (relaparotomy)	2
			Vesicovaginal fistula	1
			Bladder injury	1
Laparoscopic hysterectomy	Wound infection	1	Ureteral injury	2
	Vaginal cuff hematoma	1	Bladder injury	1
Total		31		45

Table 8. The evaluation of hysterectomy + USO/BSO according to age	
Removal of ovaries in addition to hysterectomy	**Age**
	Mean ± SD
No	42.50±4.22
BSO	50.54±7.76
USO	43.08±4.47
p	**0.000***

*p<0.05 One-way ANOVA test, Patients with vaginal hysterectomy were not included in the analysis, BSO: Bilateral salpingo-oophorectom, USO: Unilateral salpingo-oophorectomy

Table 9. The evaluation of caesarean history according to total-subtotal hysterectomy operation groups			
Caesarean History	**Operation**		**p**
	Total	**Subtotal**	
	n (%)	**n (%)**	
No	1116 (83.7%)	59 (71.1%)	**0.003***
Yes	218 (16.3%)	24 (28.9%)	

*p<0.05 chi-square test

Table 10. The distribution of postoperative histopathology results		
Pathology diagnostic groups	**n**	**%**
Leiomyoma	759	53.6
Adenomyosis	328	23.1
Ovarian/para ovarian cyst	183	12.9
Endometrial hyperplasia	40	2.8
Endometrial polyp	97	6.8
Atrophic endometrium	132	9.3
Proliferative endometrium	79	5.6
Cervical intraepithelial neoplasia	33	2.3
Salpingo-oophoritis	17	1.2
Endometriosis/endometriotic cyst	52	3.7

In our study, similar to the literature, myoma uteri had the first place (609; 43%). Adnexal mass was the second with 225 cases (15.9%), and descent of uterus was the third with 217 (15.3%) cases. In accordance with the literature, the most common indication for vaginal hysterectomy was a descent of uterus.

Karp et al. (12) studied the application of hysterectomy with BSO under 51 years of age and emphasized that BSO should not be applied, especially under 46 years of age, if there is no genetic mutation (BRCA1-2) or a pathology like endometriosis BSO should not be applied. They stated that unnecessary BSO might lead to sexual dysfunction, cardiac problems, diabetes, and early mortality. In our study, the mean age of patients who had BSO was 50.5.

In patients who had an abdominal hysterectomy, Tazegül et al. (13) found bladder injury in 4 (0.5%) patients, ureteral injury in 3 (0.37%), and bowel injury in 3 patients. Intraoperative bladder injury was observed in 1 (1.85%) patient who had a vaginal hysterectomy.

Dinçgez et al. (6) included 949 patients and bladder injury which required bladder repair in 2 patients, 1 (0.12%) in the vaginal hysterectomy group and 1 (0.12%) in the abdominal hysterectomy group. Bowel injury was observed in 0.52% of all cases.

In our study, in the abdominal hysterectomy group, one patient had ureteral injury, and six patients had bladder injury. In the laparoscopic hysterectomy group, two patients had ureteral injury, and one patient had bladder injury. The urinary complication rate was 0.6% in patients who had an abdominal hysterectomy, 0.4% in patients who had a vaginal hysterectomy, and 2.8% in patients with a laparoscopic hysterectomy. Bowel injury was seen only in 4 patients (0.28%) with abdominal hysterectomy.

CONCLUSION

Hysterectomy is the most common gynecological operation after caesarean. When choosing the operation technique, the clinical indication of the patient, previous surgeries, and the surgeon's experience should be taken into consideration. Vaginal hysterectomy should always be the first choice in cases with a decision of hysterectomy due to benign causes. In cases where vaginal hysterectomy cannot be performed, laparoscopic hysterectomy should be preferred.

Ethics

Ethics Committee Approval: This study was initiated after approval was obtained from Okmeydanı Training and Research Hospital Ethics Committee with a date of 21.11.2017 and a number of 764.

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.C.U., V.M., Data Collection or Processing: Y.K., M.İ.T., Analysis or Interpretation: H.C.U., N.Ç., Literature Search: M.İ.T., Writing: N.Ç., Y.Ç.

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A Comparative Study of Two Different Accommodative Intraocular Lenses: The Visual and Accommodative Amplitude Outcomes

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Abstract

Objective: To compare distance and near visual acuity along with accommodative amplitude in eyes implanted with the Tetraflex and the Tek-clear accommodating intraocular lenses (AIOLs).

Methods: Comparative, prospective, non-randomized study. Thirty-eight eyes of 26 patients implanted with the Tetraflex (17 eyes) and Tek-clear (21 eyes) AIOLs were enrolled. Uncorrected distance visual acuity (UCDVA), best-corrected distance visual acuity (BCDVA), uncorrected near visual acuity (UCNVA), distance corrected near visual acuity (DCNVA), best-corrected near visual acuity (BCNVA) and spherical equivalent refraction were the parameters evaluated postoperatively. Also, the accommodative amplitude was assessed with subjective defocus method and objective anterior chamber depth measurement before and after the topical application of pilocarpine using a Scheimpflug-Placido disc topographer at postoperative month 3 and 6.

Results: No statistically significant difference was found between the two AIOL types in regards to BCDVA, DCNVA, and BCNVA at months 1, 3, and 6 ($p>0.05$). The mean UCDVA was significantly better in Tetraflex implanted eyes ($p=0.001$, $p=0.002$, $p=0.008$), whereas the mean UCNVA was significantly better in Tek-clear implanted eyes ($p=0.008$, $p=0.01$, $p<0.0001$) at postoperative month 1, 3, and 6, respectively. Both subjective and objective accommodative amplitude assessments did not display a significant difference between the two groups at month 6 ($p>0.05$).

Conclusion: The Tetraflex accommodative IOL seemed to be better at UCDVA, whereas Tek-clear seemed better at UCNVA. The accommodation range of Tetraflex and Tek-clear lenses was comparable.

Keywords: Accommodation, cataract, intraocular lens, presbyopia

INTRODUCTION

Presbyopia is one of the most important problems in older patients with or without cataract (1-7). Spectacles, multifocal contact lenses, and several surgical treatment approaches were being used for the 'correction' of presbyopia (5-10). Presbyopia correction during cataract surgery is one of the important goals of anterior segment surgeons (5). Monovision correction, implantation of multifocal intraocular lenses (IOLs), and accommodative IOLs (AIOLs) are the most preferred choices for this purpose (5,10). Monovision correction has the advantage of using cheaper IOLs with a relatively simple technique. However, leaving the eyes with faint anisometropia has many drawbacks such as diminished contrast sensitivity, risk of diplopia, and stereopsis problems (5,10). On the other hand, multifocal IOLs are very popular among cataract surgeons with the advantage of simultaneous correction of far, intermediate, near vision, and also astigmatism with optional toric design (5,6,9). However, reduced contrast sensitivity, halo, glare, and waxy vision are the major limitations of multifocal IOLs (5,6,9).

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Alternatively, AIOLs are likely to mimic the accommodation reflex conceptually (5-8). There are three main types of AIOLs: single optic AIOLs, dual-optic AIOLs, and capsular bag refilling AIOLs (7,8). Single optic designs work with accommodative effort, which is called as the focus-shift principle (7,8). The lens optic of moves forward by contraction of the ciliary muscle, thereby increasing the refractive power of the IOL for better near vision (7,8). Several brands of single optic AIOLs are available in the market, and several studies have been conducted to assess and compare the efficacy of AIOLs within the class and with other types of IOLs (8-10).

The Tetraflex AIOL (Lenstec Inc., FL, US) is a single-piece (optic), spherical optic, acrylic IOL that has been designed to utilize the two forces activated during accommodation-vitreous movement and ciliary swelling to ensure maximum forward movement for clear near vision (5-8). The Tek-clear AIOL (Tekia, Irvine, California, US) is also a single-piece (optic), hydrophilic acrylic IOL with symmetric optic and square edge design that has been approved for the treatment of presbyopia, which acts with a similar mechanism to Tetraflex AIOL (5-8). This study aimed to compare distance and near visual performances in the eyes of patients implanted with Tetraflex and Tek-clear single optic AIOLs during cataract surgery. Accommodative amplitudes of two AIOLs were also evaluated.

METHODS

This prospective, comparative, non-randomized study was conducted in accordance with the tenets of the Declaration of Helsinki, and approval was obtained from local ethics and review board. Ethics committee approval was obtained from the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (2011/117). Written informed consent was received from all of the included patients. The data of the patients who underwent cataract surgery with phacoemulsification and AIOL between December 2011 and April 2014 was recorded. The following criteria were required for inclusion: a) to be between the age of 40-65 years, b) to have unilateral or bilateral senile or presenile cataract, c) to have basic literacy and good cooperation, d) to commit the follow-up visits, e) to have the unwillingness to use spectacles postoperatively. The patients were not included if one or more of the following criteria were present: a) to have a concomitant ocular disease such as diabetic retinopathy, age-related macular degeneration, b) to have a history of previous laser treatment or intraocular surgery, c) to have spherical refractive error of ±6 diopters and above, d) to have a cylindrical refractive error of ≥±1.5 diopters, e) to have signs for obsessive personality, f) to have jobs needing very concise near vision (watch repairer, jeweler, etc.), g) to show perioperative complications such as posterior capsule rupture, iris damage, irregular and large or small capsulorhexis.

Preoperative Assessment

The preoperative assessment involved a complete eye examination including uncorrected distance visual acuity (UCDVA) and best-corrected distance visual acuity (BCDVA), manifest refraction, keratometry (auto kerato-refracto-tonometer TRK-1P, Topcon, Tokyo, Japan), slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, and dilated retinal examination. Biometry was obtained via an ultrasound biometer (Optikon, Roma, Italy). Immersion technique was preferred, and the required IOL power for emmetropia was calculated with the SRK-T formula. Distance visual acuity was measured via a projection chart from 4 meters and recorded in decimals. Near visual acuity was measured via a Turkish near vision chart, which was previously described (11). All examinations were performed by a single ophthalmologist (HNT).

Surgical Technique

All patients underwent standardized phacoemulsification and AIOL implantation performed by a single surgeon under local anesthesia. A 2.8 mm clear corneal incision was placed at the steepest corneal meridian. A continuous curvilinear capsulorhexis of 5-5.5 mm was created. Phacoemulsification was performed using the Infiniti Vision system (Alcon, Fort Worth, Texas, US). The choice of AIOL type did not depend on any special consideration because we had previously bought AIOLs in our institution, and patients were non-randomly allocated to one of the two AIOL types according to the availability of the required power. AIOLs were implanted into the capsular bag with a single-use IOL injector. None of the patients required corneal suturing because a leak-proof wound was obtained with hydration for all eyes. All patients received topical prednisolone acetate and ofloxacin five times a day following the surgery. Prednisolone acetate was tapered off after the first week and stopped after four weeks. Ofloxacin was stopped after two weeks postoperatively.

Postoperative Assessment

Postoperative examinations were performed at postoperative day 1, week 1, month 1, month 3, and month 6. Each visit included assessment of visual acuity and manifest refraction, slit-lamp examination, and IOP measurement. In detail, UCDVA, BCDVA, uncorrected near visual acuity (UCNVA), distance-corrected near visual acuity (DCNVA), and best-

corrected near visual acuity (BCNVA) were evaluated. Near visual acuity measurements were performed from 35 centimeters. Measurement of accommodative amplitude was performed at postoperative month 3 and 6. Accommodative amplitude was evaluated with both subjective and objective methods. Defocus method was chosen as a subjective method, wherein minus lenses were used for stimulation of the accommodation. Under standard room illumination, the patient was seated with a full distance refractive correction while viewing the smallest letter on the visual acuity chart. Then, minus-power lenses were gradually increased in 0.25 D steps until the visual target was blurred (minus-lenses-to-blur-method), and the added diopter was defined as the amplitude of accommodation (12). Anterior chamber depth was measured objectively with Sirius Scheimpflug-Placido topographer (Costruzione Strumenti Oftalmici, Florence, Italy) (4,12). The distance between the anterior surface of the IOL and the corneal vertex was referred to as the anterior chamber depth and measured before and after pilocarpine instillation. Accommodative status was induced with two drops of pilocarpine 2% at 5 minutes interval, and the measurements were obtained after 30 minutes from the first instillation (13). Three consecutive measurements were taken and averaged before and after instillation of pilocarpine drops. The difference between the averages of two statuses, thus quantified drug-induced AIOL movement, which indirectly displayed the accommodation range objectively.

Statistical Analysis

All visual acuity values were converted to the logarithm of the minimum angle of resolution (LogMAR). Statistical analysis was performed using commercially available software (SPSS for Windows, version 20.0 SPSS Inc., Chicago, IL). Descriptive statistical results were described as the mean, standard deviation, and 95% confidence interval of the mean. The normality of the data was assessed using the Shapiro-Wilk test. According to the normality results, the Mann-Whitney U test or t-test was used for comparisons between groups or variables. The Wilcoxon test was used for repeated values. Chi-square and Fisher-exact test was used for the analysis of categorical variables. A p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 39 eyes of 26 patients were initially included. One eye was then removed from the study because of posterior capsular rupture during phacoemulsification. Therefore, a total of 38 eyes were evaluated. The baseline parameters of 2 AIOL groups were summarized in Table 1. Accordingly, two groups were homogenous concerning all parameters.

Seventeen eyes of 15 patients were implanted with Tetraflex AIOL, whereas 21 eyes of 19 patients were implanted with Tek-clear AIOL. Unilateral cataract surgery was performed in 14 patients (14 eyes), and bilateral surgery was performed in 12 patients (24 eyes). Of bilaterally operated patients, eight were implanted with Tetraflex/Tek-clear, two were implanted with Tetraflex/Tetraflex, and two were implanted with Tek-clear/Tek-clear AIOLs.

3.1. Visual Outcomes

Visual results were summarized in Table 2.

3.1.1 Uncorrected distance visual acuity (UCDVA)

The mean baseline UCDVA was not statistically different between the two groups (p=0.8); however, the mean UCDVA was better in the Tetraflex group than that of the Tek-clear group at all follow-up visits (Table 2, Figure 1).

3.1.2. Best-corrected distance visual acuity (BCDVA)

The mean baseline BCDVA was not statistically different between the two groups (p=0.8). Also, the mean BCDVA was not statistically different between the two groups after that (Table 2).

Table 1. Baseline and demographic characteristics of the patients in Tetraflex and Tek-clear groups

	Tetraflex	Tek-clear	p
Age, years (range)	55.9±7.9 (48-65)	52.3±7.9 (45-58)	0.2
Male/Female	10/5	9/10	0.1
Right/Left	7/10	11/10	0.4
IOL power, diopters (range)	21.0±1.3 (20.0-22.2)	21.5±1.3 (20.0-22.0)	0.3
Axial length, mm (range)	23.2±0.6 (22.6-23.5)	23.0±0.6 (22.5-23.5)	0.2
Mean K_{avg}, diopters (range)	43.3±1.2 (42.5-42.9)	43.5±1.3 (44.0-44.3)	0.6
Mean Baseline UCDVA	0.95±0.45 LogMAR	0.97±0.53 LogMAR	0.8
Mean Baseline BCDVA	0.71±0.43 LogMAR	0.72±0.41 LogMAR	0.8

IOL: Intraocular lens, mm: Millimeter, UCDVA: Uncorrected distance visual acuity, BCDVA: Best corrected distance visual acuity, K_{Avg}: Average keratometry values, LogMAR: Logarithm of the minimum angle of resolution

3.1.3. Uncorrected near visual acuity (UCNVA)

The mean UCNVA at month 1, 3 and 6 was better in the Tek-clear group than that of the Tetraflex group (Table 2, Figure 2). Also, at month 6, 95.2% of the eyes in the Tek-clear group vs 94.1% of the eyes in the Tetraflex group had a UCNVA ≥20/80 at month 6 (p=0.001).

3.1.4. Distance corrected near visual acuity (DCNVA)

The mean DCNVA was not statistically different between the two groups at any of the follow-up visits (Table 2).

3.1.5. Best-corrected near visual acuity (BCNVA)

The mean BCNVA was not statistically different between the two groups at any of the follow-up visits (Table 2).

Table 2. The mean visual acuity levels of the Tetraflex and Tek-clear groups

	Tetraflex	Tek-clear	p
UCDVA (Mean ± SD)			
Baseline	0.95±0.45	0.97±0.53	0.825
Month 1	0.14±0.16	0.34±0.19	0.001**
Month 3	0.12±0.15	0.30±0.20	0.002**
Month 6	0.16±0.16	0.30±0.21	0.008**
p*	0.00001*	0.00001*	
BCDVA (Mean ± SD)			
Baseline	0.71±0.43	0.72±0.41	0.813
Month 1	-0.01±0.05	0.01±0.04	0.161
Month 3	-0.01±0.05	0.00±0.05	0.713
Month 6	0.01±0.05	0.00±0.04	0.544
p*	0.00001*	0.00001*	
UCNVA (Mean ± SD)			
Month 1	0.54±0.17	0.41±0.16	0.008**
Month 3	0.49±0.16	0.38±0.17	0.011**
Month 6	0.54±0.15	0.36±0.16	0.00001**
DCNVA (Mean ± SD)			
Month 1	0.65±0.08	0.67±0.07	0.340
Month 3	0.59±0.09	0.64±0.11	0.144
Month 6	0.62±0.09	0.63±0.11	0.934
BCNVA (Mean ± SD)			
Month 1	0.05±0.05	0.04±0.05	0.798
Month 3	0.05±0.05	0.04±0.05	0.798
Month 6	0.08±0.07	0.06±0.06	0.284

UCDVA: Uncorrected distance visual acuity, BCDVA: Best corrected distance visual acuity, UCNVA: Uncorrected near visual acuity, DCNVA: Distance-corrected near visual acuity, BCNVA: Best corrected near visual acuity, SD: Standard deviation, *: Represents the in-group p values which were statistically significant, **: Represents the inter-group p values which were statistically significant

3.2. Manifest refraction

There was a statistically significant difference in mean spherical equivalent refractive error between the Tek-clear and Tetraflex groups at all of the follow-up visits. The eyes in the Tek-clear group were more myopic than the eyes in the Tetraflex group (Table 3).

3.3. The amplitude of accommodation (AA)

There was not any statistically significant difference between the two groups in regards to the mean AA determined by subjective defocus method and objective measurement of mean change in anterior chamber depth with Scheimpflug topographer before and after topical pilocarpine (Table 3).

3.4. Subjective patient satisfaction

Patients were simply asked to report about their satisfaction at postoperative month 6. The satisfaction was rated on a 3 step

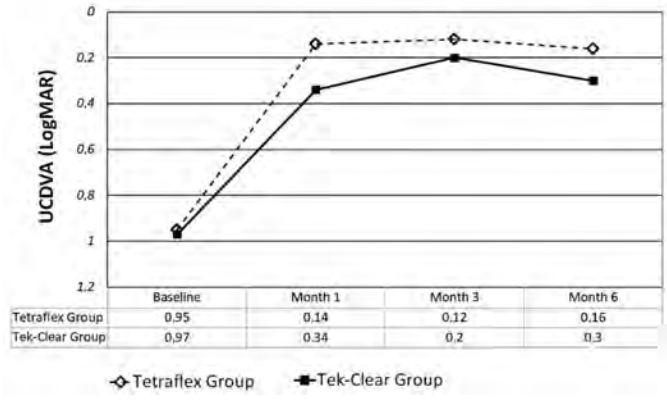

Figure 1. The uncorrected distance visual acuity levels between the two groups at different time points
UCDVA: Uncorrected distance visual acuity, LogMAR: Logarithm of the minimum angle of resolution

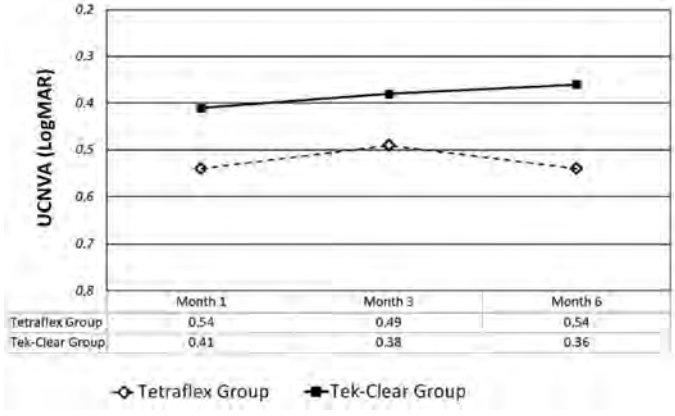

Figure 2. The uncorrected near visual acuity levels between the two groups at different time points
UCNVA: Uncorrected near visual acuity, LogMAR: Logarithm of the minimum angle of resolution

grading; very satisfactory, intermediately satisfactory, and not satisfactory subjectively. All of the included patients answered the question as very satisfactory. Also, 10 of the 12 (83.3%) bilaterally AIOL implanted patients obtained total spectacle independence at postoperative month 6.

3.5. Postoperative complications

No postoperative complications like decentration or dislocation of the AIOLs, corneal edema, inflammation, increased IOP, cystoid macular edema was detected in any of the patients. Also, any of the patients did not complain about halo or glare during the postoperative follow-up period.

At postoperative month 6, 29.4% of the patients in the Tetraflex group and 28.8% of the Tek-clear group showed mild posterior capsule opacification ($p<0.05$). None of the patients required laser capsulotomy because posterior capsule opacification (PCO) was not clinically significant and was not obscured the visual axis in any of the groups (14).

DISCUSSION

We compared the visual and functional outcomes of 2 AIOLs in this prospective study. Both of the IOLs had single optics and worked with accommodative effort. Visual outcomes were similar between the two IOLs. Both of them showed improvement in both near and distance visual acuities. No statistically significant difference was found between them in regards to visual outcomes except postoperative uncorrected distance and near visual acuities. The patients implanted with the Tek-clear AIOL showed a myopic shift, which caused better UCDVA with Tetraflex and better UCNVA with Tek-clear at postoperative month 1, 3, and 6. The two important outcomes of this study were that the Tek-clear group was found to be more myopic than the Tetraflex group (-1.27 D vs -0.18 D at month 6); therefore the uncorrected near vision was better in Tek-clear, and uncorrected distance vision was better with Tetraflex as expected. The significances between the uncorrected distance and near visual acuity levels were probably secondary to the postoperative myopic shift of the Tek-clear group. We supposed that this shift might be secondary to the keratometric/biometric errors or effective lens position or a constant of the IOL. All of the keratometric and biometric measurements were made by a single physician (HNT), and the anterior chamber parameters were similar between the two groups. Therefore, we ruled out the first two probable reasons for the myopic shift. Therefore, we supposed that this phenomenon was probably caused by a constant of the Tek-clear AIOL. Although the myopic shift in Tek-clear implanted eyes was reported in another study (15), we could not be sure about this, so we informed the company in this regard. The main anatomical outcomes of the study showed a similarity between the two IOLs, both subjective and objective AA outcomes were not statistically different between the two groups.

