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Robotic Rectal Cancer Surgery with the da Vinci Xi System: First 100 Cases

da Vinci Xi Sistemi ile Robotik Rektum Kanseri Cerrahisi: İlk 100 Olgu

Volkan Özben[1], Alper Doğruöz[2], Salih Anıl Boğa[1], Erman Aytaç[2], Bilgi Baca[1], İsmail Hamzaoğlu[1], Tayfun Karahasanoğlu[1]

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ABSTRACT

Introduction: The da Vinci Xi system, the latest model of the robotic technology, is proposed to enable multiquadrant abdominal surgery to be performed in a fully robotic approach without the need for a laparoscopic assistance, robot re-docking or re-positioning of the trocars. However, the literature has limited data on this topic. In this study, we aimed to evaluate the feasibility of the Xi robot use in rectal cancer surgery, a multiquadrant surgical procedure.

Methods: Patients undergoing robotic mezorectal excision for rectal adenocarcinoma using the da Vinci Xi system between December 2014 and June 2017 were included in this study. Data were collected prospectively and analyzed retrospectively. Demographic data, perioperative clinical findings, histopathologic data and postoperative 30-day outcomes were analyzed.

Results: One hundred patients were included in this study. There were 57 male and 43 female patients with a mean age of 61.4±12.3 years. Low anterior resection and abdominoperineal recetion were performed in 90 and 10 patients, respectively. In all the operations, the abdominal and pelvic stages of the procedure were completed robotically without a need for dual docking or trocar re-positioning. The mean operative time was 328.4±105.8 min and blood loss was 131.7±170.3 mL. Intraoperative complication occurred in 2 patients (2%). Two procedures were converted to open surgery (2%). The mean number of harvested lymph nodes was 25.3±12.0. All the surgical margins were clear except for four patients (4%). The rate of incomplete mesorectal fascia was 3.2%. The mean length of hospital stay was 6.6±3.6 days and the overall postoperative morbidity rate was 25%.

Conclusion: The da Vinci Xi model enables rectal cancer operations to be performed in a fully robotic fashion. This feature of the robot helps surgeon to benefit optimally from the advantages robotic surgery in all stages of the procedure.

Keywords: da Vinci Xi system, rectal cancer, robotik mesorectal excision

ÖZ

Amaç: Robot teknolojisinin en güncel modeli olan da Vinci Xi sisteminin multikadran karın ameliyatlarını laparoskopi yardımı olmadan, robotu tekrar konuşlandırma veya trokar pozisyonunda değişiklik gerektirmeden tamamen robot ile yapılmasını mümkün kıldığı öne sürülmektedir. Ancak bu konu üzerinde literatür verisi sınırlıdır. Bu çalışmada multikadran bir cerrahi olan rektum kanseri ameliyatında Xi robot kullanımının uygulanabilirliğini değerlendirmeyi amaçladık.

Yöntemler: Çalışmaya Aralık 2014 ile Haziran 2017 tarihleri arasında rektum adenokanseri tanısı ile da Vinci Xi sistemi kullanılarak robotik mezorektal eksizyon ameliyatı yapılan hastalar alındı. Veriler prospektif kaydedildi ve retrospektif olarak incelendi. Hastaların demografik bilgileri, intraoperatif bulgular, histopatolojik veriler ve postoperatif 30 gün sonuçları değerlendirildi.

Bulgular: Çalışmaya toplam 100 hasta dahil edildi. Hastaların 57'si erkek, 43'i kadın, ortalama yaş 61,4±12,3 yıl idi. Doksan hastaya aşağı anteriyor rezeksiyon ve 10 hastaya abdominoperineal rezeksiyon uygulandı. Tüm ameliyatlarda karın ve pelvis aşamaları robotun ikinci defa konuşlandırılmasına gerek duyulmadan ve trokarların yeri değiştirilmeden tamamlandı. Ortalama ameliyat süresi 328,4±105,8 dk ve kanama miktarı 131,7±170,3 mL idi. İki hastada intraoperatif komplikasyon gelişti (%2). İki hastada açık cerrahiye geçildi (%2). Çıkarılan ortalama lenf nodu sayısı 25,3±12,0 idi. Radyal sınır pozitifliği saptanan 4 hasta (%4) dışındaki tüm hastalarda cerrahi sınırlar temiz bulundu. İnkomplet mezorektal fasya bütünlüğü oranı %3,2 idi. Ortalama hastanede yatış süresi 6,6±3,6 gün ve postoperatif toplam morbidite oranı %25 idi.

Sonuç: da Vinci Xi modeli rektum kanseri ameliyatlarının tamamen robotik yapılmasını mümkün kılmaktadır. Robotun bu özelliği cerrahın ameliyatın tüm aşamalarında robotik cerrahinin avantajlarından optimal bir şekilde faydalanmasını sağlamaktadır.

Anahtar Kelimeler: da Vinci Xi sistemi, rektum kanseri, robotik mezorektal eksizyon

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Introduction

In the last 30 years, significant advances have been made in the treatment of rectal cancer with the use of neoadjuvant therapies and identification of total mesorectal excision technique (1,2). In the field of surgery, demonstration of the advantages of laparoscopic surgery compared to open surgery in terms of early postoperative results (3,4) led to the spread of minimally invasive surgery. However, the technical difficulties experienced due to the use of flat and rigid instruments in a narrow and deep anatomical area such as the pelvis (5), and high rates of switching to open surgery and peripheral surgical margin positivity (6,7) have made the oncological effectiveness of mesorectal excision with classical laparoscopy a matter of discussion.

In addition to the advantages of minimally invasive surgery, robotic surgery has eliminated the disadvantages of classical laparoscopy thanks to better mobility with angled instruments in the narrow space, three-dimensional high-resolution imaging and stable tissue traction (8). In the following years, the increase in interest in robotic surgery brought about technological developments in robotic systems. Rectal cancer surgery is a multiquadrant surgery involving mesorectal dissection in the pelvis and mobilization of the left colon in the abdomen. The fact that the previous robot model, da Vinci Si (Intuitive Surgical Inc., Sunnyvale, CA, USA), allowed a single quadrant surgery in the abdomen, led the surgeons to use different techniques to mobilize the left colon (9-11). It is reported that the da Vinci Xi model, which is currently the most up-to-date system, has eliminated this problem with its multiquadrant access feature. However, the experience on this subject was limited by the data reported from a small number of patients (12-15).

In our own practice, we use the da Vinci Xi system routinely as of November 2014. In this study, we aimed to present the technical details and the perioperative clinical results of the robotic mesorectal excision surgeries performed since this date.

Methods

The study was approved by the Ethics Committee of Acıbadem Mehmet Ali Aydınlar University Hospital with the decision number 2017-12/7. Patients who underwent robotic mesorectal excision due to rectum adenocarcinoma between December 2014 and May 2017 in the General Surgery Departments of Acıbadem Atakent and Maslak Hospitals were included in the study. Patients with synchronous colon tumors were excluded from the study. Informed consent was obtained from all patients included in the study and their data were used. Demographic and preoperative clinical data, intraoperative findings, histopathological data, and results of postoperative 30-day outcome were entered into the colorectal cancer database prospectively (16) and the data were evaluated retrospectively. The docking time was determined as the time between positioning of the robot and connection of the robotic arms to the trocars. The total operative time was determined as the time between the first skin incision and the closure of the incision. The conversion was defined as the completion of any stage of the surgery with an open or classical laparoscopic approach, with the exception of the abdominal incision made for removal of the specimen.

Following rectal cancer diagnosis with endoscopic and histopathological examination, clinical staging of the tumor was performed with the help of computerized tomography of the thorax and abdomen, endorectal ultrasonography and/or magnetic resonance imaging. Neoadjuvant chemotherapy/radiotherapy was administered to the patients who were diagnosed as having T3-4 or N + stage tumors that were located under the pelvic peritoneal reflection. The patients were treated with Na-phosphate soda and enema one day before the surgery and venous thrombosis prophylaxis 12 hours before the operation. Antibiotic prophylaxis was applied during general anesthesia induction and then nasogastric tube and urinary catheter were placed.

Robotic Mesorectal Excision Technique

The patient was placed in a modified lithotomy position. A Veress needle was inserted through a supraumbilical incision and pneumoperitoneum was established using CO_2 at a pressure of 12 mmHg. A 30-degree robot camera was advanced from the 8-mm robot trocar placed in this area, and three other 8-mm robots and 5-mm assistant trocars were placed under direct vision (Figure 1). The operating table was positioned to Trendelenburg with 30 degrees right side tilt, and the omentum was retracted upwards over the transverse colon and the small intestine was retracted to the right upper quadrant of the abdomen. The robot was on the left side of the patient and the assistant was on the right side. After placing a camera in Arm 2, the robot system was targeted to the left inguinal area and the robotic arms were mounted on the trocars.

The surgery was performed by medial to lateral dissection technique. Visceral peritoneum was opened with scissors after the sigmoid colon was mobilized anteriorly and laterally with tip-up grasper. The inferior mesenteric artery (IMA) was ligated 1 cm distal to the origin by using Hem-o-lok clips (Teleflex, Morrisville, NC, USA) and divided. The inferior mesenteric vein was ligated and divided at the lower limit of the pancreas (Figures 2, 3). Omental bursa was reached through the plane between the anterior surface of the pancreas and the mesocolon. Then, the Toldt fascia was dissected through the embryological avascular region, and medial to lateral mesocholic dissection was completed with preserving the left ureter and gonadal veins. The lateral peritoneal ligaments of the descending colon and splenic flexure were dissected. After the descending colon was mobilized, posterior mesorectum was dissected by protecting the autonomic nerve plexus through the plane between the presacral fascia and mesorectal fascia at the level of promontorium. After posterior mobilization was achieved, the total mesorectal excision procedure was completed by reaching to the pelvic floor through both lateral and then anterior planes (Figure 4). Partial mesorectal excision was performed in case of tumors located in the upper rectum. The trocar in the lower right quadrant was replaced by a 12 mm robotic or laparoscopic trocar, and the rectum was excised by the robotic stapler (EndoWrist 45 mm stapler, Intuitive Surgical, Inc.) or laparoscopic stapler (Echelon Flex™ 60 mm stapler, Ethicon, Cincinnati, OH, USA) advanced through this trocar. Then, a suprapubic incision was made and the wound protector/retractor (Alexis™) was inserted into the incision. Specimen was taken out of the abdomen from this incision (Figure 5). After the proximal colon was cut, the anvil of the circular stapler was inserted in the proximal end of the colon with purse string suture and left in the abdomen, and the suprapubic incision was sutured. Colorectal or coloanal anastomosis was performed with circular stapler advanced from the anus. In some patients, vascularization of the descending colon was evaluated with the FireFly™ camera of the

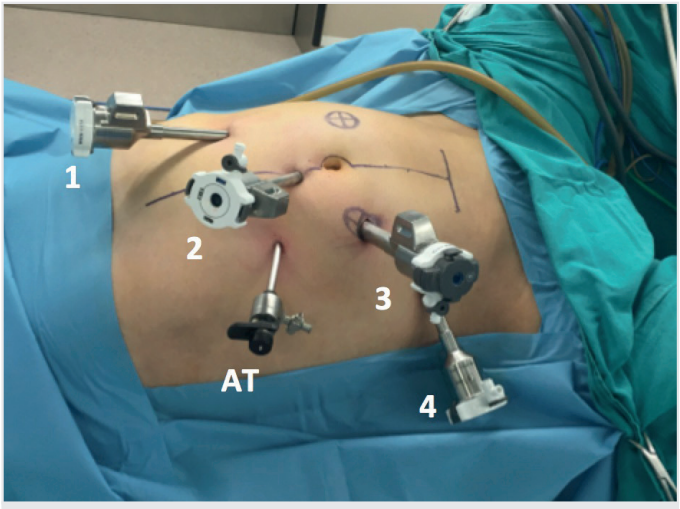

Figure 1. Trocar position in robotic rectal cancer surgery. Camera was connected to Arm 2, bipolar forceps to Arm 1, monopolar scissors to Arm 3 and tip-up grasper to Arm 4

AT: Assistant trocar

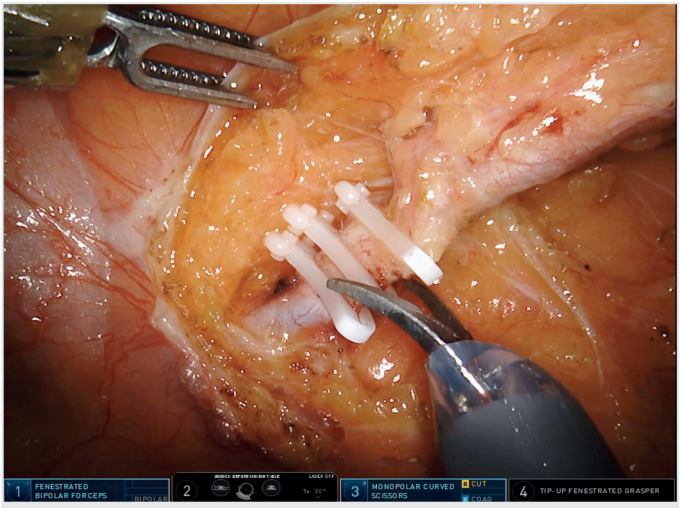

Figure 2. Ligation and division of the inferior mesenteric artery

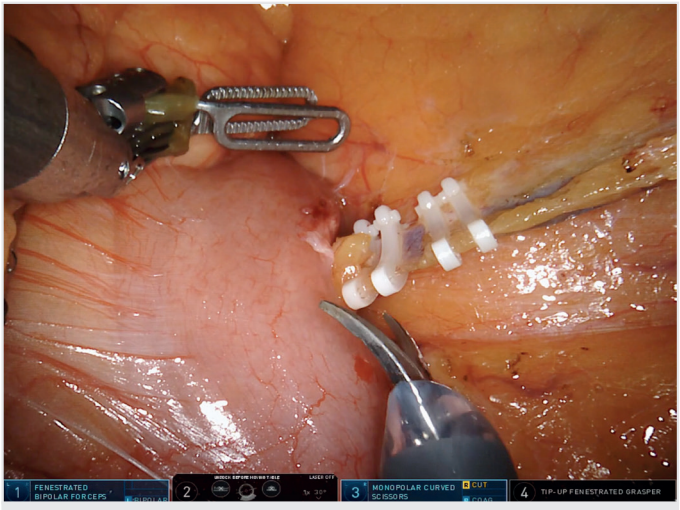

Figure 3. Ligation and division of the inferior mesenteric vein

robot following intravenous indocyanine green (2.5 mg/mL) prior to anastomosis. Anastomotic leakage control was performed by air test and a silicone drain was placed in the pelvis. Then fascia and skin incisions of 12 mm trocar location were sutured. The operations were finalized following performing a diverting loop ileostomy.

In cases where intersphincteric resection was required, perineal dissection was performed after the rectal dissection was performed to the intersphincteric plane with robot in the abdominal stage. Total mesorectal excision was completed by entering the intersphincteric plane with an incision at the dentate line. After the specimen was removed from the anus, a manual coloanal anastomosis was performed. In patients who needed abdominoperineal resection, the pelvic stage was performed with extralevator approach following completion of the abdominal stage with the robot.

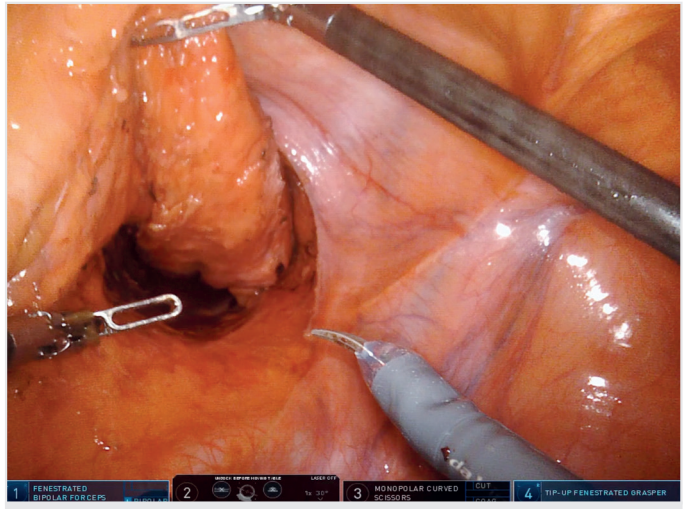

Figure 4. Completion of total mesorectal excision

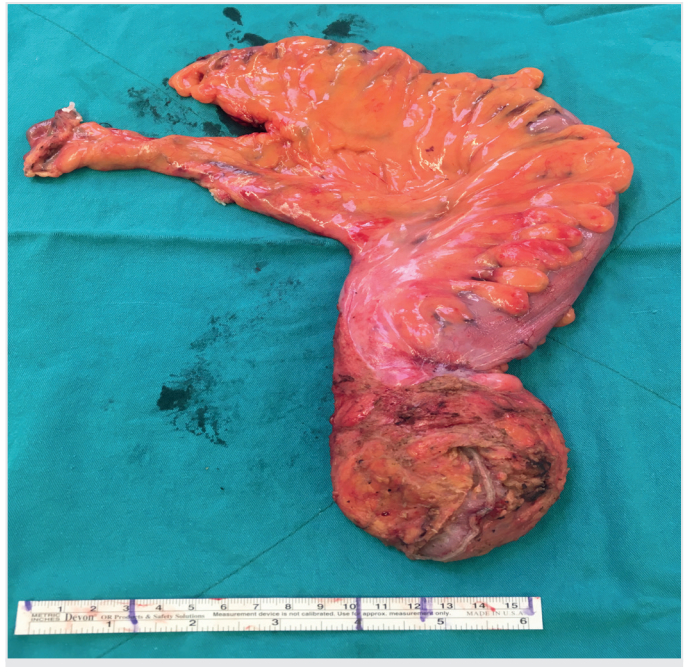

Figure 5. Total mesorectal excision specimen

Postoperative pain control was achieved with intravenous narcotic drugs. The nasogastric catheter was removed immediately after the operation and the urinary catheter was removed on the first postoperative day. Patients were discharged after adequate pain control and oral feeding.

Statistical Analysis

Statistical analysis of the data was performed by SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Categorical data were expressed as frequency and percentage (n, %) and continuous variables as mean ± standard deviation.

Results

A total of 100 patients were included in the study. Fifty-seven of all patients (57%) were male and 43 were female. Mean age was 61.4±12.3 years and body mass index was 27.3±3.6 kg/m^2. Demographic data and preoperative clinical information are presented in Table 1. In our series, the most common tumor was distal rectal tumor (44%), followed by proximal (38%) and middle rectal (17%) tumors. The operations, intraoperative data and follow-up findings of the first postoperative 30-day are presented in Table 2. Ninety patients underwent low anterior resection and 10 patients underwent abdominoperineal resection. Intersphincteric resection was performed in 15 patients who had undergone low anterior resection. In all operations, the abdominal and pelvic stages were completed without the need for robot re-docking or re-positioning of the trocars. The mean robot docking time was 4.9±1.5 minutes, mean operative time was 328.4±105.8 minutes and blood loss was 131.7±170.3 mL. Intraoperative complication occurred in two patients (2%). These complications were prostatic urethral injury and bleeding after removal of the clip placed on IMA. Urethral injury was repaired intraoperatively. The other patient who developed hemorrhage underwent open surgery. Open surgery was performed in two patients (2%), one because of the inability to continue dissection due to severe tumoral adhesion in the pelvis and the other due to bleeding from the IMA (following removal of the clip). The mean time to first defecation and oral feeding was 2.9±1.6 days and 3.3±1.7 days, respectively and mean hospital stay was 6.6±3.6 days.

Twenty five patients (25%) had morbidity within the first 30 days postoperatively (Table 2). Anastomotic leakage occurred in three patients (3%); this complication was controlled by diverting ileostomy in two patients and conservative treatment in the other one. All of 12 patients who developed ileus had paralytic origin and it regressed with conservative treatment. Percutaneous drainage was performed in one patient who developed intraabdominal abscess and diverting ileostomy was performed in one patient with rectovaginal fistula. There was no mortality.

Histopathological data and oncologic results are presented in Table 3. The mean number of harvested lymph nodes was 25.3±12.0. Lymph node metastasis was detected in 31 patients and the mean number of metastatic lymph nodes was 1.3±3.0. All the surgical margins were clear, except for radial margin positivity in four patients (4%). In 61 of 63 patients who underwent total mesorectal excision, the integrity of the mesorectal fascia was complete or near complete (96.8%).

Table 1. Demographic data and preoperative clinical information

Gender	
Male	57 (57%)
Female	43 (43%)
Age, years	61.4±12.3
BMI, kg/m^2	27.3±3.6
ASA score	
I	27 (27%)
II	62 (62%)
III	10 (10%)
IV	1 (1%)
Previous abdominal surgery	19 (19%)
Tumor location	
Proximal rectum	38 (38%)
Middle rectum	17 (17%)
Distal rectum	44 (44%)
Proximal + distal rectum	1 (1%)
Neoadjuvant chemotherapy/ radiotherapy	46 (46%)

BMI: body mass index, ASA: American Society of Anesthesiologists
Data are presented as number (%) or mean ± standard deviation

Table 2. Intraoperative and postoperative findings

Surgery	
Low anterior resection	90 (90%)
Abdominoperineal resection	10 (10%)
Mesorectal excision	
Total	63 (63%)
Partial	37 (37%)
Robot docking time, minimum	4.9±1.5
Operative time, minimum	328.4±105.8
Bleeding, mL	131.7±170.3
Intraoperative complication	2 (2%)
Conversion	2 (2%)
Time to first flatus, days	2.0±1.0
Time to first defecation, days	2.9±1.6
Time to first oral feeding, days	3.3±1.7
Length of hospital, days	6.6±3.6
30-day morbidity	
Ileus	12 (12%)
Wound infection	5 (5%)
Anastomosis leak	3 (3%)
Intraabdominal abscess	1 (1%)
Rectovaginal fistula	1 (1%)
Pulmonary embolism	1 (1%)
Atelectasis	1 (1%)
Urinary tract infection	**1 (1%)**
Mortality	0 (0%)

Data are presented as number (%) or mean ± standard deviation

Table 3. Histopathological data	
Tumor diameter, cm	3.7±2.2
Number of lymph nodes	25.3±12.0
Number of metastatic lymph nodes	1.3±3.0
pT	
T_0	13 (13%)
T_1	9 (9%)
T_2	22 (22%)
T_3	44 (44%)
T_4	12 (12%)
pN	
N_0	69 (69%)
N_1	19 (19%)
N_2	12 (12%)
pTNM staging	
0	15 (15%)
I	26 (26%)
II	27 (27%)
III	26 (26%)
IV	6 (6%)
Proximal surgical margin, cm	16.6±6.4
Distal surgical margin, cm	2.8±1.7
Radial surgical margin, cm	1.6±1.4
Surgical margin positivity	4 (4%)
The integrity of the mesorectal fascia[a]	
Complete	38 (60.3%)
Near-complete	23 (36.5%)
Incomplete	2 (3.2%)

pTNM: pathological tumor-node-metastasis

[a]Mesorectal fascia integrity was evaluated in 63 patients who underwent total mesorectal excision. Data are presented as number (%) or mean ± standard deviation

Discussion

The results of our study support the feasibility of mesorectal excision surgery in the rectum cancer surgery with a fully robotic approach with the help of the da Vinci Xi system. Compared to the da Vinci Si system, features such as thinner and longer arm structure of the Xi system, ergonomic trocar alignment, the ability to connect the camera to the desired trocar, automatic targeting of the robot arms and patient clearance allow the surgery to be performed from the splenic flexure to the pelvic floor with single robot docking.

The use of robots in colorectal surgery has increased especially in rectal surgery, which is performed in a narrow area, due to the visibility and movement area provided by the system. However, the most important disadvantage of the Si system is that it only allows working at a single quadrant in the abdomen (17), thus there is need for dual docking in rectal surgery that involves the abdominal and pelvic stages. As this increases both the operative time and the workload, it caused surgeons to prefer hybrid laparoscopic-robotic technique (9,10,17-20). In this technique, vascular ligation and mobilization of the left colon are completed by classical laparoscopy, and the robot is used only for pelvic dissection. Surgeons who do not prefer hybrid techniques have described different techniques including repositioning to robotic arms (21-24) or modification of trocar sites (23). In the period when we used the Si system, we docked the robot twice and used a total of 7 trocars. Later on, we were able to complete the operation with a fully robotic approach by repositioning the trocars, however, crossing of the robotic arms in the extracorporeal area made the operation very difficult. This situation explains why the console time is longer in the surgeries performed with the Si system as emphasized in a previous study comparing both robotic systems (12).

In the literature, there are 3 studies comparing Vinci Xi and Si system in rectal cancer surgery. In a study in which Protyniak et al. (13) compared 44 patients in Si robot group and 26 patients in Xi robot group who underwent sigmoidectomy and anterior resection surgeries, the operative time (219 vs 224 minimum), intraoperative bleeding (170 vs. 188 mL), conversion rates (3.8% vs 11.4%), length of hospital stay (5.7 vs 6 days) and total complication rates (26.9% vs 22.7%) were not significantly different. In another study comparing two robots in a total of 20 patients, Morelli et al. (15) stated that the operative time (257 vs 353 min) and length of hospital stay (6.3 vs 8.7 days) were shorter with the Xi system, however, there were no difference in terms of conversion and morbidity. Finally, in a study of 53 patients previously conducted in our clinic (12), we found that console time was shorter in the Xi group (265 vs. 317 min), but the amount of bleeding (141 vs 181 mL), conversion (3.6% vs 4.0%), length of hospital stay (6.2 vs 5.1 days) and postoperative complication rates (14.3% vs 12%) were not significantly different. The common result highlighted in these three studies is that surgeries can be completed with a fully robotic approach with the Xi system without the use of laparoscopy and without requiring the robot to be dual docked. In the present study including 100 patients, mean operative time (328 minutes), intraoperative bleeding (132 mL), conversion rate (2%), length of hospital stay (6.6 days) and total morbidity rate (25%) were consistent with the literature. The abdominal and pelvic stages of the operation were completed with a fully robotic approach in all cases.

One of the important stages of rectal cancer surgery is the excision of the rectum. The wide mobility of the robotic stapler and the ability of angulation up to 90 degrees offer significant advantages to the surgeon at this stage, especially in patients with a narrow pelvis (25). Robotic stapler is integrated in the Xi model in our country and is not available in Si model. We have been using robotic stapler routinely since November 2015. In addition, the evaluation of intestinal vascularization with the indocyanine green and the robot's FireFly™ camera vision is an increasingly common practice for the safety of the anastomosis (26). The FireFly™ camera feature is also available in the Xi system and requires an additional update for use in the Si system. The reason why the indocyanine green-FireFly™ camera system was not used routinely in the present study is the continuation of a randomized study in our clinic.

The use of new technologies in cancer surgeries leads to suspicion whether resection is sufficient oncologically. It is known that the

number of lymph nodes harvested is directly related to the prognosis of the disease. The mean number of lymph nodes harvested in our series was 25.3 and this was higher than the number of lymph nodes reported in other large series (11.7-15.0) on robotic rectal cancer surgery (27-29). Surgical margin positivity was 4% and this data is within the range of 2.5% to 7.3% in the literature (27,29,30).

Study Limitations

The retrospective nature of our study is an important limitation. No comparison with the Si system can also be regarded as a limitation. However, this comparative study was previously reported from our clinic (12) and the main objective of this study was to present that a fully robotic approach in rectum tumor surgery with the Xi system is possible. Considering the limited number of studies in the literature, increasing data on this subject may lead further prospective comparative studies.

Conclusion

The multiquadrant access feature provided by the Xi robot system enables multiquadrant abdominal surgery to be performed with a fully robotic approach without the need for a laparoscopic assistance, robot re-docking or re-positioning of the trocars. This feature allows the surgeon to make an optimal use of the advantages of robotic surgery in all stages of rectal cancer surgery.

Ethics Committee Approval: The study was approved by the Ethics Committee of Acıbadem Mehmet Ali Aydınlar University Hospital with the decision number 2017-12/7.

Informed Consent: Informed consent was obtained from all patients included in the study and their data were used.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Concept - V.Ö., A.D., S.A.B., E.A., B.B., İ.H., T.K.; Design - V.Ö., A.D., S.A.B., E.A., B.B., İ.H., T.K..; Supervision - V.Ö., A.D., S.A.B., E.A., B.B., İ.H., T.K.; Resources - V.Ö., B.B., T.K.; Data Collection and/or Processing - V.Ö., A.D., S.A.B., B.B.; Analysis and/or Interpretation - V.Ö., E.A., B.B., T.K.; Literature Search - V.Ö., E.A., T.K.; Writing Manuscript - V.Ö., E.A., T.K.; Critical Review - V.Ö., A.D., S.A.B., E.A., B.B., İ.H., T.K.