Table 3. The mean spherical equivalent and accommodation parameters of the Tetraflex and Tek-clear groups

	Tetraflex	Tek-clear	p
SE (D) (Mean ± SD)			
Month 1	-0.43±0.68	-1.32±0.57	<0.0001
Month 3	-0.29±0.74	-1.24±0.59	<0.0001
Month 6	-0.18±0.78	-1.27±0.55	<0.0001
AA (D) (Defocus method)			
Month 3	-1.04±0.30	-1.10±0.27	0.4
Month 6	-1.15±0.27	-1.17±0.29	0.8
Δ ACD (mm)			
Month 3	0.32±0.16	0.33±0.33	0.2
Month 6	0.37±0.16	0.37±0.30	0.2

SE: Spherical equivalent, D: Diopter, AA: Accommodation amplitude, Δ ACD: The difference between before and after pilocarpine induced anterior chamber depth, p: P value, SD: Standard deviation

In the literature, there are several studies regarding the outcomes of single optic AIOLs (10,16-24). The most evaluated one was Crystalens, which is the first Food and Drug Administration approved AIOL (7,8,19). In most of the reports, it was demonstrated that Crystalens showed improvement in both distance and near visual acuity (7,8). In a study by Karavitaki et al. (19), the long-term visual acuity outcomes after bilateral Crystalens implantation were evaluated. They included 50 eyes of the 25 patients and reported the visual outcomes and complications after a mean follow-up period of 42 months. The mean UCDVA was found to be improved from 0.56 to 0.19 LogMAR, and BCDVA was found to increase from 0.17 to 0.05 LogMAR at the last follow up visit. The uncorrected intermediate and near visual acuity was ≥J2. No intra-or postoperative complications were reported, except posterior capsule opacification in 12 of the 50 eyes during the first year (19). Another widely evaluated single optic AIOL is 1CU (5,20). In a randomized comparative trial by Harman et al. (20), binocular near vision performance was compared among patients who were implanted with the 1CU accommodating, multifocal, and monofocal IOL. Initially, 90 patients were included in the study, and 64 of them completed the follow-up period of 18 months. Mean uncorrected and corrected distance visual acuities were found to be increased in all of the three groups at months 3 and 18 postoperatively. The UCNVA and accommodative range were better in both 1CU than monofocal IOL group at month 3

and 18 as expected (20). The Tetraflex and Tek-clear AIOLs are the two other AIOLs in the market that were evaluated in this study (7,8). Wang et al. (21) evaluated the visual performance of Tetraflex in 23 eyes of 23 patients with cataract. After a mean follow-up period of 12 months, the Tetraflex implanted eyes showed significant improvement in regards to UCNVA and UNDVA. Total spectacle independence was achieved, %34.7 of the patients. Tan et al. (23) compared the performances of accommodative, multifocal, and monofocal IOLs in a study in which Tetraflex AIOL was used. The Tetraflex group of the study showed improvement in distance and near visual acuity at the follow-up visits at postoperative months 3 and 12, and 60% of the patients achieved total spectacle independence. The percentage of achieving total spectacle independency was nearly twice when compared with the study by Wang et al. (21). This might be due to the high bilateral operation rate of the patients who were included in the study by Tan et al. (23) in contrast to the unilaterality of the patients in the study of Wang et al. (21). Also 83.3% of bilaterally AIOL implanted patients did not require spectacle correction in our study that supported this idea. In another study by Beiko (10), the visual performances of Crystalens, Tetraflex, and monovision with a monofocal IOL were compared. No statistical difference was reported in visual outcomes among the three groups. Wolffsohn et al. (24) investigated the mechanism of action of the Tetraflex IOL by assessing the objective amplitude-of-accommodation via autorefraction, anterior chamber depth, and pupil size via optical coherence tomography, and IOL flexure via aberrometry. They reported a decrease in the pupil size was, and interestingly the IOL was found in the same position with the accommodation effort; however, the optical aberrations were found to be increased. Therefore, they postulated that the accommodative benefits of Tetraflex might be due to optical aberrations. The Tek-clear AIOL was rarely studied in the literature (15). Sadoughi et al. (15) compared the distance and near visual function after cataract surgery among the patients who were implanted with Crystalens AIOL, Tek-clear AIOL, or a monofocal IOL. After a follow-up period of 6 months, distance and visual acuity levels were found to be similar among the three groups. However, near visual acuity functions were better in both of the AIOL groups than the monofocal IOL group. The spherical and cylindrical refraction error of the Tek-clear group was -0.14 and -1.0 diopters, respectively. Moreover, this was arithmetically greater than the other two groups, which were similar to the postoperative refractive error of the Tek-clear subgroup of our study. Also, the patients with postoperative ametropia >-0.50 diopters were excluded from the study by Sadoughi et al. (15), which probably decreased the mean postoperative myopic shift among the Tek-clear implanted eyes.

No significant postoperative complications were detected in both of the groups except PCO, which was the most important complication of AIOLs (25). It was thought to be a drawback of the AIOLs because the anteroposterior movement of AIOLs was proposed to induce early PCO in the AIOL implanted eyes; also the probable change in anterior segment parameters after YAG laser capsulotomy was another hesitation about the AIOLs (25,26). However, the rate of PCO in AIOLs was reported to be similar to other hydrophilic IOLs, and the accommodative ability was reported to be unchanged after YAG laser capsulotomy. The PCO rate was similar between the Tetraflex and Tek-clear groups in our study, and none of the patients required YAG laser capsulotomy during the follow-up period of the study.

The main limitation of the study was the small number of included patients and non-randomized study design. Also, the choice of AIOL did not depend on any special consideration because we had the previously bought AIOLs in our institution and had to implant the AIOLs according to the biometry-defined power of the AIOL. However, we compared the visual and accommodative outcomes of these two different AIOLs prospectively in the literature for the first time in patients with cataracts and obtained some positive results, which were discussed in detail.

CONCLUSION

In conclusion, both AIOLs used in our group of patients showed superior performances in regards to visual outcomes. The only difference was found in the postoperative uncorrected distance and near visual acuity levels and manifest refraction. The Tek-clear group showed a myopic shift postoperatively, which caused the group to demonstrate a better outcome in uncorrected near vision. In contrast, the Tetraflex group showed a better outcome concerning uncorrected distance vision. Therefore, we might propose some recommendations according to the results of this study. If a patient requires a perfect distance visual acuity and a good or intermediate near visual acuity, then Tetraflex IOL might be the better choice. In contrast, if a patient requires a very good near visual acuity and a good or intermediate distance visual acuity, then Tek-clear IOL might be the better choice. Of course, this was a pilot study conducted with a relatively low number of patients, and we might only assume these results and recommendations. Further prospective, randomized, comparative studies are needed to clarify our results.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (2011/117).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.N.T., U.Y., İ.U.O., A.Ö., Design: H.N.T., U.Y., İ.U.O., A.Ö., Data Collection or Processing: H.N.T., U.Y., İ.U.O., Analysis or Interpretation: H.N.T., U.Y., İ.U.O., A.Ö., Literature Search: H.N.T., A.Ö., Writing: H.N.T., A.Ö.

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Cancer Susceptibility Syndromes in Childhood Cancer: Okmeydanı Experience

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Abstract

Objective: Childhood cancers form 2% of all cancers, and identified familial and genetic factors are responsible for only 5-15%. Determining the hereditary conditions that cause predisposition enables early detection of cancer.

Methods: It was aimed to determine the patients with a genetic predisposition to cancer, treatment success and drug side effects among the patients diagnosed with a non-leukemia malignancy in Okmeydanı Training and Research Hospital between 2015-2017.

Results: A Cancer Predisposition syndrome was found in 7 (5%) of 121 cases diagnosed with non-leukemia malignancy. Cancer Predisposition syndromes were Ataxia telangiectasia, Beckwith Wiedemann syndrome, Neurofibromatosis type 1, Down syndrome, Gardner syndrome, and Rothmund Thomson syndrome. Cancers observed were Non-hodgkin lymphoma, Wilms tumor, malignant glial tumor, malignant peripheral nerve sheath tumor, testicular germ cell tumor, hepatoblastoma, and osteosarcoma. Malignancy was detected at an early stage in all three patients who were followed up regularly due to Cancer Predisposition syndrome. At the last follow-up, five cases were in remission. In two cases, drug dose reduction was required due to chemotherapy side effects.

Conclusion: Detection of malignancy at an early stage indicates the importance of regular follow-up. With this study, we wanted to emphasize the importance of recognizing Cancer Predisposition syndromes and the need for regular follow-up.

Keywords: Childhood cancer, Cancer Predisposition syndromes, malignancy

INTRODUCTION

The first questions that come to the minds of the parents of children diagnosed with cancer are: "Is this disease caused by us, is there any possibility of it affecting other children?". Evidence of genetic susceptibility to cancer will enable us to answer these questions and provide genetic counseling. Childhood cancers make up 2-4% of all cancers. Every year, 200.000 children under the age of 15 are diagnosed with cancer. In general, the risk for cancer development in the first 15 years of life varies between 1/600-1/1000, and most of them occur in the first five years. No specific cause can be found in 75-90% of cases. Identified familial and genetic factors are responsible for 5-15% and known environmental contacts and exogenous factors for less than 5-10% (1). Exogenous factors are classified as external agents (physical carcinogens, ionizing radiation, non-ionizing radiation), biological carcinogens (virus infections), and chemical carcinogens (tobacco, pesticides, asbestos, aflatoxin, arsenic, food and drinking water pollutants, drugs, and medicines). Approximately 90% of all newly diagnosed cancers occur with de novo somatic mutations and 10% due to hereditary genetic features (2). There are many hereditary conditions that increase the risk of tumors in childhood and can cause a predisposition for cancer development. The frequency of cancer in children and adolescents with an underlying genetic syndrome or hereditary

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susceptibility is unclear. In the early 1990s, this rate was estimated to be 1-10% (3). In a newer publication in the Pediatric Cancer Genome Project/St. Jude Children's Research Hospital, a frequency of 16.0% in solid tumor cases, 8.6% in brain tumors, and 3.9% in leukemia was detected (4). This report focused on 23 well-known cancer susceptibility genes and genes with a high penetration rate of 8 types of cancer. The most frequently affected genes were found to be TP53, adenomatous polyposis coli (APC), and BRCA2.

Identifying the hereditary conditions that cause predisposition provides early detection of cancer by developing screening programs. It may also lead to a change in treatment in cases of increased toxicity or resistant disease. In this study, it was aimed to determine patients with a genetic predisposition to cancer who had a diagnosis of non-leukemia childhood cancer and to determine the success of treatment and drug side effects.

METHODS

The files of 121 cases diagnosed with a non-leukemia malignancy in the Pediatric Oncology Department of Okmeydanı Training and Research Hospital between 2015 and 2017 were analyzed retrospectively. The study was performed in accordance with the ethical rules based on the principles of the Helsinki Declaration. A Cancer Predisposition syndrome was found in 5% (7 cases) of these cases.

RESULTS

The demographic characteristics of the cases are given in Table 1. The mean age of Cancer Predisposition syndrome and cancer diagnosis was 5 and 10 years, respectively. In 3 of the cases, Cancer Predisposition syndrome and malignancy were diagnosed at the same time (case 1,4,6). Malignancy was detected at an early stage (stage 1-2) in all 3 cases (case 3,5,7) who were followed up regularly due to the Cancer Predisposition syndrome. All 4 cases without follow-up applied with advanced stage (stage 3-4) malignancy. At the last control, 5 cases were in remission. In two cases, drug dose reduction was required due to chemotherapy side effects (case 1,7).

Case 1: An 11-year-old male patient, who was admitted due to shortness of breath and respiratory distress, was diagnosed with T-lymphoblastic Non-hodgkin lymphoma (NHL) by biopsy. Also, ataxic gait, sclera, and telangiectasia were detected, and cerebellar atrophy findings were seen in cranial magnetic resonance imaging (MRI) examination. Alpha-fetoprotein (AFP)

Table 1. Demographic characteristics of patients

Case	Predisposing syndrome	Genetic	Family history	Regular follow-up	Age at diagnosis of the predisposing syndrome	Malignity	Age at diagnosis of malignancy	Chemotherapy side effects and drug dose reduction	Outcome
1	Ataxia telangiectasia	ATM mutation	-	-	11	Non-Hodgkin lymphoma	11	+	Diseased, alive
2	Beckwith Wiedemann	Clinical diagnosis	-	-	1	Wilms' tumor	4	-	Disease-free, alive
3	Down	Trisomy 21	-	+	1	Testicular germ cell tumor	14	-	Disease-free, alive
4	Gardner	APC mutation	Father +	-	0.5	Hepatoblastoma	0.5	-	Disease-free, alive
5	Neurofibromatosis type 1	Clinical diagnosis	Mother: NF + pancreas tumor Sister: NF	+	3	MPNST	13	-	Disease-free, alive
6	Neurofibromatosis type 1	Clinical diagnosis	Mother: NF Sister: NF+ malignant glial tumor	-	15	Glioblastoma	15	-	Diseased, alive
7	Rothmund Thomson	RECQL4	-	+	4	Osteosarcoma	13	+	Disease-free, alive

ATM: Ataxia telangiectasia mutation, APC: Adenomatous polyposis coli, NF: Neurofibromatosis type 1, MPNST: Malignant peripheral nerve sheath tumor

level, which was screened due to suspected ataxia telangiectasia (AT), was found to be high. *ATM* gene mutation was detected in the genetic evaluation of the case. Also, bronchiectatic changes were observed in both lungs due to AT. T-cell lymphopenia was detected in the immunological evaluation, and treatment disruptions occurred, and drug dose reductions were made during chemotherapy since drug side effects were seen more than expected, and frequent infections were experienced. The patient, who is still partially responsive, continues to be treated.

Case 2: The patient was admitted with severe abdominal pain after being kicked in the abdominal region while joking with his brother, and a ruptured mass of about 10 cm in diameter from the left kidney was detected after further imaging studies. Wilms' tumor was diagnosed with a biopsy. On admission, it was learned that the patient was diagnosed with Beckwith Wiedeman syndrome (BWS) at the age of 1 due to left-sided hemihypertrophy and macroglossia, but was not followed up regularly. In the abdominal ultrasonography (USG) examination, medullary nephrocalcinosis was detected in the other kidney, and the patient was scheduled for follow up by the nephrology department. The treatment of the patient who underwent tumor resection after preoperative chemotherapy was completed with postoperative radiotherapy and chemotherapy. The patient is in remission for one year.

Case 3: A 14-year-old male patient who was taken to regular follow-up examinations since the age of 1 with the diagnosis of Down syndrome was admitted with swelling in the right testicle. The patient had no distant organ metastasis, and he was diagnosed with stage 1 non-seminamatous mixed germ cell tumor after high orchiectomy. Chemotherapy was given after surgical treatment. The patient whose treatment is completed is remission for two years.

Case 4: A 6-month-old male patient with a paternal history of Gardner's syndrome was admitted with increasing abdominal swelling for the last two months. After abdominal MRI examination, multifocal masses were seen in the liver, and hepatoblastoma was diagnosed by biopsy. After genetic evaluation, APC mutation was detected. Liver transplantation was performed in the patient who was given preoperative chemotherapy and was not found suitable for the surgery. He is in remission without treatment for two years.

Case 5: A 13-year-old girl who was followed up with the diagnosis of neurofibromatosis (NF) type 1 was admitted due to the rapid growth of the previous neurofibroma in the neck area. After mass excision, the diagnosis of malignant peripheral nerve sheath tumor (MPNST) was made. The patient who was given postoperative chemotherapy is in remission without treatment for two years.

Case 6: A 15-year-old girl with an older sister with a malignant glial tumor presented with a complaint of seizure and a mass in the left frontal region was detected in the cranial MRI examination. A diagnosis of malignant glial tumor was made after mass excision. NF type 1 was considered by seeing cafe au lait spots on the patient, her mother, and her older sister, and the genetic examination continues. Postoperative radiotherapy and chemotherapy were given, and she is followed-up in remission for three months.

Case 7: A 13-year-old male patient who was followed-up due to Rothmund Thomson syndrome (RTS) was brought with the complaint of left knee swelling. MRI examination revealed a mass of left distal femur origin, and a diagnosis of osteosarcoma was made after pathological evaluation. When giving preoperative chemotherapy, especially after Doxorubicin treatments, increased signs of toxicity were observed, and dose reduction was made. After dose reduction, chemotherapy was continued without disruption. Postoperative chemotherapy was completed in the patient with a tumor necrosis rate of >90% (good chemotherapy response) in the postoperative pathological evaluation, and he is being followed up for six months without treatment.

DISCUSSION

It is a fact that cancers are caused by genetic mutations. For many childhood cancers, when age, occurrence, and cell origin are evaluated, they appear to indicate an intrauterine origin. Pediatric oncologists should evaluate children diagnosed with cancer and their families according to well-defined criteria for hereditary cancer susceptibility (5). Rare tumors associated with cancer susceptibility (adrenocortical carcinoma), bilateral or multifocal tumors (Wilms' tumor), tumors that occur earlier than expected (thyroid carcinoma), multiple synchronic, or metachronous tumors, additional symptoms for the underlying syndrome (axillary freckle) and family history should be examined. Also, the same or related cancers occurring in the same family, a cancer diagnosis in two or more first-degree relatives, tumors associated with a specific cancer susceptibility syndrome, young age, cancer in siblings, and consanguineous marriages should suspect the physician.

Many hereditary immune deficiency syndromes increase the risk of childhood cancer, especially lymphomas and leukemia. Because they are rare, they make up less than 0.1% of all childhood cancers. AT is the most common, and more than

10% of affected children develop lymphoma or leukemia before the age of 15 (6). Bloom syndrome, common variable immunodeficiency syndrome, X-linked agammaglobulinemia, immunoglobulin A deficiency, severe combined immune deficiency, Duncan disease, and Nijmegen Breakage syndrome are at high risk of NHL and leukemia. In our series, similar to the literature, NHL developed in a 14-year-old male who was not previously diagnosed with AT. Although the drug doses to be given in Chromosomal Breakage syndromes are also controversial in the literature, the general belief is to start the treatment with a full dose and to reduce the dose if the side effects are seen more (7). In our case, full-dose treatment was initiated without drug reduction. In our case, whose chemotherapy side effects were severe, dose reduction was made in the following cycles, and treatment disruptions were observed. In the literature, it has been reported that dose reduction does not lead to a disadvantage in disease control in patients with chromosomal breakage syndromes, and severe infections are prevented by reducing systemic toxicity (7).

The most common Overgrowth syndrome associated with childhood cancer is BWS, and the cumulative risk of cancer is 10% by age 4. Wilms' tumor is the most common cancer in BWS. Also, the risk of hepatoblastoma, neuroblastoma, and pancreatoblastoma is increased (8). Our patient was diagnosed with BWS at the age of 1, Wilms' tumor was diagnosed at an advanced stage as the patient was not taken to regular follow-ups. Screening is recommended at regular intervals in BWS cases (Table 2). The absence of follow-ups led to the development of malignancy and the inability to treat medullary nephrocalcinosis, which is one of the other findings in BWS. This situation may cause chronic kidney failure in the long term in our case with a single kidney. Wilms' tumor is one of the best treatment successes among childhood malignancies. Recognizing BWS and other diseases that predispose to Wilms' tumors (WAGR syndrome, Denys Drash syndrome, isolated hemihypertrophy, Bloom syndrome) and follow-up will provide treatability with early diagnosis.

Numerical chromosome abnormalities are associated with childhood cancer, among which the largest number of cases has been reported in Down syndrome to date (9). In addition to the increase in the frequency of leukemia, an increase in the frequency of germ cell tumors has also been proven. However, the frequency of solid tumors other than lymphoma and retinoblastoma is not seen in children with Down syndrome. Although seminoma is reported more frequently with Down syndrome, non-seminomatous germ cell tumor in our case is a different feature from the literature. Our patient's regular follow-up from the age of 1 caused the early detection of cancer.

Gardner's syndrome, a variant of familial adenomatous polyposis, is an autosomal dominant disease characterized by malignant altered colon polyps and benign and malign extra-colon lesions. Tumors frequently associated with Gardner's syndrome are carcinoma of the ampulla of Vater, papillary thyroid carcinoma, and hepatoblastoma in childhood. The frequency of hepatoblastoma has been reported as 1.5% (10). Family screening is required because of the autosomal dominant inheritance of the disease (11). In cases with genetically diagnosed Gardner syndrome, especially in the first five years of life, abdominal USG and AFP screening are recommended every six months. Our case has been followed up in remission for two years after liver transplantation and is being followed up for other malignancies that may accompany.

NF1 is an autosomal dominant inheritance, which is the most common familial tumor predisposition syndrome that develops as a result of the mutation in the NF1 gene located in chromosome 17 and is the most common in the society. Due to its predisposition to benign and malignant tumor development and NF1 related complications, early diagnosis and clinical follow-up are essential (12). Malignant tumors that may develop in NF1 are glial central nervous system tumors, MPNST, sarcomas, myeloid leukemia, myelodysplasia, and myeloproliferative disorders (12). In our series, MPNST and malignant glial tumors were observed in our two NF1 cases. Regular follow-up of our case with MPNST enabled early detection and treatment of malignant transformation in neurofibroma. The patient with a malignant glial tumor was admitted with advanced disease because the patient was not followed-up regularly despite having an anamnesis in the family. Close monitoring of children with NF1 will allow early detection of malignant tumors.

RTS is a syndrome of childhood cancer-associated autosomal recessive DNA repair disorders, and other diseases in this group are Fanconi anemia, AT, Bloom syndrome, Nijmegen Breakage syndrome, and xeroderma pigmentosum (13). RTS increases the frequency of skin cancer and osteosarcoma. In the largest series in which RTS cases were reported, 32% of the cases developed osteosarcoma at the age of 11.5 years (14). Hicks et al. (15) reported that increased toxicity due to doxorubicin could be observed in RTS cases. However, the general recommendation is to give the full dose of the treatment and reduce the dose in case of increased toxicity (16). In our case, a full dose of chemotherapy was initiated, and the patient showed signs of

Table 2. Cancer Predisposition syndromes screening recommendations (adapted from reference 5)		
Syndrome	**Associated cancer**	**Screening**
Ataxia telangiectasia	Lymphoma, leukemia, breast cancer	Breast cancer screening for carriers
Beckwith Wiedeman	Wilms' tumor, hepatoblastoma, neuroblastoma, adrenocortical carcinoma	Abdomen USG and full urine analysis every three months at <7 years of age Serum AFP every three months at <3 years of age
Bloom	Leukemia, lymphoma, Wilms' tumor, stomach-colon-breast cancer	Abdomen USG every three months at <7 years of age (for Wilms' tumor)
Denys Drash	Wilms' tumor	Abdomen USG every three months at <7 years of age
Down	Leukemia, germ cell tumors	Regular CBC control
Fanconi anemia	Leukemia, MDS, hepatocellular carcinoma	CBC control every six months
Frasier	Wilms' tumor, gonadoblastoma	Gonadectomy for diagnosis, Abdomen USG every three months at <7 years of age
Gardner	Hepatoblastoma, colon cancer	Serum AFP and USG every three months at <3 years of age, Colonoscopy at age 10
Genital anomalies in boys	Wilms' tumor	Consider the WT1 mutation study Abdomen USG every three months at <7 years of age
Isolated hemihyperplasia	Wilms' tumor, hepatoblastoma, neuroblastoma, adrenocortical carcinoma	Abdomen USG and full urine analysis every three months at <7 years of age Serum AFP every three months at <3 years of age
Kleinfelter	Germ cell tumors, breast cancer	Consider mastectomy for breast cancer prophylaxis if the patient has gynecomastia
Multiple endocrine neoplasia 2B	Thyroid cancer, pheochromocytoma	Prophylactic thyroidectomy
45,X/46,XY	Gonadoblastoma	Gonadectomy for diagnosis
Neurofibromatosis type 1	Malignant peripheral nerve sheath tumor, leukemia, neural tumors	Regular follow-up, informing that plexiform neurofibromas may become malignant
Nevoid basal cell carcinoma	Medulloblastoma, basal cell carcinoma	
Peutz Jeughers	Gastrointestinal and other cancers	
Rothmund Thomson	Osteosarcoma, skin cancer	Regular follow-up, information, skin examination
Rubinstein Taybi	Medulloblastoma	
Simpson-Golabi-Behmel	Wilms' tumor	Abdomen USG and full urine analysis every three months at <7 years of age
WAGR	Wilms' tumor	Abdomen USG and full urine analysis every three months at <7 years of age
Xeroderma pigmentosum	Skin and corneal tumors	Regular skin and eye examination
USG: Ultrasonography, AFP: Alpha-fetoprotein, MDS: Myelodysplastic syndromes, WT: Wild type, CBC: Complete blood count		

toxicity due to doxorubicin similar to Hicks et al. (15) After dose reduction, chemotherapy was completed without disruption.

CONCLUSION

It is an important feature to detect the cases that are regularly followed up in our series at an early stage and shows the importance of regular follow-up. Also, with the determination of hereditary conditions that cause predisposition, the treatment dose was successfully completed by reducing the drug dose in 2 of our patients who showed increased signs of toxicity due to chemotherapy. In the light of these findings, with this study, we wanted to emphasize the importance of recognizing diseases that predispose to cancer and the need for regular follow-up.

Ethics

Ethics Committee Approval: The study was analyzed retrospectively in accordance with the ethical rules based on the principles of the Helsinki Declaration between 2015 and 2017 by Department of Okmeydanı Training and Research Hospital.

Informed Consent: Informed consent was obtained from patients' parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ş., S.H., Concept: H.Ş., Design: H.Ş., S.H., Data Collection or Processing: H.Ş., Analysis or Interpretation: H.Ş., Literature Search: H.Ş., S.O., Writing: H.Ş., S.O.

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Do Endocrinopathies Cause Changes in Transverse Carpal Ligament Thickness and Carpal Tunnel Area in Carpal Tunnel Syndrome?

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Abstract

Objective: The purpose of this study was to investigate the effect of transverse carpal ligament (TCL) thickness and the size of carpal tunnel area on clinical findings and electrophysiological changes through the wrist magnetic resonance imaging (MRI).

Methods: In this prospective study, the thickness of the TCL and the carpal tunnel areas of preoperative cases diagnosed with carpal tunnel syndrome (CTS) were measured via wrist MRI results. The effect of TCL thickness and carpal tunnel area on endocrinopathies such as diabetes mellitus (DM) and hypothyroidism and the effect of these variables on clinical findings and electrophysiologic changes were evaluated in the light of the literature.

Results: TCL thickness and carpal tunnel area were not statistically significant among DM, hypothyroidism and electrophysiological changes ($p>0.05$).

Conclusion: This study include one of the limited researches comparing the carpal tunnel area and TKL thickness in cases with and without endocrinopathy CTS. However, there is a need for further researches that have a greater number of cases, including multi-centered, different-winged people.

Keywords: Carpal tunnel syndrome, diabetes mellitus, hypothyroidism, transverse carpal ligament

INTRODUCTION

Thanks to the developing technology, many branches, especially orthopedic surgeons and neurosurgeons, frequently benefit from magnetic resonance imaging (MRI) while making a clinical diagnosis (1-6). In carpal tunnel syndrome (CTS), an ankle MRI examination is auxiliary imaging used, especially in cases such as evaluation of preoperative intra-canal space-occupying lesions (SOL) and detection of postoperative complications (2,7).

From past to present, after the open CTS the weakness of the transverse carpal ligament (TCL) on the postoperative digital flexor muscles is evaluated, and the effect of the incision of the ligament on the volar migration of the median nerve and digital flexor tendons is investigated (1) or in idiopathic CTS association of morphological anomalies with the severity of this syndrome are assessed with the help of MRI (6). However, in these trials, generally live mammalians like horses and donkeys are used instead of volunteers (4,5). It is known that the sensitivity of animal tissues and human tissues is different (7,8). In line with this proven scientific fact, the results obtained from animal experiments using live mammals are different and do not always reflect the truth (7-11). Evaluation of the literature reveals that in studies where live mammal subjects are not used,

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commercial cell lines are generally preferred (12,13). However, their results are not trusted because commercial cell lines include uniform cells, they don't contain the microenvironment like the extracellular matrix around them, and their phenotypic and genotypic properties change in time (14-19).

In this article, animal tissue or commercial cell lines were not used while creating the experimental setup. We believe that the results may be strong, as the data from this study are from the human wrist MRI and electromyography (EMG) tests. The aim of this scientific research was to investigate the relationship between TCL thickness and carpal tunnel area size with endocrinopathies and electrophysiological changes in patients diagnosed with CTS and included in this research.

METHODS

This prospective research was performed after approval from the Ethics Committee of Namık Kemal University Medical School with a number of 2017/55/05/04 and consent from the volunteers. In order to minimize analysis-related errors, similar measurements were performed by similar researchers.

Tools

The EMG device which was used to record the electrical activity of muscle and peripheral nerves and measure their functions was Nihon Kodhen Corporation Tokyo, Japan (#80270), and the MRI device was 1.5 Tesla, GE HEALTHCARE-OPTIMA MRA360.

Working principle

In this prospective research, we measured TCL thickness and carpal tunnel size in wrist MRI's of preoperative CTS patients (n=40). Then, we evaluated whether TCL thickness and carpal tunnel size change with endocrinopathies like diabetes mellitus (DM) and hypothyroidism and the effects of these variables on clinical findings and electrophysiologic changes. The association of carpal tunnel size and TCL thickness with endocrinopathies, and whether these measurements have effects on EMG findings were statistically assessed and discussed considering the literature.

Inclusion and Exclusion Criteria for the Cases

The study universe consisted of 67 patients who had complaints due to the involvement of sensory fibers of the median nerve (n=67).

Biochemical and hormonal assessments were performed for those cases who had flammable pain with tingling and numbness at the distal part of the wrist, whose first three fingers and the lateral half of the fourth finger were affected, whose sleep is interrupted due to numbness and paresthesia and shake their hands to relieve the pain, whose pain radiates to forearm and shoulder but spares neck, who feels hands painful and swollen especially in the morning, who have muscle weakness and atrophy at thenar region, and especially who have clumsiness which increases with activity and weakness in grasping objects. Although the CTS occurs due to idiopathic causes, several blood tests were performed for differential diagnosis. These tests included fasting plasma glucose, erythrocyte sedimentation rate, rheumatoid factor, anti-nuclear antibody, thyroid function tests, uric acid, and predisposing metabolic storage diseases.

After biochemical laboratory tests, the subjects were taken to the EMG laboratory to be evaluated with EMG. Mild CTS patients who have slowed median distal sensory conduction and lower than normal sensory action potential amplitude by orthodromic, antidromic, or palmar pathway (n=10), moderate CTS patients who had increased median nerve distal motor latency in addition to mild CTS symptoms (n=4), and subjects who had Raynaud phenomenon (n=1), dry skin (n=2), swelling (n=2), and color changes (n=3) at median nerve distribution area were excluded. In the study group, there was no case with tumoral lesions, bone fractures, neural cyst, or ganglion cyst. If there were any, those cases also would have been excluded.

Subjects who have severe CTS (n=40) according to EMG findings such as frequently absent sensory action potential, "-" thenar response, a severe decrease in amplitude, delayed distal latencies, and partial denervation in thenar EMG were included in this study.

Electrodiagnosis and EMG

An EMG analysis was performed for all patients who were clinically thought to have CTS and included in the study to differentiate CTS from cervical spondylosis, brachial plexus lesions, peripheric polyneuropathies, thoracic outlet syndrome, multiple sclerosis, cervical (C5-6) radiculopathies, entrapment neuropathies at other sites of the median nerve, and to measure the severity of median nerve injury. During the performance of these measurements, the guidelines of the American Association of Electrodiagnostic Medicine, American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation were taken into account. The diagnosis was made by measuring distal/proximal sensory ratio, which is the ratio of digit-wrist conduction velocity and palm-wrist conduction velocity performed from the third digit. According to this sensory conduction was measured at a 13-14 cm area in which CTS symptoms are seen. These values were compared with the conduction velocities of other regions that innervate

neighboring areas. According to the EMG results, the cases were grouped into 4 categories as normal, mild, moderate, and severe CTS (20).

In radiological evaluation, multiplanar MRI was used because it demonstrates musculoskeletal system diseases and soft tissue problems with high resolution and multiplanar cross-sectional evaluation (Figure 1a). The MRI sequences to be measured were fat-suppressed proton density axial (PDA) evaluation, and axial T1 weighted evaluation. PDA evaluation parameters were TR: 2500, TE: 13, FOV: 8 cm, matrix: 512x256, slice thickness: 2 mm, gap: 0.5 mm, NEX: 2, ETL: 8, BW: 14 and axial T1A evaluation parameters were TR: 500, TE: 10, FOV: 8 matrix: 512x256, slice thickness: 2 mm, gap: 0.5 mm, NEX: 2, BW: 14. During MRI evaluation antero-posterior thickness of flexor retinaculum was performed at the level of hamulus of hamatum (Figure 1b). In addition, an increase in median nerve thickness was measured at the psiform bone level, and median nerve compression and carpal tunnel area were measured at the hamatum level (Figure 1c) (21).

The measurements were performed with Sectra pacs (version 18.2; 2017) program.

Surgical Technique

During the preoperative evaluation, all of the cases were taken to the operation table. While the patients were at a neutral supine position, the antisepsis of the surgical area was achieved by 10% polyvinylpyrolidone solution. The hand was positioned as palm facing upwards. A longitudinal, approximately 1-1.5 cm incision line was marked, starting from the Kaplan cardinal line close to the flexor retinaculum, along the imaginary line passing through the radial edge of the fourth finger. To achieve anesthesia at incision line, lidocaine and epinephrine solutions were applied in 4 mL volume after dilution within 0.9% isotonic sodium chloride solution. Skin and subcutaneous tissue were passed with a surgical incision. TCL was identified and incised. The median nerve was decompressed. Bleeding control was established, subcutaneous tissue and the skin were sutured in accordance with the anatomical origin, and the operation was terminated.

Statistical Analysis

The data were analyzed with SPSS 20.0 package program. Descriptive statistics were given as mean ± standard deviation or median and frequency. Fisher's exact test and the Fisher-Freeman Halton tests were used to compare qualitative data. Because data obtained after the exclusion of subjects who didn't meet research criteria were not normally distributed, Mann-Whitney U test was used instead of the student's t-test. Then, the association was controlled using Spearman's Rho test. The results were evaluated with a 95% confidence interval, and $p<0.05$ was accepted as the significance level.

RESULTS

Demographic features and accompanying metabolic and other diseases were classified in subjects' diagnoses as CTS (Table 1).

No significant association was detected between CTS area and TCL thickness (rs=-0.020; p=0,903; p>0.05) (Table 2). Also, there was no significant association between TCL thickness and carpal tunnel area with DM, hypothyroidism, and electrophysiological variables (p>0.05) (Table 3).

DISCUSSION

In order to diagnose CTS, anamnesis, physical, and neurological examinations of the subject are evaluated together (22), and diagnostic provocative and electrodiagnostic tests are performed

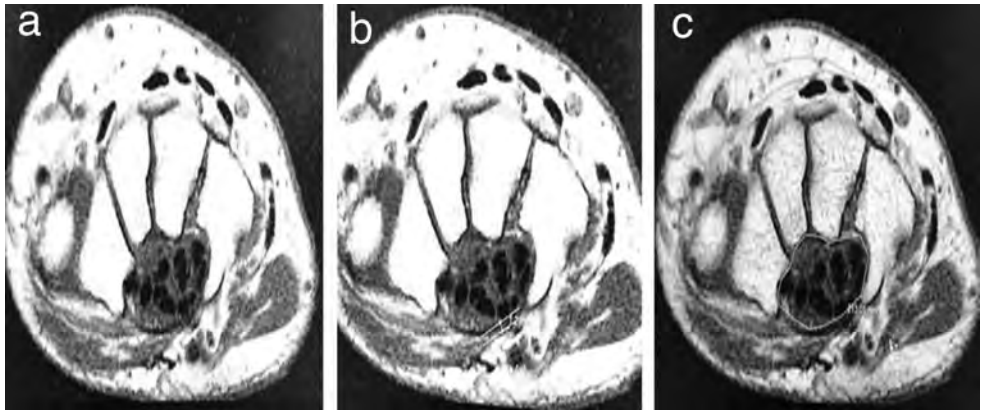

Figure 1. Noncontrast T1 Hand MRI. Axial sections through the wrist. a) Vertical section of the carpal tunnel, b) TCL thickness, c) measurement of carpal tunnel area
TCL: Transverse carpal ligament

for subjects who are believed to have CTS (23). By this way, CTS may be differentiated from other neuropathies (24).

After excluding rheumatological diseases and conditions such as sequelae of old fractures, radiological methods are used to evaluate parameters such as space occupying lesions in carpal tunnel, decreased carpal tunnel area due to osseous pathologies, and TCL thickness. (3,23). After Fornage et al. (25) detected TCL thickening in CTS patients using ultrasonography, hand MRI was started to be used in 1986, and it gained popularity in years. Neurophysiologic studies (NPS) have an important role in CTS diagnosis today, but there are studies in the literature that reported NPS does not help to diagnose typical CTS patients, and it results in more confusion than its benefits (26). Later, studies emerged that emphasized that neurophysiological studies have important roles in CTS diagnosis (27,28). Hand ultrasonography and conventional hand MRI studies during the same years demonstrated the fibrosis and edema in TCL in CTS patients (29).

With the advance in diagnostic evaluation tools, studies emerged in the literature, which demonstrated that in endocrinopathies like DM and hypothyroidism, TCL hypertrophy causes CTS. Based on this, surgical decompression for CTS cases due to DM may relieve sensory findings (30).

In this study, contrary to the literature, no statistically significant association could be found between TCL thickness and carpal tunnel area with DM, hypothyroidism, and electrophysiologic variables.

Netscher et al. (1) investigated the role of TCL in postoperative weakness and flexor digital canal system in CTS patients who were operated with open surgery. They used cadavers to study the effect of TCL on flexor tendons during the course of flexor tendons in the carpal tunnel. Using MRI imaging, they demonstrated that compared with the patients who were operated with other methods, patients who had TCL reconstruction with flap

Tablo 1. Demographic data and the distribution of systemic diseases accompanying CTS

Age (Years)	Mean ± standard deviation	55.60±11.38
Sex (Frequency)	Female	38 (95%)
	Male	2 (5%)
Height (cm)	Mean ± standard deviation	160.33±7.5
Weight (kg)	Mean ± standard deviation	77.5±14.40
Body mass Index (kg/cm^2)	Mean ± standard deviation	30.24±5.79
Accompanying diseases (frequency)	No	24 (60.0%)
	Yes	16 (40.0%)
Type of accompanying disease (Frequency)	Diabetes mellitus	8 (20.0%)
	Hypertension	9 (22.5%)
	Rheumatoid arthritis	7 (17.5%)
	Hypothyroidism	2 (5.9%)

CTS: Carpal tunnel syndrome

Table 2. Comparison of carpal tunnel area and transverse ligament thickness in cases that have or don't have accompanying endocrinopathy

			Carpal tunnel area (mm^2)	Transverse ligament thickness (mm)
DM	Yes (n=8)	Mean ± SD	206.94±27.22	0.94±0.16
	No (n=30)	Mean ± SD	202.71±28.79	0.96±0.14
		p*	0.624	0.945
Hypothyroidism	Yes (n=2)	Mean ± SD	187.47±14.80	1.00±0.17
	No (n=30)	Mean ± SD	202.71±28.79	0.96±0.14
		p*	0.095	0.282

*Alpha significance values obtained after Mann-Whitney, DM: Diabetes mellitus, SD: Standard deviation

Table 3. The association of TCL thickness, and carpal tunnel area with diabetes mellitus, hypothyroidism, and electrophysiological variables

			DM	Hypothyroidism	EDS
Spearman's rho	DM	Correlation Coefficient	1.000	-0.115	-0.120
		Sig. (2-tailed)¥	-	0.481	0.459
	Hypothyroidism	Correlation coefficient	-0.115	1.000	0.175
		Sig. (2-tailed)¥	0.481	.	0.281
	EDS	Correlation coefficient	-0.120	0.175	1.000
		Sig. (2-tailed)¥	0.459	0.281	-

¥Alpha significance values for Spearman's rho correlation test, *EDS; electrophysiological study, DM: Diabetes mellitus

transposition technique had less volar migration at 12-week follow up and less postoperative adhesions (1).

Another study retrospectively evaluated the diagnosis and treatment of 12 CTS cases that developed due to SOL inside the channel (3). Subjects who had space-occupying osseous lesions such as distal Radius fracture or lunate dislocation were excluded. The study included three males and eight females with a mean age of 51. The subjects were followed for 18 months after the operation, and the CTS diagnosis was made using clinical evaluation and EMG. In cases which were detected to have swelling and tenderness in the wrist line location, imaging studies such as wrist MRI and computed tomography (CT) were used for diagnostic evaluation. Using the classical open surgery technique, SOL was excised. Pathological evaluation of the excised SOL tissues revealed tuberculous tenosynovitis in three cases, nonspecific tenosynovitis in two cases, and gout in one case. Pathological evaluation of the other cases demonstrated CTS due to tumoral lesions in 5 cases; four of them were calcified, and 1 was originated from the ganglion. In postsurgical follow-up, all patients remitted, and no recurrence or complication was seen. The authors concluded that the presence of SOL should be excluded in cases detected to have swelling or tenderness at wrist line location, and imaging studies such as MRI or CT are required for these patients (3).

Our study results demonstrated that there were no tumoral lesions, neural compression due to bone fractures, or ganglion cyst in our study group.

Tanaka et al. (23) investigated whether high-resolution MRI could detect the triangular fibrocartilage complex injuries. High-resolution MRI was performed to subjects who had a positive ulnocarpal stress test and ulnar distal end tenderness at the wrist, and radial attachment, disc, ulnar part of triangular fibrocartilage, ulnotriquetral ligament, palmar radioulnar ligament (PRUL), and dorsal radioulnar ligament (DRUL) were evaluated. They concluded that although high-resolution MRI couldn't exactly detect DRUL, PRUL, and ulnolunate ligament, it was a safe imaging method for the radial part and disc area injuries (23).

Gray et al. (4); performed a prospective cadaver study in horses to evaluate whether CT arthrography was a useful imaging method to examine intercarpal ligament in horses. They found that CT arthrography was a useful imaging method to evaluate intercarpal ligament, and it can be used diagnostically to assess disability due carpal tunnel injury in horses (4).

We used only a wrist MRI to evaluate cases in our study.

A study that emphasized palmar metacarpal region is very important in horses and monkeys because it includes tendons and ligaments which contribute to the grasping of substances evaluated ligaments and tendons belonging to the palmar surface metacarpals of the healthy miniature monkeys (n=6) using MRI (5).

In this study, ligaments and tendons were evaluated by anatomic dissection and MRI, and the authors concluded that MRI was a very useful imaging method to evaluate soft tissues such as tendons and ligaments in the metacarpal region of living mammalian subjects. They detected that the suspensory ligament, deep digital ligament, and inferior check ligament were similar to horse ligaments. They also found that superficial digital flexor ligament has a superficial check ligament that emerges before the carpal joint in these animals. On the other hand, they found that miniature monkeys had another ligament originating from the large metacarpal bone called the second accessory ligament. The authors reported that this ligament could be detected by MRI, a monkey can grasp things thanks to this ligament, and this is a morphological feature for such monkeys (5).

Ikeda et al. (6) used 3-tesla MRI to evaluate the correlation between morphological abnormalities in idiopathic CTS and CTS severity. They evaluated the relationship between CTS severity and cross-sectional areas at multiple levels and performed nerve conduction studies and wrist MRI at both hands of unilateral CTS cases (n=35). At both the affected and unaffected hands median nerve was evaluated at 4 levels: distal radioulnar joint, the corpus of the scaphoid bone, scaphoid tubercle, and hamulus of the hamate bone. TCL thickness was evaluated at 3 regions with MRI and correlated with subjects who were detected to have severe CTS after distal motor latency study. The authors detected that in the affected hand, the median nerve cross-sectional area (MNCA) at the corpus of scaphoid bone was significantly larger than the unaffected hand. In addition, they suggested that the (MNCA) at hand was positively correlated with distal motor latency (6).

In this study, we also excluded Mild CTS patients who have slowed median distal sensory conduction and lower than normal sensory action potential amplitude by orthodromic, antidromic, or palmar pathway, moderate CTS patients who had increased median nerve distal motor latency in addition to mild CTS symptoms, and subjects who had Raynaud phenomenon, and dry skin, swelling, color changes or other autonomic sympathetic

nervous system involvement findings. The mean age of the cases included in our study was 55.60±11.38 years and involved 38 females and 2 males.

CONCLUSION

In conclusion, contrary to the literature, we couldn't detect a statistically significant association between carpal tunnel area and TCL thickness in this study (rs=-0.020; p=0.903; p>0.05). Also, no statistically significant association could be detected between TCL thickness and carpal tunnel area with DM, hypothyroidism, and electrophysiological variables. The low number of cases with endocrinopathies and the inclusion of people from the same race are the limitations of this study.

This prospective study is one of the few studies that compared the carpal tunnel area and TCL thickness using radiological evaluations in CTS patients with or without endocrinopathies. Prospective, multi-center studies that involve CTS patients with endocrinopathies from multiple races are urgently required.

Ethics

Ethics Committee Approval: Namık Kemal Üniversitesi Tıp Fakültesi (date: 25-05-2017; number: 2017/55/05/04).

Informed Consent: Not applicable.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.K., A.T.Ş., Concept: N.K., A.T.Ş., K.Ö., Design: N.K., A.T.Ş., K.Ö., Data Collection or Processing: N.K., A.T.Ş., Analysis or Interpretation: N.K., A.T.Ş., Literature Search: N.K., A.T.Ş., A.M.B., Writing: N.K., A.T.Ş., K.Ö., A.M.B.

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ORIGINAL ARTICLE

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Adrenocortical Carcinoma: Single Center Experience

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Abstract

Objective: The prevalence of adrenocortical carcinoma (ACC) is approximately 0.02% of all cancers, and the annual incidence is approximately 1-2 per million population. ACC is more aggressive, and the prognosis of ACC is poorer in adults than that in pediatric patients. We aimed to investigate the clinicopathological characteristics and factors affecting overall survival (OS) in patients with ACC who were followed-up and treated in our hospital.

Methods: The patients, who were treated and followed up in the oncology clinic between 2006 and 2018, were included in the study. The patients who were diagnosed with ACC in the pathologic evaluation were included.

Results: A total of 10 patients, five men (50%) and five women (50%), were included in the study. The mean age was 42.4 years (range=18-67). Six patients (60%) were stage 3, and four patients (40%) were stage 4. Eight patients (80%) underwent surgery. The release of glucocorticoid and/or androgen was detected in six patients (60%). Recurrence developed in six patients (100%), and seven patients (70%) died during the follow-up. The median OS was 13 months in patients with stage 3 disease, and the median OS was eight months in patients with stage IV disease (Log-rank p=0.177). The eastern cooperative oncology group performance status (ECOG PS) and performing of surgery were detected as the most significant factors affecting OS (Log-rank p=0.01, Log-rank p=0.02).

Conclusion: The significant factors for OS were found to be surgery and ECOG PS in our study.

Keywords: Adrenocortical carcinoma, overall survival, metastasis, glucocorticoids

INTRODUCTION

Adrenocortical carcinomas (ACC) are extremely rare. The annual incidence is 1-2/1000 000. Its prevalence among all cancers is approximately 0.02%. Although ACC may be detected in all ages, there is a bimodal distribution for age. The disease is most frequently detected under the age of five years and in the 4th-5th decades. The prevalence is higher in women with a ratio of 1.5-2.5/1 compared with men (1).

Approximately 60% of the patients present with the symptoms of feminization, virilization, and hypokalemia due to the release of corticosteroid, androgen, estrogen, and mineralocorticoids. Functional ACC is mostly detected in women and children; however, non-functional ACC is mostly detected in the advanced ages. Non-functional ACC symptoms are detected in the late period due to the pressure of the mass, organ invasion, and distant metastasis (2). Generally, ACC is more aggressive, and the prognosis is worse in adults compared with patients in the pediatric patients.

In the present study, we aimed to investigate the clinicopathological characteristics and factors affecting overall survival (OS) in patients with ACC who were followed-up and treated in our hospital.

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METHODS

The patients who were followed up and treated in the oncology clinic of Okmeydanı Training and Research Hospital between 2006 and 2018 were included. The patients who were diagnosed with ACC via pathologic evaluation were included in the study. The data including age, gender, the eastern cooperative oncology group performance status (ECOG PS), stage, surgical status, surgical margin status (R0=Complete resection, R1=Microscopic surgical margin positivity, R2=Macroscopic surgical margin positivity), adjuvant treatment, recurrence, the site of the recurrence, the site of metastasis at diagnosis, and the final status (Exitus-alive) were obtained from the archive files. The staging was performed in accordance with the European network for the study of adrenal tumors.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 22.0 for Windows program was used in the statistical analysis. The descriptive statistics were given as mean, standard deviation, minimum, and maximum for the numerical variables, and number and percentage for the categorical variables. The survival analyses were performed using the Kaplan Meier analysis. The predictive factors were investigated using the Cox Regression analysis. The statistical significance was regarded as $p<0.05$.

Ethics committee approval was obtained for the study (48670771-514.10).

RESULTS

A total of 10 patients, five men (50%) and five women (50%), were included in the study. The mean age was 42.4 years (range=18-67). The numbers of patients with ECOG PS 0, 1-3, and 4 were five (50%), four (40%), and one (10%), respectively. Six patients (60%) were stage 3, and four patients (40%) were stage 4. Eight patients (80%) underwent surgery, with three of whom having R2 resection. The mean dimension of the tumor was 10.6±4.3 cm. The release of glucocorticoid and/or androgen was detected in six patients (60%). Two patients (20%) received adjuvant radiotherapy (RT), and two patients (20%) received adjuvant mitotane. Recurrence developed in six patients (100%). Liver metastasis developed in four patients (66.7%), intra-abdominal recurrence in one patient (16.7%), and bone metastasis in one patient (16.7%). Liver metastasis was detected in two patients (50%), and lung/liver metastasis was detected in two patients (50%) at diagnosis. Seven patients (70%) died during the follow-up (Table 1).

The median OS was 13 months in patients with stage 3 disease, and the median OS was eight months in patients with stage 4 disease (Log-rank p=0.177) (Figure 1).

The median OS in all stages was calculated as 12 months in patients who underwent surgery; however, the median OS was three months in patients who did not undergo surgery. The difference was statistically significant (Log-rank p=0.01) (Figure 2).

A statistically significant difference was detected in OS in accordance with the ECOG PS (Log-rank p=0.02) (Figure 3).

Table 1. Demographic and clinical data of the patients

		n	%
Gender	Male	5	50
	Female	5	50
ECOG PS	0	5	50
	1	2	20
	3	2	20
	4	1	10
Stage	3	6	60
	4	4	40
Surgery	No	2	20
	Yes	8	80
Margin	R0	2	25
	R1	3	37.5
	R2	3	37.5
Tumor status	Glucocorticoid ± androgen	6	60
	Androgen	1	10
	Not evaluated	3	30
Adjuvant treatment	Mitotane	2	20
	RT	2	20
Recurrence - metastasis	Yes	6	100
Localizations of the recurrence	Liver	4	66.7
	Intraabdominal	1	16.7
	Bone	1	16.7
The localization of metastasis at diagnosis	Liver	2	50.0
	Liver + Lung	2	50.0
Status	Exitus	7	70
	Alive	3	30
Age (Years)	Mean ± SD (min-max)	10	42.4±14.5 (18-67)
Tumor size (cm)	Mean ± SD (min-max)	9	10.6±4.3 (5-18)

Cm: Centimeter, ECOG PS: Eastern cooperative oncology group performance status, R0: Complete resection, R1: Microscopic surgical margin positivity, R2: Macroscopic surgical margin positivity RT: Radiotherapy, SD: Standard deviation, Min: Minimum, Max: Maximum

The ECOG PS was detected as the most significant factor in the univariate analysis (p=0.027) (Table 2).