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

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Assessment of Risk Factors for Lymph Node Metastasis in Endometrial Cancer

Endometriyum Kanserinde Lenf Nodu Metastazı için Risk Faktörlerinin Değerlendirilmesi

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ABSTRACT

Introduction: To determine the clinical and pathologic factors that are risk factors for metastasis of the lymph nodes (pelvic and/or aortic lymph nodes) in cases who underwent staging surgery due to endometrial carcinoma.

Methods: The clinical and pathological characteristics of 143 patients who underwent staging surgery between 2007 and 2016 were retrospectively analyzed. Linear regression analysis, logistic regression analysis, Spearman correlation and Receiver operator curve tests were used to determine risk factors for lymph node metastasis. P<0.05 was considered significant in all statistical evaluations.

Results: Thirteen cases (9.1%) had lymph node metastasis [5 cases (3.5%) only pelvic, 3 cases (2.1%) only paraaortic, 5 cases (3.5%) both pelvic and paraaortic lymph node]. In linear regression analysis, there was a significant correlation between lymph node metastasis and non-endometrioid histological type, deep myometrial invasion (≥50% invasion depth), advanced histologic grade, lymphovascular space invasion, positive peritoneal cytology and tumor size (p<0.05). The correlation between tumor size and lymph node metastasis was positive, and Receiver operator curve revealed 4.25 cm tumor size was the most appropriate cut-off value for risk of lymph node metastasis (sensitivity=83%, specificity=75%). In logistic regression analysis, lymphovascular space invasion was the only independent risk factor for nodal metastasis (odss ratio: 11.8; 95% confidence interval: 1.8-75.4, p=0.009).

Conclusion: In endometrial cancer cases, lymphovascular space invasion is the only independent risk factor for lymph node metastasis. There is linear correlation between tumor size and lymph node metastasis. Further studies is needed to determine the limit value of tumor size for lymph node metastasis.

Keywords: Endometrial carcinoma, lymphatic metastasis, logistic model

ÖZ

Amaç: Endometriyum kanseri nedeni ile evreleme operasyonu yapılan olgularda lenf nodu (pelvik ve/veya paraaortik lenf nodları) metastazı için risk oluşturan klinik ve patolojik faktörlerin belirlenmesidir.

Yöntemler: Çalışmamızda 2007-2016 yılları arasında endometriyum kanseri tanısı ile evreleme cerrahisi uygulanan 143 olgunun klinik ve patolojik özellikleri retrospektif olarak incelendi. Lenf nodu metastazı için risk faktörlerinin belirlenmesinde doğrusal regresyon analizi, lojistik regresyon analizi, Spearman korelasyon testi ve işlem karakteristik eğrisi testleri kullanıldı. Tüm istatistiksel değerlendirmeler için p<0,05 anlamlı kabul edildi.

Bulgular: Beş olguda (%3,5) sadece pelvik, 3 olguda (%2,1) sadece paraaortik, 5 olguda (%3,5) ise hem pelvik hem de paraaortik lenf nodu olmak üzere 13 olguda (%9,1) lenf nodu metastazı mevcuttu. Doğrusal regresyon analizinde non-endometrioid histolojik tip, derin miyometrial invazyon (≥%50 invazyon derinliği), ileri histolojik grade, lenfovasküler alan invazyonu, pozitif peritoneal sitoloji ve tümör boyutu ile lenf nodu metastazı arasında anlamlı ilişki bulundu (p<0,05). Tümör boyutu ile lenf nodu metastazı arasında pozitif korelasyon mevcuttu ve işlem karakteristik eğrisinde 4,25 cm tümör boyutu lenf nodu metastazı için en uygun sınır değer olarak tespit edildi (duyarlılık %83, özgüllük %75). Regresyon analizinde ise lenfovasküler alan invazyonu lenf nodu metastazı için bağımsız tek risk faktörü olarak belirlendi (odss oranı: 11,8; %95 güven aralığı: 1,8-75,4; p=0,009).

Sonuç: Endometriyal kanserli olgularda lenfovasküler alan invazyonu lenf nodu metastazı için bağımsız tek risk faktörüdür. Tümör boyutu ile lenf nodu metastazı arasındaki korelasyon ise doğrusaldır. Lenf nodu metastazı için tümör boyutunun sınır değerini belirlemede yeni çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Endometriyal karsinoma, lenfatik metastaz, lojistik model

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Introduction

Endometrial cancer (EC) is the most common type of gynecologic cancer in Turkey and in other developed countries (9.8/100,000 and 14.7/100,000, respectively), and it is the second most common type of gynecologic cancer in developing countries (5.5/100.000) (1,2). Compared with other gynecologic cancers, patients with EC are diagnosed at an earlier stage (approximately 75% of cases), thus having a better prognosis (1). However, the incidence of endometrial cancer is increasing in both developed and developing countries due to increasing risk factors such as high frequency of obesity, prolonged lifetime expectancy and decreased parity (2-4).

The staging of patients diagnosed with EC has been performed surgically since 1988 according to the recommendation of the "International Federation of Gynecology and Obstetrics (FIGO)" (5). FIGO surgical staging is accepted as the most important prognostic factor in these tumors. Apart from the surgical staging, age of the patient, tumor characteristics [histology, grade, size, degree of myometrial invasion, lymphovascular space invasion (LVSI)], peritoneal cytology, and lymph node (LN) involvement also have prognostic significance (3). Among these, LN involvement is also important in initiating postoperative adjuvant treatment and also in determining radiotherapy area.

Currently, there is no definite method to detect the presence of LN metastases preoperatively or intraoperatively (6-11). For this reason, FIGO and "American Congress of Obstetricians and Gynecologists" recommend performing both pelvic and paraaortic LN sampling in surgical staging of patients with EC (12). However, there is no consensus on the extent of LN sampling area (13). On the other hand, it is accepted that the risk of LN metastasis increases in the presence of various risk factors, such as non-endometrioid histology, advanced histological grade, deep myometrial invasion, LVSI, and high preoperative serum tumor marker levels (cancer antigen 125 and 15-3) (6-8,14-16) and it is recommended to keep the LN sampling area as wide as possible (17).

In this study, we aimed to determine the risk factors for LN metastasis by examining the clinical and surgical characteristics of the patients who underwent surgical staging for EC and to compare the results with similar studies.

Methods

Patient Selection and Evaluation

Following approval of the local ethics committee (Ankara Yıldırım Beyazıt University Faculty of Medicine Ethics Committee acceptance no: 26379996/210), the patients who underwent surgical staging for EC between 2007 and 2016 at Ankara Yıldırım Beyazit University Ankara Ataturk Training and Research Hospital were retrospectively evaluated. Since our study was a retrospective case-control study, "informed consent form" was not obtained from the patients. The study was conducted in accordance with the ethical standards defined in the 1964 Helsinki declaration and its later amendments.

Clinical [age, gravida, parity and menopause status (yes or no)] and pathological features [FIGO surgical staging, histology (endometrioid or non-endometrioid), grade (low (grade I-II) or high (grade III)], tumor size (cm), degree of myometrial invasion (<1/2 or ≥1/2), LVSI (yes or no), peritoneal cytology, and LN sampling results (positive or negative) of all patients were recorded. The data were obtained from the patient files and hospital information system. Patients with incomplete surgical staging according to the FIGO recommendation (18), less than 20 harvested LNs (19), pre-operative neo-adjuvant therapy (hormone therapy, chemotherapy or radiotherapy), concurrent gynecologic malignant tumor diagnosis and mixed type histology were excluded from the study. The clinical and surgical features of the patients who were staged before 2009 were reviewed and their new stages were determined according to the recently published FIGO system (FIGO-2) (20). Then the patients were divided into two groups according to LN metastasis, and the parameters that constitute risk for LN metastasis were evaluated. We tried to determine the independent risk factors among parameters that were different between groups.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) ver. 21.0 (IBM Corp., Armonk, NY, US). Kolmogorov-Smirnov test was used to determine the normality of the data. The data with normal distribution were expressed as mean ± standard deviation (range) and data without normal distribution were expressed as median (interquartile range) (range). Linear regression analysis was used to determine the risk factors for LN metastasis and logistic regression analysis was used to determine the independent risk factors. The relationship between tumor size and LN metastasis was evaluated by Spearman's correlation test. Receiver operator curve (ROC) analysis was used to determine the cutoff value for LN metastasis. Independent sample t-test and Mann-Whitney U test were used to compare numerical data, and chi-square test was used to compare categorical data. $P<0.05$ was considered statistically significant for all statistical analysis. Odds ratios (ORs) were determined with 95% confidence interval (CI).

Results

A total of 154 patients underwent surgical staging for EC within the specified period. However, 11 patients who met the exclusion criteria were excluded from the study. Of 143 patients included in the study, pelvic and/or paraaortic LN metastases were detected in a total of 13 patients (9.1%), including five cases with only pelvic (3.5%), three cases (2.1%) with only paraaortic, and five cases (3.5%) with both pelvic and paraaortic LN metastasis. The distribution of all patients in the study is shown in the study flow chart (Figure 1).

The clinical and surgical features of the patients included in the study are presented in Table 1. Linear regression analysis revealed significant relationship between LN metastasis and non-endometrioid histology, deep myometrial invasion (≥50% invasion depth), advanced histological grade (grade III), LVSI, positive peritoneal cytology, and tumor size ($p<0.05$) (Table 2). There was a positive correlation between tumor size and LN involvement ($p=0.001$). In the ROC curve analysis, a 4.25 cm tumor size was found to be the cut-off value for LN metastasis (83% sensitivity and 75% specificity) ($p=0.001$) (Figure 2). In logistic regression analysis, LVSI was the only independent risk factor for LN metastasis (OR=11.8; 95% CI, 1.8-75.4, $p=0.009$).

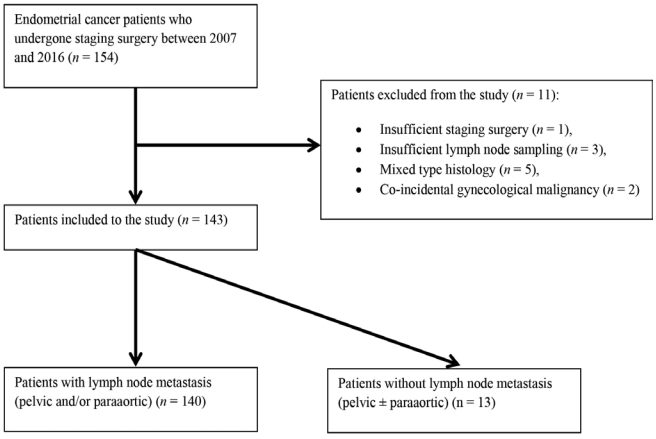

Figure 1. Flow chart of the study

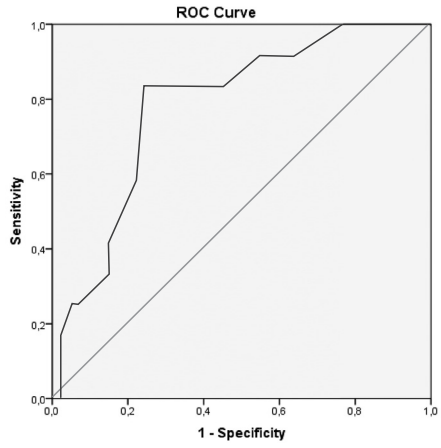

Figure 2. Receiver operator curve analysis of the relationship between tumor size and lymph node involvement in patients with endometrial cancer (area under curve=0.78; standard error=0.06; p=0.001; 95% confidence interval, 0.6-0.9)

Table 1. The clinical and pathological features of the patients

Features	Patients (n=143)
Age (year), mean ± SD (range)	60.3±10.2 (40-85)
Gravida, median (IQR) (range)	4 (3) (0-16)
Parity, median (IQR) (range)	3 (2) (0-15)
Menopause status, n (%)	
Y	113 (79%)
N	30 (21%)
FIGO staging, n (%)	
Stage IA	91 (63.6%)
Stage IB	29 (20.3%)
Stage II	8 (5.6%)
Stage IIIA	1 (0.7%)
Stage IIIB	1 (0.7%)
Stage IIIC1	4 (2.8%)
Stage IIIC2	5 (3.5%)
Stage IVA	2 (1.4%)
Stage IVB	2 (1.4%)
Histology, n (%)	
Endometrioid type	120 (83.9%)
Non-endometrioid type	23 (16.1%)
Histological grade, n (%)	
Low (grade I, II)	116 (81.1%)
High (grade III)	27 (18.9%)
Tumor size, mean ± SD (range)	3.4±2.2 (0.1-12)
Myometrial invasion, n (%)	
≥1/2	12 (8.4%)
<1/2	131 (91.6%)
LVSI, n (%)	
Y	111 (77.6%)
N	32 (22.4%)
Positive peritoneal cytology, n (%)	
Y	111 (77.6%)
N	32 (22.4%)

SD: standard deviation, IQR: interquartile range, Y: yes, N: no, FIGO: Federation of Gynecology and Obstetrics, LVSI: lymphovascular space invasion

Table 2. The comparison of clinical and pathological features of the patients with and without lymph node metastasis

Features	Patients without lymph node metastasis (n=130, 90.9%)	Patients with lymph node metastasis (n=13, 9.1%)	p
Age (year), mean ± SD (range)	60.1±10.5 (40-85)	62.1±7.9 (50-77)	0.49
Gravida, median (IQR) (range)	4 (3) (0-16)	5 (3) (0-8)	0.21
Parity, median (IQR) (range)	3 (2) (0-15)	4 (3) (0-7)	0.17
Menopause status, n (%)			
Y	101 (70.6%)	12 (8.4%)	0.3
N	29 (20.3%)	1 (0.7%)	
Histology, n (%)			
Endometrioid type	114 (79.7%)	6 (4.2%)	0.001
Non-endometrioid type	16 (11.2%)	7 (4.9%)	
Histological grade, n (%)			
Low (grade I, II)	111 (77.6%)	5 (3.5%)	0.001
High (grade III)	19 (13.3%)	8 (5.6%)	
Tumor size, mean ± SD (range)	3.3±2.2 (0.1-12)	5.2±1.8 (2-8)	0.002
Myometrial invasion, n (%)			
≥1/2	7 (4.9%)	5 (3.5%)	0.002
<1/2	123 (86%)	8 (5.6%)	
LVSI, n (%)			
Y	21 (14.7%)	11 (7.7%)	0.001
N	109 (76.2%)	2 (1.4%)	
Positive peritoneal cytology, n (%)			
Y	4 (2.8%)	4 (2.8%)	0.002
N	126 (88.1%)	9 (6.3%)	

SD: standard deviation, IQR: interquartile range, Y: yes, N: no, LVSI: lymphovascular space invasion

Discussion

In patients with EC, the presence of LN metastasis significantly reduces both the disease-free survival and overall survival by half (21). LN metastasis is reported in approximately 10% of patients with EC limited to the uterus (22). In our study, LN metastasis was observed in 9.4% of all EC patients.

In studies evaluating risk factors for LN metastasis in patients with EC, the parameters that are considered as negative prognostic factors for EC are also indicated as risk factors for LN metastasis (6-8,14-16). However, there is no consistency between the results of similar studies. For example, while non-endometrioid histology, deep myometrial invasion (≥1/2 myometrial invasion) and advanced histological grade (grade III) were found to be independent risk factors for LN metastasis in a Swedish study, only the number of harvested LNs (>30) was found to be an independent risk factor in another study (6,23). In another study, LVSI was reported to be the only independent risk factor for LN metastasis (24). In accordance with most of similar studies, a significant relationship was found between LN metastasis and non-endometrioid histology, deep myometrial invasion (≥50% invasion depth), advanced histological grade (grade III), LVSI, positive peritoneal cytology and tumor size in our study. However, only LVSI was found to be an independent risk factor for LN metastasis.

In the studies evaluating the relationship between tumor size and LN metastasis, the consensus is that the risk of LN metastasis increases with increasing tumor size. In a pioneering study on this subject, it was reported that no LN metastasis was seen with a tumor size less than 2 cm and this cut-off value was suggested to be used to determine low-risk cases for LN metastasis (25). Following this study, many studies, including SEER study, used 2 cm as a cut-off value when assessing risk for LN metastasis (26). However, in a recent study by Cox Bauer et al. (27) in patients with endometrioid type EC, it was shown that using 5 cm as the cut-off value was statistically more significant in determining the risk of LN metastasis . In our study, we found a positive correlation between tumor size and LN metastasis, and determined “4.25 cm” as the cut-off value for the risk of LN metastasis. We found a lower cut-off value than Cox Bauer et al. (27) and this might be related to including patients with non-endometrioid type EC in our study. However, both Cox Baurer et al. (27) and we found the cut-off value that is at least two times more than recommended “2 cm” cut-off value for LN metastasis.

Study Limitations

Our study has some limitations such as being a single-center and retrospective study. However, our results are important in terms of showing that LVSI is the most important risk factor for increased risk of LN metastasis in patients with EC, and that the risk in case of LVSI is at least 11 times higher. Therefore, the evaluation of LVSI status besides tumor histology and grade in intraoperative frozen section analysis might affect LN sampling decision in low-risk patients and LN sampling extent in high-risk patients.

Conclusion

On the other hand, our results show that the relationship between tumor size and LN metastasis needs to be re-evaluated. Further studies examining the relationship between tumor size and LN metastasis in different histological subtypes can restate the risk concept in these patients.

Ethics Committee Approval: Local ethics committee (Ankara Yıldırım Beyazıt University Faculty of Medicine committee acceptance no: 26379996/210).

Informed Consent: Since our study was a retrospective case-control study, “informed consent form” was not obtained from the patients.

Peer-review: Internally peer-reviewed.

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Diagnostic Performance of Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Endometrioma

Endometriomada Nötrofil/Lenfosit Oranı ve Trombosit/Lenfosit Oranının Tanı Performansı

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ABSTRACT

Introduction: To evaluate whether neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have diagnostic value in endometrioma, which is a chronic inflammatory disease.

Methods: A total of 187 patients who underwent surgery for adnexal mass, 97 patients diagnosed with endometrioma and 90 patients with benign cyst (corpus luteum, serous cysts or functional cysts), were included in this retrospective, comparative case series. NLR and PLR values obtained from preoperative complete blood count parameters were compared between the two groups.

Results: There was no statistically significant difference between endometrioma and benign cyst groups regarding mean age (34.8±8.93 and 34.0±8.59 years, respectively, p=0.88). Fourteen point four percent (n=14) of the endometriomas were bilateral. The mean endometrioma size was 6.0±2.74 cm and 27.8% (n=27) of the endometriomas was found to be smaller than 5 cm. There was no significant difference between the endometrioma and the benign cyst group in terms of median NLR values (1.848 and 1.635, respectively, p=0.124). PLR median values were significantly higher in endometrioma group than in benign cyst group (128.77 and 114.69, respectively, p=0.015). NLR ratio was found to be statistically significantly higher in bilateral endometriomas compared to unilaterals.

Conclusion: Although NLR was not found to be elevated in patients with endometrioma, it was found to be affected from bilaterality. PLR was found to be elevated in patients with endometrioma and not affected by the stage of the disease.

Keywords: Endometrioma, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio

ÖZ

Amaç: Nötrofil/lenfosit oranı (NLR) ve trombosit/lenfosit oranının (PLR) kronik enflamatuvar bir hastalık olan endometriomada tanı değerinin olup olmadığını değerlendirmektir.

Yöntemler: Bu retrospektif, karşılaştırmalı olgu serisine adneksiyel kitle nedeniyle opere edilip patoloji sonucu endometrioma gelen 97 hasta ile kontrol grubu olarak patoloji sonucu benign kist (korpus luteum, seröz kist ya da fonksiyonel kistler) olan 90 hasta dahil edildi. Hastaların preoperatif dönemde hemogram parametrelerinden elde edilen NLR ve PLR değerleri iki grup arasında karşılaştırıldı.

Bulgular: Endometrioma ve benign kist grubu yaş ortalamalarında istatistiksel anlamlı fark yoktu (sırasıyla 34,8±8,93 ve 34±8,59, p=0,88). Endometriomaların %14,4'ü (n=14) bilateraldi. Ortalama endometrioma boyutu 6±2,74 cm olarak belirlendi, %27,8'inin (n=27) 5 cm'den daha küçük olduğu saptandı. Endometrioma ile benign kist grubu arasında ortanca NLR değerleri açısından anlamlı bir fark saptanmadı (sırasıyla 1,848 ve 1,635, p=0,124). PLR ortanca değerleri endometriomada benign kiste göre anlamlı yüksek saptandı (sırasıyla; 128,77 ve 114,69, p=0,015). Bilateral endometriomalarda unilaterallere göre NLR oranının istatistiksel olarak anlamlı yüksek olduğu görüldü.

Sonuç: NLR'nin endometrioma olgularında yüksek saptanmasa da bilateral olma durumundan etkilendiği görüldü. PLR'nin ise endometriomalı hastalarda yüksek olduğu ve hastalığın evresinden etkilenmediği tespit edildi.

Anahtar Kelimeler: Endometrioma, nötrofil/lenfosit oranı, trombosit/lenfosit oranı

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Introduction

Endometriosis is defined as the presence of endometrial tissue outside the uterus and is a common disease seen in 5-10% of women in reproductive age (1). It is a common, chronic inflammatory condition and ectopic endometrial tissue and associated inflammation may cause dysmenorrhea, dyspareunia, chronic pain and infertility. The lysis of erythrocytes by inflammatory cells in hemorrhages in the endometriotic foci formed with hormonal effect during menstrual period results in the formation of pigmented histiocytes and hemosiderin-laden macrophages (2). Although endometriosis is usually seen in the pelvic region, it may be localized to any part of the body. Endometriosis lesions in the pelvis can be categorized as superficial-peritoneal, ovarian and deep infiltrating (3). Ovarian endometriosis is caused by bleeding of ectopic endometrial tissue and it results in a hematoma surrounded by ovarian parenchyma, known as endometrioma (4). One-third of cases are bilateral. Unlike most hemorrhagic physiological ovarian cysts, endometriomas typically have fibrotic walls and surface adhesions, and they are filled with syrup-like chocolate colored material, and are surrounded by over parenchyma (5). In addition, the endometrial epithelium is covered with stroma and glands (6).

Based on the inflammatory response in endometriosis, inflammation markers and lymphocyte counts were studied alone and in combination with cancer antigen 125 (CA 125) for the detection of endometriosis (7,8).

Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in peripheral blood are simple systemic inflammatory response markers assessed by blood parameters and are associated with several neoplastic conditions. NLR has diagnostic value in some pathologies characterized by systemic or local inflammatory response such as diabetes mellitus, liver failure, presence and severity of coronary artery disease, ulcerative colitis and inflammatory arthritis (9-13). A relationship was found between elevated PLR and venous thrombosis (14).

We have planned this study to evaluate the role of these markers that are associated with various inflammatory processes in the pathophysiology of endometriosis in which chronic inflammation plays a significant role and to differentiate endometriomas from benign processes.

Methods

A total of 187 patients, who underwent surgery for adnexal mass at Haseki Training and Research Hospital, Obstetrics and Gynecology Clinic between September 2008 and October 2017, were included in this retrospective, comparative case series. Ninety-seven patients diagnosed with endometrioma and 90 patients with benign cysts (corpus luteum, serous cysts or functional cysts) without histopathological findings of endometriosis were included in the study as the patient and the control groups. Ethics committee approval and patient consent were not obtained because the study was retrospective. Non-pregnant women with regular menstrual cycles, with no hormonal treatment for endometriosis, and with normal liver and renal function tests were included in the study. The definitive diagnosis was made histopathologically with laparotomy or laparoscopy. Women with pelvic inflammatory disease, myoma uteri, adenomyosis, endometrial pathology, metabolic and autoimmune disorders or history of malignancy were excluded from the study. Age, complete blood count parameters within a month before surgery, lateralization, size and histopathological definitive diagnosis of endometrioma were obtained from hospital data system for each patient. NLR ratio was obtained by dividing the neutrophil count by lymphocyte count, and PLR was obtained by dividing platelet count by lymphocyte count.

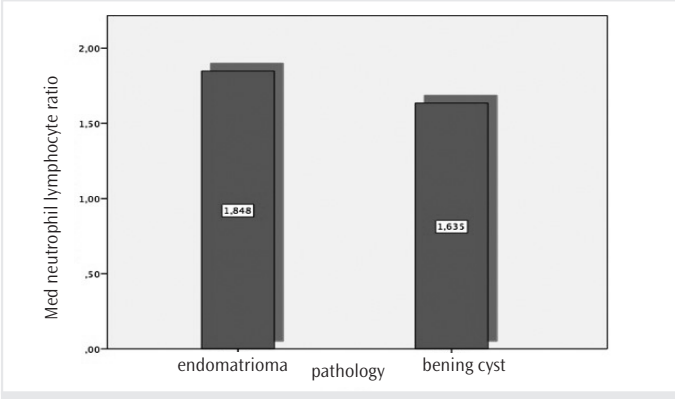
Statistical Analysis

IBM SPSS 22.0 (IBM SPSS Statistics, IL, USA) was used for all statistical analyzes. The NLR and PLR median values were compared using the median test. Continuous variables between the two groups were compared using Student's t-test. $p<0.05$ was considered significant.

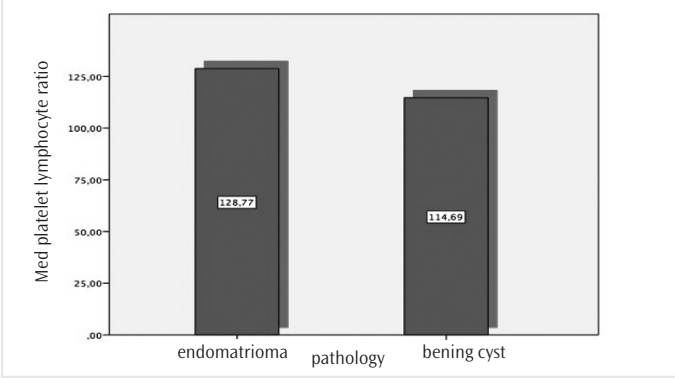
Results

The mean age of 97 patients operated for endometrioma was 34.8±8.93 years and the mean age of 90 patients with benign cyst pathology was 34±8.6 years. There was no statistically significant difference between the two groups in terms of age (p=0.88). Eighty-five point six percent (n=83) of the patients with endometrioma were unilateral and 14.4% (n=14) were bilateral. The mean cyst size in patients operated for endometrioma was 6±2.74 cm. It was detected that 27.8% (n=27) of the endometriomas were smaller than 5 cm.

When the median NLR values of endometrioma and benign cysts were compared, no significant difference was found between the two groups (1.848 and 1.635, respectively, p=0.124). Graphic 1 summarizes the median NLR values of the two groups. However, when the median PLR



Graphic 1. Comparison of median neutrophil/lymphocyte ratio values of cases with endometrioma and benign cyst



Graphic 2. Comparison of median thrombocyte/lymphocyte ratio values of cases with endometrioma and benign cyst

Table 1. Median neutrophil and platelet and p values in endometrioma and benign cyct

	Endometrioma	Benign cyst	p
Median NLR	1.85	1.64	0.124
Median PLR	128.77	114.69	0.015

NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio

values of both groups were compared, it was found that it was significantly higher in the endometrioma group than in the benign cyst group (128.77 and 114.69, respectively, p=0.015). Graphic 2 shows the median PLR values of the two groups. The median NLR and PLR and p values of the endometrioma and benign cyst groups are shown in Table 1.

When the median NLR and PLR values were compared according to bilaterality in the endometrioma group, there was a statistically significant elevation in NLR in bilateral endometriomas. In patients with unilateral and bilateral endometrioma, the median NLR values were 1.82 (minimum-maximum=0.41-3.84) and 2 (minimum-maximum=1.42-4.30), respectively (p=0.03). However, in patients with unilateral and bilateral endometrioma, median PLR values were calculated as 126.80 (minimum-maximum=60.67-588.33) and 134.85 (minimum-maximum=93.03-208.99), respectively, and there was no statistically signifacant difference between the two groups (p=0.23).

Discussion

Although endometrioma is known for the presence of chocolate colored fluid during surgery, the definitive diagnosis is made by tissue biopsy and histological verification. The combination of signs, symptoms, imaging methods and laboratory is used in the diagnosis. The patient may present with dysmenorrhea, dyspareunia, chronic pelvic pain, and symptoms of infertility and a sensitive cystic mass can be detected in the pelvic examination. The characteristic appearance of endometrioma on transvaginal ultrasound is a cystic ovarian mass with diffuse homogeneous ground-glass echoes. There are no pathognomonic laboratory findings for endometriosis. A number of urinary and endometrial biomarkers have been examined for noninvasive diagnosis of the disease, but none have been clinically useful (15). Although the role of serum CA 125 in primary diagnosis is not defined (5), it may be increased in women with endometriosis (for example more than 35 units/mL) (16,17). However, serum CA 125 concentrations are not routinely tested in women evaluated or treated for endometriosis. This is due to the high concentration of serum CA 125 in other diseases, especially in ovarian cancer.

As a result of studies on the role of inflammation in the pathogenesis of endometriosis, it was seen that macrophages, which account for 85% of peritoneal fluid leukocytes, have increased in the peritoneal fluid of patients with endometriosis. Macrophages have been associated with the onset and development of endometriosis through fibronectin, tumor necrosis factor (TNF)-alpha, cytokines and interleukin production (18-20). Activated macrophages also provide TNF-alpha and endometrial cell proliferation that stimulate collagen synthesis and fibroblast proliferation, thus leading to adhesion formation, and secrete cytokines that stimulate the activation of T and B cell (21). The cytokines detected in the peritoneal fluid of patients with endometriosis are interleukin (IL)-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, interferon gamma, TNF-alpha, transforming growth factor (TGF)-beta and vascular endothelial growth factor. TNF-alpha is secreted by activated macrophages, fibroblasts, T and B cells, and its concentration in the peritoneal fluid was positively correlated with the stage of the endometriosis by some authors (22). TGF-beta was also found to be high in the peritoneal fluid of patients with endometriosis in line with the stage of the disease. TGF-beta is most likely involved in endometrial proliferation, angiogenesis, inhibiton of lymphocyte and natural killer cells (23).

In this study, although NLR and PLR values were thought to be effective in the preoperative diagnosis of endometrioma, it was observed that only PLR values are higher in patients with endometrioma than in patients with benign cyct.

In the literature, there are conflicting results with our finding that NLR is not different in endometrioma compared to benign cysts. Similar to our study, Yavuzcan et al. (24) (33 patients) and Kim et al. (25) (219 patents) did not find a relationship between NLR and endometrioma. However, in studies by Cho et al. (26) including 231 patients and by Sayan et al. (27) including 50 patients at any stage, and in studies by Tokmak et al. (28) including 467 patients and by Yang et al. including 197 patients at stage 3-4, NLR was significantly higher in endometriosis cases. In the study with the highest number of cases, the NLR were higher in the endometrioma group (29). When the characteristics of endometrioma cases included in this study were examined, it was observed that 95% of the patients had stage 3-4 endometriosis. In the same study, the bilaterality rate was reported as 26%. It may be thought that this series may have high NLR values because of advanced endometriosis and possibly more peritoneal inflammation. In our study, we found statistically significant elevation in NLR in bilateral endometriomas. Although there was no subgroup analysis in the previous study, the ratio of bilaterality was more than our series and it might be another factor that can explain the elevated NLR.

Thrombocytosis has been associated with various proinflammatory mediators (30). Increased platelet count in response to chronic inflammation due to the nature of endometriosis is also an expected result. In this study, we detected elevated PLR as a result of chronic inflammation of endometriosis. PLR was significantly higher in a study of 197 patients with moderate and severe endometriosis (31). However, in a study in 61 cases of stage 3-4 endometriosis, there was no difference between the endometrioma and the control group in terms of PLR (32). In our study, we also found no relationship between bilaterality and elevated PLR values. Based on this finding, further studies may be conducted to demonstrate that PLR values are not affected by the stage of the disease.

Study Limitations

Our study has some limitations including (a) the stages of endometriosis cannot be reached due to retrospective nature of the study, (b) the control group including only patients operated for a mass, and (c) not including patients being followed up and recevieved medical treatment. However, it is valuable because the number of patients is higher than many studies in the literature and it has a similar control group in terms of age.

Conclusion

In conclusion, NLR was shown to be affected by bilaterality, although it was not found to be elevated in patients with endometrioma. In addition, PLR was found to be elevated in patients with endometrioma and was not affected by the stage of the disease.

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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Investigation of Superior Laryngeal Nerve Disorders with Laryngeal Electromyography in Patients with Hoarseness

Ses Kısıklığı Olan Hastalarda Superior Larengeal Sinir Bozukluklarının Larengeal Elektromiyografi ile Araştırılması

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ABSTRACT

Introduction: In this study, we aimed to investigate the laryngeal electromyography (L-EMG) findings of organic and functional laryngeal pathologies that affect superior laryngeal nerve in patients with hoarseness.

Methods: All patients underwent routine examination and videolaryngoscopy using a 70-degree 4-mm telescope. L-EMG studies were performed via portable Dantec™ Keypoint® EMG/NCS/EP Workstation with 2-channel options. For EMG, 20 mm bipolar concentric needle electrodes were used. Because the procedure was relatively painless and local anesthetics could affect the function of the muscles, no local anesthesia was administered to the patients. Cricothyroid muscle (CTM) and thyroarytenoid muscle (TAM) were tested by electromyography method.

Results: Twenty-four patients with hoarseness were included in the study. Eleven patients (46%) were male and 13 (54%) were female. The mean age was 37.62 years (range: 15-57 years). A total of 96 muscles were examined with EMG. L-EMG was pathological in 15 patients (62.5%) and bilateral pathology was observed in three patients. Twenty muscles (20.8%) were detected as pathological, with neurogenic involvement in 20 muscles (70%), poor activity or no activity in four muscles (20%) and dystonic activity in two muscles (10%). Eight right CTMs (five neurogenic involvement, two poor activity, one no activity) and five left CTMs (two neurogenic involvement, one poor activity, two dystonic activity) were pathological. TAMs had neurogenic involvement on the right side in four patients and on the left side in three patients.

Conclusion: It should be kept in mind that L-EMG may be an adjunctive application for detecting pathologies with neurogenic or myogenic involvement that affect the superior laryngeal nerve and lead to hoarseness.

Keywords: Electromyography, larynx, hoarseness, superior laryngeal nerve

ÖZ

Amaç: Bu çalışmada ses kısıklığı olan hastalarda superior larengeal siniri etkileyen organik ve fonksiyonel larengeal patolojilerin larengeal elektromiyografiye (L-EMG) yansıyan bulgularını araştırmayı amaçladık.

Yöntemler: Hastaların tamamına rutin kulak burun boğaz muayenesi ve 70 derece 4 mm'lik teleskopla larenks muayenesi yapıldı. L-EMG incelemeleri Dantec™ Keypoint® iki kanal portable cihazla yapıldı. EMG için 20 mm bipolar konsantrik iğne elektrotlar kullanıldı. İşlemin göreceli olarak ağrısız olması ve lokal anesteziklerin kasların fonksiyonlarını etkilebileceği düşüncesiyle hastalara lokal anestezi yapılmadı. Krikotiroid kas (KTK) ve tiroaritenoid kas (TAK) elektromiyografi yöntemiyle test edildi.

Bulgular: Ses kısıklığı olan 24 hasta çalışmaya alındı. Hastaların 11'i erkek (%46), 13'ü kadındı (%54). Ortalama yaş 37,62 yıl (15-57 yıl) idi. Toplam 96 kasa EMG yapıldı. L-EMG 15 hastada patolojik (%62,5), bu hastaların üçünde bilateral patolojik bulundu. Yirmi kas patolojikti (%20,8). Bunların 14'ünde nörojen tutulum saptandı (%70), 4'ünde zayıf aktivite gözlendi ya da aktivite alınamadı (%20), 2'si ise distonik aktivite gösteriyordu (%10). Sağ KTK'lerden 8 tanesi (5'i nörojen, 2'si zayıf aktivite, 1'inde aktivite alınmıyor), sol KTK'lerden 5 tanesi (2 nörojen, 1 zayıf aktivite, 2 distonik aktivite) patolojikti. TAK'lerden sağ TAK 4 hastada, sol TAK 3 hastada nörojen tutulum gösteriyordu.

Sonuç: Ses kısıklığına neden olan patolojilerde superior larengeal siniri etkileyen nörojen ya da miyojen tutulumlar olabileceği ve bunun aydınlatılmasında L-EMG'nin yardımcı bir uygulama olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: Elektromiyografi, larenks, ses kısıklığı, superior larengeal sinir

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Introduction

Laryngeal electromyography (L-EMG) is a study that evaluates the integrity of the muscles and nerves of the larynx. The movements of the vocal cords are coordinated by laryngeal muscles, laryngeal cartilages, brain and nerves innervating the laryngeal muscles. Diagnostic L-EMG is indicated in patients with signs of movement disorder in vocal cords. The aim of the diagnostic L-EMG is to elucidate the cause of these movement disorders and to guide the diagnosis. Laryngeal movement abnormalities may be due to joint dysfunction, muscular anomalies, and central or peripheral neural disorders involving the larynx. It is important to understand the etiology of movement disorder for developing an effective treatment algorithm. Although evidence-based data confirming the usefulness of L-EMG is very few, it has proved to be very useful clinically. Diagnostic L-EMG is performed to evaluate the integrity of the laryngeal neuromuscular system. L-EMG works by using electrical signal transmission of nerves. Electrodes receive electrical impulses from muscles and convert them into visual and sensory signals, and these signals are interpreted (1).

The superior laryngeal nerve (SLN) is the branch of the vagus nerve. It branches from the vagus nerve near the jugular foramen at the skull base, usually about 4 cm superior to the carotid bifurcation at the level of second cervical vertebra and ganglion nodosum. After approximately 1.5 cm, SLN branches into the larger internal and the smaller external branches. The external branch lies on the surface of the inferior constrictor muscle and innervates cricothyroid muscle (CTM) (2). The CTM is responsible from the tension on the vocal folds and allows patients to create high-pitched sounds. Damage to SLN makes it difficult for patients to create high-pitched sounds. This is a big problem especially for singers and women (3).

In this study, we aimed to investigate the EMG findings of organic and functional laryngeal pathologies that affect superior laryngeal nerve in patients with hoarseness.

Methods

Twenty-four patients with hoarseness were included in the study. Patients with hoarseness due to laryngeal malignancy and patients with previous history of thyroid or laryngeal surgery were excluded. However, three patients who had had radiotherapy due to nasopharyngeal carcinoma about one year ago and had no relapse were not excluded from the study. All patients underwent routine examination and videolaryngoscopy using a 70-degree 4-mm telescope. L-EMG studies were performed via portable Dantec™ Keypoint® EMG/NCS/EP Workstation (Medtronic Co, Skovlunde, Denmark) with 2-channel options. This study was appoved by the Local Ethics Committee of İstanbul University Cerrahpaşa Faculty of Medicine (date: 2005, number: 08). Informed consent was signed by all patients. Because the procedure was relatively painless and local anesthetics could affect the function of the muscles, no local anesthesia was administered to the patients. For EMG, 20-mm bipolar concentric needle electrodes (Myoline, Spes Medica, Genova, Italia) were used. In order to test CTM, the skin over the cricothyroid membrane was pierced 1 cm lateral to the midline with a monopolar needle electrode. The CTM was tested by moving the needle to the upper lateral part of the cricothyroid membrane until the electrical activity was observed on the oscilloscope and heard from the speaker system. We placed the needle electrode over the midline of cricothyroid membrane in order to measure the activity of the thyroarytenoid muscle (TAM). The needle electrode was inserted through the cricothyroid membrane and then oriented at an angle of 30° laterally and 60° superiorly. We reached TAM with a submucosal approach. The patient was asked to phonate /e:/ several times.

Results

Twenty-four patients with hoarseness were included in the study. Eleven patients (46%) were male and 13 (54%) were female. The mean age was 37.62 years (range: 15-57 years). A total of 96 muscles were examined with EMG (Table 1).

L-EMG was pathological in 15 patients (62.5%) and bilateral pathology was observed in three patients. Twenty muscles (20.8%) were detected as pathological, with neurogenic involvement in 20 muscles (70%), poor activity or no activity in four muscles (20%) and dystonic activity in two muscles (10%). Eight right CTMs (five as neurogenic involvement, two as poor activity, one as no activity) and five left CTMs (two as neurogenic involvement, one as poor activity, two as dystonic activity) were pathological. Neurogenic involvement was observed in the right TAMs in four patients and in the left TAMs in three patients. The right CTM showed neurogenic involvement in one patient who had had radiotherapy due to nasopharyngeal carcinoma. In endoscopic laryngeal examination, we detected adduction failure in six patients (25%), adduction failure and bowing in eight patients (33.3%), atrophy of the vocal cords in three patients (12%), hypertrophy of the vocal cords in two patients (8.33%), edema in one patient, irregularity in one patient, paralysis in one patient, and polyp in one patient (20%). Regarding endoscopic examination, fourteen patients with abnormalities such as adduction failure and bowing were evaluated as functional disorder, and 10 patients with abnormalities such as nodules, polyps and paralysis were evaluated as organic disorders. L-EMG was normal in two of 14 patients, and 12 patients (85%) had neurogenic involvement. Neurogenic involvement was detected in one patient with Reinke's edema, in three patients with hypertrophic cord, and in 3 patients with atrophy of the vocal cords (30%). Endoscopic examinations and L-EMG findings of the patients with organic and functional pathology were consistent. While two patients had neurogenic involvement and decreased activity in bilateral CTMs, they also had adduction failure and bowing in the endoscopic examination. The right vocal cord was paralytic in one patient and neurogenic involvement was observed in the right TAM in EMG. The patient, who had atrophy of the right vocal cord in the endoscopic examination, had loss of activity in the right CTM and neurogenic involvement in the TAM in EMG.

Discussion

The importance of L-EMG is based on its diagnostic ability to examine the major peripheral sensory nerves and motor unit, anterior horn cells, axons, and muscle fibers. The structure examined in EMG is the motor unit. The muscle may be normal, or may exhibit neurogenic or myogenic involvement in EMG. The lesion is outside the muscle component of the motor unit in neurogenic involvement. The duration of the motor unit action potential (MUAP) is prolonged, the amplitude increases,

Table 1. The endoscopic examination and electromyography findings of patients

Patient	Right CTM	Right TAM	Left CTM	Left TAM	Examinaton	Laryngoscopy
O.T.	N	N	Polyphasia	N	N	AF
A.K.	N	N	N	N	N	AF
M.M.	Neurogenic MUAP	N	N	N	N	AF
A.K.	N	N	N	Neurogenic MUAP	N	AF
E.D.	N	Polyphasia	N	N	N	AF, B
Y.Y.	Decreased activity	N	N	N	N	AF
S.K.	N	Neurogenic MUAP	N	N	N	Bilateral edema
F.K.	N	Neurogenic MUAP	N	N	N	Right sided paralysis
M.K.	Neurogenic MUAP	N	N	N	N	AF, B
Ş.O.	Neurogenic MUAP	N	Neurogenic MUAP	N	N	AF, B
M.D.	N	N	N	N	N	Right sided irregularity
A.C.	N	N	N	N	N	AY, B
N.Ö.	N	N	N	N	N	AY, B
C.Ş.	Neurogenic MUAP	N	N	N	N	Bilateral hypertrophy
A.D.	N	N	N	N	N	Bilateral hypertrophy
D.T.	N	N	N	N	N	Bilateral edema and hypertrophy
H.B.	N	N	N	N	N	Right sided polyp
Z.B.	Decreased activity	N	Decreased activity	N	N	AF, B
Ş.K.	No activity	Neurogenic MUAP	N	N	N	Right sided atrophy
L.B.	N	N	Dystonic activity	Neurogenic MUAP	N	AF, B
Y.K.	N	N	N	N	N	Left sided atrophy
M.C.	N	N	N	Neurogenic MUAP	N	Left sided atrophy
N.A.	Polyphasia	N	Dystonic activity	N	N	AF, B
C.H.	N	N	N	N	N	Right sided AF

CTM: cricothyroid muscle, TAM: thyroarytenoid muscle, N: normal, AF: adduction failure, MUAP: motor unit action potential, B: bowing

the number of phases increases, and the number of observed MUAPs decreases in case of neurogenic involvement. However, in myogenic involvement, the amplitude decreases, the duration is shortened, the number of phases increases, and the early recruitment pattern is observed (4). In our study, we observed that 12 of 14 patients with functional disorder and 3 of 10 patients with organic disorders in the endoscopic examination had neurogenic involvement in L-EMG.

L-EMG is a diagnostic method that can be used not only to investigate vocal cord paralysis, but also to confirm the location of the lesion, possible etiology, and neuroanatomy. The results may vary depending on the type of electrodes used (5). In a study performed with 110 patients, transcartilaginous electrodes and endotracheal electrode EMG recordings were compared. EMG recordings performed with both electrodes were reported to be reliable. In addition, it was reported that transcartilaginous EMG recordings had higher amplitude and more stable waves. Although there was significant amplitude reduction in endotracheal tube records, there was no significant amplitude reduction in transcartilaginous recordings (6). L-EMG is also used for intraoperative recurrent laryngeal nerve monitoring (7). In a study in ten patients, the researchers used a technique called “airway scope” to monitor recurrent laryngeal nerve and SLN intraoperatively. In this study, vocal cord motion, which occurred by stimulation given to recurrent laryngeal nerve and SLN, was visualized by “airway scope” device and it was reported to be an important technique for surgical safety (8). In this study, we observed the polyphasic MUAPs in L-EMG of one patient with vocal cord paralysis. In accordance with the literature, this made us think that prognosis of the patient would be good. In another retrospective study in 137 patients, L-EMG results showed that SLN, recurrent laryngeal nerve or both were damaged in 94 patients, while 43 patients had normal findings. Twenty five percent of the neurogenic involvement has been reported to be idiopathic, while others have been reported after the treatment of thyroid, parathyroid, lung and pancreatic malignant tumors (9). In our study, we found that 12 of 14 patients with functional disorder and 4 of 10 patients with organic disorder had neurogenic involvement in L-EMG. Radiotherapy induced neuropathy in nasopharyngeal carcinoma was reported as 0.3% to 9% (10). Vestibulocochlear apparatus, hypoglossal nerve and vagus nerve are the most frequently damaged structures. Although vocal cord paralysis due to vagus nerve injury is usually unilateral, bilateral paralysis may occur and may lead to life-threatening airway obstruction (11). Three patients in our study had had radiotherapy for nasopharyngeal carcinoma one year ago and one of these patients had neurogenic involvement in CTM.

Conclusion

L-EMG is a safe procedure to detect possible etiology in patients with hoarseness. It should be kept in mind that L-EMG may be an adjunctive application for detecting pathologies with neurogenic or myogenic involvement that affect the superior laryngeal nerve and lead to hoarseness.

Ethics Committee Approval: This study was approved by the Local Ethics Committee of İstanbul University Cerrahpaşa Faculty of Medicine (date: 2005, number: 08).

Informed Consent: Informed consent was signed by all patients.
Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.Ö.; Design - A.K.; Supervision - F.Ö.; Resources - N.U.A.; Data Collection and/or Processing - Ş.Ö.; Analysis and/or Interpretation - N.U.A.; Literature Search - M.Ş.; Writing Manuscript - Ş.Ö.; Critical Review - F.Ö.

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

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Functional Results of Surgery for Otosclerosis

Otoskleroz Cerrahisi Fonksiyonel Sonuçları

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ABSTRACT

Introduction: To evaluate the audiological variables and to investigate the factors affecting hearing improvement in patients who underwent stapedotomy with the diagnosis of otosclerosis.

Methods: The data of 114 patients who had middle ear exploration were retrospectively reviewed. Air conduction thresholds between 250-6000 Hz and bone conduction thresholds between 500-4000 Hz were examined in pure tone audiometry. Postoperative air-bone gap (ABG), change in ABG, and change in bone conduction threshold at high frequency were primarily examined. The results of different piston diameters were compared.

Results: Eighty-three patients with stapedial footplate fixation were included in the study. While post-operative air conduction thresholds decreased significantly at all frequencies, bone conduction thresholds decreased significantly only at 2000 Hz (p=0.001). The most notable gain in ABG was obtained at 500 Hz. The post-operative air conduction pure tone average was significantly higher in patients with 0.6 mm diameter prosthesis. Postoperative mean ABG and ABG values at 2000 and 4000 Hz were found to be significantly lower in patients with 0.8 mm diameter prosthesis (p<0.05). The change in ABG at 2000 Hz was significantly lower in patients with 0.6 mm diameter prosthesis (p=0.029). The mean change in bone conduction thresholds at high frequencies was positive in 58 patients (70%) and negative in 25 patients (30%). There was no difference between different piston diameters regarding bone thresholds at high frequencies.

Conclusion: Improvement was achieved at all frequencies in air conduction thresholds following stapedotomy. In our study, it was found that the lower the pre-operative bone conduction thresholds were, the more the improvement in ABG. A significant advantage was achieved at 2000 and 4000 Hz frequencies in patients with 0.8 mm piston diameter compared to 0.6 mm piston diameter.

Keywords: Air-bone gap, otosclerosis, stapedotomy

ÖZ

Amaç: Otoskleroz tanısıyla stapedotomi yapılmış olan olgularda odyolojik değişkenleri değerlendirmek ve işitme kazancını etkileyen faktörleri incelemektir.

Yöntemler: Orta kulak eksplorasyonu yapılmış 114 hastanın retrospektif taraması yapıldı. Saf ses odyometrik incelemede hava iletim eşikleri 250-6000 Hz arası, kemik iletim eşikleri ise 500-4000 Hz arasında incelendi. Postoperatif hava-kemik aralığı (HKA), HKA değerindeki değişim ve yüksek frekans kemik iletimindeki değişim primer olarak incelendi. Farklı çapta piston kullanılan hastaların sonuçları kıyaslandı.

Bulgular: Stapes taban fiksasyonu tespit edilen 83 hasta çalışmaya dahil edildi. Postoperatif hava yolu eşiklerinde tüm frekanslarda anlamlı azalma tespit edilirken, kemik yolu eşiklerinde sadece 2000 Hz'te anlamlı bir azalma tespit edildi (p=0,001). HKA'da en yüksek kazanç 500 Hz'te elde edildi. Postoperatif hava yolu saf ses ortalaması 0,6 mm çaplı protez kullanılan hastalarda anlamlı olarak daha yüksek tespit edildi. Postoperatif HKA ortalaması ile 2000 ve 4000 Hz'teki değerleri, 0,8 mm piston çapı kullanılan hastalarda anlamlı olarak daha düşük bulundu (p<0,05). HKA değişimi 2000 Hz'te 0,6 mm çaplı piston kullanılan hastalarda anlamlı olarak daha düşük idi (p=0,029). Yüksek frekans kemik eşikleri ortalamasındaki değişim 58 hastada (%70) pozitif iken, 25 hastada (%30) negatif değerdeydi. Farklı piston çapları arasında yüksek frekans kemik eşikleri açısından fark saptanmadı.

Sonuç: Stapedotomi sonrasında hava yolu eşiklerinde tüm frekanslarda kazanç sağlanmıştır. Çalışmamızda, preoperatif kemik yolu eşikleri ne kadar düşükse, HKA kazancının o kadar fazla olduğu tespit edilmiştir. 0,8 mm çaplı piston kullanılanlarda, 0,6 mm çaplı piston kullanılan hastalara göre 2000 ve 4000 Hz'te anlamlı avantaj elde edilmiştir.

Anahtar Kelimeler: Hava-kemik aralığı, otoskleroz, stapedotomi

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Introduction

Otosclerosis is an otic capsule disease characterized by bone resorption and replacement that causes fixation in the stapes footplate (1). Otosclerosis, which is one of the common causes of conductive hearing loss in adults, is seen more frequently in women and between the ages of 30-40 years (2). Two-thirds of otosclerosis cases have a family history of hearing loss (3).

Three different treatment modalities have been defined for otosclerosis: wait - see, hearing aid, and stapes surgery. The effect of stapes surgery on conductive hearing loss due to otosclerosis is well known. Stapedectomy, defined by John Shea, has been replaced by stapedotomy over time. The risk of sensorineural hearing loss with stapedotomy is reported to be less (4-7).

Although some prognostic factors have been emphasized in the pre-operative evaluation of otosclerosis, these factors are not clear as in tympanoplasty (5,6). Surgical experience, patient characteristics and intra-operative findings have an important place among prognostic factors (8-10).

In our study, the functional results of patients who underwent stapedotomy with the diagnosis of otosclerosis were evaluated through an audiological perspective and a prognostic point of view. The effect of stapedotomy surgery on bone and air conduction hearing thresholds, and change in frequency-specific air-bone gap (ABG) were investigated.

Methods

Patient Selection and Evaluation

A retrospective analysis of 114 patients who underwent middle ear exploration with a preliminary diagnosis of otosclerosis between 2007 and 2013 was performed. Patients with tympanic membrane perforation or retraction and patients without intra-operative stapedial footplate fixation were excluded from the study. Stapedotomy was performed in all patients. Patients who had undergone revision surgery, ear surgery for another reason, and had juvenile otosclerosis were not included in the study. Age, gender, pre-operative and post-operative audiogram data, diameter of the prosthesis used during surgery, and hearing status of the other ear were recorded. The study was approved by the Local Ethics Committee of İstanbul Training and Research Hospital (513-25/07/2014).

The audiometric examinations (AC 40; Interacoustics A / S, Assens, Denmark), which were performed before the surgery and at least 1 year after surgery, were evaluated. In the pure tone audiometric examination, air conduction thresholds were examined at 250, 500, 1000, 2000, 4000 and 6000 Hz frequencies, and bone conduction thresholds at 500, 1000, 2000 and 4000 Hz frequencies. The pure tone average (PTA) values were calculated by taking the arithmetic average of both air and bone conduction thresholds at 500, 1000, 2000 and 4000 Hz. ABG at 500, 1000, 2000 and 4000 Hz was calculated by subtracting the bone conduction threshold value from the air conduction threshold value at these frequencies. The mean ABG (mean ABG) value was calculated by taking the arithmetic average of the ABG values at four frequencies. The change in postoperative ABG (gain) was determined by subtracting the postoperative ABG value from preoperative ABG value, and it was calculated separately for meanABG and for the four frequencies examined. The difference between pre-operative and post-operative bone conduction thresholds at 1000, 2000 and 4000 Hz were determined and the effect of surgery on bone conduction was evaluated. Positive value indicated improvement in bone conduction and negative value indicated damage in inner ear (11).

Speech reception threshold (SRT) and speech discrimination score (SDS) values in the speech audiometry were recorded. The post-operative changes in SRT and SDS values were determined.

The primary aim was to investigate post-operative ABG, the change in ABG and changes in mean of bone conduction thresholds at 1000, 2000 and 4000 Hz. The secondary aim was to investigate the frequency-specific changes in bone and air conduction thresholds, and changes in speech audiometry (SRT and SDS) values. The differences between the patients with 0.6 and 0.8 mm stapes prosthesis diameter were evaluated.

Statistical Analysis

SPSS 15.0 for Windows (IBM Corporation, Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were expressed as number and percentage for categorical variables and mean ± standard deviation (minimum-maximum) for numerical variables. The comparisons of non-normal distributed numerical variables between two independent groups were performed by using Mann-Whitney U test. Dependent group comparisons were evaluated using the dependent sample t-test for normal distribution and Wilcoxon test for non-normal distribution. The relationships between the numerical variables were examined by Spearman's correlation analysis because of the non-parametric test condition. Statistical significance was accepted as $p<0.05$.

Results

Eighty-three patients (49 men and 34 women) who underwent stapes surgery were included in the study. Surgeries were performed by three different surgeons. The mean age of the patients was 41.3±11.11 (minimum-maximum: 20-68) years. Hearing loss was accompanied by tinnitus in 49.4% of the patients, dizziness in 6% and pain in 2.4%. The operated ear was on the left side in 47% and on the right side in 53%. Hearing loss was detected in the other ear in 73.2% of the patients. 0.6 mm stapes prosthesis was used in 48 patients (58%) and 0.8 mm stapes prosthesis was used in 35 patients (42%). The main factor determining the diameter of the prosthesis was the size of the fenestration created at the base of the stapes.