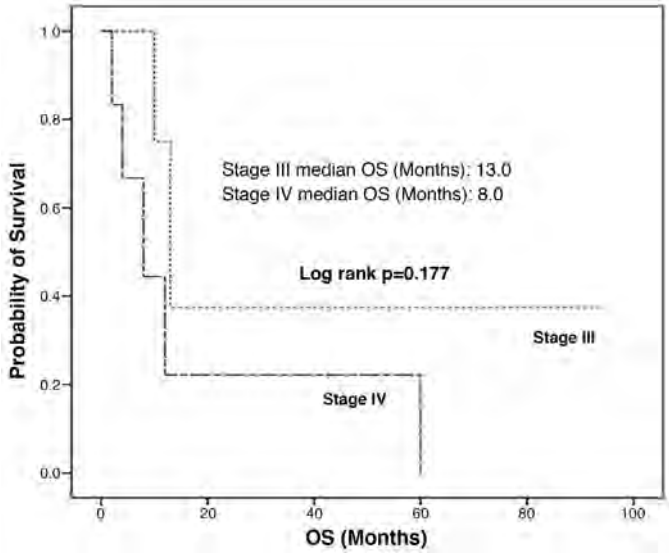

Figure 1. The overall survival in accordance with the stage
OS: Overall survival

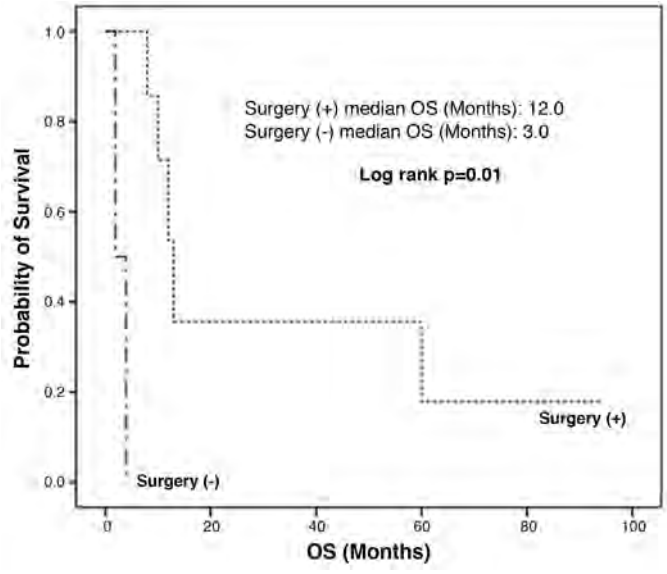

Figure 2. The overall survival in accordance with the surgical status
OS: Overall survival

Table 2. Univariate analysis for overall survival				
	HR	**95% CI**		**p**
Sex (Female vs male)	1.221	0.243	6.122	0.809
Age at diagnosis (Years)	1.018	0.972	1.066	0.451
ECOG PS	4.145	1.173	14.650	**0.027**
Stage (4 vs 3)	3.000	0.567	15.883	0.186
Tumor size (cm)	1.078	0.847	1.372	0.540
Cm: Centimeter, ECOG PS: Eastern cooperative oncology group performance, HR: Hazard ratio, CI: Confidence interval				

DISCUSSION

Complete surgical resection is the only potentially curative treatment for ACC. The first recommendation for the patients, who were candidates for surgery with resectable stage 1 to 3 disease, is the complete surgical resection. Before the surgery, the hormonal evaluation of all patients must be conducted to identify the secretory activity of the tumor. The identification of cortisol-producing tumors is particularly essential. The suppression of the Hypothalamic pituitary adrenal axis might have been developed in these patients, even in patients with mild hypercortisolism. To avoid postoperative adrenal insufficiency, glucocorticoid therapy must be initiated in these patients (3). Surgery was performed in eight patients (80%) in our study, and complete resection (R0) could be achieved only in two patients (25%). The tumors of seven patients (70%) were functional in our study, and six (60%) of them released glucocorticoid.

Although resection is technically possible in most patients with stage 1 to 3 disease, resection is not curative for most patients (4). Metastasis developed within two years in patients with stage I to 3 disease in a study, including 202 cases (5). Recurrence developed in all stage 3 patients in our study.

Although some clinicians suggested that the maximal debulking surgery improved survival, even if the tumor is unresectable (4,6,7), other clinicians suggested that this strategy had no advantage for survival (8,9). There are no adequate data to support the routine surgery for unresectable tumors. Debulking surgery in functional larger tumors may help control the hormone hypersecretion and increase the efficacy of the other

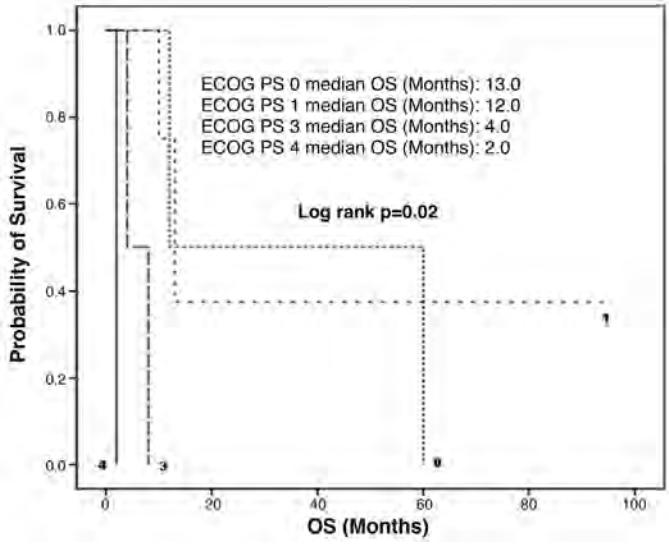

Figure 3. The overall survival in accordance with the ECOG PS status
ECOG PS: Eastern cooperative oncology group performance, OS: Overall survival

therapies (10). However, the prognosis is worse in patients with an unresectable disease than in those resectable counterparts. The OS generally ranges between three and nine months (1,11). The OS was three months in patients who could not undergo surgery, and the OS was 12 months in patients who underwent surgery in our study. Debulking surgery could be performed in only two patients (20%) in the metastatic stage in our study.

The most important factors identifying the prognosis in ACC are the disease stage and complete resection (12,13). In a series of 253 patients, The French Association of Endocrine Surgeons Study group found the five years OS as 66%, 58%, 24%, and 0% for stage I, II, III, and IV disease, respectively (12). Inadequate resection is associated with a poor prognosis, independently of the stage. The effect of surgical margin on the prognosis was demonstrated in a study using the national cancer database. The 5- years OS rates were found as 46%, 21%, and 10% for R0, R1, and R2 resection, respectively, in this study (13). R0 resection could be achieved in two patients (25%), R1 resection in three patients (37.5%) and R2 resection in three patients (37.5%) in our study and the median survival was calculated as 60, 10, and 8 months, in R0-, R1- and R2-resected groups, respectively.

ACC was suggested to be a radio-resistant tumor in the past. However, this may not be true for modern RT techniques (14). There is no randomized study that demonstrated the efficacy of adjuvant RT in resected-ACC patients. Some studies supported the benefit of RT in patients who had a high risk of local recurrence (14-16).

The results of 14 patients (stage I, II, and III) with no macroscopic residual disease who were treated with adjuvant RT were compared to 14 patients not receiving adjuvant RT, in terms of resection status, the use of adjuvant mitotane, disease stage, and tumor size. Local recurrence developed in two patients out of 14 who were treated with adjuvant RT compared to 11 patients out of 14 who received no RT. Despite this difference, the disease-free survival (DFS) and OS were not significantly better in patients who received RT (15). In a retrospective study from Michigan University, the results of 20 patients with R0 or R1 resection without adjuvant RT was compared to 20 patients who received adjuvant RT, and the results for both groups were similar for the stage, surgical margin, and the use of adjuvant mitotane. In a median 34 months of follow-up time, local recurrence was detected higher in patients without RT (60% vs %5%). However, this benefit did not affect DFS and OS (16). Only two patients (20%) received adjuvant RT in our study.

Because of the rarity of the disease and lack of larger prospective randomized clinical studies, the benefit of the routine postoperative adjuvant therapy for ACC is not clear. Although some uncontrolled non-randomized studies suggested that the adjuvant mitotane might delay or prevent the recurrence in non-metastatic disease (17-19), the other studies suggested that there was no benefit for DFS or OS (20,21).

The retrospective analysis of 177 stage I to III patients with complete macroscopic resection, which were collected from 55 centers between 1985 and 2005, showed that adjuvant mitotane therapy was associated with significantly longer DFS in comparison with the control group (42 months vs 10-25 months). Less number of patients died in the mitotane-receiving group compared with the control group (55% vs 25-41%) (18). Only two patients (20%) were initiated adjuvant mitotane in our study.

Although our study involved a follow-up time of 12 years, the number of patients was inadequate. The multivariate analysis could not be performed due to the small number of patients. Although the tumor stage was not statistically significant due to the small number of cases, it was clinically significant.

CONCLUSION

In conclusion, the most significant factors, which affected the survival, were detected as performing surgery and ECOG PS. The increase in ECOG PS increased the mortality risk by four-folds.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Istanbul Okmeydanı Training and Research Hospital (approval no: 48670771-514.10).

Informed Consent: Patients were not required to give informed consent, because the study was retrospective and anonymous data were used, which were obtained after each patient agreed to treatment by written consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S., Ş.S., Ç.G., Ş.S., Concept: S.A., Ç.G., Ay.S., Ş.C., Design: A.S., S.A., C.D., Ş.C., Data Collection or Processing: Ş.S., O.C., N.Y., C.D., Analysis or Interpretation: A.S., O.C., Ş.C., Literature Search: Ş.S., O.C., S.A., Ç.G., Writing: A.S., S.A., Ay.S., Ş.C. .

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ORIGINAL ARTICLE

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Factors Associated with Postoperative Chronic Pain and Recurrence After Laparoscopic Total Extraperitoneal Inguinal Hernia Repair

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Abstract

Objective: To assess the risk factors for chronic pain and recurrence after laparoscopic total extraperitoneal (TEP) inguinal hernia repair.

Methods: Data of the patients who underwent laparoscopic TEP repair were analyzed. Clinical and surgical characteristics, including learning curve, mesh weight, the pore size of the mesh, use of mesh fixation, and fixation methods, were assessed. Fixation by absorbable or non-absorbable tackers was performed in all procedures except for self-fixating meshes. Mesh brands were tiered into groups regarding pore size and weight. Operative time was defined as the duration between skin incision and dressing. The minimum follow-up was 24 months. Postoperative chronic pain was defined as moderate to severe groin pain, which was accepted as a Visual Analog score ≥3 longer than three months. Pain and recurrence were evaluated at 1 and 6 weeks in clinic visits and at 3, 12, and 24 months by telephone questionnaires. The occurrence of a fascial defect in physical examination or ultrasound was defined as recurrence.

Results: Three-hundred and eighty-two procedures were included. Postoperative chronic pain was seen in 31 (8.1%) patients and was higher with micropore mesh (p=0.004), mesh fixation (p=0.002), fixation with titanium tacks (p<0.001) and at first 50 cases (p=0.043). Fifteen (3.9%) patients had a recurrence. Older age (p=0.046), prolonged operative time (p=0.040), body mass index (BMI) (p=0.008) and learning curve (p=0.034) were significantly associated with higher recurrence rate. In multivariate analysis pore size [Odds ratio (OR): 2.911, 95% confidence interval (CI): 1.153-7.351, p=0.024] and fixation with titanium tacks (OR: 8.776, 95% CI: 4.040-14.893, p=0.004) were independent risk factors for chronic pain; BMI (OR: 1.307-95% CI:1.138-1.501, p<0.001) was the only independent risk factor for recurrence.

Conclusion: The outcome of laparoscopic TEP repair is related to the technic as well as patient-based factors. Titanium tacks and micropore meshes increase postoperative pain risk without any benefit on recurrence. Patients with higher BMI have an increased recurrence risk.

Keywords: Laparoscopy, hernia repair, inguinal hernia, total extraperitoneal repair, groin hernia

INTRODUCTION

The main goal of the on inguinal hernia repair has been the better surgical outcome, particularly regarding chronic pain and recurrence during recent years. Approximately 10% of the patients suffer from chronic pain (longer than three months), and 10-15% require reoperation for recurrence after open or laparoscopic inguinal hernia repair (1). Minimally invasive approaches that provide reduced nerve damage and postoperative pain with satisfactory recurrence rates have been emerged to improve quality of life after inguinal hernia repair (2). In a meta-analysis comparing laparoscopic transabdominal preperitoneal and total extraperitoneal (TEP) technics with Lichtenstein procedure revealed no difference in recurrence rates but fewer wound infection and chronic pain and earlier return to work with laparoscopic technics (3). Laparoscopic TEP is the most preferred minimally invasive repair with fewer complications, including visceral injury, ileus, and port-site hernia, shorter hospital stay, and reduced postoperative pain (4,5). In a prospective study, 10.555 Lichtenstein and 6.833 TEP procedures were compared,

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and no difference in recurrence and chronic pain was found, however postoperative complications ($p<0.001$) and early pain at rest ($p=0.011$) and exertion ($p<0.001$) were lower in TEP group (6).

Despite several randomized trials and meta-analyses, guidelines still do not mention any of those procedures as the standard of care (7). Either Lichtenstein or laparoscopic technics can be chosen based on resources and expertise. Moreover, there is no consensus on mesh selection and fixation (7). There is still a need for large-scale, controlled studies comparing different types of surgical materials. This study presents the mid-term results of TEP repair in a single center with an analysis of risk factors for chronic pain and recurrence.

METHODS

Prospectively collected database of patients who underwent laparoscopic TEP inguinal hernia repair between January 2012 and January 2017 was reviewed. Patients older than 18 years old with primary inguinal hernia were included in the study. All the procedures were performed under general anesthesia by the same team. The preoperative condition of the patients was recorded according to the American Society of Anesthesiologists classification. Age, gender, body mass index (BMI), type of hernia (unilateral and bilateral), type of defect (direct, indirect and combined), mesh weight, pore size of the mesh, use of mesh fixation and fixation methods (absorbable tackers and titanium tackers) were retrospectively gathered from the registry.

Mesh brands were tiered into groups regarding pore size and weight. BARD 3Dmax™ (Bard Davol Inc., RI, USA) and Prolene™ (Ethicon, LLC, USA) mesh comprised micropore group, where ProGrip™ (Medtronic, MN, USA) and Parietex™ (Medtronic, MN, USA) meshes were included in macropore group. BARD 3Dmax™, Prolene™, Parietex Hydrophilic Anatomical Mesh™ and ProGrip™ mesh were included in heavy-weight (>50 g/m^2) group. The light-weighted group was comprised of Parietex Lightweight Mesh™. Tacker fixation by Protack™ or Absorbatack™ was used in all procedures except for those performed using ProGrip™. The selection of mesh and tacker brands was due to the subjective choice of the surgeon and the availability of the materials at present.

Operative time was defined as the duration between skin incision and dressing. The procedures were divided into two groups (first 50 cases and after 50 cases) to assess the effect of the learning curve. Postoperative analgesia was provided with paracetamol and diclofenac sodium. All patients were assessed for Visual Analog scale score (VAS) and examined for seroma and recurrence at 1 and 6 weeks. At 3, 12 and 24 months, telephone questionnaire was performed, and VAS scores were recorded. Patients with any complaints were invited to the outpatient clinic for an in-person examination. Postoperative chronic pain was defined as moderate to severe groin pain, which was accepted as a VAS score lasting greater than 3 for 3 months. Recurrence was evaluated by physical examination, and ultrasound was performed for confirmation in case. Any fascial defect in the previous hernia site determined by the surgeon was recorded as recurrence. If the physical examination did not reveal a finding associated with a recurrent hernia, ultrasound was performed in patients with symptoms.

Statistical Analysis

Statistical analysis was done using IBM SPSS Statistics for Windows, Version 24.0. Categorical data were compared by chi-square or Fisher's exact tests. Continuous data were compared using the Student's t-test. A multivariate logistic regression model was conducted to determine risk factors for chronic pain and recurrence. $P<0.05$ was considered statistically significant.

Approval of the local Ethics committee was received for the study (İstanbul Medipol University Ethics committee number: 10840098-604.01.01-E.53651). All the patients gave written consent for the surgery and permission for the use of data in studies.

RESULTS

Two hundred and fourteen patients were meeting the inclusion criteria. Bilateral repairs were assessed individually, and 382 procedures were analyzed. The demographic and surgical characteristics of the patients are given in Table 1. The brand of the mesh was BARD 3Dmax mesh in 64 (16.8%) patients, Parietex Lightweight mesh in 44 (11.5%), Parietex Hydrophilic Anatomical mesh in 77 (20.2%), ProGrip Laparoscopic self-fixating mesh in 69 (18.1%) and Prolene mesh in 128 (33.5%) patients. There were 192 (50.3%) and 190 (49.7%) patients in micropore and macropore groups. High-weighted meshes were used in 338 (88.5%) patients; 44 (11.5%) patients had light-weighted mesh. No fixation was performed in 69 (18%) patients who underwent hernia repair using self-fixating mesh.

The mean VAS score at one week was 3.6 ± 1.9; at six weeks was 1.4 ± 0.8; at three months was 0.57 ± 0.4; at six months was 0.32 ± 0.3, at 12 months 0.22 ± 0.5 and 0.1 ± 0.2 at 24 months. Postoperative chronic pain was seen in 31 (8.1%) patients. Conservative treatments were given to those patients. At 12 months, only 5 (1.3%) patients had remaining chronic pain.

The mean BMI was 26.4±3.2 in patients with chronic pain and significantly higher than the mean BMI of patients having no pain (24.8±2.7, p=0.010). Type of the hernia or defect and mesh weight was no effect on postoperative pain. Postoperative chronic pain was seen in 23 (12%) patients in the microporous mesh group and 8 (4.2%) patients in the macroporous group (p=0.004). Mesh fixation significantly increased postoperative pain rate. None of the patients with self-fixating meshes suffered chronic pain. The chronic pain rate was significantly higher with mesh fixation (0% vs 9.9%, p=0.002). Among 31 patients with chronic pain, 30 had titanium tacks, and 1 had absorbable tacks. Titanium tacks were associated with higher pain rate (p<0.001) (Table 2).

The median follow-up was 26 (24-62) months. The recurrent hernia was seen in 15 (3.9%) patients who had significantly higher mean BMI (27.9±3.8 vs 24.8±2.7, p=0.008). Female patients had no recurrence (p=0.387). The mean age was significantly higher in patients with recurrence (51±18.4 vs 43.2±16.1, p=0.046). None of the patients with unilateral hernia suffered a recurrence, where 15 recurrences out of 337 procedures (4.5%) were seen, but the difference between patients with unilateral and bilateral

Table 1. Demographic and clinical characteristics of the patients

Number of patients	382
Age (mean ± SD)	50.8±14.9
Sex	
Male	359 (94%)
Female	23 (6%)
BMI (kg/m², mean ± SD)	24.9±2.8
ASA class	
1-2	303 (79.3%)
2-4	79 (20.7%)
Type of hernia	
Unilateral	45 (11.8%)
Bilateral	337 (88.2%)
Type of defect	
Direct	146 (38.2%)
Indirect	220 (56.7%)
Combined	16 (4.2%)
Type of mesh	
Highweight	338 (88.5%)
Lightweight	44 (11.5%)
Pore size	
Micropore	192 (50.3%)
Macropore	190 (49.7%)
Mesh fixation	
No	69 (18%)
Yes	313
Titanium	187 (49%)
Absorbable	126 (33%)
Operative time (min ± SD)	39.6±14.1
Learning curve	
First 50 cases	50
After 50 cases	332 (86.9%)

ASA: American Society of Anesthesiologists classification, BMI: Body mass index, SD: Standard deviation, Min: Minute

Table 2. Univariate analysis of the factors associated with pain

n=382	Pain		p
	No (n=351)	Yes (n=31)	
Age (mean ± SD)	50.6±14.3	52.7±19.7	0.457
Sex			0.575
Male	330	29 (8.1%)	
Female	21	2 (8.7%)	
BMI (kg/m², mean ± SD)	24.8±2.7	26.4±3.2	**0.010**
ASA class			0.349
1-2	277	26 (8.6%)	
2-4	74	5 (6.3%)	
Type of hernia			0.264
Unilateral	43	2 (4.4%)	
Bilateral	308	29 (8.6%)	
Type of defect			0.895
Direct	135	11 (7.5%)	
Indirect	201	19 (8.6%)	
Combined	15	1 (6.3%)	
Type of mesh			0.490
High weight	311	27 (8%)	
Lightweight	40	4 (9.1%)	
Pore size			**0.004**
Micropore	169	23 (12%)	
Macropore	182	8 (4.2%)	
Mesh fixation			**0.002**
No	69	0	
Yes	282	31 (9.9%)	
Titanium	157	30 (16%)	**<0.001**
Absorbable	125	1 (0.8%)	
Operative time (min ± SD)	39.9±14.1	36.4±14.2	0.277
Learning curve			**0.043**
First 50 cases	43	7 (14%)	
After 50 cases	308	24 (7.2%)	

SD: Standard deviation, BMI: Body mass index, ASA: American Society of Anesthesiologists classification, Min: Minute

hernias was not statistically significant (p=0.147). Alike as hernia type, the difference in recurrence rates in light-weighted (0%) and high-weighted (4.4%) mesh groups (p=0.154) and also microporous (5.7%) and macroporous (2.1%) groups (p=0.058) did not reach a statistical significance. The recurrence rate was similar in patients with and without mesh fixation. There were 3 (4.3%) recurrences in the self-fixating mesh group and 12 (3.8%) recurrences in patients who underwent titanium or absorbable tack fixation (p=0.074). In the first 50 cases, 5 (10%) recurrences were seen, which was significantly higher when compared with the following cases (n=10, 3.1%) (p=0.034) (Table 3).

Multivariate analysis was performed for factors predicting postoperative chronic pain (mesh fixation, fixation material, pore size, and BMI) and recurrence (BMI and learning curve). Using microporous meshes [Odds Ratio (OR): 2.911, 95% confidence interval (CI): 1.153-7.351, p=0.024] and fixation with titanium tacks (OR: 8.776, 95% CI: 4.040-14.893, p=0.004) were independently associated with postoperative pain. BMI was the only independent predictor of recurrence (OR: 1.307, 95% CI: 1.138-1.501, p<0.001) in multivariate analysis (Table 4).

DISCUSSION

Postoperative chronic pain and recurrence are the major problems of inguinal hernia repair. Our results indicated the inessentiality of mesh fixation, which has already been shown before. Apart from confirming previous literature, this study revealed the predictive factors for postoperative pain and recurrence. We found an increased risk of pain with microporous mesh and fixation with titanium tacks. The only independent predictor of recurrence was BMI.

The incidence of chronic pain after inguinal hernia repair has been reported up to 30% (8,9) and decreased less than 3% since laparoscopic technics emerged (10). This benefit may be associated with direct vision and protection of inguinal sensory nerves. In a study of 626 TEP repair published by Patel et al. (11) in 2016, significant and severe pain incidences were reported as 25% and 0.09% at the end of 2 years. They used Surgical Outcomes Measurement system and Carolinas Comfort scale and defined significant pain as mild but bothersome or worse on either specific tool. Mesh brand (Parietex anatomic, parietexprogrip, and physiomesh), size of the mesh, and fixation method had no effect on pain. Poor quality of life and general health status were predictors of pain longer than six months. In another study, Westin et al. (9) reported that 20% of the patients suffered from some degree of pain after TEP at one year, but severe pain was reported by 2.1%. The Inguinal Pain Questionnaire was used in this study. In our study, the VAS score >3 lasting longer than three months was accepted as chronic

Table 3. Univariate analysis of the factors associated with recurrence

n=382	Recurrence		p
	No (n=367)	Yes (n=15)	
Age (mean ± SD)	51±18.4	43.2±16.1	**0.046**
Sex			0.387
Male	344	15 (4.2%)	
Female	23	0	
BMI (kg/m², mean ± SD)	24.8±2.7	27.9±3.8	**0.008**
ASA class			0.623
1-2	291	12 (4%)	
2-4	76	3 (3.8%)	
Type of hernia			0.147
Unilateral	45	0	
Bilateral	322	15 (4.5%)	
Type of defect			0.368
Direct	138	8 (5.5%)	
Indirect	214	6 (2.7%)	
Combined	15	1 (6.3%)	
Type of mesh			0.154
High weight	323	15 (4.4%)	
Lightweight	44	0	
Pore size			0.058
Micropore	181	11 (5.7%)	
Macropore	186	4 (2.1%)	
Mesh fixation			0.074
No	66	3 (4.3%)	
Yes	301	12 (3.8%)	
Titanium	176	11 (5.9%)	
Absorbable	125	1 (0.8%)	
Operative time (min ± SD)	39.8±14.2	32.3±7.9	
Learning curve			**0.034**
First 50 cases	45	5 (10%)	
After 50 cases	322	10 (3.1%)	

SD: Standard deviation, BMI: Body mass index, ASA: American Society of Anesthesiologists classification, Min: Minute

Table 4. Multivariate analyses of the factors predicting pain and recurrence

	Variable	OR (95% CI)	p
Pain	Pore size	2.911 (1.153-7.351)	0.024
	Mesh Fixation with titanium tacks	8.776 (4.040-14.893)	0.004
Recurrence	BMI	1.307 (1.138-1.501)	<0.001

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

pain, as defined before by The International Association for the Study of Pain. Our chronic pain rate was 8.1% and seemed to be higher than previous studies; however, the measurement tools and the definition of severe or chronic pain were quite different between our study and those others. Our mean VAS score at two years was compatible with the literature. The main drawback of our study may be the lack of quality of life questionnaires. Indeed, this is also a drawback of the literature that there are no standard definitions and measurement tools of postoperative pain and quality of life after inguinal hernia repair. There are few studies assessing the predictors of pain after TEP repair. Onlay mesh placement, fixation of the mesh, strenuous physical activity, young age, and poor general health have been suggested to increase postoperative chronic pain incidence (11-14). In our study, we found higher pain incidence with higher BMI, using microporous mesh, mesh fixation, fixation with titanium tacks, and at the beginning of the learning curve.