The mean air conduction value was 56.1±9.9 dB hearing level (HL) in the preoperative period, and 34.1±17.5 dB HL in the postoperative period. The difference was statistically significant ($p<0.001$). The reduction in air conduction thresholds at 250, 500, 1000, 2000, 4000 and 6000 Hz were similarly significant ($p<0.05$) (Table 1). The difference between the frequency-specific air conduction thresholds of different stapes prosthesis diameters was not significant. However, the PTA value of postoperative air conduction was significantly higher in patients with a 0.6 mm diameter stapes prosthesis ($p=0.042$).

The mean bone conduction value was 18.1±7.3 dB HL in the preoperative period, and 16.7±12.9 dB HL in the postoperative period.

Table 1. Preoperative and postoperative air conduction hearing thresholds

	Preoperative			Postoperative		
AC threshold	Total	0.6 mm	0.8 mm	Total	0.6 mm	0.8 mm
250 Hz	64.5±13.1	64.8±11.8	64.5±14.8	37.8±17.6	42.2±19.7	36.9±16.3
500 Hz	62.2±10.7	62.9±10.0	61.7±11.1	35.2±17.0	38.2±19.0	32.0±16.5
1000 Hz	58.5±10.2	59.4±11.3	57.4±7.8	32.5±17.6	35.0±19.2	29.9±17.3
2000 Hz	51.5±12.6	52.1±14.4	50.6±11.7	32.0±18.2	35.1±19.4	30.5±19.0
4000 Hz	52.0±16.7	53.5±17.8	47.7±15.1	36.6±22.6	42.8±24.9	34.0±23.2
6000 Hz	55.4±19.3	58.4±22.6	49.9±16.9	47.2±23.4	55.1±27.8	43.9±15.9
PTA	56.1±9.9	57.8±11.0	54.3±8.6	34.1±17.5	29.1±23.2	19.9±20.6
SRT	54.6±10.5	57.7±10.5	52.3±10.2	33.5±18.1	35.5±19.6	29.2±18.3
SDS	91.7±7.9	90.8±9.2	93.4±6.3	90.5±8.6	90.9±8.6	92.7±9.9

AC: air conduction, PTA: pure tone average, SRT: speech reception threshold, SDS: speech discrimination score

Table 2. Preoperative and post-operative bone conduction hearing thresholds

	Preoperative			Postoperative		
BC threshold	Total	0.6 mm	0.8 mm	Total	0.6 mm	0.8 mm
500 Hz	16.5±8.0	17.9±9.8	15.4±5.4	14.9±12.9	15.6±15.7	11.7±10.1
1000 Hz	17.1±8.3	18.7±8.9	15.3±6.7	15.6±13.7	16.4±16.3	13.2±12.2
2000 Hz	21.5±10.4	22.5±11.4	19.3±8.4	17.2±13.9	17.6±17.3	17.0±13.2
4000 Hz	17.2±12.4	18.0±13.4	15.1±12.1	19.1±15.7	20.5±18.1	17.0±17.0
PTA	18.1±7.3	19.3±8.2	16.3±5.7	16.7±12.9	13.5±15.5	9.3±11.8

BC: bone conduction, PTA: pure tone average

Table 3. Air-bone gap values before and after otosclerosis surgery

	Preoperative			Postoperative		
ABG	Total	0.6 mm	0.8 mm	Total	0.6 mm	0.8 mm
500 Hz	45.8±11.3	45.1±12.5	46.5±11.3	20.2±11.6	17.4±14.4	11.7±12.5
1000 Hz	41.3±9.0	40.8±8.9	42.2±8.0	16.9±9.6	14.4±11.6	9.9±10.1
2000 Hz	30.1±8.7	29.7±10.0	31.0±8.2	14.8±9.9	13.5±11.1	7.6±8.5
4000 Hz	34.8±11.9	35.3±13.1	32.5±11.1	17.4±12.3	17.3±13.9	9.7±11.0
Mean ABG	38.0±7.6	38.1±8.3	38.1±6.5	17.3±9.2	15.6±11.6	9.7±9.6

ABG: air-bone gap, mean ABG: mean air-bone gap

Table 4. Distribution of air-bone gap according to different frequencies

ABG change	Total	0.6 mm	0.8 mm
500 Hz	25.5±15.4	27.9±18.3	34.9±16.2
1000 Hz	24.5±13.6	26.8±14.9	32.4±13.6
2000 Hz	15.3±13.6	16.2±15.2	23.3±13.1
4000 Hz	17.3±14.9	18.3±18.3	22.8±14.0
Mean ABG	20.7±11.4	22.7 ±13.7	28.3±11.6

ABG: air-bone gap, mean ABG: mean air-bone gap

The difference was not statistically significant (p=0.07). While the change in bone conduction thresholds at 500 Hz, 1000 Hz and 4000 Hz were not statistically significant, the change at 2000 Hz was statistically significant (p=0.001). Bone conduction thresholds were not significantly different between patients with different stapes prosthesis diameters (p>0.05) (Table 2).

The mean ABG value was 38±7.6 dB HL in the preoperative period, and 17.3±9.2 dB HL in the postoperative period (p<0.001). Mean ABG and ABG values at all frequencies showed a statistically significant decrease (Table 3). The ABG values at 2000 and 4000 Hz in the postoperative period and mean ABG values were significantly higher in patients with a 0.6 mm stapes prosthesis diameter compared to patients with a 0.8 mm prosthesis diameter (p<0.05).

The mean ABG change was 20.7±11.4. The highest ABG change was found at 500 Hz and the lowest value was at 2000 Hz. The change at 2000 Hz was found to be significantly lower in patients with a 0.6 mm stapes prosthesis diameter compared to patients with a 0.8 mm prosthesis diameter (p=0.029). Regarding ABG, there was no significant difference between the patients with different stapes prosthesis diameters, except at 2000 Hz. The change in ABG is given in Table 4.

There was no statistically significant relationship between age, gender, and change in ABG (p>0.05). Preoperative bone conduction threshold

values were significantly ($p<0.05$) negatively correlated with ABG change at all frequencies, except 2000 Hz ($p=0.092$).

There was no statistically significant relationship between bone conduction at high frequency and age ($p=0.597$) and gender ($p=0.985$). This value was positive in 58 patients (70%) and negative in 25 patients (30%). Two patients with negative values were diagnosed with total hearing loss after surgery. This variable was positively correlated with bone conduction hearing thresholds and mean bone conduction threshold values at 500 Hz and 1000 Hz ($p=0.011$, $p=0.004$, $p=0.010$, respectively). On the other hand, no significant relationship was found with bone conduction hearing thresholds at 2000 and 4000 Hz ($p=0.098$ and $p=0.259$, respectively). The mean of bone conduction threshold change at high frequency was found to be 5.8 dB HL in the 0.6 mm prosthesis diameter group, and 7.2 dB HL in the 0.8 mm prosthesis diameter group ($p=0.64$).

While the postoperative change in SRT was statistically significant ($p<0.001$), there was no significant change in SDS ($p=0.43$) (Table 1). There was a negative correlation between the change in SRT and bone conduction hearing threshold level at 4000 Hz ($p=0.046$), and positive correlation with air conduction hearing threshold levels at 500 and 1000 Hz ($p=0.024$ and $p=0.005$, respectively). There was also a positive correlation between this change and ABG at 1000 Hz ($p=0.005$). There was no statistically significant relationship between the change in SDS and the other parameters. There was also no statistically significant difference between SRT ($p=0.682$) and SDS ($p=0.648$) change in gender groups.

Discussion

Stapedotomy is known to cause gains in air conduction hearing thresholds in patients with otosclerosis. In our study, gain is obtained at all frequencies in the postoperative air conduction hearing threshold values compared to the preoperative values, while gain was achieved only at 2000 Hz in bone conduction. Both the significant gain in the bone conduction at 2000 Hz and the lower gain in the ABG at 2000 Hz compared to other frequencies are consistent with the principle of formation of the Carhart's notch. When the Carhart's notch was first described by Carhart (12) in 1950, it was reported as a worsening at the pure tone threshold of bone conduction at maximum 2000 Hz (500 to 4000 Hz). Although the Carhart's notch formation mechanism, which was reviewed after that period, has not been fully elucidated, some studies have been reported to support the association with the resonance frequency of the ossicular chain (13-15). After a successful otosclerosis surgery, Carhart's notch disappears. Therefore, this is thought that bone conduction thresholds at 2000 Hz do not reflect the cochlear reserve.

In our study, a significant negative correlation was found between ABG gain and preoperative bone conduction hearing thresholds at all frequencies, except 2000 Hz. In other words, preoperative bone conduction thresholds were determined as a prognostic factor affecting the gain in ABG. The data we have obtained suggest that the individuals who have better bone conduction thresholds will be more likely to have ABG gain.

The highest gain in ABG was detected at 500 Hz and 1000 Hz. When the preoperative ABG values were examined, the highest values were found at 500 and 1000 Hz similarly. These data are interpreted as being compatible with the fact that otosclerosis causes more hearing loss at lower frequencies. Otosclerosis acts on the rigidity of middle ear and affects especially low frequencies. However, high frequencies are also affected in the presence of progressive disease (16). In the studies examining the relationship between ABG gain and age, Marchese et al. (3) reported low functional results at age 50 and older and Bittermann et al. (8) stated that ABG gain was advantageous in patients over 40 years of age. In our study, there was no relationship between ABG gain and age.

There was a statistically significant change between pre- and postoperative ABG values at all frequencies (500, 1000, 2000 and 4000 Hz). The highest gain was achieved at 500 Hz, while the lowest gain was at 2000 Hz. In our study, a significant improvement was observed at all frequencies in postoperative air conduction hearing thresholds. Gerard et al. (5) and Meyer (17) reported that there might be no significant improvement at high frequencies due to the effect of cochlear otosclerosis. On the other hand, Ueda et al. (18) reported a significant ABG gain at 2000 and 4000 Hz, and poor gain at higher frequencies and below 1000 Hz.

Postoperative changes in the ossicular chain after a successful stapes surgery are known as overclosure (11). In case of a worsening in this value, which is calculated as the change in mean bone conduction threshold at 1000, 2000 and 4000 Hz, a surgical damage to the cochlea can be interpreted (11). This change, calculated as negative in 30.1% (25 patients) in our patient group, gives the rate of internal ear damage that occurred during or after surgery.

Conflicting findings have been obtained in studies on the effect of stapes prosthesis diameter on hearing gain in otosclerosis surgery. There are studies reporting that the prosthetic diameter does not have an effect on hearing gain, and there are studies reporting that large-scale prostheses provide more gains at lower frequencies and small-diameter prostheses at higher frequencies (19-23). In cases where small fenestration is made at the stapes base, the risk of internal ear damage and prosthesis migration is reported to be less (24). In our study, no significant difference was found between the bone conduction thresholds of groups with a 0.6 or 0.8 mm stapes prosthesis diameter. When the frequency-specific air conduction thresholds were examined, there was no significant difference between the two groups, while the mean air conduction was significantly higher in the patient group with 0.6 mm diameter prosthesis. The change in ABG was found to be significantly higher at only 2000 Hz in the 0.8 mm prosthesis diameter group. Postoperative ABG values were found to be significantly lower in the 0.8 mm prosthetic diameter group at 2000 and 4000 Hz. The change in mean bone conduction at high frequency that is used to detect inner ear damage did not show a significant difference between the groups. These findings can be interpreted as partially better results with 0.8 mm stapes piston diameter.

Conclusion

In our study, gain was obtained at all frequencies in air conduction thresholds after stapedotomy. The significant gain in the bone conduction thresholds at 2000 Hz reflects the Carhart's phenomenon. Otosclerosis is associated with conductive hearing loss at low frequencies, especially

at the beginning. Observing the highest change at 500 Hz is consistent with this fact. In our study, it was found that ABG gain increased with decreasing preoperative bone conduction threshold. It was determined that the postoperative ABG was less with 0.8 mm stapes prosthesis diameter, especially at 2000 and 4000 Hz. There was no significant difference in hearing gain between patients with 0.6 and 0.8 mm stapes prosthesis diameter.

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Outcomes of Cataract Surgery with Iris Hook: Our Experience

İris Kancası Aracılı Gerçekleştirilen Katarakt Cerrahisi Sonuçlarımız

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ABSTRACT

Introduction: We aimed to evaluate the clinical results of cataract surgery performed using iris hook in our clinic.

Methods: The medical records of patients who underwent cataract surgery via phacoemulsification with intraocular lens implantation (PHACO+IOL) that was performed using iris hook were reviewed retrospectively. The patients were evaluated in terms of cataract type, associated ocular diseases, pre-operative and post-operative best-corrected visual acuity (BCVA) and intraocular pressure (IOP).

Results: Out of 3020 eyes treated with PHACO+IOL, iris hook was used in 21 eyes. The mean age of these patients (15 men/8 women) was 71.9±12.1 (range=30-90) years. Thirteen percent of patients had mature cataract, 65.2% had nuclear cataract and 21.7% had nuclear+posterior subcapsular cataract. Regarding associated ocular diseases, it was shown that 43.5% of patients had pseudoexfoliation syndrome and 30.4% had primary open-angle glaucoma. Additionally, 34.8% of patients had hypertension, 4.3% had diabetes mellitus and 17.4% had hypertension+diabetes mellitus. Forty-three point five percent of patients had no history of systemic diseases. Capsular tension ring was used in 13% of surgeries. No posterior capsular perforation was detected. A 3-piece hydrophobic, acrylic, foldable IOL was implanted in-the-bag position in all eyes. Mean pre-operative BCVA was 0.18±0.13 (Snellen visual acuity chart) and mean post-operative BCVA was 0.32±0.23. The mean change in BCVA was 0.15±0.25 and this change was statistically significant (p=0.010). BCVA increased in 65.2% of the patients (n=15), decreased in 21.7% (n=5) and remained the same in 13% (n=3). Mean preoperative IOP was 19.65±5.07 and mean post-operative IOP was 17.26±5.76. The decrease in IOP was not statistically significant (p=0.078).

Conclusion: Although cataract surgery is a risky condition in patients with narrow pupils, our results with iris hook were satisfactory.

Keywords: Phacoemulsification, iris hook, pupil stretching

ÖZ

Amaç: Kliniğimizde yapılan katarakt ameliyatlarında iris kancası kullanımı sonuçlarını değerlendirmektir.

Yöntemler: 2014-2016 yılları arasında fakoemülsifikasyon ve göz içi lens implantasyonu (FAKO+IOL) esnasında iris kancası kullanılan hastaların dosyaları incelendi. Olgular katarakt tanı tipi ve eşlik eden göz patolojileri, hastalıkları, ameliyat öncesi ve sonrası erken dönemde görme keskinlikleri (GK) ve göz içi basınç (GİB) açısından değerlendirildi.

Bulgular: FAKO+IOL yapılan 3020 gözden 21'ine (%0,7) iris kancası kullanıldığı tespit edildi. İris kancası kullanılan olguların yaş ortalaması 71,9±12,1 yıl (30-90 arasında) idi. Hastaların 15'i erkek (%65), 8'i kadındı (%34). Hastaların %13'ünde matür katarakt, %65,2'sinde nükleer katarakt (NK), %21,7'sinde ise NK+arka subkapsüler katarakt mevcuttu. Oftalmolojik muayenede %43,5 oranında psödoeksfoliasyon, %30,4 oranında glokom gözlendi. Anamnezde hastaların %34,8'inde hipertansiyon (HT), %4,3'ünde diabetes mellitus (DM), %17,4'ünde HT+DM olduğu görüldü. Hastaların %43,5'inde sistemik hastalık yoktu. Operasyonlarda kapsül germe halkası takılma oranı %13 idi. Hiçbir olguda arka kapsül perforasyonu saptanmadı. Tüm olgularda üç parçalı hidrofobik akrilik katlanabilir. Göz içi lens implantasyonu kapsül içine yapıldı. Hastaların Snellen eşeline göre GK ortalaması preoperatif dönemde 0,18±0,13, postoperatif dönemde 0,32±0,23 olarak saptandı. GK değişim ortalaması 0,15±0,25 idi. Postoperatif GK'de artış istatistiksel olarak anlamlıydı (p=0,010). Hastaların %65,2'sinde (n=15) arttı, %21,7'sinde (n=5) azaldı, %13'ünde (n=3) aynı kaldı. Hastaların GİB ortalaması preoperatif dönemde 19,65±5,07, postoperatif dönemde 17,26±5,76 idi. Postoperatif GİB düşüşü istatistiksel olarak anlamlı değildi (p=0,078).

Sonuç: Dar pupillalı olgularda katarakt cerrahisi komplikasyonlar açısından riskli bir durum olmakla birlikte, iris kancası kullanılan olgularda sonuçlarımızın tatmin edici olduğu görüldü.

Anahtar Kelimeler: Fakoemülsifikasyon, iris kancası, pupil germe

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Introduction

Cataract surgery via phacoemulsification (PHACO) becomes more difficult and more complications are encountered when the pupil width is smaller than ideal. Pupil dilatation may be inadequate despite the use of pre-operative mydriatic eyedrops or intraoperative injection of 0.1 cc adrenaline solution (adrenaline was diluted into balanced salt solution (BSS) to prepare an adrenaline concentration of 0.20 mg/mL) into the anterior chamber prior to capsulorhexis in case of pseudoexfoliation syndrome, uveitis, diabetes mellitus, systemic alpha-1A adrenoreceptor blocker use, previous ocular trauma and iridoschisis (1).

Preoperative mydriatic eyedrops are used to ensure the ideal width of the pupil. These eyedrops may be instilled even when the patient is admitted to the operating table. Diluted adrenaline injection into the anterior chamber helps the pupil to dilate. For a more rigid dilatation of the pupil, this should be done in such cases. However, caution should be taken in patients with cardiac disease and severe aortic stenosis. Pupillary stretching is a method used when these methods do not work. Sector and radial iridectomy with sphincterotomy are methods that can be used to provide pupillary dilatation, but cause permanent effects on iris anatomy. In order to dilate the pupil mechanically, ring-shaped pupil expanders and iris hooks placed separately from small corneal incisions may be used. Iris hooks were first used by McReynolds in 1977. The first used iris hooks were metallic and non-foldable, and nylon and foldable hooks have been used in the following years. Foldable hooks were first used in vitreoretinal surgery, but Nichamin was first to use foldable hooks for cataract surgery in 1993. Iris hooks are used to increase the pupil width and contribute to the reduction of complication rates.

In this study, the surgical results of patients, in whom the pupil dilatation was inadequate during the cataract surgery via PHACO and foldable iris hooks were used, were investigated retrospectively.

Methods

The medical records of patients who underwent cataract surgery via PHACO with intraocular lens implantation (IOL) that was performed using iris hook between January 2014 and December 2015 in our clinic were reviewed retrospectively. Age, gender, cataract types, concomitant pseudoexfoliation, concomitant systemic diseases, ophthalmic and systemic drugs, additional devices used during operation and peroperative complications were recorded. All surgical methods and per-operative conditions were recorded from the patients' detailed discharge forms. Postoperative visual acuity, intraocular pressure (IOP) and anterior segment examination findings of the patients were obtained from patient follow-up cards. The data were evaluated statistically.

Ethics committee approval (İstanbul Training and Research Hospital no: 1016) was obtained for the study. The study was conducted in accordance with the Declaration of Helsinki. All patients were informed about the study and their consent was obtained.

The surgeries were performed by a single surgeon. Tropicamide (tropamid® 1%, Bilim İlaç Sanayi ve Ticaret AŞ, İstanbul, Turkey), cyclopentalate hydrochloride (sikloplejin® 1%, Abdi İbrahim İlaç, İstanbul, Turkey) and phenylephrine hydrochloride (mydfrin® 2.5%, Alcon Laboratories Inc., Texas, USA) were administered to each subject's eye to be operated with a half-hour intervals beginning two hours before the surgery. The last drops were administered when the patient was admitted to the operating table. Diluted adrenaline was injected into the anterior chamber after the first side entrance to the cornea. The volumetric effect of the viscoelastic material was used to increase the pupillary dilation. The viscoelastic agent was injected into the pupilla border. Pupillary stretching was performed in order to increase pupil dilatation. In cases where adequate pupillary dilatation could not be achieved with all these procedures, 4 iris hooks were implanted from the lateral corneal incisions. The side entries made for implantation were more perpendicular and smaller in width. In order to have a symmetrical pupillary dilatation, the incisions from which the iris hook will be implanted were performed at a 90-degree angle between the two incisions. After IOL implantation, the iris hooks were taken out of the pupil before the viscoelastic material was removed from the eye. After the viscoelastic material was cleaned, the incisions other than lateral incisions used for the passage of the iris hooks were sealed with BSS.

Statistical Analysis

SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis. Descriptive statistics were expressed as number and percentage for categorical variables, and mean, standard deviation, minimum and maximum for numerical variables. Comparison of two related groups was performed using Paired t-test or Wilcoxon test, where appropriate. Comparison of two or more independent groups was performed using One-Way ANOVA, Kruskal-Wallis test, Mann-Whitney U test or Student's t-test, where appropriate. Relations between numerical variables were examined by Spearman tests correlation analysis since the parametric test condition could not be provided. Statistical significance was accepted as $p<0.05$.

Results

A total of 3020 PHACO+IOL implantation were performed in our clinic between January 2014 and December 2015, and iris hook was used in 21 (0.7%) cases. The mean age of these patients was 71.9±12.1 (minimum-maximum=30-90) years. Fifteen (65%) of the patients were male and 8 (34%) were female. Regarding cataract type, 3 (13%) had mature cataract, 15 (65.2%) had nuclear cataract and 5 (21.7%) had nuclear + posterior subcapsular cataract (Figure 1). Seven (30.4%) of the patients had a pre-diagnosed glaucoma and these patients were under antiglaucoma treatment. Biomicroscopic evaluation revealed pseudoexfoliation in 10 eyes (43.5%) (Figure 2).

Systemic disease evaluation revealed hypertension in 8 patients (34.8%), diabetes mellitus in one (4.3%) and hypertension + diabetes mellitus in four (17.4%) patients. There was no history of systemic disease in 8 (43.5%) patients.

It was determined that 3 (13%) patients had capsular tension ring implantation due to insufficient zonular support. None of the patients had posterior capsule perforation and no aphakic patients were observed (Table 1).

When the recorded ophthalmologic examinations were evaluated, it was observed that mean preoperative visual acuity was 0.18±0.13 (Snellen visual acuity chart) and mean post-operative visual acuity was 0.32±0.23.

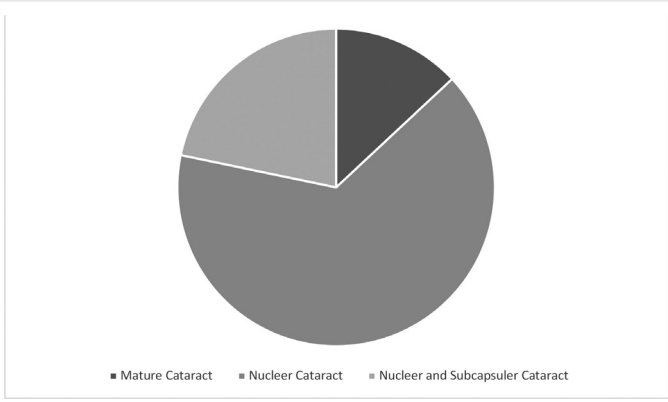

Figure 1. Cataract types in patients operated with iris hook

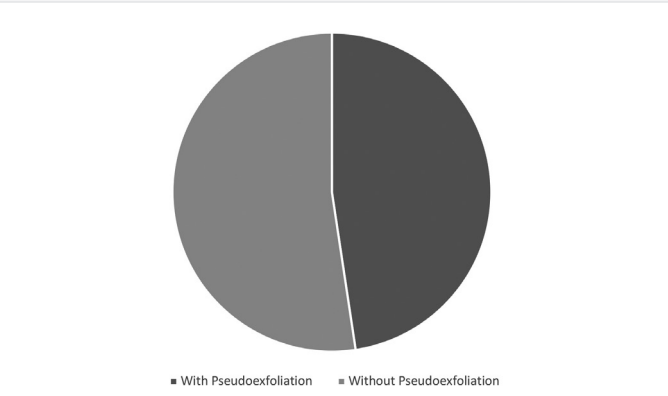

Figure 2. The rate of pseudoexfoliation in patients operated with iris hook

Table 1. Use of capsule tension ring, posterior capsule tear and aphakia development rates in cases with iris hook

Capsular tension ring (%)	3 (13.0)
Posterior capsular tear (%)	0 (0)
Aphakia n (%)	0 (0)

Tablo 2. Evaluation of preoperative and postoperative intraocular pressures and visual acuity in cases with iris hook

	Avg. ± SD (min-max)
Preoperative visual acuity	0.18±0.13 (0.05-0.4)
Postoperative visual acuity	0.32±0.23 (0.05-1)
Visual acuity change	0.15±0.25 (-0.8-0.3)
p value	0.010
Preoperative ıntraocular pressure	19.65±5.07 (14-35)
Postoperative ıntraocular pressure	17.26±5.76 (11-30)
Intraocular pressure change	2.39±6.65 (-10-22)
p value	0.078

SD: standard deviation, min: minunmum, max: maximum

The mean change in visual acuity was 0.15±0.25. Postoperative visual acuity improvement was statistically significant (p=0.010). Regarding IOP measurement with applanation tonometer, mean preoperative IOP was 19.65±5.07 and mean postoperative IOP was 17.26±5.76. The mean change in IOP was 2.39±6.65. This decrease in postoperative IOP was not statistically significant (p=0.078). IOP decreased in 16 patients (69.6%), increased in 4 patients (17.4%) and remained the same in 3 patients (13%) (Table 2).

Tablo 3. Evaluation of preoperative and postoperative intraocular pressures and visual acuity changes in the cases using iris hooks which were classified according to cataract type, capsular tension ring, pseudoexfoliation and whether there was glaucoma or not

Avg. ± SD		V change		IP change	
		p	Avg. ± SD	p	
Cataract type	Mature cataract	-0.17±0.08	0.964	4.00±15.59	0.849
	NC	-0.15±0.29		2.33±4.42	
	NC+PSC	-0.12±0.19		1.60±7.13	
Capsular tension ring	Positive	-0.07±0.15	0.564	-3.33±7.64	0.215
	Negative	-0.16±0.26		3.25±6.26	
Pseudoexfoliation	Positive	-0.10±0.16	0.400	4.90±7.36	0.201
	Negative	-0.18±0.30		0.46±5.59	
Glaucoma	Positive	-0.06±0.16	0.265	4.00±9.42	0.591
	Negative	-0.18±0.27		1.69±5.26	

V: vision acuity, IP: intraocular pressure NC: nucleer cataract, PSC: posterior subcapsular cataract, SD: standard deviation

When the patients were classified according to cataract type, capsular tension ring implantation, presence of pseudoexfoliation and glaucoma, no statistically significant difference was observed in the rates of changes in pre-operative and postoperative visual acuity and IOP values between the groups with and without these conditions (Table 3).

Discussion

Complications can occur during PHACO surgery even if the ideal ophthalmologic and surgical instruments are provided. Complications are related to the surgeon's knowledge, experience, and immediate motivation, as well as preoperative systemic and ocular preparations (2). The most important ophthalmological preparation for ease of surgery and reduction of complication rates is to provide pupil dilatation before surgery. It has been shown in many studies that the complication rates have increased in case of insufficient pupillary width during cataract surgery (3). Complications such as iris trauma, iris tissue damage due to aspiration, iridodialysis, hyphema, zonular damage, posterior capsule rupture and the replacement of cataract material into the vitreous and resulting vitreous loss can be observed in cases with narrow pupils (4). In general, this preparation with preoperative mydriatic eyedrops may not always work completely alone. Some surgeons do not do dilatation at the examination one day before the surgery to prevent pupil fatigue. Again, some surgeons do not start dilatation procedures in the early morning hours for surgeries scheduled to start later in the day.

Local anesthesia performed for the operation has an effect on pupil dilatation. Vielpau et al. (5) reported that subtenon anesthesia was a

more effective method in providing pupil dilatation compared to other types of local anesthesias. Subtenon anesthesia may be preferred in such cases.

If the pupil is not dilated sufficiently, the surgeon will not be able to see the capsule area enough for capsulorhexis; however, even though the pupil is dilated up to 4 mm, it will be difficult to select the area where the capsule is opened during capsulorhexis, as the fundus reflux is insufficient. In this case, the risk of capsulorhexis tip to go to the periphery is arisen. There is a risk that the capsulorhexis tip heading to the periphery is entangled to the posterior capsule and this may cause fragmented lens materials to fall into the vitreous during PHACO surgery. During the PHACO surgery with narrow pupils, some of the lens materials and cortex fragments may be retained by the iris and these fragments may remain in the eye as a residue. Since it is more difficult to observe the effect of the manipulations on the capsule in cases where the pupil is narrow, the development of tears in the capsule and the damage of the zonules affected by the forces acting on the capsule can be possible (6). During the surgery, the formation of tears may cause dislocation of the lens particles into the vitreous. In cases where capsule integrity deteriorates, it is difficult to implant the IOL into the capsule. In cases with zonular damage, a capsular tension ring may be required for the capsule tension to be 360 degree balanced (7). The capsular tension ring can also be used many years after surgery in order to fix the ring to the sclera and return the lens to the pupillary cavity if the implanted IOL is subluxated (8). In our study, the capsular tension ring was implanted in 3 cases (13%) due to insufficient zonular support. It has been reported in many publications that the possibility of post-operative inflammation increases in patients with narrow pupils (6). It has been described that prostaglandin release, which is defined in the mechanism of progressive myosis, a component of the floppy iris syndrome described in patients using systemic alpha-1A adrenoreceptor blocker, occurs by manipulations during iris surgery (9). Based on this information, it can be said that prostaglandin release will increase due to the increased manipulation of iris in patients with narrow pupils. Prostaglandin, which has an inflammatory effect in the development of postoperative anterior chamber reaction, therefore triggers the development of post-operative inflammation (10).

Some systemic diseases should be questioned by surgeons, which may prevent the idealization of pupil dilatation. Diabetes mellitus disease is the most important among these diseases. Because of the accumulation of glucose products in the iris, the iris dilator muscles are exposed to stronger resistance and iris dilatation becomes more difficult (11). A second important disease is benign prostatic hypertrophy. Systemic alpha-1A adrenoreceptor blockers used for the treatment of this disease are irreversibly linked to iris dilator muscles. Atrophy occurs in dilatator muscles in the long term (12). Another condition associated with the use of this drug is the development of floppy iris syndrome (13). The components of the floppy iris syndrome are a flaccid iris during the surgery, a propensity for iris to prolapse towards the area of cataract extraction, and progressive intraoperative pupil miosis despite standard procedures to prevent this. In patients using systemic alpha-1A adrenoreceptor blocker, progressive narrowing of the pupillary diameter during the operation has been associated with prostaglandin analogues, which have been secreted due to microtraumas in the narrow pupil (9,12). In these cases, there is some information that the use of non-steroidal anti-inflammatory drugs topically prior to surgery may be useful in preventing progressive miosis (14). It should be noted that patients on systemic alpha-1A adrenoreceptor blockers should not undergo iris stretching to increase intraoperative pupil diameter. Iris stretching in these patients leads to further loss of the iris tone, making it easier for the iris to loosen and prolapse. The incidence of complications is higher when iris prolapse is seen in patients with narrow pupilla. In a study conducted in our clinic, it was observed that the rate of use of iris hooks in patients using systemic alpha-1A adrenoreceptor blockers was significantly higher than in our study.

Since the ideal of pupillary dilatation is very important for the surgery, surgeons have searched for additional methods during the years when all other procedures failed to provide ideal pupil dilatation. The process of mechanically opening the environment to be operated is an important condition in every field of medical science. The use of mechanical effect and expanding tools has emerged in the light of these considerations. Pupillary expanding devices are annular devices and iris hooks. The ring-shaped devices dilate the iris more symmetrically and closer to the physiological state. The iris hooks pull the iris from the point of contact with the iris and increase the pupil width. In a study, Birchall and Spencer (15) compared the use of 5 iris hooks and 4 iris hooks. In the cases using five iris hooks, the total length of the pupilla opening was decreased by 17% compared to the cases using 4 iris hooks. Iris hooks are generally used to pull the pupil from 4 points. However, in cases where the iris is prolapsed from the main entry site, iridodialysis ocuured by attaching the iris to the PHACO end, the iris damage caused by maneuvers to insert the iris into the eye at the main entry site and decreasing the need for a corneasecular suture, a 5th iris hook can be used to stabilize the iris by subincisional implantation.

Conclusion

Iris hooks can be used to mechanically provide pupil dilatation in order to avoid the difficulties and the complications that the narrow pupil will bring to the surgeon for PHACO surgery. The use of the iris hook is a tool that can be used as a weapon against the narrow pupil because of the relatively easy surgical training. However, surgeons should always be reminded that patients may have additional ocular pathologies and that surgical complications may be encountered despite the use of this device.

Ethics Committee Approval: İstanbul Training and Research Hospital no: 1016.

Informed Consent: All patients were informed about the study and their consent was obtained.

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Clinical Results of a Violet-light Filtering Aspheric Intraocular Lens

Mor Işığı Filtre Eden Asferik Bir Göz İçi Lensinin Klinik Sonuçları

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ABSTRACT

Introduction: To evaluate the visual and refractive outcomes after implantation of a monofocal aspheric yellow chromophore intraocular lens (Eyecryl Plus ASHFY600, Biotech Vision Care Pvt. Ltd., Ahmedabad, India).

Methods: Medical records of patients, who underwent cataract surgery and had intraocular lens implantation, were retrospectively analyzed. One eye of each patient was evaluated. Subjective manifest refraction and visual acuity results at 1 week and 1, 3 and 6 months, and intraoperative and postoperative complications were analyzed.

Results: Forty-nine eyes (25 right and 24 left) of 49 patients (31 male and 18 female) were included in the study, At postoperative week 1, best corrected distance visual acuity (CDVA) was significantly increased and within an acceptable range. Uncorrected distance visual acuity (UDVA) and best CDVA were stabilized at the 1st month examination, and there was no significant difference in visual acuity between the 1st month and the 3rd and 6th month examinations. The best CDVA and UDVA at 6th months were 20/25 or better in 93% and 79% of patients, respectively. The spherical equivalent of the manifest refraction was within ± 1.00 D emmetropia in 96% of the patients. No complication occurred during or after surgery.

Conclusion: CDVA and UDVA and postoperative refractive results were similar to non-chromophore lenses. The implantation of the Eyecryl Plus ASHFY600 intraocular lens has been evaluated as effective and safe.

Keywords: Cataract surgery, emmetropia, violet light, visual acuity, yellow chromophore

ÖZ

Amaç: Sarı kromoforlu, mor ışığı kısmen filtre eden, asferik monofokal bir göz içi lensinin (Eyecryl Plus ASHFY600, Biotech Vision Care Pvt. Ltd., India) klinik sonuçlarını değerlendirmektir.

Yöntemler: Katarakt cerrahisi geçirip cerrahi sonunda Eyecryl Plus ASHFY600 model intraoküler lens implantasyonu uygulanan hastaların dosyaları retrospektif olarak incelendi. Her hastanın bir gözü çalışma kapsamında değerlendirildi. Birinci hafta, 1. ay, 3. ay ve 6. ay muayenelerindeki subjektif manifest refraksiyon ve görme keskinliği sonuçları ile intraoperatif ve postoperatif komplikasyonlar analiz edildi.

Bulgular: Kırk dokuz hastanın 49 gözü çalışma kapsamına alındı (25 sağ göz ve 24 sol göz, 31 erkek ve 18 kadın). Ameliyat sonrası 1. hafta muayenesinde en iyi düzeltilmiş uzak görme keskinliği anlamlı derecede artmış ve kabul edilebilir derecedeydi. Düzeltilmemiş ve en iyi düzeltilmiş görme keskinlikleri 1. ay muayenesinde stabilize olmuştu ve 1. ay muayenesi ile 3. ve 6. ay muayeneleri arasında görme keskinlikleri açısından anlamlı fark yoktu. Altıncı ayda düzeltilmemiş ve en iyi düzeltilmiş görme keskinlikleri hastaların sırasıyla %79 ve %93'ünde 20/25 veya daha iyiydi. Manifest refraksiyonun sferik eşdeğeri hastaların %96'sında ±1,00 D emetropi aralığındaydı. Hiçbir hastada ameliyat esnasında veya sonrasında komplikasyon gelişmedi.

Sonuç: Düzeltilmiş ve düzeltilmemiş görme keskinlikleri ve ameliyat sonrası refraktif sonuçlar kromoforsuz lenslerle benzer olarak tespit edilmiştir. Eyecryl Plus ASHFY600 göz içi lensinin implantasyonu etkili ve güvenli olarak değerlendirilmiştir.

Anahtar Kelimeler: Katarakt cerrahisi, emetropi, mor ışık, görme keskinliği, sarı kromofor

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Introduction

Ultraviolet light (below 400 nm) does not provide useful vision and can lead to retinal damage; so, ultraviolet-blocking intraocular lenses (IOL) have been dominant in cataract surgery after 1980s (1). These lenses are now standard of care and effectively block most of the radiation below 400 nm. In addition, it has been suggested that increasing the absorption spectrum of the IOL to violet or further to blue spectrum may result in better contrast sensitivity and better protection against retinal phototoxicity and associated age-related macular degeneration (AMD) (2).

Although a blue or violet-light filtering IOL may help prevent phototoxic damage that is thought to contribute to the pathogenesis of AMD, it has been suggested by some researchers that such lenses may also result in impaired scotopic vision and color perception (3). However, major differences in the absorption capacities were observed in the violet and blue light range among commercially available violet or blue light filtering IOLs depending on their material properties (4). Thus, it is not correct to think all these lenses as a homogenous subgroup. Filtering properties of each IOL and corresponding clinical effects must be tested individually.

Eyecryl Plus ASHFY600 (Biotech Vision Care Pvt. Ltd., Ahmedabad, India) is a hydrophobic acrylic, aspherical IOL that does not affect quality of scotopic vision due to its unique Natural Yellow Chromophore filters 400 nm to 440 nm of light spectrum only. There are no published studies describing clinical outcomes following implantation of this lens.

In this study, we retrospectively analyzed the visual and refractive results after implantation of Eyecryl Plus ASHFY600.

Methods

This study followed the tenets of the Declaration of Helsinki, and approval was obtained from the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (approval number: HHEAH-KAEK 2017/193). Medical records of patients, who underwent cataract surgery and had IOL implantation, were retrospectively analyzed. Patients with diabetes and patients with previous retinal or other ocular pathology were excluded from the analysis. Only one eye of each patient was included in the study.

Uncorrected and corrected visual acuity testing and routine preoperative and postoperative ocular examinations were performed at 1 week, and 1, 3, and 6 months postoperatively. At the preoperative visit, uncorrected distance visual acuity (UDVA), best corrected distance visual acuity (CDVA), manifest refraction, corneal topography, biometry, ocular health evaluation, and other standard preoperative testing were performed. At postoperative week 1, UDVA, CDVA and manifest refraction was performed. UDVA, CDVA, uncorrected near visual acuity and distance corrected near visual acuity (DCNVA) measurements were performed at the 1st, 3rd and 6th month examinations. A back-illuminated 19" LED LCD monitor chart with a decimal notation (CC-100 XP, Topcon, Tokyo, Japan) was used for UDVA and DCVA visual acuity measurements. The visual acuities were converted to logMAR for statistical analysis and converted back to Snellen/decimal notation for presentation. UNVA and DCNVA were measured using a Jaeger test chart at 40 cm.

Surgical Technique

All surgeries were performed using phacoemulsification with Infiniti Vision System (Alcon Laboratories Inc., Fort Worth, Texas, United States) and R-Evolution (Optikon 2000 SpA, Rome, Italy). After topical anesthesia (Proparakain hydrochloride 0.5%), a temporal clear corneal incision (2.75 mm) was made. A central, continuous, curvilinear capsulorhexis, approximately 5.5 mm in diameter was created. Phacoemulsification was performed using torsional or longitudinal ultrasound, followed by irrigation and aspiration of the cortex. The IOL was then implanted in the capsular bag.

Intraocular Lens

The Eyecryl Plus ASHFY600 IOL is a hydrophobic acrylic lens with a natural chromophore to filter 400 nm to 440 nm of violet-blue light spectrum only, so it does not affect the quality of scotopic vision. It has a single piece, aspheric optic and a 360-degree square edge. The optic was designed with negative spherical aberration to compensate for the cornea's positive spherical aberration. The IOL has "C" loop haptics with an overall diameter of 13.00 mm and an optic size of 6.00 mm. The Abbe value is 49 in order to reduce chromatic aberrations, and the refractive index is 1.48 (5).

Statistical Analysis

Statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL, US). Mean (± standard deviation) was reported for continuous variables. Median (minimum, maximum) was reported for near visual acuity (Jaeger). Following tests of normality using Shapiro-Wilks test, Friedman analysis and Wilcoxon signed-ranks test were used to evaluate differences in visual acuity at the follow-up visits.

Results

Forty-nine eyes (25 right and 24 left) of 49 patients (31 male and 18 female) were included in the study, The mean age of patients was 68.2 years, with a range of 40-84 years.

Visual Acuity

The visual outcomes are presented in Table 1 and Figure 1. There was a statistically significant improvement in UDVA and CDVA from 1 week to 1 month (Table 1, p=0.007). UDVA and CDVA were stabilized at the 1st month examination, and there was no significant difference between the 1st month and the 3rd and 6th month examinations (Table 1). At 6th month, median DCNVA was J3 (Table 2). The best CDVA and UDVA at 6th months were 20/25 or better in 93% and 79% of patients, respectively (Figure 1).

Refractive Outcomes

The mean spherical equivalent of the manifest refraction (SE) was significantly decreased from the preoperative examination to the 6th month examination (Table 3, p<0.001). Mean SE was stable across the 1st, 3rd, and 6th month examinations, and there were no statistically significant differences between the postoperative examinations. At 6th month, the SE was within ±0.50 D of emmetropia in 36 of 49 eyes (74%)

Table 1. Uncorrected and corrected distance visual acuities during follow-up

	Preoperative (n=49) Mean ± SD	1st week (n=49) Mean ± SD	1st month (n=49) Mean ± SD	3rd month (n=49) Mean ± SD	6th month (n=49) Mean ± SD	p*
UDVA (Decimal)	N/A	0.72±0.24	0.81±0.20	0.83±0.18	0.83±0.19	0.03**
CDVA (Decimal)	0.33±0.15	0.89±0.19	0.98±0.07	0.97±0.08	0.97±0.08	<0.00†

UDVA: uncorrected distance visual acuity, CDVA: corrected distance visual acuity, SD: standard deviation

*Global p value (overall all groups comparison)

**1st week-1st month: p=0.007; 1st week-3rd month: p=0.004; 1st week-6th month: p=0.002; 1st month-3rd month: p=0.470; 3rd month-6th month, p=0.962 (Wilcoxon signed-ranks test)

†Preoperative-1st week: p<0.001; 1st week-1st month: p<0.001; 1st week-3rd month: p=0.001; 1st week-6th month: p=0.002; 1st month-3rd month: p=0.751; 3rd month-6th month, p=0.314 (Wilcoxon signed-ranks test)

Table 2. Uncorrected and distance corrected visual acuities during follow-up

	1st month (n=49) Median (min-max)	1st month (n=49) Median (min-max)	6th month (n=49) Median (min-max)
UCNVA (Jaeger)	13 (3-14)	13 (3-14)	13 (3-14)
DCNVA (Jaeger)	3 (3-19)	3 (3-13)	3 (3-13)

UCNVA: uncorrected near visual acuity, DCNVA: distance corrected near visual acuity, min: minimum, max: maximum.

UCNVA: 1st month-3rd month: p=0.220; 1st month-6th month: p=0.180; 3rd month-6th month, p=0.750 (Wilcoxon signed-ranks test). DCNVA: 1st month-3rd month: p=0.420; 1st month-6th month: p=0.285; 3rd month-6th month, p=0.670 (Wilcoxon signed-ranks test)

Table 3. Spherical equivalent of manifest refraction during follow-up

	Preoperative (n=49) Mean ± SD	1st week (n=49) Mean ± SD	1st month (n=49) Mean ± SD	3rd month (n=49) Mean ± SD	6th month (n=49) Mean ± SD	p*
SE (Diopters)	-1.60±2.21	0.15±0.56	-0.14±0.55	-0.14±0.55	-0.15±0.57	<0.001

SE: spherical equivalent of manifest refraction, SD: standard deviation

*Global p value (overall all groups comparison)

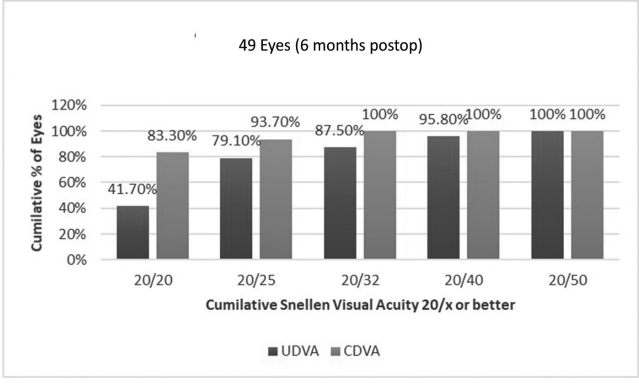

Figure 1. Cumulative monocular UDVA and CDVA at postoperative 6th month

UDVA: uncorrected distance visual acuity, CDVA: corrected distance visual acuity

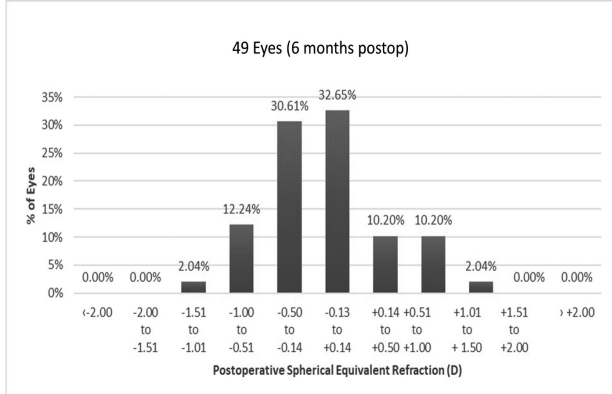

Figure 2. Predictability of refraction at 6th month examination

and within ±1.00 D in 47 of 49 eyes (96%) (Figure 2). At 6th month, the refractive cylinder was 0.50 D or less in 30 (61.22%) of 49 eyes and 1.00 D or less in 42 eyes (85.71%) (Figure 3).

Complications

No preoperative or postoperative complications were observed in our cohort. No patients lost any lines of DCVA.

Discussion

This retrospective study assessed the refractive and visual outcomes in cataract surgery patients who had hydrophobic aspheric ASHFY600 IOL implantation. The results revealed good visual acuity at postoperative 6th month. Specifically, mean UDVA, CDVA and SE improved significantly over the postoperative period to a UDVA, CDVA and SE of 0.83±0.19, 0.97±0.08, and -0.15±0.57 D at postoperative 6th month, respectively.

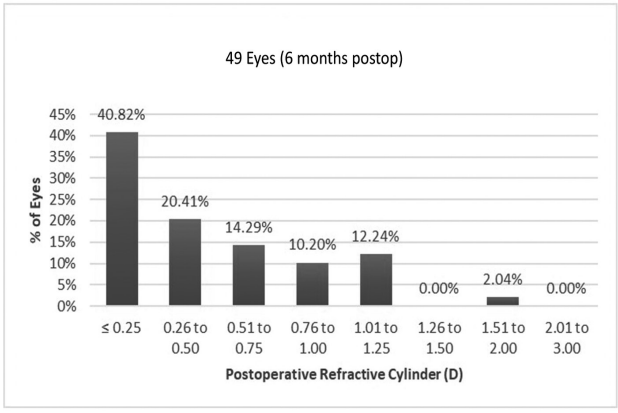

Figure 3. Residual refractive cylinder at 6th month examination

In our study 74% of the eyes were within ±0,50 D of emmetropia and 96% (47/49) were within ±1.00 D of emmetropia and UCDVA was 20/25 or better in 79% of the eyes. The Royal College of Ophthalmologists Cataract Surgery Guidelines state that a refractive outcome within ±1.00 D of the target should be achieved at ≥85% of the eyes with appropriate formula selection, optical axial length measurement, and optimization of IOL constants (6). Gale et al. (7) have set the refractive benchmark of more than 55% within ±0.50 D and Hahn et al. (8) has set the refractive benchmark of more than 80% within ±0.50 D. Our refractive results are comparable with these results and benchmarks in the literature.

In our study 7 of 49 (14%) eyes had astigmatism more than 1.00 D postoperatively and UCVA was relatively lower in these eyes. A 2.75-mm temporal clear corneal incision was used in all patients and this may have resulted in astigmatism of more than 1.00 D in the eyes which already have astigmatism close to 1.00 D. Placement of the incision site on the steep corneal meridian or implantation of a toric IOL may have reduced the amount of post-operative astigmatism and increase UCDVA.

UNVA and DCNVA were not satisfactory, however, we consider it reasonable that a monofocal IOL does not result in a satisfactory near vision. Although the IOL is monofocal, it is noteworthy that a significant number of patients had DCNVA of J3 or more. Relatively better near vision in these eyes might be due to the aspheric nature of the IOL, pseudoaccomodative mechanisms such as a small pupil size (which is frequently seen in this age group) or a combination of these factors. Also, it must be underlined that reading speed was not assessed, thus, these results might not reflect functional near vision accurately.

Retrospective nature and lack of a control group are weaknesses of our study. However, this study adequately shows the safety and efficacy of ASHFY600 IOL. Close and frequent follow-up all consecutive patients implanted with the IOL and having follow-up values of all patients are the strong sides of this study.

Conclusion

In conclusion, this preliminary study shows that ASHFY600 IOL provides excellent UDVA, CDVA and refractive stability.

Ethics Committee Approval: The approval was obtained from the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (approval number: HHEAH-KAEK 2017/193).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.Y., A.D., B.A., M.T., O.Ö., U.Ü., A.A., A.D.; Design - D.Y., A.D., B.A., M.T., O.Ö., U.Ü., A.A., A.D.; Supervision - D.Y., A.D., B.A., M.T., O.Ö., U.Ü., A.A., A.D.; Resources - A.A., A.D. B.A.; Materials - D.Y., A.D., M.T., O.Ö., U.Ü.; Data Collection and/or Processing - D.Y., A.D., M.T., O.Ö., U.Ü.; Analysis and/or Interpretation - D.Y., A.D., B.A., M.T., O.Ö., U.Ü., A.A., A.D.; Literature Search - M.T., O.Ö., U.Ü.; Writing Manuscript - D.Y., A.D., B.A., M.T., O.Ö., U.Ü., A.A., A.D.; Critical Review - D.Y., A.D., B.A., M.T., O.Ö., U.Ü., A.A., A.D.

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

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The Effect of Tibialis Anterior Tendon Transfer on Metatarsus Adductus Deformity in Children with Clubfoot

Pes Ekinovarusu Olan Çocuklarda Tibialis Anterior Tendon Transferinin Metatarsus Adduktus Deformitesine Etkisi

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ABSTRACT

Introduction: Tibialis anterior tendon transfer (TATT) is a common treatment method used in the dynamic supination of the foot due to sequelae or relapse of pes equinovarus (PEV). In this method, the TAT is transferred from its insertion on the medial cuneiform to the lateral cuneiform. Therefore, TATT surgery may have a corrective effect on metatarsus adducus deformity by creating a force vector that pushes the middle of the foot from medial to lateral. However, there is limited literature on the effect of TATT on metatarsus adductus deformity, which is one of the components of clubfoot. The aim of our study was to investigate the effect of TATT on metatarsus adductus deformity.

Methods: Sixteen feet of 11 patients who underwent TATT with the diagnosis of PEV between 2007-2015 were included in the study. Pre- and postoperative talus-1.metatarsal angle, talocalcaneal angle and 4. metatars-metaphyseal angle were measured on standing antero-posterior radiographs. The correction rate of metatarsus adductus deformity was statistically analyzed.

Results: After a mean follow-up of 26±15 months, the mean talus – 1st metatarsal angle decreased from 18.8±1 degrees to 10.9±6 degrees, the mean talocalcaneal angle from 22.5 degrees ±8.6 to 24.4±9.3 degrees and the mean 4th metatarsal-metaphyseal angle from 38±14 degrees to 27±11 degrees after TATT. While there were statistically significant radiological corrections in talus – 1st metatarsal angle and 4th metatarsal-metaphyseal angle ($p<0.05$), there was no statistically significant change in the talocalcaneal angle ($p=0.51$).

Conclusion: TATT provides radiological improvement in the metatarsus adductus deformity in children with PEV. The reason for this is that the Tibialis in PEV works as an invertor rather than dorsiflexor/evertor of the ankle. In conclusion, the need for additional surgery for metatarsus adductus deformities in patients undergoing TATT should be reviewed.

Keywords: Clubfoot, metatarsus adductus, pes equinovarus, tibialis anterior tendon transfer

ÖZ

Amaç: Pes ekinovarus (PEV) sekellerine ve nükslerine bağlı ayağın dinamik süpinasyonun tedavisinde tibialis anterior tendon transferi (TATT) oldukça sık uygulanan bir tedavi yöntemidir. Bu yöntemde TAT'nin insersyosu ayak medialinden orta hatta taşınmaktadır. Dolayısı ile tibialis anteior kasının ayak ortasını medialden laterale doğru iterek metatarsus adduktus deformitesini düzeltici yönde etki gösteren bir kuvvet vektörü oluşmaktadır. Ancak TATT'nin PEV'in komponentlerinden biri olan metatarsus adduktus deformitesi üzerine olan etkisi hakkında yeterli literatür bilgisi bulunmamaktadır. Çalışmamızın amacı TATT'nin metatarsus adduktus deformitesi üzerine olan etkisini araştırmaktır.

Yöntemler: Kliniğimiz dijital arşivinden faydalanılarak 2007-2015 yılları arasında PEV tanısı ile TATT yapılan 11 hastanın 16 ayağı çalışmaya dahil edildi. Hastaların basarak çekilmiş olan ayak anteroposterior grafileri üzerinden operasyon öncesi ve sonrası talus-1. metatars açısı, talokalkaneal açı ve 4. metatars metafizyel açı ölçümler yapılararak metatarsus adduktus deformitesinin düzelme miktarı istatiksel olarak değerlendirildi.

Bulgular: Ortalama 26±15 aylık takip sonrası tendon transferi cerrahisinden sonra talus-1. metatars açısı 18,8±1 dereceden 10,9±6 18,8±1 dereceye, talokalkaneal açı 22,5±8,6 dereceden 24,4±9,3 deceye, 4. metatars-metafizial açı ise 38±14 dereceden 27±11 dereceye geriledi. Talus-1. metatars açısı ve 4. metatars-metafizial açıda istatiktiksel olarak anlamlı radyolojik düzeltme gözlemlenirken ($p<0,05$), talokalkaneal açıda istatistiksel olarak anlamlı değişiklik gözlenmedi ($p=0,51$).

Sonuç: PEV'li çocuklarda TATT, metatarsus adduktus deformitesinde radyolojik düzelme sağlamaktadır. Bunun nedeni, PEV'de TAT'nin ayakta dorsifleksor/evertor olarak değil invertör olarak çalışmaya başlaması olarak düşünülebilir. Sonuç olarak TATT uygulanan hastalarda metatarsus adduktus deformitesi için ek cerrahi uygulaması gerekliliği yeniden gözden geçirilmelidir.

Anahtar Kelimeler: Çarpık ayak, metatarsus adduktus, pes ekinovarus, tibialis anterior tendon transferi

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Introduction

Idiopathic clubfoot deformity remains a common pediatric orthopedic problem with an incidence of 1/1000 live birth (1). Successful outcomes can be achieved by serial manipulations and casting following the principles of the Ponseti method. However, relapses can be seen up to 50% in clubfoot treatment, regardless of initial treatment outcomes and correction achieved (2). Relapse is the result of the same pathology that causes the primary deformity and is usually associated with non-compliance with the Ponseti brace protocol (3). Manipulation and re-casting are usually the initial treatments for relapses, but operative treatment may be needed for residual deformities after serial casting (4).

In our study, we hypothesized that by transferring tibialis anterior tendon (TAT) into lateral cuneiform in TAT transfer (TATT) procedure, transforms the supination vector of the TAT to a dorsiflexion vector that may gradually reduce metatarsus adductus deformity in relapsed clubfoot. The purpose of this study was to evaluate the radiologic outcomes and the reducing effects of TATT procedure on metatarsus adductus deformity in relapsed clubfoot.