Risk factors for a recurrent inguinal hernia include female gender, direct versus indirect inguinal hernia, limited surgical experience, and low volume centers (7). Compatible with the literature, the recurrence rate was 10% at the beginning of our learning curve and decreased to 3.1% after the first 50 cases (p=0.034). Similarly, postoperative chronic pain was 14% and 7.2% before and after the 50th case (p=0.043). In a recent study, Berndsen et al. (14) reported a 2.5% recurrence after 485 laparoscopic inguinal hernia repairs at a 5-year follow-up. Strenuous work (OR: 13.7), technically challenging repairs (OR: 7.2), and chronic discomfort (OR: 6.7) were the risk factors for recurrence in their study. We did not assess the technical difficulty of the operation; however, operative time, which may be a predictor of difficulty, was associated with recurrence in our study (p=0.040). Another drawback was the lack of records regarding postoperative activity and strenuous work of the patients; instead, we found higher BMI (p=0.008) and older age (0.034) were risk factors for recurrence.

There is an important heterogeneity among surgical technics and used materials, particularly in fixation fashion and mesh brands in TEP inguinal hernia repair. Recent guidelines strongly state that in almost all cases, any type of mesh fixation is unnecessary (7). Mesh fixation is recommended in only large direct hernias and with atraumatic fixation technics such as fibrin glue and cyanoacrylate (7,15). Consistent with these recommendations, none of the patients with no-fixation in our study had chronic pain (0% vs 9.9%, p=0.002). The recurrence rates were similar between no-fixation (4.3%) and tack-fixation (3.8%) groups (p=0.074). Fixation with titanium tack was the only independent risk factor for chronic pain in our study. The main conflicting issue in laparoscopic TEP repair is selecting the best mesh material. Despite several published randomized trials and meta-analysis, there are no standardized recommendations. The porosity, elasticity, strength, and the material of the mesh all influence tissue reaction; however, a general classification, which is based on a specific property of the mesh and which can reflect all risks, is not currently available, and even hardly conceivable. The limited literature on those properties mostly focused on the weight classification (lightweight versus heavyweight), and no further details of the meshes were given in the published data. The Herniasurge group 2018 Guideline stated that there is no single perfect mesh, and a mesh classification reflecting all possible risks or benefits does not exist and is not possible to develop (7). Small pore and heavyweight meshes are considered to carry a high-risk for fibrotic bridging and long-term mesh-related problems. Only a few studies in the literature have compared lightweight and heavyweight meshes and shown the superiority of lightweight mesh regarding better pain scores, comfort, and sexual dysfunction over conventional heavyweight polypropylene (13). However, long-term results have raised concerns about an increased risk of mesh displacement and recurrence with the use of lightweight mesh (16,17). A recent Swedish nationwide population study, including 13.839 laparoscopic TEP hernia repairs, revealed that lightweight meshes were associated with an increased risk of reoperation for recurrence (HR 1.56, p<0.001) compared to highweight meshes. This difference was more distinct in direct hernias and larger defects. In our study, there was no difference in chronic pain (p=0.895) and recurrence (p=0.368) rates between direct and indirect hernias. The chronic pain rates were also similar to lightweight (8%) and highweight (9.1%) meshes (p=0.490). There was no recurrence at two years with lightweight meshes, where in the highweight mesh group, our recurrence rate was 4.4%, but this difference did not show a statistical significance (p=0.154).

CONCLUSION

Laparoscopic TEP repair is a safe and effective method for inguinal hernia treatment. Mesh fixation is associated with a high risk of postoperative chronic pain with no benefit on long-term recurrence rates. Macroporous meshes provided favorable early postoperative outcome regarding pain. Mesh weight, pore size, and the brand did not affect recurrence. There is a need for large randomized trials in order to find the best classification of mesh materials and identify the perfect mesh.

Ethics

Ethics Committee Approval: Approval of the local Ethics committee was received for the study (İstanbul Medipol University Ethics committee number: 10840098-604.01.01-E.53651).

Informed Consent: All the patients gave written consent for the surgery and permission for the use of data in studies.

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Authorship Contributions

Surgical and Medical Practices: Y.Ö., P.B., Concept: Y.Ö., O.O, Design: Y.Ö., N.Ç.A., Data Collection or Processing: P.B., O.O., Y.Ö., Analysis or Interpretation: N.Ç.A., Literature Search: N.Ç.A, Y.Ö., Writing: N.Ç.A., Y.Ö.

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Comparison of Cesarean Sections Performed in the Second Stage of Labor and Vacuum-assisted Vaginal Delivery

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Abstract

Objective: Cesarean section or operative vaginal delivery can be performed in the second stage of labor. The aim of our study was to compare cesarean deliveries performed in the second stage of labor and vacuum assisted vaginal deliveries in terms of maternal and neonatal outcomes.

Methods: Between January 2017 and January 2018, the patients who delivered by cesarean section in the second stage of labor and vacuum assisted vaginal deliveries were retrospectively evaluated. Neonatal and maternal outcome parameters were compared between the two groups.

Results: A total of 113 patients, 53 patients in the vacuum delivery group and 60 patients in the cesarean section group, were included in the study. There was no difference between the groups in terms of maternal adverse outcomes. In terms of neonatal outcomes, umbilical cord pH was lower in the vacuum assisted delivery group (p=0.026).

Conclusion: Since maternal and neonatal complications are similar, operative vaginal delivery may be considered as an alternative mode of delivery in the second stage of delivery in the appropriate patient group.

Keywords: Vacuum, cesarean section, second stage of labor

INTRODUCTION

In recent years, cesarean delivery rates have increased worldwide (1). Among the reasons for this increase are medicolegal problems, increased number of multiple pregnancies due to an increased number of pregnancies with assisted reproductive techniques, and maternal desire. In addition to planned cesarean deliveries, emergency cesarean deliveries in the second stage of labor also increased. One of the most important reasons for this increase is the hesitation of the doctors to perform vaginal deliveries with intervention in the second phase of labor due to medicolegal issues (2,3).

Operative vaginal delivery is known to be associated with various maternal and neonatal complications (4,5). The belief that cesarean is safer in terms of maternal and especially neonatal outcomes led to a decrease in operative vaginal deliveries. Many trials have compared forceps and vacuum-assisted delivery outcomes (6-9). Only a few studies evaluated maternal and neonatal outcomes after operative vaginal delivery and cesarean delivery.

Our study aims to compare maternal and neonatal results of cesarean deliveries performed in the second stage of birth and vacuum-assisted vaginal deliveries.

METHODS

Our study was planned as a retrospective cohort study at Kanuni Sultan Süleyman Training and Research Hospital, Department of Obstetrics and Gynecology, between January 2017 and January 2018. The study was started after approval from the Kanuni Sultan Süleyman Education and Research Hospital Ethics Committee.

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This study included live singleton pregnancies that were delivered by vacuum-assisted vaginal delivery or cesarean delivery in the second phase of labor after the 34th week of gestation. Multiple pregnancies, those with a gestational week <34, pregnancies with congenital fetal anomalies, and patients whose data were not fully available were excluded. Vacuum deliveries were performed with the number 5 or 6 metal bell cap.

Maternal and neonatal data and birth results were obtained from the hospital database. Maternal features were gestational week, maternal age, gravida, and parity. The main maternal outcome parameters were blood loss during labor and hemoglobin and hematocrit values after delivery. Postpartum bleeding was defined as >500 mL for vacuum-assisted deliveries and >1000 mL for cesarean section. Other maternal results were lacerations (vaginal, cervical, perineal), ureteric damage, and hysterectomy.

Primary endpoints for newborns were birth weight, APGAR score at 1st and 5th minutes, arterial cord blood pH <7.05, and neonatal intensive care unit requirement.

Short-term outcome parameters of newborns and mothers after vacuum-assisted vaginal delivery were compared with outcome parameters of newborns and mothers after cesarean section at the second phase of labor.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences 20.0 (SPSS Inc.; Chicago, IL, USA) package program. Distribution of quantitative data was evaluated with the Kolmogorov-Smirnov test. Student's t-test was used for normally distributed variables and the Mann-Whitney U test was used for non-normally distributed variables. The chi-square test was used for the evaluation of quantitative data. A sample size calculation was performed at the G-power program with an effect size of 0.5, α error of 0.05, and power of 0.95. The calculation showed that at least 45 patients were required for each group. Statistical significance was achieved when $p<0.05$.

RESULTS

Between the study dates, there were 55 vacuum-assisted deliveries and 63 cesareans at the second phase of labor in our hospital. Two patients in the vacuum group and three patients in the cesarean group were excluded because their data can't be reached. The study included 53 patients in the vacuum assisted labor group and 60 patients in the cesarean group.

Comparison of the demographic data of the patients is listed in Table 1. No difference could be detected between the groups in maternal age, gravida, parity, gestational age, prepartum hemorrhage, and hematocrit ($p>0.05$).

No difference could be detected between the groups in neonatal outcomes like birth weight, hospitalization at neonatal intensive care unit, and 1st and 5th minute APGAR scores. Umbilical cord pH was significantly lower in vacuum-assisted vaginal delivery group ($p=0.026$). But no difference could be detected between the two groups in newborns with fetal pH <7.05 ($p>0.05$) (Table 2).

No difference could be found between the groups in maternal adverse results ($p>0.05$). Uterus rupture occurred in one patient in each group. A patient in the cesarean group had ureteral damage, and three patients in the vacuum group had perineal laceration (Table 3).

DISCUSSION

The rates of operative vaginal delivery have decreased over the years, while cesarean rates in general and during the second

Table 1. Comparison of demographic data

	Vacuum-assisted vaginal delivery (n=53)	Cesarean delivery (n=60)	p
Maternal age	27.00±6.72	25.76±6.47	0.323*
Gravida	2 (1-5)	2 (1-4)	0.324**
Para	1 (0-4)	0 (0-3)	0.212**
Gestational age (week)	39.05±1.02	38.83±1.12	0.275*
Prepartum hemoglobin (g/dL)	12.42±1.18	12.61±1.05	0.375*
Prepartum hematocrit (%)	37.60±3.75	38.13±3.49	0.439*

*Student's t-test and **Mann-Whitney U test were used

Table 2. Comparison of neonatal results

	Vacuum-assisted vaginal delivery (n=53)	Cesarean delivery (n=60)	p
Newborn weight (g)	3378.67±393.56	3316.25±366.41	0.385*
Umbilical cord pH	7.20± 0.17	7.26±0.07	0.026*
Admission to newborn intensive care unit	3 (5.7%)	2 (3.3%)	0.548**
1st minute APGAR score <5	4 (7.5%)	3 (5.0%)	0.575**
5th minute APGAR score <7	2 (3.8%)	0 (0%)	0.129**
Fetal blood pH <7.05	2 (3.8%)	1 (1.7%)	0.487**

*Student's t-test and **chi-square test were used

phase of labor have increased (10). The results of our study showed that short term maternal and neonatal complications of vacuum-assisted vaginal delivery and cesarean section during the second phase of labor were similar.

Current literature that compare operative vaginal delivery and cesarean delivery during the second phase of labor is conflicting (11-15). A study comparing operative vaginal delivery and cesarean delivery during the second phase of labor found more short term neonatal and maternal complications with operative vaginal delivery (11). Another study reported different results; no difference could be found in maternal adverse outcomes, and even less neonatal adverse results were reported for nulliparous women who delivered with forceps assistance (13). Another study showed that intracranial trauma was more frequent in newborns who had cesarean during labor (16).

According to neonatal results, our findings showed that there was no difference in 1st and 5th minute APGAR scores between vacuum-assisted delivery and cesarean section during labor. In our study, although there was a statistically significant difference between umbilical cord pH values, no difference was found between neonates with clinically significant pH <7.05. This result is similar to the previous study results (11,14). In a previous study compared with forceps deliveries, cesarean group had more newborns with a 5th minute APGAR score <7 (16). Another study also showed more newborns with 5th minute APGAR scores <7 in the cesarean group compared with operative vaginal deliveries, but the difference was not statistically significant (14). A factor contributing to the low APGAR score in this study may be the type of anesthesia. APGAR score at 5th minute, and arterial pH value were lower in the group which had cesarean section with general anesthesia compared with the group which had cesarean section with spinal anesthesia (17). In our study, anesthesia was not used in vacuum-assisted deliveries. Cesarean deliveries were performed under general anesthesia. We believe that, although not routinely reported in previous trials, general anesthetic agents may affect neonatal results.

Table 3. Comparison of maternal results

	Vacuum assisted vaginal delivery (n=53)	Cesarean delivery (n=60)	p
Blood transfusion	3 (%5.7)	4 (%6.7)	0.825**
Uterus rupture	1 (%1.9)	1 (%1.7)	0.929**
Hysterectomy	1 (%1.9)	0 (%0)	0.285**
Ureteral injury	0 (%0)	1 (%1.7)	0.345**
Vaginal laceration	3 (%5.7)	0 (%0)	0.062**
Postpartum hemorrhage	3 (%5.7)	3 (%5.0)	0.786**
Postpartum hemoglobin (g/dL)	10.69±1.30	10.91±1.31	0.366*
Postpartum hematocrit (%)	32.28±4.03	32.75±3.69	0.522*

* Student's t-test and **chi-square test were used

Compared with vaginal deliveries, respiratory distress was higher in cesarean deliveries. Another study showed that increased cesarean rates didn't increase short term results, but admission to a neonatal intensive care unit increased with cesarean deliveries (18). However, no difference was found in neonatal intensive care unit admissions in our study. Previous studies also demonstrated that bell caps also affected neonatal and maternal results (16). Only a metal bell was used in our study.

No difference was found between the two groups regarding short-term maternal results. However, this result differs from the literature because there was no significant difference in maternal postpartum bleeding (11,13). In the literature, a significant factor that contributed to high rates of anemia in an operative vaginal delivery is episiotomy, and blood loss comparable to that in a cesarean section was reported for an episiotomy (19-21). Whether vaginal, perineal, and cervical lacerations increase in forceps and vacuum-assisted deliveries is still debated (11). An episiotomy is frequently applied in operative vaginal deliveries.

The results of our study demonstrated that operative vaginal delivery is not associated with worse neonatal and maternal results compared with cesarean section during the second phase of labor. Operative vaginal delivery can still be regarded as a successful method with rare adverse neonatal outcomes when administered safely and carefully. However, the results of our study and other previous studies demonstrated that the cesarean section didn't increase the maternal complication risk significantly (22).

World Health Organization Global Survey on Maternal and Perinatal Death demonstrated that compared with spontaneous vaginal death, all other delivery methods, including operative vaginal delivery and cesarean increase risk for adverse maternal results, including death and intensive care unit admission. Blood transfusion and hysterectomy are more frequent with cesarean section compared with vacuum-assisted vaginal delivery (23).

The limitations of our study are its retrospective design and inability to obtain data about fetal head level and duration of the second phase when a decision was made for interventional delivery. The main strength of our study is the performance of vacuum-assisted deliveries and cesareans by experienced specialists.

CONCLUSION

In conclusion, alternative vaginal delivery may be thought of as an alternative method of delivery to cesarean section in an appropriate patient group, because they have similar maternal and neonatal complications. Extensive studies with large sample sizes are required to evaluate the outcomes of delivery methods at the second phase of labor.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital (2017).

Informed Consent: Informed consent is not obtained due to the retrospective nature of this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A.Ç., Concept: İ.T.Y., Design: A.A., Data Collection or Processing: G.Ş., Analysis or Interpretation: A.A., Literature Search: B.A.Ç., Writing: İ.T.Y., B.A.Ç.

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

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Comparison of Short-term Efficacy of Ranibizumab to Dexamethasone in the Treatment Naive Pseudophakic Diabetic Macular Edema: A Real-Life Study

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Abstract

Objective: This study aimed to compare the short-term efficacy of dexamethasone (Dex) implant with those of three consecutive ranibizumab (Rzb) injections in the treatment-naive diabetic macular edema patients.

Methods: In this retrospective study, 30 eyes of 30 diabetic macular edema (DME) patients were enrolled in the intravitreal Rzb (IVR) group; 29 eyes of 29 patients were enrolled in the Dex implant (DI) group. The IVR group was treated with three consecutive monthly Rzb injections; the DI group was injected one single DI. Both groups underwent ophthalmological examinations and optical coherence tomography exams at baseline and 1st, 2nd, and 3rd month visits. Data were analyzed with SPSS 22.0, statistically.

Results: Mean age, duration of diabetes, baseline best-corrected visual acuity, and central macular thickness (CMT) of both arms were statistically indifferent. The intraocular pressure (IOP) changes were within and between groups insignificant. The comparison of visual gain at the final visit showed no difference ($p>0.05$). The final CMT reduction in both groups was statistically insignificant (145 µm vs 110.5 µm $p>0.05$). In the DI group, two eyes (7%) had to be treated with topical anti-glaucomatous agents in the follow-up.

Conclusion: Both monthly Rzb injections and DI are equally effective in the initial treatment of DME. Although the treatment effect of the DI was seen earlier in the follow-up, the IOP elevations may be a clinical concern in some cases.

Keywords: Dexamethasone, diabetic macular edema, ranibizumab

INTRODUCTION

Diabetes is an emerging public health issue worldwide, and its complications are predicted to be one of the major problems of medical care in the upcoming years. Macular edema secondary to diabetic retinopathy is the leading cause of visual impairment at any stage of the disease. Ischemia-induced up-regulation of inflammatory mediators causes the breakdown of the blood-retinal barrier (BRB), leading to increased vascular permeability and macular edema. In the last decade, vascular endothelial growth factor (VEGF) is found to be the main factor of this pathogenesis. Thus, anti-VEGF treatment strategy-starting with the off-label usage of bevacizumab (1) improved itself to be superior to monotherapy with laser photocoagulation (2) or steroids in several studies (3). Following bevacizumab, ophthalmologically introduced anti-VEGF agents such as ranibizumab (Rzb) and aflibercept have proven them as effective in the treatment of diabetic macular edema (DME) (4,5). Today, the first-line therapy for center-involving macular edema is anti-VEGF agents (6) that are competing with each other as it is reported recently in DRCR.net's comparative trial (7). However, corticosteroids-an old actor in the management of diabetic macular edema e.g., triamcinolone-returned with a slow-releasing biodegradable

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implant of dexamethasone (Dex) (Ozurdex; Allergan, Irvine, CA, USA) into our armamentarium (8). Although concerns about well-known steroid-induced complications such as cataract formation or elevation of intraocular pressure (IOP) remain, clinicians consider this effective treatment modality as a second-line option reserved especially for anti-VEGF resistant DME cases rather than a first-line therapy.

In the literature, only a few reports are comparing anti-VEGF drugs with Dex implant (DI) head-to-head, based on real-life experience. In this present study, we aimed to compare the efficacy of a single DI to the intravitreal Rzb (IVR) loading phase in treatment-naive DME patients, to make a real-life analysis.

METHODS

This retrospective single-center study was conducted in the Retina Department of Okmeydanı Education and Research Hospital (OERH), University of Health Sciences, İstanbul. Ethical approval was approved by the Local Ethical Committee (48670771-514,10). The study has adhered to all aspects of the tenets of the Declaration of Helsinki. Informed consent was obtained from all the participants before each interventional procedure.

First of all, electronic and hardcopy records of ninety-eight treatment-naive DME patients-treated with either three consecutive IVR injections or a single DI between January 2017 and December 2018-were reviewed retrospectively. Our exclusion criteria were phakic lens status, the presence of co-existing ophthalmic pathologies such as glaucoma, retinal vein occlusions, the existence of vitreomacular interface disorders, or any prior treatment for DME such as any intravitreal injections or laser photocoagulation. Diffuse macular edema cases in the form of degenerative foveal thickening were also excluded to eliminate the effect of possible chronic foveal dysfunction. We included only the pseudophakic eyes into this study to subside the interference of cataract formation on visual results. According to our inclusion and exclusion criteria, fifty-nine eyes of 59 patients were enrolled finally into our study. 30 eyes of 30 patients were recruited into the Rzb (IVR) group and 29 eyes of 29 patients into the DI group.

While the IVR-group has undergone 3 consecutive intravitreal 0.5 mg Rzb injections (IVR) in a loading dose fashion, the DI-group was injected one single 0.7 mg DI. All intravitreal injections were performed in an operating room; single-use intravitreal injection sets were used, 5% povidone-iodine solution was applied at ocular surface minimum 5 minutes before injection, detailed informed consent forms were signed by each patient for any intervention, separately.

All patients underwent a baseline fluorescein angiography and spectral-domain optical coherence tomography (SD-OCT) (Cirrus; Zeiss, Germany) examination. Ophthalmic evaluation, including best-corrected visual acuity (BCVA) assessment in Snellen decimals, biomicroscopy, measurement of IOP by goldmann tonometry, funduscopy, and SD-OCT, were performed at baseline and 1st, 2nd, and 3rd month visits in the follow-up. We defined our primary outcome as changes in central macular thickness (CMT) and BCVA in both groups at the final visit.

Statistical Analysis

SPSS version 22.0 was preferred for statistical analysis. The variables were investigated using visual and analytical methods to determine whether or not they are normally distributed. The effect of the therapeutic agent on the change in BCVA, CMT, and IOP by time was investigated using repeated measures analysis of variance. The Greenhouse-Geisser correction was used when the sphericity assumption was violated. A multiple linear regression model was used to identify independent predictors of BCVA gain and CMT reduction. A p value <0.05 was defined as statistical significant.

RESULTS

In this retrospective study, 30 eyes of 30 patients (IVR-group) and 29 eyes of 29 patients (DI- group) were studied. Both groups were similar in terms of sex, age, duration of diabetes, glycosylated HbA, initial BCVA, CMT and IOP at baseline ($p=0.821$, $p=0.344$, $p=0.436$, $p=0.764$, $p=0.089$, $p=0.658$ and $p=0.460$, respectively). Table 1 summarizes the demographical and clinical features of both groups. The p values represent the significance of the comparisons; both groups were found statistically indifferent in all pre-mentioned demographic and clinical features.

Visual Outcomes

At 1st month visit, the mean BCVA logarithm of the minimum angle of resolution increased in both study groups significantly [0.73 vs 0.57 (IVR); 0.94 vs 0.63 (DI); $p=0.02$ and $p<0.001$; respectively]. Although a significant increase in the mean BCVA compared to baseline continued in DI group at 2nd month visit (0.94 vs 0.53; $p<0.001$), that upward trend did not reach a statistical significance in IVR group (0.54; $p=0.465$) at this time point. At the final visit, while the mean BCVA in DI group remained stable and statistically significant (0.54; $p=0.959$; 0.94 vs 0.63 $p<0.001$), a slight increase in BCVA continued in IVR group (0.46; $p=0.051$) still significant compared to baseline value (0.73 vs 0.46; $p=0.01$).

When the groups were compared with each other, the mean BCVA gain was found comparable through follow-up at every

time point (Table 2; p=0.080; repeated measures analysis of variance). Figure 1 depicts the mean BCVA changes of both groups throughout the study period.

Anatomical Outcome

The mean CMT in both groups decreased from their baseline values significantly at the 1st month visit (from 448 to 316 µm (DI), from 437 to 363 µm (IVR); both p<0.001; respectively). At 2nd month time point, CMT reduction continued in both groups, although significant compared to baseline (448 to 301µm (DI); from 437 to 348 µm (IVR); both p<0.001), these changes were statistically insignificant relative to previous visit (301 µm (DI), 348 µm (IVR); p=0.057, p=0.155; respectively). At 3rd month, the mean CMT value of DI group remained stable (301µm, p=0.974), but it decreased in IVR group significantly (321 µm, p<0.001).

The intergroup comparison aspect of CMT reduction revealed that patients in DI group had a more significant CMT reduction at 1st and 2nd month visits; (75 µm vs 132 µm; 90 µm vs 147 µm; Table 2; p=0.028, repeated measures). However, at the final visit (month 3), the decrease of mean CMT value was statistically insignificant between groups (117 µm (IVR) vs 147 µm (DI); p>0.05). Although DI resulted in a faster improvement of CMT than IVR, the IVR group ended with a similar CMT reduction at the final visit. Figure 2 presents the mean CMT changes of both groups in the follow-up.