Methods

After approval (approval number 08/02/2017-67) from the Institutional Review Board of Metin Sabancı Baltalimanı Osteopathic Hospital, a retrospective review of the operative logs from 2006 to 2015 was undertaken to identify all idiopathic clubfoot patients who underwent TATT procedure with at least one year follow-up. Patients who had additional congenital anomalies, neuromuscular disease, and a history of previous surgery other than percutaneous achillotomy were excluded from the study. Also patients who did not have appropriate radiographs and patients with less than one-year follow-up after surgery were excluded from study. Concomitant procedures as achilles tendon lengthening and plantar fasciotomy were noted. Because of the retrospective study design, no approval form was obtained from the patients.

Sixteen feet of 11 patients (2 girls) were identified from the medical records. All patients were initially treated for idiopathic clubfoot deformity with Ponseti method. The decision to perform TATT procedure was based on the clinical findings of dynamic supination gait, which was observed during swing and heel strike phases of gait and accompanying the dynamic heel varus deformity.

All surgeries were performed under general anesthesia and pneumatic tourniquet in supine position by one of the three authors. According to Ponseti and Smoley technique, two incisions were made on dorsal aspect of the foot (2). First incision was made longitudinally along the path of the TAT near its insertion. After dissecting TAT, the tendon was totally detached from its insertion and a Krackow stitch was placed into the distal portion of the tendon. The second incision was made over lateral cuneiform under fluoroscopic guidance. Then the tendon was pulled out and moved to the lateral side of the foot subcutaneously. Thus, the tendon remains under the retinaculum. Under fluoroscopic guidance, a drill hole, which was large enough to accommodate the tendon, was made in the middle of the lateral cuneiform. Krackow stitch was threaded into a straight needle and the needle was passed to the plantar aspect of the foot through the drill hole on lateral cuneiform. After that, needle was passed through a felt pad and then through different holes in a button to secure the tendon on the plantar aspect of the foot. Achilles tendon lengthening was performed if the passive dorsiflexion was less than 10 degrees and plantar fasciotomy was performed if needed. A long leg cast was applied keeping the foot in abduction and dorsiflexion for six weeks. Cast and button was removed after six weeks and no additional therapy or bracing was performed thereafter.

Medical records were reviewed to document the age at surgery, gender and follow-up period. Anteroposterior (AP) weight-bearing radiographs of foot and ankle were evaluated on INFINITT Healthcare Picture Archiving Communication System (INFINITT Healthcare Co., Ltd., Seoul, South Korea) by a board certified orthopedic surgeon (Figure 1). Preoperative AP radiographs of the foot and final follow-up radiographs were evaluated and measurements of talus – 1st metatarsal angle (TM_1), talocalcaneal angle (TC) and (III) 4th metatarsal – metaphyseal angle (M_4M) were made on AP radiographs of foot (Figure 1).

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences Software version 17 (SPSS, Inc., Armonk, NY, USA). Normality of the variable distribution was tested with Kolmogorov-Smirnov test. Continuous variables were displayed as means ± standard deviation. Continuous variables were compared using the paired sample t-test. p values <0.05 were considered to be statistically significant.

Results

Sixteen feet of 11 relapsed clubfoot patients were evaluated. The mean age at the time of surgery was 4.4±1.1 years. The mean follow-up time was 26±15 months. Measurements of preoperative and final follow up AP radiographs of foot are listed in Table 1.

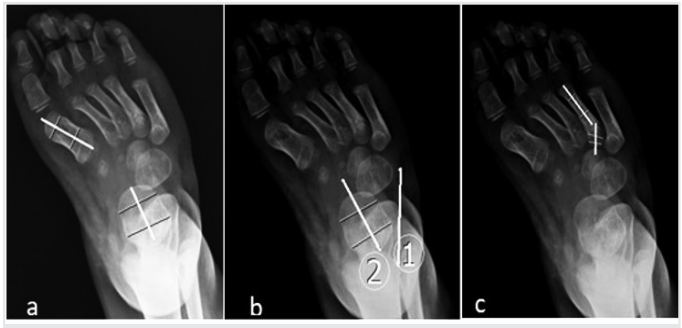

Figure 1. Measurements of (a) talus – 1st metatarsal angle (TM_1), (b) talocalcaneal angle (TC) and (c) 4th metatarsal – metaphyseal angle (M_4M) on AP radiographs of foot

Table 1. Radiographic measurement results

	Preoperative	Final follow-up	p
TM_1 angle	18.8 ±1	10.9 ±6	0.009*
TC angle	22.5±8.6	24.4±9.3	0.512
M_4M angle	38 ±14	27 ±11	0.023*

Tm_1: talus – 1st metatarsal angle, m_4m: 4th metatarsal – metaphyseal angle

The mean TM_1 angle was decreased from 18.8±1 degrees to 10.9±6 degrees with statistically significant difference ($p<0.05$). Also the mean M_4M angle was decreased from 38±14 degrees to 27±11 degrees with statistically significant difference ($p<0.05$). Changes in TC angle were not statistically significant ($p>0.05$).

Discussion

The results of the TATT procedure in the treatment of relapsed clubfoot have been investigated in various studies (2,5,6). The TATT procedure primarily improves dynamic supination gait by providing muscle balance (7). As a consequence of transferring TAT into lateral cuneiform, the cuneiforms and the cuboid are shifted more laterally than normal and that corrects and stabilizes relapsing clubfoot (2). In 1940, Garceau first described the TATT procedure in the treatment of relapsed clubfoot and reported good and excellent results in forefoot adduction correction (6). In our study, we also observed the metatarsus adductus reducing effect of TATT procedure on relapsing clubfoot.

The metatarsus adductus is evaluated by the angle between the longitudinal axis of the metatarsus and the navicular, cuboid and cuneiform bones (8). Farsetti et al. (2) presented the results of TATT procedure in relapsing clubfoot by evaluating the changes of the angles formed by the longitudinal of the navicular - the first cuneiform, the calcaneus - the fifth metatarsal, and the calcaneus - the cuboid by plain radiographs and computed tomography scans (2). After analyzing the outcomes, they observed that the foot abduction occurs after TATT procedure. They stated that the changes in angles might be due to the abducting/everting force caused by the transfer that was able to shift the cuneiforms, cuboid, and the whole forefoot more laterally. It is difficult to evaluate metatarsus adductus in the pediatric age due to insufficient ossification centers of the navicular, cuboid and cuneiform bones (8). Therefore, it is recommended to use TM_1 angle and M_4M angle on radiographs to evaluate metatarsus deformity in children (5,8). For this reason, unlike the study of Farsetti et al. (2), we evaluated different radiological measurements assessing the metatarsus adductus deformity in our study. Nevertheless, we observed that metatarsus adductus decreased after the TATT procedure.

In a long-term study that evaluates results of the TATT procedure in the treatment of relapsed clubfoot, Holt et al. (1) observed no differences in TM_1 angle with the reference group. Similarly, we observed decrease in TM_1 in our study. The changes in TC angle were not remarkable in our study. In the same study, authors observed a smaller TC angle, but they stated that TC angle noted in patients who had been treated with the TATT procedure resulted in no clinically detectable differences between the groups as demonstrated by similar outcomes measured with questionnaires (1). Therefore, we believe that the absence of significant changes in TC angle will not lead any clinical problems in future.

Kuo et al. (6) reported their outcomes of TATT procedure performed in relapsed clubfoot with an average follow-up time of 10.3 (±3.5) years (6). They evaluated the forefoot adduction with measurements of TC and TM_1 angles performed on the AP radiographs. They observed that the TM_1 angle was corrected a mean of 24.2 degrees (6). In our study, we observed that the TM_1 was corrected a mean of 7.9 degrees with statistical significance, which was relatively lower than the study of Kuo et al. (6). We think that this difference is due to our relatively short follow-up period, which was about 2 years. We believe that gradual correction of metatarsus adductus deformity will be observed and long-term results of our study will show similar correction rates with previous studies (6).

Metatarsus adductus deformity in relapsed clubfoot are also treated by osteotomies of metatarsal, cuneiform and cuboid bones (5,9,10). But these procedures may have serious complications as delayed wound healing, malunion, nonunion and shortening of the metatarsal (11). Knörr et al. (5) described a percutaneous method of correcting of severe metatarsus deformity in children. They observed 5.83 degrees correction in M_4M, which was stated to be successful. In our study, we observed 11 degrees of correction, which was higher than referral study. Therefore, we think that results of TATT procedure on M_4M changes was sufficient to reduce metatarsus adductus deformity. We think that complications related to the osteotomy procedures can be avoided by choosing TATT procedure in the treatment of metatarsus adductus in relapsed clubfoot.

Study Limitations

Our study has some limitations. Due to retrospective nature of this study, the outcome evaluation was only conducted with radiological measurements. As a limitation of this study, we were not able to provide functional assessment of the TATT. Because of our short-term results, we are unable to report the results of the TATT procedure in skeletal maturity.

Conclusion

We think that the TATT procedure provides similar results with simpler intervention compared to osteotomy procedures. Considering the complications of osteotomies in the treatment of metatarsus adductus deformity for relapsed clubfoot, we believe that surgeons should reconsider the necessity of osteotomy for metatarsus adductus deformities in patients undergoing TATT surgery.

Ethics Committee Approval: For this study, approval is taken from the Institutional Review Board of Metin Sabancı Baltalimanı Osteopathic Hospital (approval number: 08/02/2017-67).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Concept – A.İ.B., O.N.Ö.; Design – A.İ.B., E.A.; Supervision - A.İ.B., O.N.Ö.; Data Collection and/or Processing- A.K., E.A.; Literature Search – B.Ö., Y.M.D.; Writing Manuscript A.İ.B., O.N.Ö.; Critical Review – B.Ö., Y.M.D.

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

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Comparison of Infraclavicular and Supraclavicular Brachial Plexus Block in Upper Extremity Surgery

Üst Ekstremite Cerrahisinde İnfraklaviküler ve Supraklaviküler Brakiyal Pleksus Bloğunun Karşılaştırılması

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ABSTRACT

Introduction: In this study, we aimed to compare the efficacy of infraclavicular and supraclavicular brachial plexus block in patients undergoing upper extremity surgery.

Methods: After obtaining ethics committee approval, 50 patients who were between the ages of 18-80 years with an "American Society of Anesthesiologists (ASA)" score of I or II and who would undergo elective upper extremity surgery in the orthopedics and traumatology clinic were included in the study. Patients were randomly divided into two groups; 25 patients in infraclavicular block group (group I) and 25 patients in supraclavicular block group (group S). In both groups, nerves were searched using peripheral nerve stimulator and a total of 20 mL of 0.5% levobupivacaine and 20 mL 2% lidocaine were injected into the brachial plexus sheath. Demographic data, ASA scores, operative indications, time to block point, needle depth, onset of block time, operative time, duration of motor and sensory block, and onset of postoperative initial pain were recorded.

Results: There was no statistically significant difference regarding the demographic data and operative time between the patients. The time to block point, needle depth and onset of block time were significantly longer in group I than group S ($p<0.001$, for all). No significant difference was found between the groups in terms of duration of motor block and sensory block, and onset of postoperative initial pain.

Conclusion: In our study, we found that the supraclavicular block is more advantageous in terms of time to block point, needle depth and onset of block time.

Keywords: Brachial plexus block, infraclavicular, regional anesthesia, supraclavicular

ÖZ

Amaç: Çalışmamızda üst ekstremite cerrahisi uygulanacak hastalara, infraklaviküler ve supraklaviküler bölgede brakiyal pleksus blokajı uygulamalarının etkinliğinin karşılaştırılmasını amaçladık.

Yöntemler: Hastanemiz etik kurul onayı alındıktan sonra ortopedi ve travmatoloji kliniğinde üst ekstremitesinden elektif olarak ameliyat olacak, "American Society of Anesthesiologists (ASA)" I-II aralığında, yaşları 18-80 yıl arası 50 hasta çalışmaya dahil edildi. Olgular infraklaviküler blok (grup İ) ve supraklaviküler blok (grup S) olarak rastgele 25'er kişilik iki gruba ayrıldı. Grupların her ikisinde de periferik sinir stimülatörü yardımıyla ameliyat bölgesine göre iki ayrı sinir aranarak, toplamda 20 mL %0,5 levobupivakain ve 20 mL %2 lidokain brakiyal pleksus kılıf içerisine enjekte edildi. Hastaların demografik verileri, ASA skorları, ameliyat endikasyonları, blok noktasına ulaşma süreleri, iğne derinliği, blok başlama süresi, ameliyat süresi, motor ve duysal blok süresi ile ilk ağrı başlama süresi kaydedildi.

Bulgular: Olguların demografik verilerinde ve ameliyat sürelerinde istatistiksel olarak anlamlı bir fark yoktu. Blok noktasına ulaşma süresi, iğne derinliği ve blok başlama süresi grup İ'de grup S'ye göre anlamlı derecede daha uzun bulundu (hepsi için; $p<0,001$). Gruplar arasında motor blok süresi, duysal blok süresi ve ameliyat sonrası ilk ağrı başlama süresi bakımından anlamlı bir fark bulunmadı.

Sonuç: Çalışmamızda supraklaviküler bloğun infraklaviküler bloğa göre blok noktasına ulaşma süresi, iğne derinliği ve blok başlama süresi açısından daha avantajlı olduğunu tespit ettik.

Anahtar Kelimeler: Brakiyal pleksus bloğu, infraklaviküler, rejyonal anestezi, supraklaviküler

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Introduction

There are important advantages of regional anesthesia, including (a) the patient being conscious during the surgery, (b) spontaneous breathing of the patient, (c) maintaining airway reflexes, (d) analgesia in the post-operative period and (e) early mobilization of the patient (1).

Different regional anesthesia methods may be preferred to general anesthesia in upper extremity surgery (2,3). The economic and environmental approach in daily anesthesia practice as in all areas of life has been accepted by almost all of our colleagues and therefore regional anesthesia methods have been increasingly preferred for appropriate surgeries in recent years. Having an advantage of avoiding possible complications due to general anesthesia increases the frequency of use of regional anesthesia (4).

Upper extremity blocks are more common than lower extremity blocks. The brachial plexus can be blocked by interscalene, supraclavicular, infraclavicular and axillary approaches. The brachial plexus is formed by anterior primary rami of the nerves from C5 to T1. Each of these nerves exits the intervertebral foramina and extends anterolaterally and caudally. This structure, which extends in 3 trunks in the interscalen region, is divided into lateral, medial, and posterior branches, and forms 5 peripheral nerves. Because the brachial plexus is more compact in the upper levels, it is easier to block, and therefore supraclavicular and infraclavicular approaches are used more frequently (1,2,5).

Supraclavicular brachial plexus block is a popular technique for surgeries below shoulder level due to rapid onset of action and high success rate. However, complications such as vascular injection, pneumothorax, phrenic nerve palsy and Horner's syndrome are high. The most important advantages of the infraclavicular brachial plexus block are that it has fewer complications and that a catheter can be placed. However, the brachial plexus is located deeper in the infraclavicular region (6).

In our study, we aimed to compare the effectiveness of infraclavicular and supraclavicular brachial plexus blocks, which are similar approaches that provide anesthesia for the entire upper extremity in cases that will be operated for fracture and soft tissue pathology.

Methods

Patients Selection and Block

Following ethics committee approval (Bezm-i Alem Vakıf University Faculty of Medicine Hospital), patients who would undergo unilateral upper extremity surgery under elective conditions in the orthopedics and traumatology clinic were selected for the study. Fifty patients between the ages of 18-80 years with an "American Society of Anesthesiologists (ASA)" score of I or II were included in the study. Written consents were obtained from all patients.

Patients with neurological deficits, mental retardation, alcohol or drug addiction, local anesthetic substance allergy, coagulopathy, morbid obesity and pregnant women were not included in the study.

The patients included in the study were randomly divided into two groups as group I including 25 patients with infraclavicular brachial plexus block and group S including 25 patients with supraclavicular brachial plexus block.

The patients were taken to the regional anesthesia practice room inside the operating theater. Peripheral vascular access was performed with intravenous cannulae (20 G) from the dorsum of the contralateral hand and balanced electrolyte solution was given at a dose of 5-7 mL/kg/h. 0.03 mg/kg intravenous midazolam was administered to all patients as standart premedication.

Patients in group I underwent infraclavicular brachial plexus block with coracoid approach. The block was typically performed with the patient in the supine position. The arm was adducted and the elbow flexed with the palm in contact with the patient's belly. The coracoid process of the scapula was marked. Two cm below and two cm medial of the coracoid process was determined and was marked as the point of peripheral block injection (2).

Supraclavicular brachial plexus block was applied to patients in group S. The block was typically performed with the patient in the supine position with the head turned away from the side to be blocked. The arms were coupled to the body on both sides. A 2 cm thick pillow was placed under the shoulder of the block side. Thus, the lung apex was removed from the intervention region (4). The head was extended to stretch the neck muscles. The mid-point of the clavicle was marked. The lateral edge of the clavicular head of the sternocleidomastoid muscle was found. The point of injection was determined as 1-1.5 cm above the mid-point of the clavicle and 1.5-2 cm from the lateral edge of the clavicular head of the sternocleidomastoid muscle. If this point hits the jugular vein, the entrance point was moved medially or laterally (4).

In both groups, an electrocardiogram (ECG) electrode was attached to the deltoid muscle of the arm to be blocked. Skin cleansing was performed with povidone iodine and local anesthesia was performed with 2 cc 2% lidocaine. Multistimuplex® (Pajunk, Germany) was used as nerve stimulator and 21 G, 50 mm or 100 mm Stimuplex A® (B. Braun Melsungen AG, Japan) needles that are custom made for plexus anesthesia were used. The cathode pole of the nerve stimulator was connected to the conductive end of the needle, and the anode pole was connected to the ECG electrode attached to the deltoid muscle. The stimulator was initially set to 1.0 mA, 2 Hz, 0.1 mS parameters. From the marked point, 100 mm needle was inserted into the skin anthroposteriorly by forming a 90 degrees angle to the floor where the patient was lying in group I. Fifty mm needle was inserted from the marked point in group S, and the needle was advanced caudally, slightly to medially and to dorsally. Skin, subcutaneous tissue and muscles were passed and fasciculations of the muscles innervated by the brachial plexus nerves (median nerve, ulnar nerve, radial nerve, musculocutaneous nerve) were searched. The fasciculation response of one of the nerves was obtained and it was considered as a successful localization indicator that the fasciculation was shown to continue when the current was decreased to 0.4 mA. After the aspiration test, a total of 10 mL of 0.5% levobupivacaine and 10 mL 2% lidocaine were administered by repeating aspiration at every 5 mL. Similarly, 10 mL 0.5% levobupivacaine and 10 mL 2% lidocaine were administered by looking for another nerve. In each patient, two nerves out of median nerve, ulnar nerve, radial nerve and musculocutaneous nerve were located and 20 mL of local anesthetic combination was injected in each of them.

At the end of the procedure, the time to block point and the needle depth were recorded in each patient. Five minutes after the procedure, the operation area was controlled at 5-minute intervals with pinprick test and cold-hot test. The onsets of motor and sensory block times were recorded. When the block was completed, the surgery was started. Quality of anesthesia and motor block were evaluated with the Hollmen scale (Table 1). Indications of surgery, operative time and onset of postoperative initial pain were recorded. Complications were also recorded in both groups.

Statistical Analysis

SPSS for Windows 15.0 (Statistical Package for Social Sciences Inc., Chicago, IL, USA) was used to evaluate the findings of the study. In addition to descriptive statistical methods (mean, standard deviation), Student's t-test and Mann-Whitney U test was used to compare quantitative data, where appropriate. Chi-square test was used to compare qualitative data. The results were evaluated at 95% confidence interval with a significance level of $p<0.05$.

Results

There was no statistically significant difference between the groups in terms of demographic data and operative time (Table 2). The indications for surgery are given in Table 3.

The time to block point, needle depth, onset of block time, duration of motor and sensory block, and onset of postoperative initial pain are shown in Table 4.

The time to block point, needle depth and onset of block time were significantly longer in group I compared to group S ($p<0.001$, for all).

There was no significant difference between the groups in terms of duration of motor block, duration of sensory block, and onset of postoperative initial pain.

In both groups, regional anesthesia was switched to general anesthesia in one case due to insufficient block. The rate of failed block was 4% in both groups.

In our study, none of our patients had arrhythmia, bradycardia, hypotension, cardiogenic shock, central toxicity, phrenic nerve block, pneumothorax, major vascular injury, Horners syndrome and neurological damage.

Table 1. Hollmen scale

Quality of anesthesia	
0	Full sensation with pinprick
1	Weak sensation compared to other extremity
2	Recognized as light touch
3	Loss of sensation
Quality of motor block	
0	Normal motor function
1	Weak motor function compared to before block
2	Very weak motor function
3	Complete loss of motor function

Table 2. Demographic features and operative time of the groups

	Group I		Group S		p
Age	40.96±	10.69	41.96±	15.76	0.794
Height (cm)	170.16±	8.43	169.48±	7.52	0.765
Weight (kg) gender	72.28±	11.57	77.88±	13.18	0.117
(Female/male)	8/17		6/19		0.753
Operative time	70.80±	31.81	7.20±	39.11	0.852

Group I: infraclavicular brachial plexus block group, group S: supraclavicular brachial plexus block group (Data were given as n, mean ± standard deviation)

Table 3. Indications for surgery of the patients

Surgery	Grup I		Grup S	
	n	%	n	%
Wrist fracture	4	(16)	1	(4)
Phalanx fracture	3	(12)	11	(44)
Humerus fracture	3	(12)	5	(20)
Carpal tunnel syndrome	5	(20)	3	(12)
Olecranon fracture	4	(16)	2	(8)
Radius fracture	6	(24)	3	(12)

Group I: infraclavicular brachial plexus block group, group S: supraclavicular brachial plexus block group (Data were given as n, percentage)

Table 4. Time to block point, needle depth, onset of block time, duration of motor block, duration of sensory block and onset of post-operative initial pain

	Grup I		Grup S		p
Time to block point (min)	6.36±	4.18	2.52±	2.62	<0.001
Needle depth (cm)	4.74±	0.90	2.49±	0.41	<0.001
Onset of block time (min)	16.76±	0.88	15.16±	1.72	<0.001
Duration of motor block (min)	434.00±	15.55	448.80±	17.15	0.105
Duration of sensory block (min)	485.60±	18.04	502.00±	26.14	0.090
Onset of post-operative initial pain (min)	538.80±	23.15	563.20±	29.40	0.112

Group I: infraclavicular brachial plexus block group, group S: supraclavicular brachial plexus block group (Data were given as n, mean ± standard deviation), min: minimum

Discussion

The advantage of avoiding possible complications due to general anesthesia increases the frequency of application of regional anesthesia. It should be remembered that along with the problems that will be caused by the use of multiple drugs, which are mandatory for general anesthesia applications, we could protect the world we live in from fluoride gas wastes to be discharged into the atmosphere (4).

If adequate analgesia and optimum surgical conditions are achieved, performing any intervention under regional anesthesia is considered to be a more reliable method than general anesthesia (5).

Schulz-Stubner (7) argue that brachial plexus block is an effective and safe method for anesthesia or analgesia in hand and upper extremity surgery. In our study, we similarly found that the brachial plexus block was safe and effective with both approaches.

Considering the fact that an important part of hand surgery interventions are constituted by urgent and satiated patients, it is possible to avoid the side effects of general anesthesia by applying brachial plexus block to these patients.

In a study of Hadzic et al. (8), general anesthesia and infraclavicular block were compared in outpatient hand surgery attempts, and it was found that analgesia score was better with infraclavicular block, that there was no need for additional analgesia, and that it provided earlier ambulation and it was superior in terms of adverse effects.

Rodriguez et al. (9) suggested that two-nerve injection technique increased the success rate in infraclavicular brachial plexus block. In their study with 60 patients, they found that double injection using nerve stimulator was more successful than single injection. In our study, we used double injection in both infraclavicular and supraclavicular technique.

Pneumothorax may occur at a rate of 0.6 to 5% in the supraclavicular block (10). Horner syndrome, phrenic nerve block and hematoma due to injury of the major vessels can also be seen. Reversible diaphragmatic paresis of the intervened side at a rate of 28% to 80% can be seen with this technique (10,11). For these reasons, the application of supraclavicular technique may cause various disadvantages especially in outpatients (10-12). None of our patients developed respiratory distress during and after surgery. Horner's syndrome, pneumothorax, nerve damage and hematoma were not seen in any of our patients.

In a study conducted in 48 volunteer men and women, Neuburger et al. (13) measured the distance of the block needle to the pleura with magnetic resonance imaging in vertical infraclavicular block and found a mean of 5.3 cm (3.1-8.7 cm). Therefore, they showed that the infraclavicular technique is reliable against the risk of pneumothorax. In our study, the mean of needle depth was 4.74 cm in the infraclavicular group and 2.49 cm in the supraclavicular group. Although none of our patients developed respiratory distress, the possibility of pneumothorax development was considered and the chest radiographs were obtained at the 6th hour postoperatively. No pneumothorax was observed in any of our patients.

Cox et al. (14) reported a significant reduction in the incidence of systemic toxicity with local anesthetics from 0.2% to 0.01% over the last thirty years. In addition, they stated that although the incidence of systemic toxicity in peripheral nerve blocks was highest with 7.5 per ten thousand, the neural damage rate was lowest with 1.9 per ten thousand. None of our patients developed systemic toxicity and neural damage.

De Jose Maria B et al. (15) performed a study in 80 children, aged between 5 and 15 years, and compared supraclavicular and infraclavicular brachial plexus block. Similar to our study, he found that the supraclavicular technique was performed in a shorter time and could be preferred to infraclavicular technique.

Conclusion

Brachial plexus block with infraclavicular and supraclavicular approach is safe and effective in upper extremity surgery. In our study, we found that the supraclavicular block is more advantageous in terms of time to block point, needle depth, and onset of block time.

Ethics Committee Approval: The approval was obtained from Bezm-i Alem Vakıf University Faculty of Medicine Hospital.

Informed Consent: Written consents were obtained from all patients.

Peer-review: Externally peer-reviewed.

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

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Drug-Eluting Balloon Angioplasty for Complex Femoropopliteal Lesions in Patients with End-Stage Renal Disease

Son Dönem Böbrek Yetersizliği Hastalarında Kompleks Femoropopliteal Lezyonların İlaç Salınımlı Balon Anjiyoplasti ile Açılması

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ABSTRACT

Introduction: The aim of this study was to investigate the safety and efficacy of drug-elicited balloon (DEB) use in the interventional treatment of patients with end-stage renal disease (ESRD) and complex femoropopliteal artery lesions.

Methods: A retrospective chart review identified 30 ESRD patients who were treated for symptomatic peripheral artery disease with DEB angioplasty between September 2012 and February 2016. The inclusion criteria were having Rutherford class 2 to 6 symptoms and a critical stenosis or occlusion of the femoropopliteal artery. While restenosis or reocclusion was the primary end point, major or minor amputation was the secondary end point.

Results: A total of 36 diabetic patients with complex femoropopliteal lesions who underwent endovascular therapy with DEB were identified. Four patients were lost during follow-up and 30 patients were included in the study. The mean lesion length was 114.6±27.8 mm. Primary patency was 73.1% and the secondary end point was 10.7% at 1-year. After a mean follow-up of 16.0±5.0 months, all-cause mortality was 7.1% (n=2). Ankle-brachial index increased from 0.42±0.04 to 0.88±0.05 postoperatively.

Conclusion: DEB angioplasty is efficient and safe even in long and calcified obstructive lesions including the distal superficial femoral and popliteal artery in patients with ESRD.

Keywords: Balloon angioplasty, drug-eluting balloon, end-stage renal disease, peripheral interventions

ÖZ

Amaç: Bu çalışmada son dönem böbrek yetersizliği (ESRD) ve kompleks femoropopliteal arter lezyona sahip hastaların girişimsel tedavisinde ilaç salınımlı balon (DEB) kullanımının güvenilirliği ve etkinliğini araştırmaktadır.

Yöntemler: Kabul edilme kriterleri, Rutherford sınıf 2 veya üstü semptoma sahip olmak ile birlikte hastalarda femoropopliteal arterde kritik darlık veya tıkanıklık olması idi. Hedef damar tıkanıklığı veya daralması primer sonlanma iken majör ve minör amptütasyon sekonder sonlanım olarak kabul edildi.