Table 1. The demographical and clinical features of the both groups in study population

	IVR	DEX implant	p
Number of patients	30	29	-
Gender, male (%)	14 (46%)	15 (51%)	0.821
Age, years ± SD	62.7±7.9	64.7±7.8	0.344
Duration of diabetes, years ± SD	12.2±2.3	11.8±3.4	0.436
Serum HbA1c (mg/dL) level	7.9±1.3	8.1±1.2	0.764
Baseline BCVA (LogMAR)	0.73±0.28	0.94±0.56	0.089
Baseline CMT (µm)	437.6±86.5	448±93.1	0.658
Baseline IOP (mmHg)	16.3±2.6	15.8±2.9	0.460

BCVA: Best-corrected visual acuity, CMT: Central macular thickness, IOP: Intraocular, pressure, SD: Standard deviation, LogMar: Logarithm of the minimum angle of resolution, DEX: Dexamethasone, IVR: Intravitreal ranibizumab

Table 2. Comparison of both groups in BCVA, CMT and IOP changes in follow-up revealed a statistically significant difference in favor of DI group only in CMT reduction at 1st and 2nd month visits*

	IVR group	DI group	p value
BCVA* (LogMAR)			
Baseline	0.73±0.28	0.94±0.56	0.089
1 month	0.57±0.35	0.63±45	0.600
2 month	0.54±0.46	0.53±0.42	0.703
3 month	0.46±0.35	0.54±0.44	0.449
CMT (µ)**			
Baseline	437.6±86.5	448±93.1	0.658
1 month	362.5±80.6	316.4±86	**0.038***
2 month	347.6±88	301.1±67.6	**0.027***
3 month	320.6±70.2	300.7±74.2	0.297
IOP* (mmHg)**			
Baseline	16.3±2.6	15.8±2.9	0.460
1st month	15.5±3.3	17±4.5	0.144
2nd month	15.8±3.9	18±5.4	0.077
3rd month	15.3±3.2	16.6±4.4	0.49

BCVA*: Best-corrected visual acuity, CMT**: Central macular thickness, IOP***: Intraocular pressure, LogMar: Logarithm of the minimum angle of resolution, IVR: Intravitreal ranibizumab, DI: Dexamethasone implant

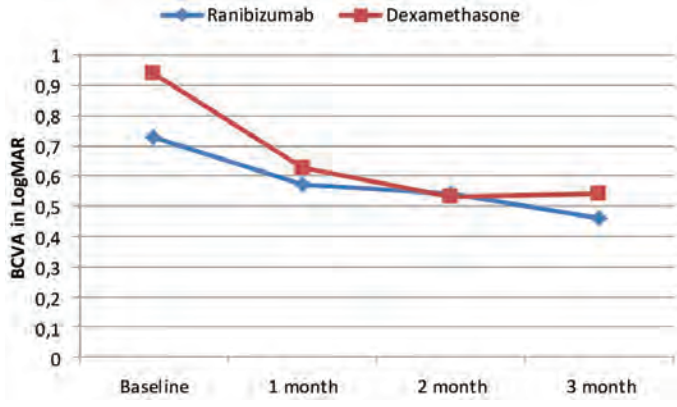

Figure 1. Comparison of BCVA through 3-month follow-ups revealed no significant difference between groups
BCVA: Best-corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution

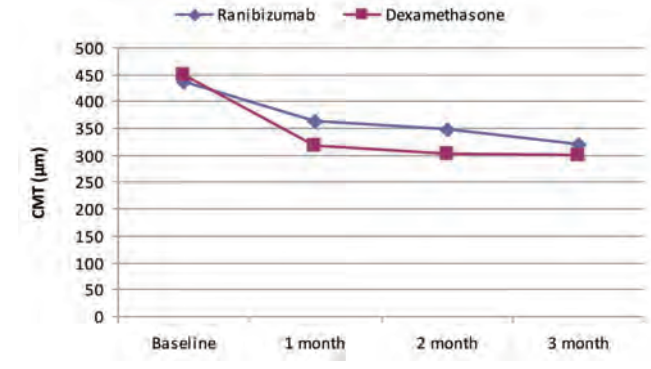

Figure 2. Regression of DME in both groups; the mean CMT value decreased in DI group at 1st and 2nd month visits significantly higher than in IVR group, but there was no statistical difference between groups at the 3rd month visit
DME: Diabetic macular edema, CMT: Central macular thickness, DI: Dexamethasone implant, IVR: Intravitreal ranibizumab

IOP Changes

The mean IOP increased in DI group at 1st month from its baseline value of 15.8±2.9 mmHg to 17±4.5 mmHg (p=0.311) and at 2nd month to 18±5.4 mmHg (p=0.020). However, mean IOP was still found within normal ranges. At the 2nd month visit, two eyes in the DI group had an IOP elevation higher than 5 mmHg, and these patients were started with topical anti-glaucomatous treatment in the follow-up. At 3rd month, a decline of IOP was remarkable in DI group (16.6±4.4 mmHg; p=0.060). Conversely, the mean IOP in IVR group did not change significantly at any time point of the study period (p=0.654, p=0,373; respectively).

The Comparison of IOP changes between groups revealed that-unlike IVR treatment DI leads to a significant rise in IOP, especially at months 1 and 2 (p=0.043; repeated measures). Figure 3 demonstrates the mean IOP changes in three months follow-up.

DISCUSSION

The major cause of visual loss in the diabetic population is currently center-involving diabetic macular edema. Theoretically, regarding the role of chronic inflammation in the BRB disruption and DME pathogenesis, corticosteroids should be considered as first-line therapy (9). However, with the introduction of intravitreal anti-VEGF therapy, these agents dominated -with their safety and effective profile-the choice of treatment of this clinical problem in the last decade. Corticosteroids, however, came back late into our armamentarium in the form of a biodegradable sustained-release DI. In this current study, we aimed to compare a potent corticosteroid -Dex- with an anti-VEGF agent, in a retrospective fashion in the aspect of efficacy.

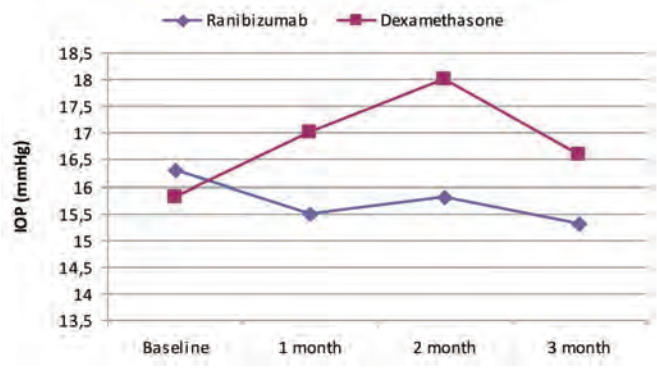

Figure 3. The mean IOP in DI group increased at 2nd month visit significantly; a decline of IOP levels was observed after introducing topical anti-glaucomatous treatment in two cases of this group; on the other hand, the IOP remained stabile in IVR group throughout the study period
DI: Dexamethasone implant, IVR: Intravitreal ranibizumab, IOP: Intraocular pressure

DI proved itself clearly as an effective agent in reducing DME in a combined treatment arm versus laser monotherapy in the PLACID trial (8). However, three-year results of the MEAD study-a randomized, sham-controlled pivotal trial - revealed also corticosteroids' well-known side-effects as cataract formation (67.9%) and IOP elevation of ≥10 mmHg (27.7%) in 0.7 mg Dex arm, one patient even underwent incisional glaucoma surgery (10). These potential side effects of Dex limited its wide-use in DME cases, worldwide.

In persistent macular edema, however, inflammatory mediators other than VEGFs are suspected to be the leading cause of suboptimal response to anti-VEGF therapy and corticosteroids' broad anti-inflammatory effect may lead to promising results especially in anti-VEGF refractory DME cases. Thus, some recent studies emphasize this second-line therapy positioning of DI (11,12).

Regarding the way of different therapeutic mechanisms of anti-VEGFs and steroids, there are only a few studies comparing these agents head-to-head in DME patients. In the first-year results of the BEVORDEX trial, a randomized, multicenter, prospective study DI administrations in every 16 weeks were compared to monthly bevacizumab injections (13). Although anatomical results were superior with fewer injections (2.7 vs 8.6) in the DI group (122 vs 187 µm reduction in CMT), functional results did not differ significantly, due to the impairing fact of cataract formation in the DI arm. The problem of cataract interference also raised in Callanan et al. (14) prospective, randomized, multi-centered study comparing Rzb with DI implant in a one-year follow-up. Sub-group analysis in this study revealed a better relative efficacy of DI compared with Rzb in baseline pseudophakic patients rather than in the total study population. Thus, despite our short follow-up, we enrolled only pseudophakic eyes into both our groups to subside the interaction of cataract formation on visual outcome.

In the comparative studies in diabetic population, one of the main issues is to find clinically equal groups for the enrollment. In this retrospective study, we carefully enrolled patients, evaluating systemic factors as gender, age, diabetic duration, HbA1c levels or ophthalmological findings as CMT or preoperative BVCA, aiming a statistically indifference in both arms. However, additional systemic or local factors may have affected our results. Thomas et al. (15), however, reported a contralateral eye-to-eye Rzb vs DI comparison in recalcitrant DME patients, eliminating the effects of systemic factors on their results. Similar to our study design, while Rzb group continued with monthly injections, DI group received one-single implant

for 3-month follow-ups. They found in this refractory DME group that DI was superior both in anatomical and functional results over IVR therapy. In contrast to their findings, Aydın et al. (16) found IVR treatment anatomically and functionally superior to DI in chronic diabetic macular edema patients. In our treatment-naive study group, however, we found IVR and DI statistically indifferent in the name of anatomical or functional results at the final visit.

Several studies in the literature reported promising results with DI in treatment of refractory DME patients (17,18,12). In these preliminary case series reports, the "magical" therapeutic effect of DI started as early as 3rd postoperative day (19) and reserved its efficacy up to 4th month (12). These findings positioned DI naturally into a second-line therapy reserved for refractory DME cases. With this current study, however, we aimed to change this clinical approach, showing the fact that one-single DI reveals similar clinical results to 3 consecutive IVR injections in treatment-naive patients. As Wallick et al. (20) reported in their large-cohort retrospective study, patients with DME averaged more than 10 health care visits more than those with diabetes but no DME (25.5 vs 14.9; $p<0.001$) in a 4-year interval, DI may be a preferable first-line therapy alternative to reduce the treatment cost and visit burden of this population.

The well-addressed concern of IOP elevation remains a problematic issue in selecting the treatment choice. We found a slight but significant elevation of mean IOP value at the 2nd month visit, deriving partially from the IOP elevation of higher than 5 mmHg in two cases. In the follow-up, IOP values of these two eyes were under control with topical anti-glaucomatous medications, leading to a decline of mean IOP at the 3rd month visit. Yılmaz et al. (21) reported in a large retrospective case series (n=1110) that IOP was elevated in only 168 eyes (15%), and topical therapy was started in 65 cases (5%). They concluded DI proved itself relatively safe in means of IOP elevations. Actually, the glaucomatous effect of Dex is mainly encountered in the steroid-responder subgroup of the population and is reversible and transient, especially after a single implant, (21) DI may not be continued in such cases, as we did in these two patients in further follow-up.

In the aspect of anatomical results, the DI group revealed a characteristic response profile, with an early reduction of CMT, leading to a significant difference in favor of DI at 1st and 2nd month visits, similar to Callanan et al. (14) results. In IVR group, however, the mean CMT continued to decrease after the third IVR injection and caught up with the stabile DI group at the 3rd month visit. This anatomical result at the final visit controversies to our general expectations that corticosteroids might be a more powerful treatment alternative. In visual gain, both groups revealed similar results through the study period.

CONCLUSION

The limitations of this current study are its lack of randomization due to its retrospective design, but we aimed to report our real-life experience in a comparative study. Although the short duration of our follow-up limits a reliable comparison of these both agents in long-term treatment, the comparable results of DI in naive DME patients support the idea of choosing this alternative for the first-line therapy in selected pseudophakic cases. We believe that this approach may have its benefits in reducing treatment burden and costs in the diabetic population.

Ethics

Ethics Committee Approval: This retrospective single-center study was conducted in the Retina Department of Okmeydanı Education and Research Hospital (OERH), University of Health Sciences, İstanbul. Ethical approval was approved by the Local Ethical Committee (48670771-514,10).

Informed Consent: Informed consent was obtained from all the participants before each interventional procedure.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.E., S.E., S.B., A.Ç., Concept: B.E., M.N.E., S.B., A.Ç., Design: B.E., M.N.E., S.B., S.E., G.K., Data Collection or Processing: B.E., G.K., A.Ç., S.E., S.B., Analysis or Interpretation: B.E., S.E., A.Ç., S.B., G.K., Literature Search: B.E., G.K., A.Ç., S.E., M.N.E., Writing: B.E., S.E., A.Ç., S.B., G.K.

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ORIGINAL ARTICLE

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Clinical and Electroencephalographic Findings in Patients with Sepsis-associated Encephalopathy and the Evaluation of Their Effects on Survival

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Abstract

Objective: Acute brain dysfunction is common in sepsis patients and is associated with increased mortality. This study aimed to investigate the clinical and electroencephalographic (EEG) findings of patients with acute neurological dysfunction due to sepsis and to evaluate their relationship with prognosis.

Methods: Sixty-one patients with sepsis were included in this prospective observational study. All patients underwent a daily neurological examination. EEG monitoring was performed in patients with delirium, coma, clinical seizures, and focal neurological findings. The patients were divided into two groups as survivors and non-survivors.

Results: Sixty-one patients included in the study had a median age of 60 years (range=21 to 81), Acute Physiology and Chronic Health Evaluation 2 score of 24 (range=14 to 39), and Sepsis-related Organ Failure Assessment score of 10 (range=3 to 24). During the EEG examination, coma was detected in 23 patients (38%), delirium/confusion in 20 patients (33%), clinical seizures in 16 patients (26%) and focal neurological findings in two patients (3%). The overall mortality rate was 42% (n=26). The EEG examination showed slowing of background activity in all patients. Also, among three patients who had seizure activity, two showed findings of an electrophysiological seizure. The EEG examination revealed a relationship between low-amplitude non-reactive background activity and mortality.

Conclusion: EEG monitoring may be indicated in the follow-up of encephalopathy in sepsis, the determination of the severity of the disease, the presence of an accompanying seizure or status, and prognosis.

Keywords: Sepsis, brain dysfunction, electroencephalography, prognosis

INTRODUCTION

Acute brain dysfunction is a severe complication of sepsis and often occurs before alterations in other organ functions in the early period (1,2). Clinically, it manifests itself in the form of acute neurological changes, such as altered consciousness, which may vary from delirium to coma, or a seizure activity (3). The relationship between these neurological findings in sepsis and increased mortality has been shown in several studies. The complication draws attention as an essential risk factor for the development of long-term cognitive impairment in survivors (4,5).

The pathophysiology of brain dysfunction in sepsis is multifactorial. In these patients, where infection does not directly affect the central nervous system (CNS), brain dysfunction is associated with neuroinflammatory and ischemic processes that result in impaired neuronal function (3,6). Also, the clinical picture is aggravated by the dysfunction of other organs, electrolyte disturbances, and the use of potential neurotoxic drugs such as antibiotics. Electroencephalography (EEG) changes observed in sepsis patients may reflect these neurotoxic processes (7-9). Although EEG in sepsis is a monitoring method used to diagnose

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brain dysfunction and to determine its severity and prognosis, the literature does not have sufficient data on this subject (10). During sepsis, various EEG findings are observed, such as the absence of reactivity, slowing of the background activity (the presence of theta and delta activity), electrophysiological seizures and periodic discharges (8,11,12). The frequency of these changes varies according to the design of the study (prospective or retrospective), the studied patient population [surgical or medical intensive care unit (ICU)], the severity and duration of sepsis (acute phase or late period), and the recording method of EEG (standard EEG recording or continuous EEG recording). Although some abnormalities, such as a triphasic wave pattern, a delta frequency, or a burst-suppression pattern, seen in the EEG examinations of sepsis patients are thought to be associated with poor prognosis, these findings need to be supported by prospective studies (10). Also, since non-convulsive seizures and status epilepticus are common in sepsis patients, the presence of ictal EEG findings may be guiding in diagnosis and treatment as well as be a potential prognostic marker (10,13).

This study aimed to investigate the clinical and EEG findings of patients who were hospitalized in the ICU due to sepsis and who had acute changes in their neurological status, and to evaluate their relationship with prognosis.

METHODS

Patients and Protocol

This prospective observational study was performed between February 2013 and February 2017 at the Medical and Surgical ICU of the İstanbul Faculty of Medicine at İstanbul University. Patients over 18 years of age, who were diagnosed with severe sepsis and septic shock according to the international diagnostic criteria for sepsis (14) and who were hospitalized in the ICU for more than 48 hours and who showed clinical signs of acute brain dysfunction, were included in the study. Acute brain dysfunction was defined as delirium/confusion, coma, clinical seizure, and the presence of focal neurological findings in neurological examination (15). Patients with a known CNS disease (neurodegenerative, inflammatory, cerebrovascular, neoplastic, traumatic brain injury) or CNS infection before the critical disease were excluded from the study. Also, patients with severe dementia, acute or chronic hypoxic brain injury affecting the neurological assessment, and patients with the presence of clinical evidence of brain death were excluded from the study. Patients who had severe hepatic insufficiency, who continuously needed muscle relaxants or who had a body temperature of <35 °C were also excluded from the study. The study was approved by the Institutional Review Board (approval number: 2013-98), and written consent was obtained from patients or their close relatives for creating medical records and applying the study protocol.

After the patients were included in the study, their clinical and demographic data, including age, gender, co-morbidities, the reason for admission to the ICU and admission category (medical or surgical), history of neurological disease, days in the ICU and duration of hospitalization were recorded. Acute Physiology and Chronic Health Evaluation (APACHE 2) score and the Simplified Acute Physiology score (SAPS 2) were used to assess the disease severity at enrollment. The Sepsis-related Organ Failure Assessment (SOFA) score was used to assess the severity of organ dysfunction from the time of admission to the ICU to discharge, and the evaluations were made daily. During the EEG monitoring, the renal and hepatic SOFA scores were calculated to evaluate the renal and hepatic failure, respectively.

From the time of admission to the ICU and throughout the study, vital and clinical examination findings of the patients were recorded. Patients were regularly followed-up with a standard laboratory protocol, including complete blood count, blood biochemistry, and blood gas analysis. From admission to the day of discharge, vital parameters, use of continuous sedation and the type of administered drug, days of sedation, duration of septic shock, days of mechanical ventilation, and days of hemofiltration were recorded daily. The infection focus that caused sepsis was noted along with culture results. Sepsis-induced hypotension was defined as a systolic blood pressure (SBP) of <90 mmHg or a mean arterial pressure of <70 mmHg, or as a decrease in SBP >40 mmHg or, in the absence of other causes, a decrease of beyond two standard deviations below the normal range for that age. Septic shock was defined as persistent sepsis-induced hypotension despite adequate fluid resuscitation in the absence of other causes of hypotension (14).

Neurological Examination

After the patients were admitted to the ICU, a detailed neurological examination was performed. All patients were followed up with a sedation protocol, except for the daily sedation discontinuation periods in the ICU. In patients receiving sedation, the depth of sedation was evaluated with the Richmond Agitation-Sedation scale (RASS) after the daily sedation was discontinued (16). The delirium/confusion assessment of the patients responding to the verbal stimulus during the RASS examination was made using the confusion assessment method for the ICU (CAM-ICU) (17), and the assessment was performed twice daily by a trained ICU nurse or

an ICU specialist. Patients who responded to the verbal stimulus and had a RASS score of ≥-3 (for example, a RASS score between -3 and +4) were diagnosed with delirium when at least one test was positive on the CAM-ICU test. Patients with a RASS score of -4 (responding only to physical stimulus) and -5 (completely unresponsive) were considered to be in a coma, and their level of consciousness was assessed using the Glasgow Coma scale (GCS). Coma was defined as GCS ≤8 in non-sedated patients or after three days of discontinuation of sedation in previously sedated patients (18). The presence of generalized or focal, tonic or clonic, short or long term and recurrent movement on the face or extremities was defined as an epileptic seizure. Any lateralized deficit was considered a focal neurological deficit.

EEG Monitoring and Analysis

Following the discontinuation of the sedation protocol as described above for the neurological evaluation of the patients that received sedation, sedation was discontinued at the time of EEG recording in patients with appropriate clinical and neurological status in ICU follow-up and treatment period. During the EEG recording, continuous sedative drug infusion was performed following internationally accepted standards in patients who required sedation, and the type of sedative drug used was recorded. The EEG monitoring of all patients with acute brain dysfunction as a result of the neurological examination was performed by an EEG technician using a portable EEG device (MICROMED SAM 32 RFO c1, 2008) at the bedside in the ICU. Twenty-one electrodes placed according to the international 10-20 system were used in scalp recording. EEG recording was performed for a median of 51 (range=20-1482) minutes. The analysis of the EEG recordings was performed by a neurologist (NB) who was a specialist in clinical neurophysiology. The American Clinical Neurophysiology Society's standardized "Critical Care EEG Terminology" guidelines were used in evaluating the EEG (19). The Salzburg consensus criteria were used in evaluating the non-convulsive seizures (20).

Statistical Analysis

Basic demographic and clinical data were presented as median and minimum-maximum for the continuous variables, and frequency and percentage for the categorical variables. The patient group was divided into two groups as survivors and non-survivors. In intergroup comparisons, the chi-square test was used for the categorical variables and the Mann-Whitney U test for the quantitative variables. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows 15.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and Clinical Data of the Study Patients

Between February 2013 and February 2017, 448 patients were admitted to our ICU with the diagnosis of sepsis. Three hundred and eight patients with acute brain dysfunction were evaluated for the study, and as a result, 61 sepsis patients (30 females, 31 males) who underwent EEG monitoring were included in the study. The flowchart of the study is shown in Figure 1. The median age of the patients was 60 (range=21-87) years, 51% (n=31) of the patients were admitted to the ICU for medical reasons, and 49% (n=30) for surgical reasons. During the ICU follow-up, 52 patients (84%) developed septic shock, 27 patients (44%) underwent hemofiltration, and all patients underwent mechanical ventilation. Baseline median APACHE 2, SOFA and SAPS 2 scores were 24 (range=14-39), 10 (range=3-24) and 53 (range=15-90), respectively. Twenty-six patients (42%) died during the ICU follow-up (Table 1).

Clinical and Neurological Findings of the Patients during EEG Monitoring

A total of 83 EEG recordings were performed in 61 patients included in the study (14 patients underwent a second EEG, seven patients a third, one patient a fourth one). The median EEG recording time was 51 (range=20-1482) minutes. The median time until the development of acute brain dysfunction was 6 (range=1-30) days after admission to the ICU. During the EEG monitoring, the most common neurological finding was coma (38%), followed by delirium/confusion (33%), clinical seizure (26%), and focal neurological findings (3%). The EEG examinations revealed that 90% of the patients had a significant slowing in background activity, with the most common wave frequency being the combination of theta/delta (n=24, 41%) followed by theta (n=24, 39%), and delta slow waves (n=6, 10%). Two patients with an EEG wave frequency of theta/delta and one patient with a delta frequency were accompanied by frontal intermittent rhythmic delta activity. No reactivation was observed in EEG in 47 patients (77%). In six patients (10%), background activity was observed to consist of low amplitude non-reactive rhythms. Generalized periodic epileptiform discharge was observed in one patient, periodic lateralized epileptiform discharge (PLED) in one, and a triphasic wave pattern in four patients. During the EEG examination in three patients, the presence of seizure activity, two of them being electrophysiological, was observed (Table 2). It was noteworthy that one of these patients was accompanied by PLEDs for a few seconds at the beginning of the electrophysiological seizure activity. The other patient had a recurrent twitching in the half of the face, which resolved after

intravenous injection of midazolam. Considering this finding as a focal motor seizure, levetiracetam treatment was begun, and the seizures disappeared in the following period. The clinical, neurological, and prognosis findings of the patients with specific EEG findings are presented in Table 3, and the EEG recording samples are presented in Figures 2-4. The follow-up EEG examination revealed that EEG findings had improved in five patients, remained the same in four patients, and worsened in five patients. During the EEG monitoring, the median SOFA score, which indicated the severity of organ dysfunction, was 9 (2-20), the median renal SOFA was 2 (0-4), and the median hepatic SOFA was 0 (0-4). During the EEG monitoring, 41% of the patients (n=25) received continuous sedative infusion, and 36% of the patients (n=22) were given remifentanil, 7% (n=4) dexmedetomidine, and 2% (n=1) midazolam for sedation. When the EEG findings of the patients who were given sedation during EEG recording were compared to those who were not given sedation, no difference was found in terms of background activity (p=0.575), amplitude (p=0.669), and the absence of reactivation (p=0.871).