Bulgular: Eylül 2012 ve Şubat 2016 tarihleri arasında, diyabetik ve kompleks femoropopliteal lezyonu olan ve girişimsel tedavide DEB kullanılmış 36 hasta tanımlandı. Dört hasta takibi bıraktığından dolayı 30 hasta ile devam edildi. Ortalama lezyon uzunluğu 114,6±27,8 mm idi. On iki ay sonunda primer açık kalım %73,1 sekonder sonlanım %10,7 gözlendi. Ortalama 16,0±5,0 aylık takip sonrası tüm sebeplere bağlı mortalite %7,1 olarak gözlendi (n=2). Ayak bileği brakial indeksi operasyon öncesi 0,42±0,04'den operasyon sonrası 0,88±0,05'e yükseldi.

Sonuç: ESRD ile birlikte uzun kalsifik ve distal yüzeyel femoral ve popliteal darlığı olan hastalarda dahi girişimsel tedavisinde DEB kullanımı etkilidir.

Anahtar Kelimeler: Balon anjiyoplasti, ilaç kaplı balon, son dönem böbrek yetersizliği, periferik girişim

Introduction

Peripheral arterial disease (PAD) is more common in patients with end-stage renal disease (ESRD) undergoing hemodialysis compared to the general population. By-pass surgery is mostly not suitable since most patients with ESRD have multiple comorbidities with distal occlusions (1). Endovascular treatment (EVT) is the preferred method of revascularization in patients with femoropopliteal lesions. Percutaneous transluminal angioplasty (PTA) is mostly preferred for revascularization of femoropopliteal disease due to its relatively low risk. However, the results of balloon angioplasty alone for the complex femoropopliteal disease have been disappointing (2,3). The possibility of treating superficial femoral artery obstruction and maintaining patency rates has dramatically increased because of further device and technique

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development in recent years (4). Recently, drug-eluting balloon (DEB) angioplasty has been introduced to reduce femoropopliteal restenosis compared to plain old balloon (POB) angioplasty. Therefore, we analyzed our experiences with 30 femoropopliteal DEB angioplasties in ESRD patients.

Methods

Patient Population

This study was a retrospective single-center study of 34 ESRD patients (hemodialysis patients, four patients lost to follow up leaving 30 patients) with femoropopliteal arterial disease and life-style-limiting claudication who underwent DEB angioplasty between September 2012 and February 2016. The presence of Rutherford Becker class 2 or greater (Fontaine IIB) symptoms and femoropopliteal critical lesions were the inclusion criteria for our study. Mean age was 58.4±6.2 years, and 55% of patients were men. Hypertension (83.3%) and diabetes (66.7%) were the most common risk factors in this patient cohort. Baseline characteristics are summarized in Table 1.

The present study complies with the principles outlined in the Declaration of Helsinki and was approved by the Emsey Hospital Ethics Committee (no: AEK 17/009) and consent was obtained from all patients for participation in the study.

Procedures

Arterial access was obtained by antegrade puncture in 24 patients and contralateral femoral puncture in 4 patients. In 2 patients, retrograde popliteal approach was preferred because of failed antegrade approach. Duplex ultrasonography (USG) and digital subtraction angiography were used for evaluation of infra-inguinal vessel calcifications. Ankle-brachial index (ABI) was measured before and after the intervention.

Intravenous heparin (100 IU/kg) was given after diagnostic angiography was performed (Figure 1A-C, 2A, 2B). Atherectomy was preferred by operator's choice in severely calcified six lesions with suitable vessel diameter. We used a support catheter with hydrophilic guide wire for chronic total occlusions. All lesions were pre-dilated before treatment with DEB angioplasty (3 minutes inflation time, 4-7 mm 20-120 mm). The ratio of DEB to vessel diameter was planned to be 1:1. The overlap zone was more than 10 mm if multiple balloons were used per lesion. Another dilation of up to 3 minutes was performed if flow-limiting dissection or residual stenosis of more than 50% was seen. A self-expandable stent was deployed when there was flow-limiting dissection or >50% residual stenosis after DEB angioplasty. A completion angiogram concluded the procedure (Figure 2C, 3A, 3B). Patients with additional below the knee lesions were treated with DEB angioplasty (n=5). Arterial access site was managed with digital pressure. Procedural details are summarized in Table 2. Proper medication for risk factors (coronary artery disease, hypertension, and hyperlipidemia) was given with dual antiplatelet therapy (DAPT) (3 months with aspirin 100 mg + Clopidogrel 75 mg then with aspirin alone). At each follow-up visit, a duplex USG of the treated femoropopliteal site (peak systolic velocity ratio 2.5 and >50% decrease in vessel diameter was an angiography indication) and additional peripheral angiography was performed when indicated.

Table 1. Baseline characteristics

Variable		n=30
		n (%)
Age, years	Mean ± SD	57.4±6.1
Gender	Male	19 (63)
	Female	11 (37)
Diabetes mellitus		21 (70.0)
Hypertension		26 (86.7)
Hypercholesterolemia		15 (50.0)
Coronary artery disease		22 (73.3)
Cerebrovascular disease		1 (3.3)
Congestive heart failure		4 (15.9)
Current smoker		18 (60)

SD: standard deviation

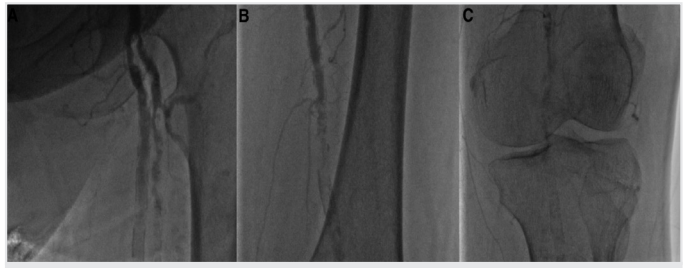

Figure 1. Preinterventional angiogram of superficial femoral artery with critical osteal stenosis and severe calcification (A). Femoropopliteal artery with critical stenosis and severe calcification (B) and popliteal artery occlusion (C)

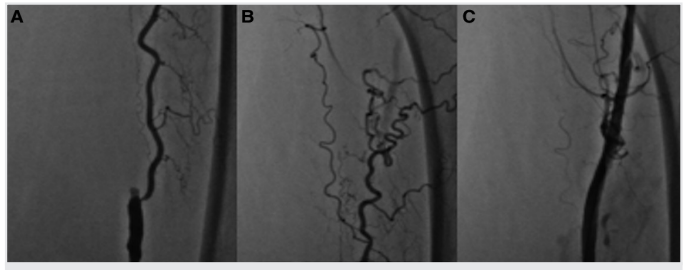

Figure 2. Superficial femoral artery chronic total occlusion (A). Popliteal artery is barely visible with collaterals (B). Superficial femoral artery after intervention (C)

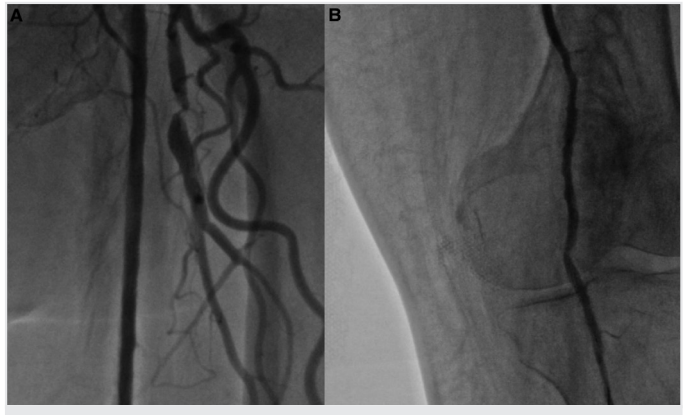

Figure 3. Superficial femoral artery after intervention (A). Popliteal artery after intervention (B)

Table 2. Procedural details

Variable		n=30
		n (%)
Mean length, mm	Mean ± SD	135.56±46.02
Total occlusion		11 (36.7)
Atherectomy performed		6 (20.0)
Severe calcification		14 (46.7)
TASC	A	4 (13.3)
	B	11 (36.7)
	C	10 (33.3)
	D	5 (16.7)
Lesion type	De novo	25 (83.3)
	Restenosis	3 (10.0)
	In-stent stenosis	2 (6.7)
BTK lesion that needed intervention		5 (16.7)
Multiple DEB		16 (53.3)

TASC: the Trans-Atlantic Inter-Society Consensus document on management of peripheral arterial disease
BTK: below the knee, DEB: drug eluting balloon, SD: standard deviation

Table 3. Clinical outcomes, 12 months

Variable	n (%)
Primary endpoint	19 (73.1)
All-cause mortality	2 (6.7)
Minor amputation	2 (7.7)
Major amputation	1 (3.8)

Definitions

Technical success was defined as restoration of straight line of blood flow to the foot with a residual stenosis less than 30%. Restenosis is defined as >%50 lesion. Major amputation was defined as limb loss above the ankle, whereas minor amputation referred to below the ankle amputation or removal of more distal parts of the lower extremity.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for the statistical analysis. Data were reported as mean, standard deviation, median, frequency, and ratio. Wilcoxon signed-ranks test was used to test the difference between preop and postop values. The results were evaluated in 95% confidence interval and at a significance level of $p<0.05$.

Results

Thirty ESRD patients (hemodialysis patients, four patients were lost during follow-up) who underwent EVT with DEB angioplasty for femoropopliteal lesions were enrolled. The mean follow-up time was 16.0 months. The technical success rate was 93.3%. Procedural details are summarized in Table 2. Stent implantation was needed in 2 patients because of flow limiting dissection. Two patients died due to acute myocardial infarction (10th, 11th month). These four patients were excluded from the primary and secondary end points. Seven patients with restenosis and reocclusion (73.1% patency in 26 patients, >%50 at narrowest point) were diagnosed by clinical investigation and duplex USG (Table 3). Peripheral angiography was performed in these cases after diagnosis. These patients were revascularized with EVT where bailout stent was not needed in any of them. Three amputations involving three patients were seen in this patient cohort (two minor and one major). Minor extravasation occurred when crossing a total occlusion with guide-wire in two patients. Obviously these extravasations were not seen after normal treatment protocol with balloon angioplasty. Access related hematoma occurred in three patients that resolved with manual digital pressure. The mean baseline ABI increased after the intervention, which demonstrated a hemodynamic success, and a clinical improvement with significant decrease in rutherford becker classification was seen in the patients (0.43±0.06, $p<0.001$) (Tables 4, 5).

Table 4. Rutherford becker classification pre-post (12 months) treatment

		n (%)
Preop RBC	0.1	0 (0)
	2	5 (16.7)
	3	17 (56.7)
	4	5 (16.7)
	5	2 (6.7)
	6	1 (3.3)
Mean ± SD		3.33±0.60
12 months follow up RBC	0	0 (0)
	1	3 (11.5)
	2	20 (77)
	3	3 (11.5)
Mean ± SD		2±0.49
		p<0.01

RBC: rutherford becker classification, SD: standard deviation *p<0.01

Table 5. Change in ankle brachial index

ABI	n=30
	Mean ± SD
Before procedure	0.45±0.04
After procedure	0.88±0.05
	p 0.001**
Difference	0.43±0.06

**p<0,01 ABI: ankle brachial index, SD: standard deviation

Discussion

ESRD is a strong determinant of atherosclerotic vascular disease and is associated with a high incidence of cardiovascular diseases. EVT of infra-inguinal lesions in ESRD patients remains a controversial issue; thus we examined the clinical and procedural outcomes of DEB angioplasty of femoropopliteal lesions in this patient cohort.

ESRD patients on dialysis with DM, frequently have calcific, long and diffuse arteriosclerotic disease in the femoropopliteal site. Therefore, these patients are often not suitable for surgery due to other comorbidities and advanced age, thus making EVT preferable. However, primary patency rate of POB angioplasty is low in multiple studies compared to DEB (3,5-8). Therefore we preferred DEB angioplasty for the treatment of femoropopliteal lesions in this study.

Nitinol or drug-eluting stents have provided better results compared to standard PTA for femoropopliteal disease, but they change the structure of the vessel and it still carries a relevant risk of restenosis, especially in long and complex lesions commonly seen in ESRD patients (5,6). Another important issue is that in-stent restenosis is more difficult to treat than restenosis in non-stented segments. Studies with DEB angioplasty have patency outcomes at least similar to stents but without leaving permanent metallic implants (9-11). Due to these facts, we preferred DEB angioplasty instead of stent deployment in our study.

EVT for PAD in ESRD patients may be technically hard because of the calcified nature of very tight stenosis or mostly occlusion, which makes the crossing by a balloon catheter and even with guide wire problematic. Through mostly antegrade femoral approach (80.0%) with using a support catheter and a hydrophilic guide wire, we crossed the lesions with a high technical success rate of 93.3% in this setting of patients.

Revascularization for peripheral arterial lesions in patients with ESRD has been controversial because of the low rates of limb preservation and short life expectancy and increased risk of dissection in this patient cohort with severe calcification (12-14). EVT, particularly with DEB angioplasty is costly. Although it seemed expensive, in a cost-effectiveness study, it appears to be better compared to local wound care alone, primary amputation or even surgical approach, especially in patients with non-healing foot wounds. (15). A recent analysis came to the conclusion that DEB angioplasty offers the lowest budget impact in the treatment of femoropopliteal lesions (16).

An alternative concept to potentially improve DEB efficacy in lesions with severe calcification (instead of pre-dilatation with a standard balloon) is to combine DEB angioplasty with directional atherectomy. After reducing plaque burden, paclitaxel can potentially inhibit cell proliferation more effectively. The DEFINITIVE AR, which is a pilot study, suggest that there is a benefit with adjuvant directional atherectomy in patients with long and calcified femoropopliteal lesions prior to using a DEB in comparison to the DEB angioplasty alone. However, the study was not sufficiently powered to detect differences in clinical outcomes. In our study, there was only one patient who needed re-intervention out of 6 patients treated with atherectomy before DEB angioplasty (16.7%). Studies with larger population are needed to evaluate the efficacy, safety, and cost-effectiveness of atherectomy as an adjuvant therapy in this patient cohort.

There is still no consensus about the duration of DAPT following DEB angioplasty (ranging from 1 to 3 months or more in different studies) (17,18). We administered a 3-month DAPT in our study. Such duration appeared safe and no acute thrombosis or major bleeding was observed during the follow-up period.

Study Limitations

This study has some limitations. First, it was a retrospective study with relatively small patient population lacking a control group. Second, we could not perform follow-up angiography in all patients and third, toe brachial index was not measured although it is needed for reliable diagnosis for PAD in this patient group (19).

Conclusion

DEB seems efficient and safe in the treatment of complex femoropopliteal lesions in ESRD patients. Larger and longer studies are needed to evaluate the efficacy, safety and cost-effectiveness of DEB angioplasty in this patient cohort.

Ethics Committee Approval: The present study complies with the principles outlined in the Declaration of Helsinki and was approved by the Emsey Hospital Ethics Committee.

Informed Consent: Consent was obtained from all patients for participation in the study.

Peer-review: Externally and internally peer-reviewed.

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Changing Trends in Radiotherapy for Glioblastoma Multiforme and Effects on Normal Tissue Doses

Glioblastoma Multiforme Radyoterapisinde Değişen Eğilimler ve Normal Doku Dozlarina Etkileri

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ABSTRACT

Introduction: The aim of the study is to reveal the changing trends in radiotherapy (RT) for glioblastoma multiforme (GBM) from past to present and to show the changes in organs at risk (OARs) doses.

Methods: We re-planned 10 GBM patients who were previously irradiated. Rigid fusion was performed through pre- and postoperative magnetic resonance imaging (MRI) and simulation computed tomography, and 9 separate volumes were created. While volumes varied from whole brain RT (WBRT) to postoperative two-phase irradiation, RT application ranged from 2-dimensional Co-60 treatment to 3-dimensional volumetric modulated arc therapy (VMAT). OARs were contoured, and doses were noted. A 3 dimensional-conformal RT (3D-CRT) plan of the volume created by preoperative MRI was compared to 3D-CRT and VMAT plans generated by postoperative MRI. Statistical analysis was performed using Paired sample t-test.

Results: During the time of WBRT, normal brain tissue was receiving 45-60 Gy. Through VMAT, the median brain-planning target volume (PTV) D_{mean} decreased to 35 Gy. According to both PTV-Radiation Therapy Oncology Group $(RTOG)_{preop}$ and PTV-$RTOG_{preop}$ 3D-CRT plannings, there was no difference in all OARs doses between plans, including brain-PTV initial volume D_{mean} and brain-PTV boost D_{mean} doses. Significantly lower OARs doses were obtained from 3D-CRT plans based on both PTV-$RTOG_{preop}$ and PTV-$RTOG_{postop}$ volumes with the VMAT planning.

Conclusion: With changing trends in RT for GBM, there has been a significant decrease in treatment volumes and normal tissue doses. According to the postoperative volume definition of RTOG, lower normal tissue doses are obtained from VMAT plans, compared to the conformal treatment plans.

Keywords: 3D conformal radiotherapy, intensity modulated radiotherapy, glioblastoma multiforme, volumetric modulated arc therapy

ÖZ

Amaç: Çalışmanın amacı glioblastoma multiforme (GBM) radyoterapisindeki (RT) geçmişten günümüze değişen eğilimlerin ortaya konulması ve risk altındaki organ dozlarındaki değişimin gösterilmesidir.

Yöntemler: GBM tanısı ile postopereatif temozolamid ve RT ile tedavi edilen 10 hastanın simülasyon bilgisayarlı tomografi görüntüleri retrospektif olarak incelenerek pre- ve postoperatif manyetik rezonans görüntüleri (MRG) ile rjiid füzyon yapıldı ve 9 ayrı volüm oluşturuldu. Volümler total kranyum ışınlamadan postoperatif iki fazlı ışınlamaya değişkenlik gösterirken, RT uygulaması 2-boyutlu (2B) Co-60 tedavisinden 3-boyutlu (3B) volumetrik ark tedaviye (VMAT) değişiyordu. Risk altındaki organlar (organs at risk - OAR) konturlandı. Beyin-hedef hacmi planlama (PTV) D_{mean}, beyin sapı D_{max}, göz D_{max} ipsilateral/kontralateral, kiazma D_{max}, koklea D_{mean} ipsilateal/kontralateral, lakrimal gland D_{max} ipsilateral/konrtalateral, lens D_{max} ipsilateral/kontralateral, pituiter gland D_{max} dozları kaydedildi. 7, 8, 9. planlar (preop MRG'den oluşturulan volümün 3B-konformal RT-3B-KRT planı ile postop MRG'den oluşturulan 3B-KRT ve VMAT planları) karşılaştırıldı. Paired sample t-testi ile istatistiksel analiz yapıldı.

Bulgular: Total kranyum RT uygulandığı dönemlerde normal beyin dokusunun hepsi 45-60 Gy alırken VMAT ile beyin-PTV D_{mean} medyan 35 Gy'e düşmüştür. Aynı zamanda göz ve lensler dışında risk altındaki organlar verilen tüm dozu alarak 60 Gy uygulanan gruplarda doz sınırlamaları aşılmıştır. Hem PTV-Radyasyon Terapisi Onkoloji Grubu $(RTOG)_{preop}$ hem de PTV-$RTOG_{postop}$ 3D-CRT planına göre beyin-PTVinitial volüm D_{mean} ve beyin-PTV_{boost} D_{mean} dozları dahil olmak üzere tüm OAR dozlarında iki plan arasında istatistiksel anlamlı fark yoktu. VMAT planı ile hem PTV-$RTOG_{preop}$ hem de PTV $RTOG_{postop}$ volümlerine göre yapılan 3D-CRT planlarından istatistiksel anlamlı daha düşük OAR dozları elde edildi.

Sonuç: Tarihsel süreçte ışınlanan volüm ve normal doku dozlarında belirgin azalma olmuştur. RTOG'nin postoperatif volüm tanımına göre konformal ve VMAT planları karşılaştırıldığında VMAT planlamada daha düşük normal doku dozları elde edilmektedir.

Anahtar Kelimeler: 3D konformal radyoterapi, yoğunluk ayarlı radyoterapi, glioblastoma multiforme, volümetrik ark tedavisi

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Introduction

Glioblastoma multiforme (GBM) is the most deadly and frequent primary brain malignancy in adults (1). Since temozolomide was added to adjuvant radiotherapy (RT), the survival rate has improved (2). Standard treatment of GBM includes surgery, RT, and chemotherapy (3-5). RT has been routinely used in the treatment of brain tumors since the 1940s (6). The use of three-dimensional conformal radiation therapy (3D-CRT) is regarded as the standard treatment (7,8). Intensity-modulated radiation therapy (IMRT) is accepted as an alternative to 3D-CRT and it can minimize treatment-associated side effects (9). The use of proton RT is also increasing (10). Initially, RT for GBM began as whole brain irradiation. The techniques in RT have improved with the development of different doses and applications and with the determination of organs at risk (OARs) and dose limits. The aim of our study was to reveal the changing trends in RT for GBM from past to present and to show the changes in OARs doses.

Methods

Simulation computerized tomography (simCT) and cranial magnetic resonance imaging (MRI) scans of 10 patients, who were treated with adjuvant temozolomide following concomitant temozolomide and RT after surgical resection, were selected from patient database of İstanbul University Institute of Oncology Hospital. After the selection, previous basic scans of the patients were called back to the RT simulation station. No patient actually joined to the simulation process and neither names nor any identifying information related to the study population were used. Due to the retrospective and simulative nature of our study, no informed consent and no ethical approval were obtained. However, the study was performed in compliance with the Declaration of Helsinki. A rigid fusion was performed through MIM software ver. 6.5 (MIM Software Inc., Ohio, USA) using simCT images, pre- and postoperative contrast-enhanced T1 and T2/flair sequences MR images. OARs and dose constraints were determined according to the European Organization for Research and Treatment of Cancer-Advisory Committee on Radiation Oncology Practice guide and the study of Scoccianti et al. (11,12). Optic chiasm, bilateral eyes, bilateral lenses, brainstem, bilateral cochlea, bilateral lacrimal glands, and pituitary gland were determined as the OARs. Brain-planning target volume (PTV) volume was generated through PTV excluded from brain tissue. In two-dimensional planning (2D), fields were manually created using multi-leaf collimators. Two-phase target volumes yielded from pre-operative MR images were determined according to the Radiation Therapy Oncology Group (RTOG) 9710 protocol. The $RTOG_{preop}$ phase 1 volume contained the volume of contrasted tumor with peripheral edema on preoperative MRI scan plus a 2 cm extra-margin. The $RTOG_{preop}$ boost volume covered the contrasted lesion (without edema) on the preoperative MRI scan plus a 2.5 cm extra-margin. The $RTOG_{postop}$ phase 1 volume included the volume of the postoperative cavity and +/- residual tumor in contrast enhanced T1-weighted MRI scans and edema in the postoperative T2-weighted MRI scans plus a 2 cm margin. The $RTOG_{postop}$ boost volume included the resection cavity +/- residual tumor in contrast enhanced T1-weighted MRI scans plus a 2 cm margin. 2D treatment planning was used to create plans 1 to 6. 3D planning was made in plans 7 to 9. Plans 7 and 8 were performed through 3D-CRT, whereas plan-9 was generated through VMAT. The XIO v4.60 treatment planning system was used for all plans except the VMAT plan. The Eclipse V8.9 treatment planning system (Varian Medical Systems, Palo Alto, CA, USA) was used for VMAT. Treatment plans were prepared with 3 full rotation VMAT fields with different collimator angles. VMAT doses were prescribed according to ICRU 83.

Co-60 was used for generating plans 1 and 2, and 6 MV was used for the remaining plans. Plan 1: Whole brain RT (WBRT), Co-60 energy, total dose 45 Gy in 25 fractions (fr); Plan 2: WBRT, Co-60 energy, total dose 60 Gy in 30 fr; Plan 3: WBRT, 6 MV energy, total dose 45 Gy in 25 fr; Plan 4: WBRT, 6 MV energy, total dose 60 Gy in 30 fr; Plan 5: WBRT in phase 1 followed by tumor bed boost in phase 2, 6 MV energy, phase 1 dose 40 Gy in 20 fr plus boost dose 20 Gy in 10 fr; Plan 6: PTV-$RTOG_{preop}$ phase 1, 6 MV energy, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr; Plan 7: PTV-$RTOG_{preop}$ phase 1, 6 MV energy, 3D-CRT, phase 1 dose 46 Gy in 23 fr boost dose 14 Gy in 7 fr, Plan 8: PTV-$RTOG_{postop}$ phase 1, 6 MV energy, 3D-CRT, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr; Plan 9: PTV-$RTOG_{postop}$ phase 1, 6 MV energy, VMAT, 46Gy in 23 fr plus boost 14 Gy in 7 fr. Brain-PTV D_{mean}, brainstem D_{max}, bilateral eye D_{max}, optic chiasm D_{max}, bilateral cochlea D_{mean}, bilateral lacrimal gland D_{max}, bilateral lens D_{max}, and pituitary gland D_{max} doses were recorded. The plans 7, 8 and 9 were compared.

Statistical Analysis

SPSS software version 20 was used for the statistical analysis (IBM Corp., Armonk, NY, USA) using the paired sample t-test. A p value <0.05 was considered statistically significant.

Results

Through VMAT, the median brain-PTV D_{mean} decreased to 35 Gy while all normal brain tissues received 45-60 Gy. At the same time, the OARs, except for the eye and the lenses, received overdoses in groups given 60 Gy. In Figure 1, the changes in four parameters of 9 plans are presented. Because both PTV-$RTOG_{preop}$ and PTV-$RTOG_{postop}$ had large treatment volumes, 3D-CRT planning was possible using two opposing coplanar fields. There was no statistically significant difference between the two plans for all OARs doses, including brain-PTV phase 1 D_{mean} and brain-PTVboost D_{mean} doses. In addition, optic chiasm D_{max}, bilateral cochlea D_{mean}, brainstem D_{max}, pituitary gland D_{max}, bilateral eye D_{max} median dose values were over the dose constraints. The PTV-$RTOG_{preop}$ 3D-CRT, PTV-$RTOG_{postop}$ VMAT plans were compared; doses of brain-PTV phase 1 D_{mean} (median 41.7 Gy vs. 24.1 Gy, p=0.001), brain-PTV boost D_{mean} (median 44 Gy vs 34.4 Gy, p=0.021), chiasm D_{max} (62.1 Gy vs. 52.9 Gy, p=0.030), contralateral cochlear D_{mean} (median 59 Gy vs. 13.8 Gy, p=0.002), ipsilateral cochlear D_{mean} (median 61 Gy vs. 28.5 Gy, p=0.006) and contralateral eye D_{max} (median 36.2 Gy vs. 23.2 Gy, p=0.022) were statistically lower in the $RTOG_{postop}$ VMAT plan. The lens D_{max} doses were within dose constraints except for one value in both groups, although the $RTOG_{postop}$ VMAT dose was higher in the lens D_{max} dose (median 3.9 Gy vs. 7.9 Gy, p=0.005). The PTV-$RTOG_{postop}$ 3D-CRT plan was compared to PTV-$RTOG_{postop}$ VMAT; the doses of Brain-PTV initial D_{mean} (median 43.5 Gy vs. 24.1 Gy, p<0.001), brain-PTV boost D_{mean} (median 45.5 Gy vs. 34.4 Gy,

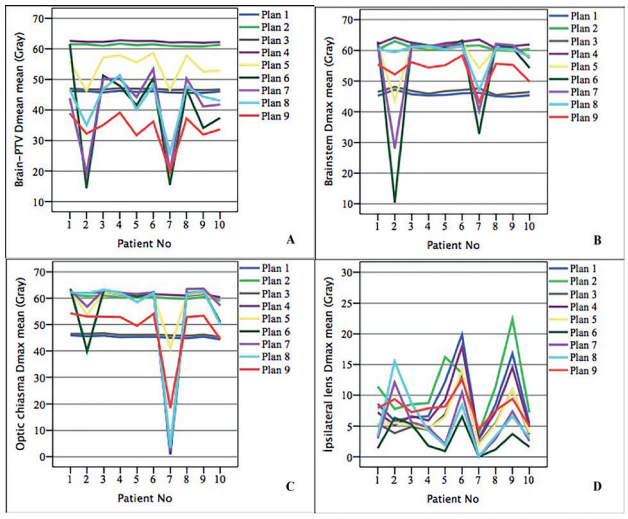

Figure 1. The doses of four organs at risk generated from 9 different plans

Plan 1: Whole brain radiotherapy (WBRT), 2D planning, Co-60, total dose 45 Gy in 25 fractions; Plan 2: WBRT, 2D planning, Co-60 energy, total dose 60 Gy in 30 fractions; Plan 3: WBRT, 2D planning, 6 MV energy, total dose 45 Gy in 25 fractions; Plan 4: WBRT, 2D planning, 6 MV energy, total dose 60 Gy in 30 fractions; Plan 5: WBRT in phase 1 and tumor bed in phase 2, 2D planning, 6 MV energy, phase 1 dose 40 Gy in 20 fractions plus boost dose 20 Gy in 10 fractions; Plan 6: planning target volume (PTV)-Radiation Therapy Oncology Group ($RTOG)_{preop}$, 2D planning, 6 MV energy, phase 1 dose 46 Gy in 23 fractions plus boost dose 14 Gy in 7 fractions; Plan 7: PTV-$RTOG_{preop}$, 3D planning, 6 MV energy, 3D-CRT; phase 1 dose 46 Gy in 23 fractions plus boost dose 14 Gy in 7 fractions; Plan 8: PTV-$RTOG_{postop}$, 3D planning, 6 MV energy, 3D-CRT, phase 1 dose 46 Gy in 23 fractions plus boost dose 14 Gy in 7 fractions; Plan 9: PTV-$RTOG_{postop}$, 3D planning, 6 MV energy, VMAT, phase 1 dose 46 Gy in 23 fractions plus boost dose 14 Gy in 7 fractions

p<0.001), optic chiasm D_{max} (62 Gy vs. 52.9 Gy, p=0.029), contralateral cochlea D_{mean} (median 48.3 Gy vs. 13.8 Gy, p=0.029), ipsilateral cochlea D_{mean} (median 57.2 Gy vs. 28.5 Gy, p=0.002), brainstem D_{max} (median 60.4 Gy vs. 55.3 Gy, p<0.001), pituitary gland D_{max} (median 61.4 Gy vs. 46.7 Gy, p=0.005), contralateral eye D_{max} (median 40.1 Gy vs. 23.2 Gy, p=0.007), and contralateral lacrimal gland D_{max} (median 36.4 Gy vs. 22.1 Gy, p=0.0232) were statistically lower in the $RTOG_{postop}$ VMAT plan. 3D-CRT, made in two phases according to PTV $RTOG_{preop}$ and $RTOG_{postop}$ volumes, and the OARs doses, made in two phase VMAT plan according to the $RTOG_{postop}$ volume, are given in Table 1.