Evaluating the Relationship Between Clinical Features and EEG Findings and Clinical Outcomes

When the survivors (n=35) and non-survivors (n=26) were compared, the age of the non-survivors was higher than the survivors (p=0.014), and the distribution of genders was similar (p=0.051). The SOFA score (p=0.017) was higher at admission to the ICU, and no significant difference was found between other the disease severity scores. The total SOFA and renal SOFA scores of non-survivors during the EEG monitoring were significantly higher (p=0.001 and p=0.005, respectively); there was no difference between the groups in terms of hepatic SOFA score (p=0.084). The survivors had a higher prevalence of delirium/confusion (p=0.013), while coma was a more common neurologic finding in the non-survivors (p=0.025). There was no significant difference in terms of clinical seizure rates (p=0.915). The non-reactive EEG pattern consisting of low amplitude non-reactive rhythms was more prevalent in the EEG examination of the non-survivors (p=0.034); however, there was no difference between the groups in terms of background activity (p=0.192), low amplitude (p=0.108), and the absence of reactivation (p=0.984) (Table 4).

DISCUSSION

In this prospective observational cohort study using EEG in sepsis patients with acute brain dysfunction, we found that: 1) all patients had abnormal EEG findings, primarily the slowing of background activity; 2) the presence of low-amplitude non-reactive rhythms on EEG were correlated with mortality; 3) advanced age, the SOFA score at admission and a high SOFA score at the time of EEG were correlated with mortality.

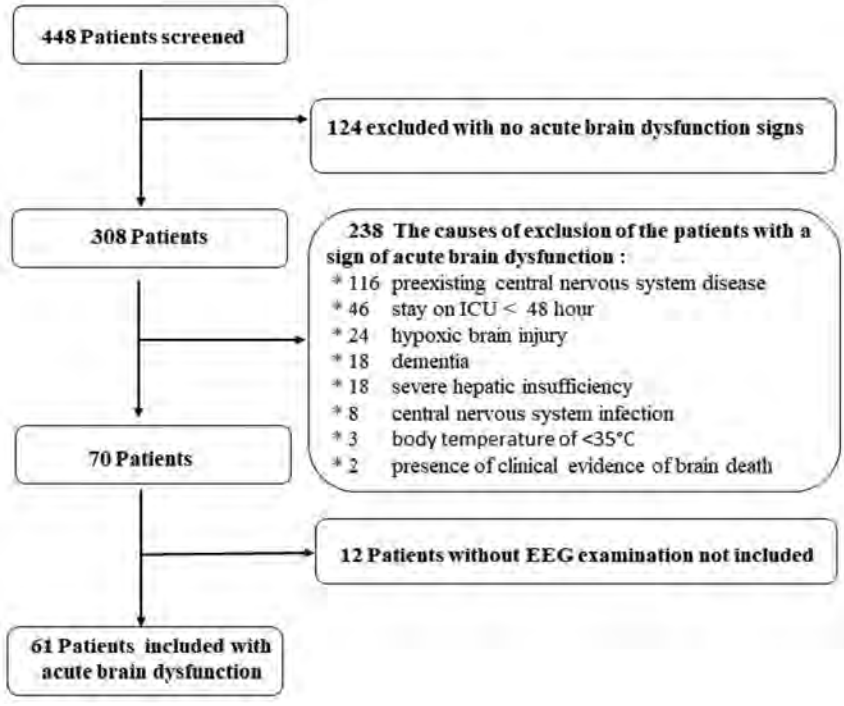

Figure 1. Flow chart of inclusion and exclusion of patients
EEG: Electroencephalography, ICU: Intensive care unit

It is known that acute neurological dysfunction developing in ICU patients with sepsis is associated with morbidity and mortality. Acute brain dysfunction in sepsis may involve different pathophysiological pathways (3,6). Whatever the underlying mechanism, various examination methods are used in addition

Table 1. Basic demographic and clinical data of the study patients

Variables	n= 61
Age (years)	60 (21-87)
Female, n (%)	30 (49)
APACHE 2 at admission	24 (14-39)
SAPS 2 at admission	53 (15-90)
SOFA at admission (from 0 to 24)	10 (3-24)
Maximum SOFA (from 0 to 24)	12 (4-24)
Glasgow Coma score at admission	15 (4-15)
Admission category, n (%)	
Medical	31 (51)
Surgery	30 (49)
Systemic diseases, n (%)	
Cardiac disease	29 (48)
Diabetes mellitus	22 (36)
Chronic renal failure	14 (23)
Cancer	20 (33)
Respiratory disease	4 (7)
Site of infection, n (%)	
Pneumonia	38 (62)
Intraabdominal	12 (20)
Soft tissue infection	5 (8)
Urinary tract infection	4 (7)
Pathogen, n (%)	
Pure gram negative	41 (67)
Pure gram positive	3 (5)
Polymicrobial	7 (12)
Positive blood culture, n (%)	17 (28)
Septic shock	
Prevalence, n (%)	52 (84)
Duration (days)	7.5 (1-36)
Duration of mechanical ventilation (days)	15 (1-41)
Duration of sedation (days)	11 (1-36)
Hemofiltration	
Prevalence, n (%)	27 (44)
Duration (days)	6.5 (1-36)
Mortality, n (%)	26 (42)
Days in the intensive care unit	19 (3-103)
Duration of hospitalization (days)	41 (6-120)

APACHE 2: Acute Physiology and Chronic Health Evaluation score, SOFA: Sepsis-related Organ Failure Assessment score, SAPS 2: Simplified Acute Physiology score, n: The number of patients (values are given as median and minimum-maximum, and the qualitative data are given as frequency and percentage)

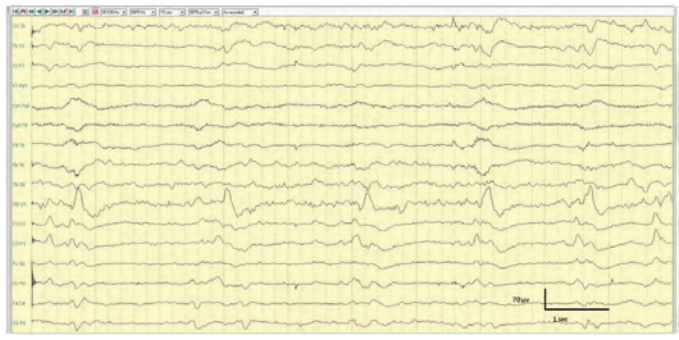

Figure 2. A representative example of EEG showing a periodic lateralized epileptiform discharge in a sepsis patient. Distinct and acute wave discharges, periodically repeating every 1.5-2 seconds, were detected in the occipital region in the posterior half of the left hemisphere during the EEG examination of a sepsis patient who had coma on the sixth day of admission to the intensive care unit. (Circular montage. Sensitivity: 70 microvolts/cm, low frequency filter: 0.5 Hz, high frequency filter: 70 Hz, paper speed: 10 seconds)

EEG: Electroencephalography

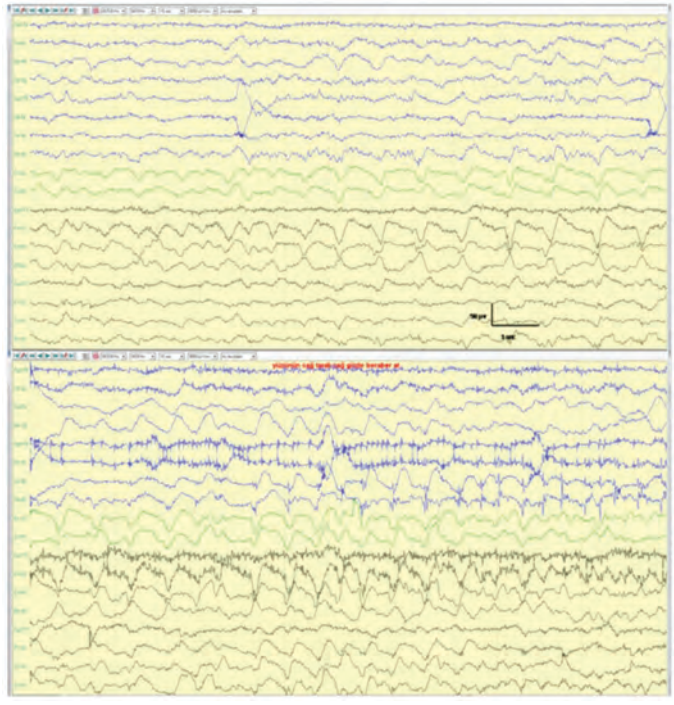

Figure 3. A representative example of EEG showing the onset of an electrographic seizure in a sepsis patient. Seizure activity in the left centro-parietal region manifested with a rhythmic, acute, slow-wave activity at 1 Hz of frequency, which showed evolution and was spread overall the hemisphere and the opposite hemisphere, was detected during the EEG examination of a sepsis patient who had a clinical seizure on the first day of admission to the intensive care unit. Clinically, the right side of the face was accompanied by recurrent twitching involving the eye. (Bipolar-double banana montage. Sensitivity: 70 microvolts/cm, low frequency filter: 0.5 Hz, high frequency filter: 70 Hz, paper speed: 15 seconds)

EEG: Electroencephalography

to clinical neurological examination in order to diagnose brain dysfunction and evaluate its severity (21). EEG is a neuromonitoring method that provides information about the electrical activity of the brain and can be performed at the bedside. EEG provides the possibility of evaluating the causes of brain dysfunction either due to structural diseases such as traumatic brain injury, intracranial hemorrhage, cerebral ischemia, and encephalitis or to functional disorders such as metabolic and sepsis-associated encephalopathy (22). The test can be used to take early potential therapeutic measures in patients with a tendency to develop brain dysfunction, to investigate the unexplained changes in consciousness and to determine the prognosis of developing neurological complications (13,23). EEG is the only examination method that can detect non-convulsive epileptic seizures (or subclinical) in critically ill patients (22). EEG is also used in the ICU to monitor the effect of sedative drugs during status epilepticus treatment (13,22,23).

EEG abnormalities in sepsis patients have been evaluated in a few studies, and the number of prospective studies in the literature is limited. The type, frequency, and the prognostic value of the EEG abnormalities associated with sepsis vary in the current studies. EEG findings of sepsis-associated encephalopathy are characterized by a generalized slowing in the background activity of EEG, and the presence of theta and delta waves, which are the indicators of diffuse cortical dysfunction (24). Concerning the severity of encephalopathy, theta waves often appear in patients with mild and moderate encephalopathy (confusion, delirium), while delta activity appears in a coma, where the impairment in consciousness level is more severe. The presence of triphasic waves and a burst-suppression pattern indicates the dysfunction of deeper brain structures such as basal ganglia and diencephalon (10). Prospective studies on sepsis patients have reported that abnormalities in the background activity of EEG are very often (7,11,25). In a prospective case series evaluating 62 patients with sepsis, 87% of the patients had abnormal EEG findings, including continuous theta and delta waves or a burst-suppression pattern, and these EEG findings have been shown to have a relationship with the diagnosis and severity of encephalopathy, as well as other organ dysfunctions and increased mortality (7). Similarly, a high prevalence in background activity abnormalities was observed in another study, but no relationship was detected between these EEG findings and the presence of sepsis-associated encephalopathy (25). A recent study in patients with sepsis demonstrated the relationship of predominant delta activity with the presence of delirium and increased mortality (11). Studies conducted on general ICU patients with and without sepsis showed that some EEG abnormalities, such as the presence of triphasic waves, delta waves, or a burst-suppression pattern, were associated with poor prognosis (11,26,27). In our study, during the EEG monitoring performed upon the detection of acute brain dysfunction, we observed a slowing in the background activity in all patients, related to the presence of sepsis-associated encephalopathy. However, a significant relationship could not be established between these changes observed in the background activity and the clinical outcome. This is probably due to the small number of patients in our study.

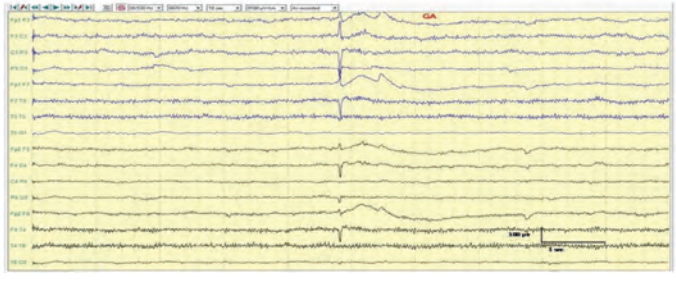

Figure 4. A representative example of EEG showing a low amplitude non-reactive rhythm in a sepsis patient. A monotone, low amplitude background activity mixed with artifacts was observed over both hemispheres during the EEG examination of a sepsis patient who had a clinical seizure on the first day of admission to the intensive care unit. It was notable that the patient's alertness did not change with noise and painful stimuli. (Bipolar-double banana montage. Sensitivity: 100 microvolts/cm, low frequency filter: 0.5 Hz, high frequency filter: 70 Hz, paper speed: 10 seconds)
EEG: Electroencephalography

In our study, we evaluated the EEG reactivity after giving standard noise and painful stimuli (23). The presence of reactivation in EEG requires the functional integrity of peripheral sensory pathways, the brainstem, subcortical structures, and the cerebral cortex. The absence of reactivation in EEG may be caused by the dysfunction that has developed in any of these structures, especially in the brainstem (28). The absence of reactivation in EEG with external stimulation is a sign of severe encephalopathy, and two recent studies on ICU patients with sepsis have shown its association with an increase in mortality (11,12). In our study, reactivation was absent in 77% (n=47), and although a higher rate was found than the two studies mentioned above, no relationship with mortality could be established. A possible explanation for this situation is the presence of sedation, or the ongoing effects of sedative drugs, which are shown to be one of the most critical factors affecting the evaluation of reactivation during EEG recording (11,12). However, in our study, there was no significant difference in terms of amplitude, slow-wave frequency, and reactivation between sedated and non-sedated patients.

It is expected to observe the specific EEG findings less often in sepsis cases in which the CNS is indirectly affected by diseases in comparison to the cases in which the CNS is directly affected. Although it is observed less frequently, these patients have different degrees of encephalopathy, and in patients with clinical improvement, recovery from encephalopathy should be confirmed with EEG. In our study, seizures were recorded in three patients in the EEG examination. One of these patients had a clinical seizure. One case had no signs of a clinical seizure, whereas the recurrent twitching on the face of the other case was thought to be a seizure, and upon EEG examination, the presence of an electroclinical seizure was confirmed. The seizures were brought under control with treatment. Also, the presence of PLED in a patient was noted as a specific EEG finding. Furthermore, it is noteworthy that patients with a non-reactive EEG, which presents with a low amplitude and lack of reactivation, may have a worse prognosis.

It is known that the EEG findings of ICU patients are affected by sedative drugs (10,11,13). Sedation is given to sepsis patients with a high disease severity score in order to ensure their safety and comfort during the treatment process. A decrease in the clearance of sedative drugs is observed during sepsis with the accompanying dysfunction

Table 2. Electroencephalography findings and simultaneous clinical variables of the patients

		Neurological findings during EEG monitorization				Death
		Delirium/ Confusion	Coma	Clinical seizure	Focal neurological findings	
EEG findings	**n (%)**					
Background activity-n (%)						
Theta	24 (39)	9	6	8	1	10
Theta/delta*	25 (41)	10	11	3	1	9
Delta**	6 (10)	-	3	3	-	2
Low amplitude non-reactive background activity	6 (10)	1	3	2	-	5
Low amplitude, n (%)	48 (79)	15	18	13	2	23
Absence of reactivity, n (%)	47 (77)	17	19	9	2	20
Triphasic waves, n (%)	4 (7)	2	1	1	-	1
Periodic anomalies, n (%)	2 (3)					
Generalized periodic epileptiform discharge	1	-	1	-	-	1
Periodic lateralized epileptiform discharge	1	-	1	-	-	1
Presence of seizures during EEG examination, n (%)	3 (5)	-	1	1	-	2
Electrophysiological seizure	2 (3)					
Variables during EEG recording	**n=61**					
Delay from admission to neurologic signs (days)	6 (1-30)					
Neurological status during EEG recording, n (%)						
Delirium/confusion	20 (33)					
Coma	23 (38)					
Presence of clinical seizure	16 (26)					
Focal neurological findings	2 (3)					
Duration of EEG recording, minutes	51 (20-1482)					
SOFA (from 0 to 24)	9 (2-20)					
Renal SOFA (from 0 to 4)	2 (0-4)					
Hepatic SOFA (from 0 to 4)	0 (0-4)					
Presence of sedation, n (%)	25 (41)					
Type of sedation, n (%)						
Remifentanil	22 (88)					
Dexmedetomidine	4 (16)					
Midazolam	1 (4)					

*Two patients with a theta/delta basic activity had an accompanying frontal intermittent rhythmic delta activity, **Two patients with a delta background activity had an accompanying frontal intermittent rhythmic delta activity, EEG: Electroencephalography, SOFA: Sepsis-related Organ Failure Assessment score, n: Number of patients (values are given as median and minimum-maximum, and the qualitative data are given as frequency and percentage)

of the organs such as liver or kidney, which play an essential role in the elimination of drugs. However, studies conducted on the critically ill patient group showed that EEG recordings continued to be informative about encephalopathy despite sedation (10). In our study, we applied the sedation protocol in line with international recommendations. During the EEG recording, we discontinued sedation in patients with an appropriate clinical and neurological status, and in a significant portion of patients that required sedation, we used remifentanil, which is rapidly metabolized in the plasma and the tissues. However, the effects of sedation cannot be completely ignored, even despite its discontinuation during EEG recording. In order to more clearly evaluate this condition, which is a limitation of our study, the sedative level should be measured, the neurophysiological changes during the EEG recording should be monitored, and the dose of the sedative should be determined using more advanced clinical parameters, such as the RASS score, during the EEG recording.

One of the limitations of our study was the lack of continuous EEG monitoring in all patients. An EEG with a short duration (less than 1 hour) makes the detection of the concomitant electrophysiological seizures particularly difficult. A continuous EEG provides more reliable detection of the changes in EEG,

Table 3. Clinical, neurological, and prognostic data of the patients with specific electroencephalography findings

Case	Age (years)	Gender	Major clinical problem and site of infection	SOFA Maximum	SAPS 2	Neurological findings	Lesion on brain MRI or CT	EEG background activity	Specific EEG patterns	Prognosis
1	59	F	Gastric surgery, anastomotic leak	19	84	Clinical seizure	No	Theta	Generalized tonic-clonic seizure record	Death
2	51	F	Liver transplant recipient, pneumonia	20	65	Coma	No	Theta/delta	Periodic lateralized epileptiform discharge and electrophysiological seizure	Death
3	49	F	Soft tissue infection	12	86	Clinical seizure	No	Delta	Electrophysiological seizure	Death
4	72	M	Radical prostatectomy, pneumonia	13	52	Coma	No	Delta	Generalized periodic epileptiform discharge	Death
5	73	M	Hepatocellular carcinoma, pneumonia	16	68	Coma	No	Low amplitude non-reactive rhythm	-	Death
6	22	F	Acute lymphoblastic leukemia, pneumonia	9	53	Clinical seizure	No	Low amplitude non-reactive rhythm	-	Death
7	61	F	Gastric surgery, anastomotic leak	9	49	Coma	No	Low amplitude non-reactive rhythm	-	Survival
8	65	M	Diabetic foot infection	21	64	Delirium	No	Low amplitude non-reactive rhythm	-	Death
9	62	M	Gastric surgery, anastomotic leak, pneumonia	12	66	Delirium	No	Low amplitude non-reactive rhythm	-	Death
10	81	F	Congestive heart failure, pneumonia	7	51	Clinical seizure	No	Low amplitude non-reactive rhythm	-	Death

SOFA: Sepsis-related Organ Failure Assessment score, SAPS: Simplified Acute Physiology score, MRI: Magnetic resonance imaging, CT: Computed tomography, EEG: Electroencephalography, F: Female, M: Male

Table 4. Comparison of the demographics and clinical and electroencephalographic findings of the survivors and non-survivors			
Variables	**Survivors (n=35)**	**Non-survivors (n=26)**	**p**
During admission to ICU			
Age (years)	56 (22-68)	63 (21-87)	**0.014**
Gender F/M	21/14	9/17	0.051
APACHE 2 score	22 (14-35)	25 (3-39)	0.083
SOFA at admission	9 (3-15)	12 (5-24)	**0.017**
SAPS 2 at admission	45 (15-90)	58.5 (16-78)	0.220
Clinical findings during acute brain dysfunction			
SOFA (0-24)	7 (2-17)	10.5 (4-20)	**0.001**
Renal SOFA (0-4)	0 (0-4)	2.5 (0-4)	**0.005**
Hepatic SOFA (0-4)	0 (0-3)	1 (0-4)	0.084
Delirium/Confusion	16 (46)	4 (15)	**0.013**
Coma	9 (26)	14 (54)	**0.025**
Presence of clinical seizures	9 (26)	7 (27)	0.915
EEG findings during acute brain dysfunction			
Background activity			0.192
Theta	14 (40)	10 (39)	-
Theta/delta	16 (46)	9 (35)	-
Delta	4 (11)	2 (7)	-
Absence of reactivation	24 (69)	20 (77)	0.984
Low amplitude non-reactive background activity	1 (3)	5 (19)	**0.034**
Low amplitude	25(71)	23 (88)	0.108
Generalized periodic epileptiform discharge	-	1	-
Periodic lateralized epileptiform discharge	-	1	-
Electrophysiological seizure	-	2	-
Days in the intensive care unit	21 (3-103)	16 (4-72)	0.470
Duration of hospitalization (days)	44 (17-120)	36 (6-80)	**0.026**

ICU: Intensive care unit, F: Female, M: Male, APACHE 2: Acute Physiology and Chronic Health Evaluation score, SOFA: Sepsis-related Organ Failure Assessment score, SAPS: Simplified Acute Physiology score, EEG: Electroencephalography, n: Number of patients (values are given as median and minimum-maximum, and the qualitative data are given as frequency and percentage)

although studies conducted with EEG examinations with short durations in septic ICU patients were able to predict the clinical outcome (11,26). Ideally, a continuous EEG should be performed in a separate room for a minimum of 24 hours. However, even though the precision in detecting the presence of intermittent electrophysiological seizures decreases in EEG examinations with short durations, EEG examination is still an important method to detect brain dysfunction, determine its severity, and to demonstrate the presence of non-convulsive status epilepticus in sepsis patients.

CONCLUSION

In conclusion, it should be noted that EEG monitoring can help determine the severity of sepsis-associated encephalopathy, in following up the encephalopathy, in determining whether it is accompanied by seizure or status epilepticus, and in prognosis.

Acknowledgements

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Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (15.02.2012-2013/98).

Informed Consent: Written informed consent was obtained from the patients or their close relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.O., NB., F.E., Design: G.O., NB., F.E., Data Collection or Processing: G.O., N.B., P.E.Ö., A.A., F.E., Analysis or Interpretation: G.O., N.B., A.A., F.E., Literature Search: G.O., N.B., Writing: G.O., N.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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Eur Arch Med Res 2020; 36 (1):83-5

Fracture of Collum Femoris Secondary to Gunshot Wound: A Lucky Patient Who Didn't Have Any Additional Injury

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Abstract

Gunshot injuries are rising in most countries in the last decades. Gun shot wounds in extremities result complicated bone fractures and related complications like infection, nonunion, malunion. Also, vascular and nerve injuries result from gunshot wounds. We report the case report of a 32-years male who underwent gunshot to the proximal femur. He had only nondeplase collum femoris fracture which was treated succesfully without any complication. We think that it is a big chance for patient having this progress in this severe trauma.

Keywords: Gunshot wound, collum femoris fracture, chance

INTRODUCTION

Firearm injuries (FAI) are encountered more and more every day amid military conflicts, increased terror incidents, easy access to weapons, and an increase in crime rates in modern civil societies. All extremity FAI are considered Gustilo type 3 open fractures. In addition to severe bone lesions and direct effects due to high-energy trauma, gunshot wounds cause additional morbidities such as amputations due to severe soft tissue injuries, vascular and nervous injuries and mortalities due to additional organ injuries (1,2).

CASE REPORT

We present a 32-year-old male patient who was brought to Okmeydanı Research and Education Hospital Emergency Department due to a FAI in October 2015. Physical examination of the patient who had an FAI in the right hip region after a close shot with a pistol demonstrated that his vital signs were stable. There was an entrance hole laterally over the right trochanter major. The neurovascular examination of the extremity was normal (Figure 1). In the radiological evaluation, there was a non-displaced right femoral neck fracture (Figure 2). No pathological sign was detected in lower extremity vascular assessment (Figure 3). The bullet core was found in the anterior part of the bladder. No additional organ injury was observed. After the local and systemic evaluation of the patient, he was prepared for surgery 6 hours after injury. Lateral decubitus position was given after spinal anesthesia. After the inlet and outlet holes were debrided, they were washed with saline with rifocin. A 2-3 cm lateral incision extending from the tip of trochanter major to distal part was made (Figure 1). The femoral neck fracture was fixated with three cannulated screws under scopy control (Figure 4). The operation was terminated after the stability was tested with scopy. Triple antibiotic therapy was applied for five days, and the patient was discharged after training about crutch use. Partial load was started to be applied after eight weeks. Full load was started to be applied at 3rd month. No problem was observed at 4th, 5th, and 6th-month follow-up visits.

DISCUSSION

Gunshot wounds are increasingly encountered in modern life in recent years. Due to the high energy, and blastic and thermal

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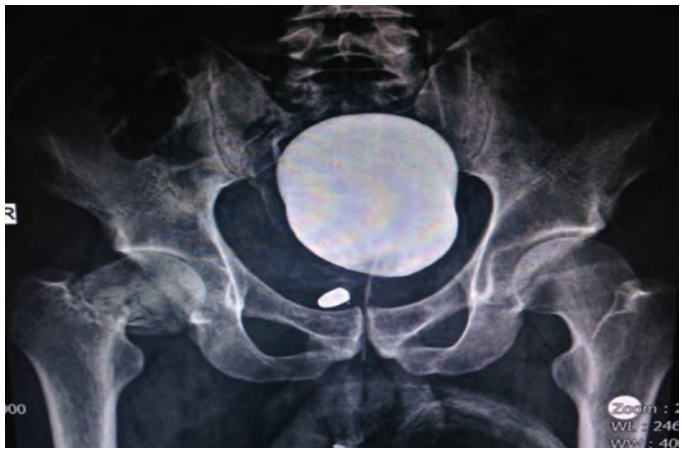

Figure 1. Pre-operation X-ray of the patient

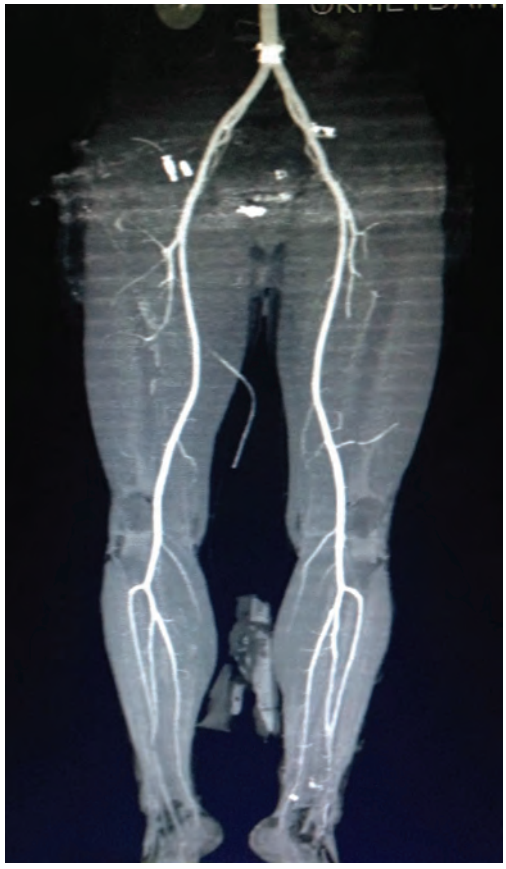

Figure 2. No pathological sign was observed in the vascular evaluation of the lower extremity

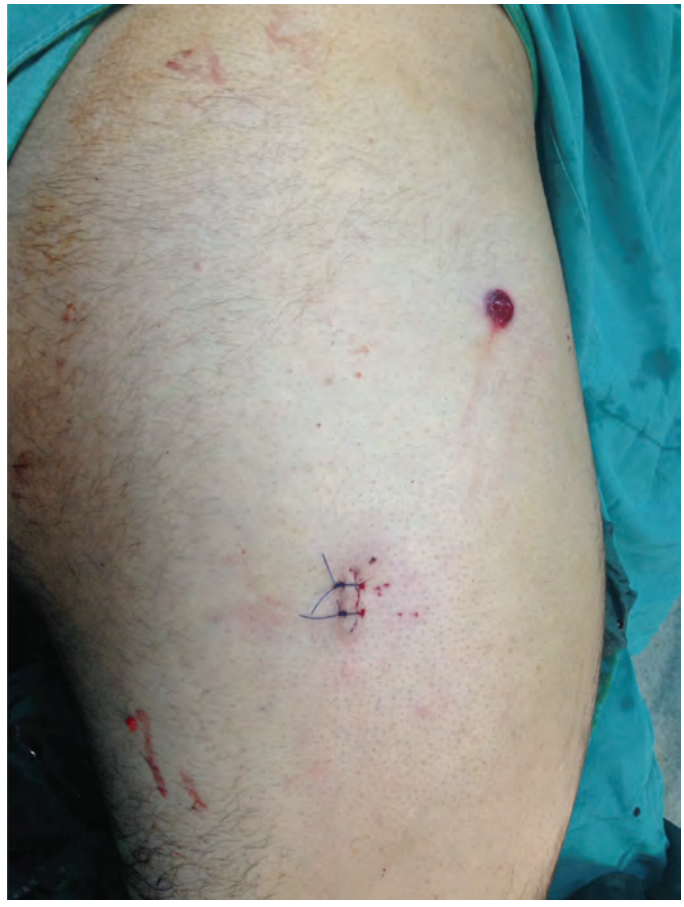

Figure 3. Clinical image of the patient

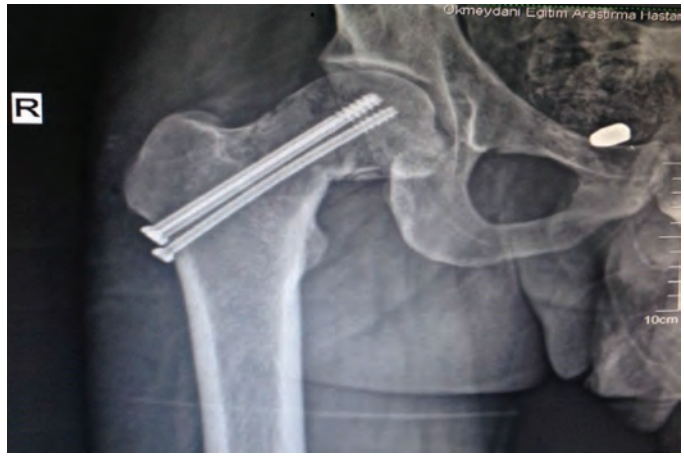

Figure 4. Post-operation X-ray of the patient

effects they create, FAI cause serious morbidity as well as mortality (1-4).

Since extremity injuries occur in half of the FAI, orthopedists also frequently face FAI (2). Bone fractures are seen in a high rate of these cases, and these cases are accepted as type 3 fractures according to the Gustilo classification (5). In most cases, fractures are fragmented in which treatment is long and complicated, recurrent surgical interventions are required, serious sequelae remain, and infections are frequently observed during follow up. Previous studies reported a 2-11% infection and up to 5% nonunion in extremity injuries due to FAI (2,6-8). In this case, a non-displaced fracture occurred at the femur neck, and the

fracture was fixated with early surgical intervention. No infection was seen during patient follow-up. Nonunion or malunion was not observed.

In cases of FAI, in addition to soft tissue and bone injuries at extremities, peripheric vascular injuries are seen up to 6% due to the direct effect of high-energy created by firearms, and blastic and thermal injuries. Vascular injuries, especially arterial injuries, may cause serious problems that threaten the extremities and also the life of the patients. In such cases, exploration should be done without any delay (5,9). Although the injury was due to a close shot, and it was at femur neck which is a vascularly important region, no peripheric vascular injury was seen.

Previous studies have reported that peripheric nerve injuries may be seen in up to 9% of FAI. There is no consensus in the literature about performing a nerve exploration and timing of it after peripheric nerve injuries. However, more commonly, an exploration is not recommended (10,11). Especially in proximal thigh injuries, as in our case, because the reinnervation distance from the first motor point to endpoint is long, the chance of success is low. In our case, the absence of peripheral nerve injury was a great chance for the patient.

In the FAI affecting the extremities, additional organ injuries can also be seen along the path that the bullet takes in the body, which will increase the risk of mortality and morbidity. In this case, the bullet nucleus that entered from the right hip region laterally made an internal advance to the anterior bladder by moving towards the medial, and the bullet nucleus was detected in the anterior part of the bladder.

CONCLUSION

Although it caused femur neck fracture, it didn't cause additional organ injuries like femoral vascular or nervous injury, or bladder injury.

In this case, the patient, fortunately, survived without many sequelae, although he had a close distance shot at proximal thigh, which is a region where severe bone, vascular, nerve, and organ injuries can occur.

Ethics

Informed Consent: Was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç.T., Concept: B.K., Design: A.Ç.T., Data Collection or Processing: E.T., Analysis or Interpretation: H.G., Literature Search: B.K., Writing: B.K.

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CASE REPORT

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Intraductal Papilloma of Buccal Mucosa Minor Salivary Gland Origin

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Abstract

Ductal papillomas are rarely seen in salivary glands. They are largely classified under the term "ductal papillomas" and generally further categorized as intraductal papilloma, sialadenoma papilliferum, and inverted ductal papilloma. Intraductal papilloma, which usually arises from the major lactiferous duct and localized in minor salivary glands, is an uncommon lesion. We report a case of intraductal papilloma of the buccal mucosa.

Keywords: Salivary glands, intraductal papilloma, benign

INTRODUCTION

Ductal papillomas are rarely seen in salivary glands. Ductal papillomas are benign papillary tumors and originate from the neoplastic proliferation of any epithelium of the ductal system. Intraductal papilloma is a rare lesion and mostly arises from the major lactiferous duct (1-3).

CASE REPORT

A 65-year-old male patient referred to the otolaryngology department with the complaint of a mass in the right cheek for 3 years. There was no pain. Head and neck examination revealed the presence of an easily noticeable mass in both skin and mucosal surfaces of the right cheek. Bi-manual examination showed a 4x2 cm oval-shaped, firm, and mobile mass.

Under general anesthesia, via a buccal mucosal incision, the tumor was removed without any complication and sent to the pathology department.

Radiologic Features

The patient was referred to the radiology department for magnetic resonance (MR) exam. MR exam was performed with a 1.5-T system MR scanner (Intera, Philips Medical Systems, Best, The Netherlands). Axial, coronal, and sagittal T1 TSE -T2 TSE weighted images, axial T2 weighted SPIR images, diffusion-weighted series, and post-contrast series were taken. Post-contrast images were acquired after administration 0.1 mmol/kg gadolinium diethylenetriamine pentaacetic acid. On MR imaging, a 42x28x14 mm multilobulated, T1WS isointense, T2WS hyperintense, heterogeneous subcutaneous mass adjacent to right corpus mandibula (Figure 1a-b). Diffusion was restricted, and the lesion showed homogeneous contrast enhancement on contrast series (Figure 2). There was no mandibular bony defect.

The lesion was excised, and the specimen was sent for histopathological evaluation.

Microscopic features (Figures 3,4): a dilated, unicystic structure was located below the mucosal surface. Cystic space was

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lined by two layers of cuboidal epithelium. Papillary growths protruded into the lumina. There was a branching and anastomosing pattern. Each papilla was composed of double-layered columnar epithelial cells, with a fibrovascular core. The nuclei of the cells were basally located, and they had a monotonous appearance. No mitotic figures and no evidence of atypia were examined. The tumor cells were limited within the ductal space. There was no cellular proliferation beyond the cyst wall.

Immunohistochemistry

The tumor cells expressed pan-cytokeratin and epithelial membrane antigen but were negative for smooth muscle actin, and the Ki-67 labeling index was low.

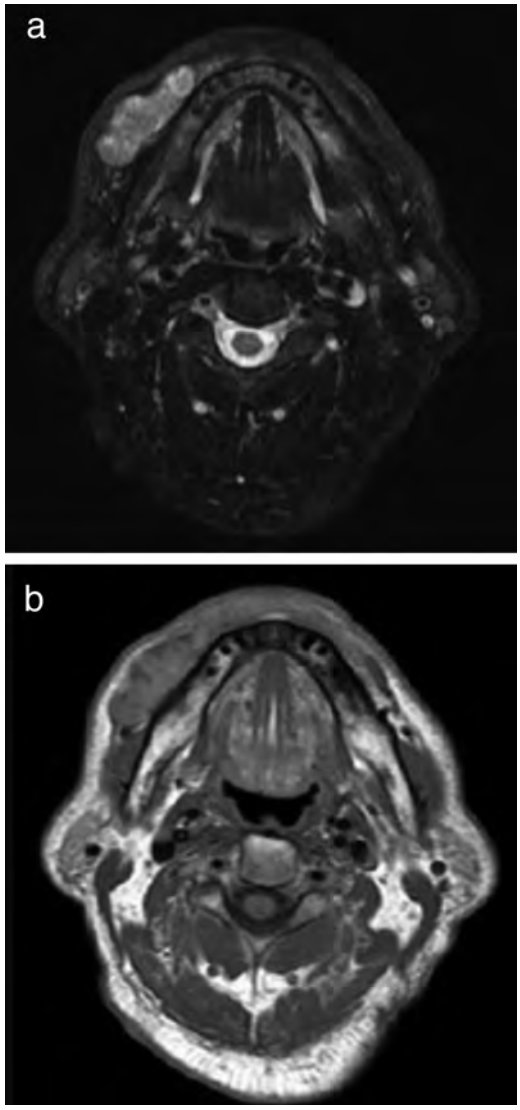

Figure 1. a, b) On MRI, a 42x28x14 mm multilobulated, T1WS (a) isointense, T2WS (b) hyperintense, heterogeneous subcutaneous mass adjacent to right corpus mandibula
MRI: Magnetic resonance imaging

DISCUSSION

Benign papillary tumors confined to the ducts in salivary glands are rare and categorized under the term "ductal papillomas". These lesions further classified as three distinct types of tumors: intraductal papilloma, sialadenoma papilliferum, and inverted ductal papilloma (1,2).

According to the literature, Brannon et al. (4) reported the largest survey with 19 cases about ductal papillomas in 2001. Three out of 19 cases were intraductal papillomas. They reviewed the

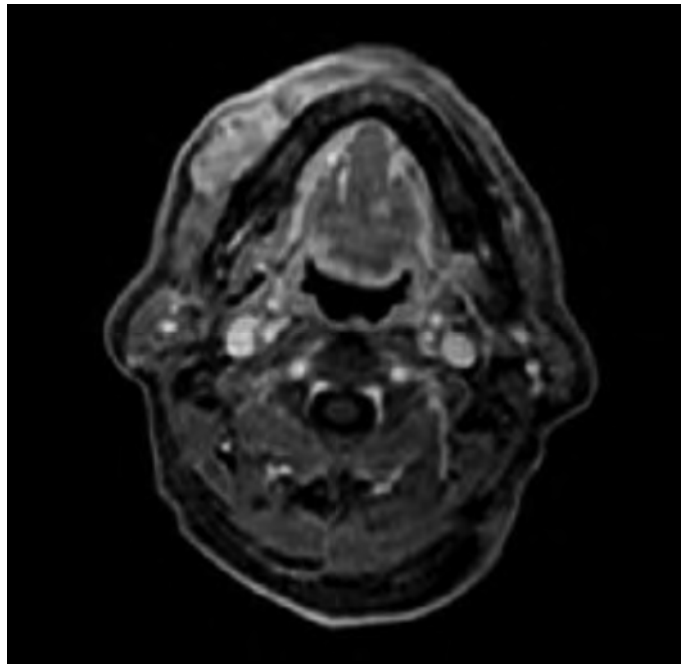

Figure 2. The lesion showed homogeneous contrast enhancement on contrast series

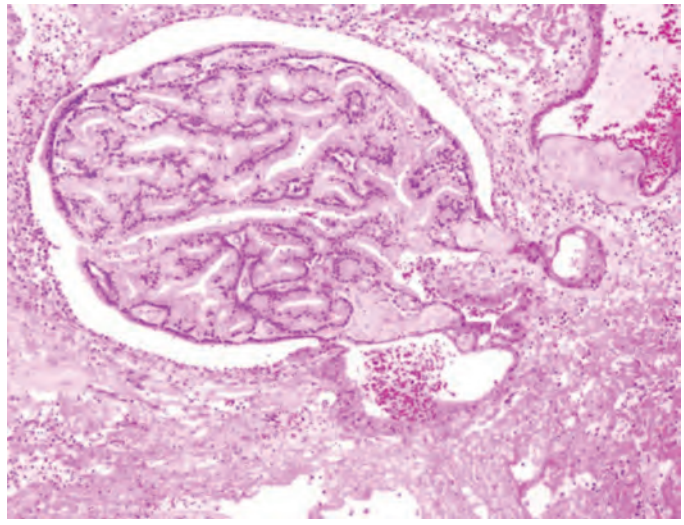

Figure 3. (Haematoxylin and eosin, x100). Cystic space is lined by a double row of cuboidal epithelium. A papillary growth protrudes into the lumina

literature and reported that with their 3 cases, slightly over 40 cases of ductal papilloma have been reported to date.

The minor salivary glands are more frequently involved than are the major glands. The locations of the reviewed cases by Brannon et al. (4) were as follows: the upper lip (6 cases), the lower lip (6 cases), lip location-not otherwise specified (1 case), the buccal mucosa (7 cases), the soft palate (2 cases), the hard palate (1 case), palate-location not otherwise specified (3 cases), ventral tongue (1 case), and oral cavity-location not otherwise specified (1 case). Major gland involvement has also been recorded, with 4 cases in the parotid gland, 3 in the submandibular gland, and 2 in the sublingual gland.

After the review of the cases by Brannon et al. (4), 2 cases of minor salivary glands, located in the sublingual region and a case located in the parotid gland, were reported (5-7).

Age range was found to be 29 to 77 years, with a mean of 63. It was seldom reported in children (6).

Most of the authors in medical literature compromised on the fact that the histogenesis of these lesions as originating from the salivary gland duct epithelium-most likely the excretory duct. Immunohistochemical studies have pointed out an origin in ductal luminal cells ductal epithelium, and excretory duct epithelium (4,8).

There are several reported cases of malignancy that share a similar morphologic pattern with intraductal papillomas. The differences are that they have atypical cellular features and a high K-67 level (9,10).

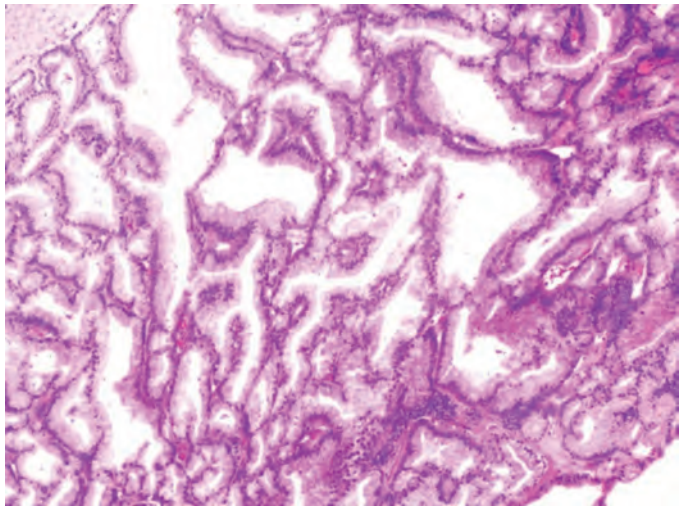

Figure 4. (Haematoxylin and eosin, x400). Each papilla, with a branching and anastomosing pattern, was composed of double-layered columnar epithelial cells. The nuclei of the cells were basally located, and they had a monotonous appearance

The intraductal papilloma usually occurs in adults and is usually located in the minor salivary glands. Lower lip and mandibular vestibule are the most frequent locations. The lesion usually appears as an asymptomatic submucosal nodule (1-3).

The majority of the patients are in their sixth or seventh decades, with a mean age of 63 years (1-3). Tumor size ranges from 0.5 to 2.0 cm (1-3).

Before making a diagnosis of intraductal papilloma, it is essential to rule out several papillary and cystic salivary gland tumors, including papillary cystadenoma (1-3), low-grade cribriform cystadenocarcinoma (LGCCC) (11), and the papillary cystic variant of acinic cell carcinoma (12). The histologic differential diagnosis for intraductal papilloma, take place between 3 lesions: papillary cystadenoma, salivary gland duct blockage phenomenon, and inverted ductal papilloma (3).

Papillary cystadenoma is a multicystic lesion composed of multiple papillary structures consisting of different epithelial cell types, which take part in the differentiation of intraductal papilloma that is a unicystic intraluminal papillary proliferation of neoplastic ductal epithelium (1).

A salivary gland duct may enlarge and form a cyst because of inflammation and obstruction. During this process, epithelial hyperplasia can occur and may form intraluminal papillary structures mimicking intraductal papilloma. The non-papillary lining may contain areas of stratified squamous epithelium. There is usually chronic inflammation, fibrosis, and acinar atrophy around the salivary glands near to the lesion (3).

Inverted ductal papilloma is lined by epidermoid cells, which is the most important different part of this lesion helps distinguish from intraductal papilloma. İnverted ductal papilloma is located near to the mucosal surface, whereas intraductal papilloma is found at deeper levels (13,14).

LGCCC is characterized by multiple ductal in situ lesions. The ductal lesions have micropapillary, tufted, and plaque-like intraluminal projections, rather than frank papillary projections with fibrovascular cores protruding into a cystically dilated duct (11).

Acinic cell carcinomas rarely show prominent papillary and cystic structures. A variant of acinic cell carcinoma, called “papillary-cystic variant of acinic cell carcinoma” has a delicate fibrovascular core, and should be kept in mind in the differential diagnosis. Lack of acinar differentiation in ductal papilloma helps to exclude the possibility of acinic cell carcinoma (12).

Despite the benign nature of the lesion, surgical resection is necessary. Malignant transformation can occur in intraductal papilloma, which is also architecturally similar to the benign counterpart, accompanied by cytological atypia, intraductal extension, microinvasion, and lymph node metastases (9). Therefore resection of the tumor with an adequate safety margin in our case was done.

CONCLUSION

In conclusion, intraductal papilloma is a rare entity in salivary glands that should be kept in mind and should be excised in order to rule out the suspicion of malignancy.

Ethics

Informed Consent: The patient was operated in Maltepe University Hospital and the informed consent was received before the operation.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Ö.Y., Y.P., G.A., Ç.V., G.K., D.D.A., Design: Ö.Y., Y.P., G.A., Ç.V., G.K., D.D.A., Data Collection or Processing: D.D.A., Y.P., Ç.V., G.A., Analysis or Interpretation: Ö.Y., G.K., Literature Search: Ö.Y., G.K., D.D.A., Writing: D.D.A., Ö.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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LETTER to the EDITOR

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Use of Smartphone Applications in Herbal Poisoning

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Dear Editor,

In November 2019, many patients applied to the Emergency Department of Okmeydanı Training and Research Hospital, with various complaints after eating spinach. Patients' complaints included hallucination, speech disorder, dry mouth, confusion, and agitation. Meanwhile, some cities such as Ankara, Edirne, and Tekirdağ were reported to have had similar cases. The common features of all the patients were that they had eaten a spinach-like vegetable (1). In the physical examination of the patients, there were anticholinergic findings such as tachycardia, mydriasis, flushing. Therefore, patient relatives were asked to bring the sample of the plant that the patients had eaten. Photos of the plant samples brought were uploaded to a plant recognition application called PlantSnap®. Using plant recognition application, it was determined that our patients were poisoned not from spinach but from the plant called datura stramonium, which is known as pipe grass among the people. This plant grows in the harvest period of spinach and is very similar to spinach.

Approximately 40 thousand tons of spinach has been produced in Ankara of Turkey. This product is sold up to the Trakya region. This is the main reason why patients are reported from Ankara, Edirne, and Tekirdağ. We thought that this poisoning was due to Datura stramonium possibly the spinach being mixed into the during harvest.

The chemical structure of the plant named Datura stramonium contains tropane group alkaloids, atropine, hyoscyamine, and scopolamine, which are responsible for hallucinogenic effects and anticholinergic findings in our patients (2). Supportive treatments, gastrointestinal decontamination therapy, and physostigmine were given to our patients according to their clinical status, and all of our patients were discharged healthily.

Smartphone applications have started to take place more frequently in our lives recently. Health-related practices, in particular, attract the attention of both healthcare professionals and others. Such practices also facilitate some interventions for our patients. For example, Kalkan and Yigit (3) argued that patients would be referred with Whatsapp®, which is a smartphone application in their studies. PlantSnap® is an application that interprets the photograph of the plant and gives information about the plant with an accuracy of up to 90%. This application makes the researched plant compared to the plants it has previously recorded in its own database. By using this application, we found out which plant our patients were poisoned and made appropriate interventions.

Although this is the opinion of a biologist who is sure in such poisonings, we think that such applications will be useful in the emergency room. We think that smartphone applications such as PlantSnap® can be used, especially in herbal poisoning requiring rapid diagnosis and treatment if the poisoning plant can be reached.

Mobile health is a rapidly developing field, and various applications can be used in the diagnosis and follow-up of patients (3). PlantSnap®, etc. to diagnose and start treatment faster in poisonings with plants, plant identification applications can be used.

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