Discussion

The routine use of RT in brain tumors began in the 1940s with kilovoltage X-rays (13,14). In the 1960s, 45-60 Gy RT was applied to the entire brain with megavoltage X-rays or Co-60 teletherapy devices (15,16). We found that all the OARs and whole brain tissue received a median [standard deviation (SD)] dose of 45 (3) Gy, except for lenses, when 45 Gy WBRT was delivered after 2D planning through Co-60 or linear accelerators. The lenses were the only normal tissue that could be protected with protection blocks anatomically because of being away from the brain tissue. In 1979, Walker et al. (13) found that 50-60 Gy doses were associated with increased survival when compared with doses ≤45 Gy. In those days, 50 - 60 Gy was applied to the whole brain. When we performed 60 Gy 2D WBRT with Co-60 and linear accelerators, we found that all the OARs and the whole brain were receiving a median (SD) dose of 60 (3) Gy, except for the lenses. All of the OARs exceeded the dose constraints that need to be considered today. In the 1970s, some centers were delivering an initial dose of 30-46 Gy as WBRT, followed by 20-30 Gy irradiation to the tumor bed, so two-phase treatment was used (17-21). Initially, CT (in the 1970s and 1980s) and then MRI (in the late 1980s) was used for delineating RT target volumes (22). Afterwards, two-phase treatment plans including phase 1 and boost volumes were used by abandoning WBRT. Previously, two-phase target volumes were created with the aid of preoperative imaging, predominantly considering preoperative tumor and edema volumes. In this study, we compared two different two-phase plans using 6 MV energy through WBRT (40 Gy/20 fr) + boost (20 Gy/10 fr), PTV-$RTOG_{preop}$ phase 1 (46 Gy /23 fr) + PTV-RTOGboost (14 Gy/7 fr) volumes generated according to RTOG 9710. Between these two plans, there were no significant differences in terms of Brain-PTVinitial D_{mean}, chiasm D_{max}, and brainstem D_{max} doses. However, in the plans generated according to RTOG 9710, the brain-PTV boost D_{mean}, contralateral cochlear D_{mean}, contralateral eye D_{max}, contralateral lacrimal gland D_{max}, ipsilateral lacrimal gland D_{max}, contralateral lens D_{max}, and ipsilateral lens D_{max} doses were significantly lower, so normal OARs were better spared. In addition to technological advances, approaches in generating irradiation volumes for GBM were changing in accordance with clinical evaluations. The side effects of RT in neurological tissues have led to this change. Brain irradiation is associated with neurotoxic side effects including radionecrosis and cognitive impairment (23,24). For the first time, Chang et al. (25) compared the RTOG volume, including peritumoral edema in preoperative MRI and target volumes in which peritumoral edema is not taken into consideration, but in which the residual tumor in the postoperative MRI +/- is targeted. According to both RTOG and MD Anderson Cancer Center plans, they revealed that 90% of the recurrences were central and within the area. Today, guidelines recommend using a postoperative MRI while defining/delineation target volume for RT in GBM. Different cooperative groups have target volume delineation that includes or excludes peritumoral edema (26). In this study, we compared the 3D-CRT plan of preoperative volume based on RTOG, the 3D-CRT plan of postoperative volume based on RTOG, and the VMAT plan of postoperative volume based on RTOG. The doses of OARs obtained in the VMAT plan, made in two phases according to PTV-$RTOG_{preop}$ and PTV-$RTOG_{postop}$ volumes, and made in two phases according to the $RTOG_{postop}$ volumes with 3D-CRT and brain-PTV initial / boost D_{mean} were significantly lower. Although 3D-CRT is accepted as the standard in general use, IMRT and VMAT use are increasingly used in tumors with large volume and near OARs (9-11). 3D-CRT is often sufficient in cases of spherical frontal or parietal tumors, whereas more successful plans can be made with IMRT or VMAT in irregularly shaped brainstem or near-orbit-like tumors (27,28). VMAT is usually preferred, because it provides a faster treatment plan and treatment application with conformality similar to IMRT. Today, the dose to be preferred in a young patient, who is fit and whose performance score is good, is 60 Gy in 30 fractions with concomitant temozolomide (11). Hypofractionated schedules are suitable for elderly or patients with a poor performance status (such as 40 Gy in 15 fractions or 34 Gy in 10 fractions) (29,30).

Conclusion

RT for disease control of GBM is important. With changing trends in RT for GBM, there has been a significant decrease in the treatment volumes and normal tissue doses. Today, the volume is generated according

Table 1. Comparison of normal tissue doses generated from 3 different radiotherapy plans according to Radiation Therapy Oncology Group volumes

	A Mean (SD) median (min-max)	B Mean (SD) median (min-max)	C Mean (SD) median (min-max)	A-B p value	A-C p value	B-C p value
Brain-PTV phase I D_{mean}	39.6 (12) 41.7 (18.1-52.4)	40.2 (8.4) 43.5 (22.6-48.7)	24.3 (3.3) 24.1 (16.9-28.5)	0.693	0.001	<0.001
Brain-PTV boost D_{mean}	41.4 (12.2) 44 (19.3-53.4)	42.9 (7.6) 45.5 (25.8-51.4)	33.6 (5.6) 34.4 (19.8-39.1)	0.458	0.021	<0.001
Optic chiasma D_{max}	55.5 (18.9) 62.1 (2.2-63.6)	54.8 (18.5) 62 (3.4-63.2)	48.6 (11) 52.9 (18.5-54.3)	0.463	0.030	0.029
Contralateral cochlea D_{mean}	42.2 (28.1) 59 (0.7-60.9)	38.4 (22.2) 48.3 (1.7-56.8)	12 (6.9) 13.8 (2.3-20.2)	0.183	0.002	0.001
Ipsilateral cochlea D_{mean}	43.6 (29.3) 61 (0.6-63)	42.7(25.3) 57.2 (1.5-60.8)	22.9 (11.5) 28.5 (2.8-33.5)	0.624	0.006	0.002
Brainstem D_{max}	55.8 (11.9) 61.6 (28-62.1)	59 (4.4) 60.4 (47-61.4)	53.6 (4.3) 55.3 (43.2-58.4)	0.349	0.484	<0.001
Pituitary gland D_{max}	48.1 (24.4) 62.1 (1.8-63.1)	53.5 (18.6) 61.4 (2.4-62.6)	41.9 (12.6) 46.7 (15.1-51.8)	0.289	0.151	0.005
Contralateral eye D_{max}	35 (21.3) 36.2 (0.1-58.4)	37.9 (21) 40.1 (0.2-60)	23.4 (9) 23.2 (7.9-38.2)	0.097	0.022	0.007
Ipsilateral eye D_{max}	38.3 (23.5) 41.3 (0.1-62.6)	42 (22.8) 46.5 (0.2-62.3)	34.5 (13.2) 35.7 (8.5-49.4)	0.100	0.333	0.053
Contralateral lacrimal gland D_{max}	30.3(21) 34.3 (0.2-58.2)	32.4(20.5) 36.4 (0.2-60)	21.9(8) 22.1 (10.1-35.5)	0.166	0.079	0.032
Ipsilateral lacrimal gland D_{max}	35.7 (23.6) 40.6 (0.1-61.4)	39.9 (22.9) 47.6 (0.2-62.2)	32.3(10.6) 36.5 (9.8-44)	0.063	0.475	0.095
Contralateral lens D_{max}	5.9 (4.2) 5.4 (0.06-12.7)	6.2 (4.2) 6 (0.1-15.3)	7.7(2) 7.7 (4.2-11.9)	0.619	0.084	0.183
Ipsilateral lens D_{max}	5.1(3.8) 3.9 (0.05-12)	5.5(4.4) 3.9 (0.1-15.5)	7.9(2.3) 7.9 (4.4-12.5)	0.415	0.005	0.066

A. Radiation Therapy Oncology Group $(RTOG)_{preop}$, Two-phase conformal radiotherapy plan using preoperative volumes according to RTOG 9710; B. $RTOG_{postop}$, Two-phase conformal radiotherapy plan using postoperative volumes according to actual RTOG recommendations; C. $RTOG_{postop}$, Two-phase volumetric modulated radiation therapy plan using postoperative volumes according to actual RTOG recommendations; X: mean value, SD: standard deviation, PTV: planning target volume, min-max: minimum-maximum

to the post-operative cranial MRI in the target volume delineation. When conformal and VMAT plans are compared according to the post-operative definition of RTOG, lower normal tissue doses are obtained in VMAT plans. 3D-CRT can be used depending on tumor location, while VMAT is advantageous when the treatment volume is close to OARs.

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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Neutrophil Lymphocyte Ratio in Estimating Response to Corticosteroid Treatment in Immune Thrombocytopenia Patients

Nötrofil Lenfosit Oranı İmmün Trombositopeni Hastalarında Kortikosteroid Tedavisine Yanıtı Öngörebilir mi?

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ABSTRACT

Introduction: We aimed to investigate the association between neutrophil lymphocyte ratio (NLR) and response and loss of response to corticosteroid treatment in immune thrombocytopenia patients (ITP).

Methods: We retrospectively analyzed the data of 47 ITP patients treated with corticosteroid therapy at Istanbul Training and Research Hospital Clinic of Hematology between 2007 and 2016. NLR was calculated using complete blood count of patients at the time of diagnosis. The cut-off score for NLR was determined at 2.5 according to median NLR level.

Results: Twenty-three (48.9%) patients had NLR <2.5 and 24 (51.1%) patients had NLR ≥2.5. There was no statistically significant relationship between NLR and treatment response, response duration and loss of response (p=0.74, p=0.869, p=0.315, respectively).

Conclusion: Although NLR was found to be associated with the prognosis and activity of various diseases in several studies, we could not verify such an association between NLR and response to corticosteroid therapy in ITP patients.

Keywords: Corticosteroid, immune thrombocytopenia patients, neutrophil lymphocyte ratio

ÖZ

Amaç: Bu çalışmada immün trombositopeni (ITP) hastalarında nötrofil lenfosit oranı (NLO) ile kortikosteroid tedavisine yanıt ve yanıt kaybı arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: 2007 ile 2016 yılları arasında İstanbul Eğitim ve Araştırma Hastanesi Hematoloji Kliniğinde kortikosteroid ile tedavi edilmiş 47 ITP hastasının verileri retrospektif olarak incelendi. NLO, hastaların tanı anındaki hemogramları kullanılarak hesaplandı. Medyan NLO düzeyine göre NLO için eşik değer 2,5 olarak belirlendi.

Bulgular: Yirmi üç hastada (%48,9) NLO<2,5 ve 24 hastada (%51,1) NLO ≥2,5 idi. NLO ile tedavi yanıtı, yanıt süresi ve yanıt kaybı arasında istatistiksel anlamlı ilişki yoktu (p=0,74; p=0,869; p=0,315).

Sonuç: NLO birçok çalışmada çeşitli hastalıkların prognozu ve aktivitesi ile ilişkili bulunmuştur. Çalışmamızda ise NLO ile ITP hastalarında kortikosteroid tedavisine yanıt arasındaki ilişki doğrulanamamıştır.

Anahtar Kelimeler: Kortikosteroid, immün trombositopeni, nötrofil lenfosit oranı

Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by isolated thrombocytopenia which is attributed to enhanced destruction and impaired production of platelets, often without a definable specific stimulus (1-3). Despite the implementation of novel agents such as thrombopoietin receptor agonists, corticosteroids (CSs) are still the first line recommended therapy for ITP patients who need treatment (1,3,4). Initial response rate to CS treatment is promising, varying from 50 to 90%; however, durable platelet response could be maintained in only 10-30% of patients, when the CS treatment is tapered off or ceased (5).

Inflammation is known to have a significant role in the course of many benign (6) and malignant diseases (7). Neutrophil lymphocyte ratio (NLR), being an inexpensive and easily available parameter, has been used frequently as a marker of systemic inflammation in recent years (6). The association between elevated NLR and the disease course, prognosis and treatment response has been established in several benign (8-14) and malignant (15,16) diseases.

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Even though ITP is an autoimmune disease, the data regarding the relationship between ITP and inflammatory markers is not sufficient. Also, there is limited data with respect to the factors affecting response to CS treatment (17-19). So, we aimed to investigate the association between NLR and response, and loss of response to CS treatment in ITP patients who needed treatment.

Methods

We retrospectively analyzed the data of 47 ITP patients treated with CS therapy at Istanbul Training and Research Hospital, Clinic of Hematology between 2007 and 2016. The data including age, gender, bleeding history, complete blood count at the time of diagnosis, NLR at the time of diagnosis, treatment response, loss of response, and duration of response were recorded for each patient. ITP diagnosis and treatment demand were defined according to The American Society of Hematology practice guidelines (1). We started treatment for patients with platelet count below $30x10^9$/L or patients with bleeding. Response to treatment was assessed according to the recommendations of the international working group (20). Response was defined as a platelet count greater than $30x10^9$/L and no response was defined as a platelet count less than $30x10^9$/L, while loss of response (LOR) was defined as a platelet count less than $30x10^9$/L or a less than 2-fold increase in the platelet count from baseline or the presence of bleeding. We did not further evaluate the patients according to complete remission, since the cohort was not large enough for such a detailed analysis. Forty-five patients received methylprednisolone and 2 patients received dexamethasone treatment as first line therapy. NLR was calculated using complete blood count of patients at the time of diagnosis. The cut-off score for NLR was determined at 2.5 according to median NLR level.

The study protocol has been approved by the Istanbul Training and Research Hospital Ethics Committee (date: 06.01.2017 no: 924) and written informed consent was obtained from all patients.

Statistical Analysis

Statistical analysis was performed using SPSS version 24 (IBM Corp., Armonk, NY, USA) software. Data were described as numbers and percentage or median and range, where appropriate. Chi-square test or Fisher's exact test was used for evaluating categorical values and Mann-Whitney U test for continuous values in patient groups. Spearman test was used for correlation analysis. A p value of <0.05 was considered statistically significant.

Results

Patient characteristics are summarized in Table 1. The median age of the patients at the time of diagnosis was 44 years (range, 18-74). Twenty-seven (57%) patients were female and 20 (43%) were male. Ten (21.3%) patients had a history of bleeding at the time of diagnosis. The median white blood cell count was 7,850/mm^3 (4.710-21.090/mm^3), hemoglobin level was 13.2 g/dL (8.3-17.80 g/dL), platelet count was 9.000/mm^3 (0-37.000/mm^3), neutrophil count was 5.200/mm^3 (2.210-16.900/mm^3), and lymphocyte count was 1.970/mm^3 (610-5.430/mm^3). Thirty-five (74.5%) patients responded to first line treatment, however, LOR developed in 19 (54.2%) of these patients during follow-up. The median NLR was 2.51 (range, 1.15-11.35), and the cut-off for NLR was assigned as 2.5 according to the median NLR level. Twenty-three (48.9%) patients had NLR <2.5 and 24 (51.1%) patients had NLR ≥2.5. There was no statistical significant difference between two groups regarding age, gender, treatment response, response duration and LOR (p=1, p=0.92, p=0.74, p=0.869, p=0.315) (Table 2). Also there was no correlation between NLR and response duration (p=0.918, r=0.018).

Table 1. Patient characteristics

Characteristic	
Gender, n, (%)	
Female	27 (57%)
Male	20 (43%)
Age, years, median, (range)	44 (18-74)
Bleeding, n, (%)	
Yes	10 (21.3%)
No	37 (78.7%)
WBC, /10^3/mm^3, median (range)	7.850 (4.710-21.090)
Hgb, /g/dL, median (range)	13.2 (8.3-17.80)
Plt, /10^3/mm^3, median (range)	9.000 (0-37.000)
Neu, /10^3/mm^3, median (range)	5.200 (2.210-16.900)
Lym, /10^3/mm^3, median (range)	1.970 (610-5.430)
NLR, median, (range)	2.51 (1.15-11.35)
Response to corticosteroid therapy, n, (%)	
Yes	35 (74.5%)
No	12 (25.5%)
Loss of response, n, (%)	
Yes	19 (54.3%)
No	16 (45.7%)

WBC: white blood cell count, Hgb: hemoglobin, Plt: platelet, Lym: lymphocyte, Neu: neutrophil, NLR: neutrophil lymphocyte ratio

Table 2. Comparison of patients with neutrophil lymphocyte ratio <2.5 and neutrophil lymphocyte ratio ≥2.5

	NLR <2.5 n=23	NLR ≥2.5 n=24	p
Gender, n, (%)			
Female	13 (57%)	14 (58%)	1
Male	10 (43%)	10 (42%)	
Age, years, median, (range)	44 (18-73)	44 (26-74)	0.92
Response to corticosteroid therapy, n, (%)			
Yes	18 (78.3%)	17 (70.8%)	0.740
No	5 (21.7%)	7 (29.2%)	
Response duration to corticosteroids, months, median, (range)	8.5 (1-60)	7 (1-105)	0.869
Loss of response, n, (%)			
Yes	8 (44.4%)	11(64.7%)	0.315
No	10 (55.6%)	6 (35.3%)	

NLR: neutrophil lymphocyte ratio

Discussion

While impaired platelet production plays a role in the pathogenesis of ITP, the fundamental step in occurrence of the disease is the production of abnormal autoantibodies specific to platelet membrane antigens. Subsequently, those antibodies bind to the membranes of circulating platelets (2,3,21). Autoantibody-bound platelets induce Fc receptor-mediated phagocytosis by macrophages primarily in spleen, leading to increased destruction of platelets (2,3,21). The triggering event in the development of antibody production remains unclear; however direct interaction of monocyte subgroups with T helper/T regulatory lymphocytes has been implicated in eliciting the events (22,23). This autoimmune nature of the disease makes CSs as the first-line therapy, which acts through decreasing the production of autoantibodies and suppressing the reticuloendothelial phagocytosis of antibody-coated platelets in ITP (2,24). Of note that, the response rate particularly sustained platelet response to CSs is not excellent different than anticipated (2,5). Nowadays, identifying risk factors has become important for tailoring individualized treatments in the majority of the diseases. Several factors such as age (17), gender (17), platelet count at diagnosis (17), abnormal platelet morphology (18) were investigated whether they affected response to corticosteroid treatment or not in ITP patients. Among them, abnormal platelet morphology was found to be associated with poor response to CS therapy. Although the data about the factors affecting the response to CS treatment is not obvious, infectious agents like *H. pylori*, human immunodeficiency virus, hepatitis C virus, cytomegalovirus (CMV), have been reported to augment thrombocytopenia in refractory ITP patients (3). In our study, we evaluated the association of NLR with response to CS treatment in ITP patients and we did not find an association. While 35 (74.5 %) patients responded to first line treatment, LOR developed in 19 (54.2%) of these patients during follow-up.

The association of elevated NLR with advanced disease and prognosis has been elucidated quite well in various malignancies (15,16). In addition, NLR has been elevated in autoimmune diseases like systemic lupus erythematosus (SLE) (9,25,26), rheumatoid arthritis (RA) (10), Sjögren's syndrome (27), and autoimmune thyroiditis (28,29). Also, increased NLR was shown to be an indicator of disease activity in SLE (26), RA (10,30), and Sjögren syndrome (27). On the contrary, the data concerning the role of NLR in some other autoimmune diseases such as Behçet's disease (11,12) and psoriasis (13,14) is conflicting. According to our knowledge, the role of NLR in adult ITP patients has not been explored previously. On the other hand, the association of low lymphocyte and leukocyte count with disease course in pediatric ITP patients were studied in two studies (31,32). Ahmed et al. (31) showed that low leukocyte and lymphocyte count at the time of diagnosis was a predictive parameter for persistence in pediatric ITP patients. Nevertheless, the treatment details of the patients were not noted in the study. Similarly, Deel et al. (32) found that low lymphocyte count at 3rd month was correlated with progression to chronic ITP. Also, majority of the patients were not treated with steroids in that study. In the current study, when we compared ITP patients who responded to first-line therapy with non-responders, we did not find a significant difference in NLR values between two groups.

Accordingly, several issues can be proposed to explain the insignificant results in our study. First, we did not have adequate data concerning the infection history of the patients, particularly *H. pylori* and CMV infection, which might have played a role in refractoriness. Secondly, subsets of lymphocytes asserted to have role in the pathogenesis of the disease constitutes only minority of the lymphocytes (33), thus any structural or quantitative abnormality in these cells would not allow alteration in lymphocyte count and also NLR. Unfortunately, we could not evaluate these factors due to the retrospective nature of the study. Lastly and the most important one according to us is that, ITP is not a systemic disease affecting the other organs leading to systemic inflammation.

Conclusion

In conclusion, although NLR was found to be associated with the prognosis and activity of various diseases in several studies, we could not verify such an association between NLR and response to corticosteroid therapy in ITP patients.

Ethics Committee Approval: The study protocol has been approved by the Istanbul Training and Research Hospital Ethics Committee (date: 06.01.2017 no: 924).

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

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Role of Hypoxia Inducible Factor-1 Alpha in Early Stage Renal Failure and Its Relationship with Biochemical and Inflammatory Parameters

Erken Dönem Böbrek Yetmezliğinde Hipoxia İnducible Factor-1 Alfa Düzeyinin Rolü ve Biyokimyasal ve Enflamatuvar Parametrelerle İlişkisi

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ABSTRACT

Introduction: Hypoxia-inducible factor-1 (HIF-1) is the protein product of the gene with the same name that is induced by hypoxia and induces a series of reactions that act in the adaptive response of the cell. HIF-1 activation is a primary defense mechanism against the hypoxia of the tissue. In general, it is activated when tissue oxygenation is disrupted. Tissue hypoxia in kidney disease provides adaptation to the current situation by activating the HIF-1 alpha level. In this report, it was aimed to measure HIF-1 alpha levels in early stage renal failure patients, compare them with healthy volunteers, and evaluate the relationship between HIF-1 alpha and other biochemical and inflammatory parameters.

Methods: This study included 22 healthy subjects (male/female; 8/14) as the control group and 25 patients (male/female; 11/14) who are followed up in the outpatient clinic with the diagnosis of early stage renal failure (glomerular filtration rate 60-90 mL/min/1.73m²). HIF-1 alpha level, biochemical parameters [glucose, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT)], hemoglobin and inflammatory parameters [C-reactive protein (CRP), neutrophil/lymphocyte ratio], platelet count (PLT), platelet parameters [mean platelet volume (MPV), plateletcrit (PCT) and platelet distribution width (PDW)] were viewed in venous blood samples in both groups, and results were compared using descriptive statistical methods as well as Mann-Whitney U, chi-square, student t-test.

Results: HIF-1 alpha, glucose, AST, ALT, gamma-glutamyl transpeptidase (GGT), PLT, MPV, PCT and PDW values were not statistically significantly different (p>0.05) among the case and control groups. There was no statistically significant correlation (p>0.05) between HIF-1 alpha and glucose, urea, creatinine, AST, GGT, CRP, neutrophile/lymphocyte ratio, PLT, MPV, PCT, PDW values.

ÖZ

Amaç: Hypoxia-inducible factor-1 (HIF-1) aynı isimli genin proteini olup hipoksiyle indüklenerek hücrenin adaptif cevabını sağlayan bir dizi reaksiyonu başlatır. Aktivasyonu dokudaki hipoksiye karşı primer defansif mekanizmadır. Genellikle doku oksijenasyonunun bozulduğu patolojik durumlarda aktive olur. Böbrek hastalığında oluşan doku hipoksisi HIF-1 alfa düzeyini yükselterek mevcut duruma adaptasyonu sağlar. Burada erken dönem böbrek yetmezliğinde HIF-1 alfa düzeyine bakılarak sağlıklı gönüllülerle karşılaştırılması ve HIF-1 alfa düzeyinin diğer biyokimyasal ve enflamatuvar parametreler ile olan ilişkisinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Çalışmaya ayaktan takipli, erken dönem böbrek yetmezliği tanısı almış (glomerular filtration rate 60-90 mL/min/1,73m²) olan hastalardan randomize edilmiş (erkek/kadın; 11/14) 25 hasta ile 22 sağlıklı (erkek/kadın; 8/14) gönüllü alınmıştır. Her iki grupta venöz kan örneklerinde HIF-1 alfa düzeyi, biyokimyasal parametreler [glukoz, kreatinin, ürik asit, aspartat transaminaz (AST), alanin transaminaz (ALT)], hemoglobin ve enflamatuvar parametreler [C-reaktif protein (CRP), nötrofil/lenfosit oranı], trombosit sayımı (PLT), trombosit parametreleri [ortalama trombosit hacmi (MPV), plateletcrit (PCT) and (PDW)] bakıldı. Sonuçlar tanımlayıcı istatistik metotların yanı sıra Mann-Whitney U, ki-kare ve student t-testi kullanılarak karşılaştırıldı.

Bulgular: Olgu ve kontrol grubunda HIF-1 alfa değeri, glukoz, AST, ALT, GGT, PLT, MPV, PCT, PDW değerleri anlamlı (p>0,05) farklılık göstermemiştir. HIF-1 alfa ile glukoz değeri, üre, kreatinin, AST, GGT, CRP, nötrofil/lenfosit oranı, PLT, MPV, PCT, PDW değerleri arasında anlamlı (p>0,05) korelasyon gözlenmemiştir. HIF-1 alfa ile ürik asit değeri arasında anlamlı (p<0,05) negatif korelasyon gözlenmiştir. HIF-1 alfa ile ALT ve hemoglobin değeri arasında anlamlı (p<0,05) pozitif korelasyon gözlenmiştir.

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Conclusion: It is known that chronic hypoxia is an important factor in the progression of chronic renal diseases regardless of the underlying cause. It was assumed that the factors including normotension, normal hemoglobin level and the presence of medical therapy reducing oxidative stress (angiotensin converting enzyme inhibitors and angiotensin receptor blockers) in the patientsimproved renal hypoxia and therefore affected the results of this study.

Keywords: Hypoxia-inducible factor-1 alpha, early stage renal failure, renal hipoxia

Sonuç: Kronik hipoksinin altta yatan sebepten bağımsız olarak kronik böbrek hastalıklarının ilerlemesinde önemli bir faktör olduğu bilinmektedir. Hasta grubunun normotansif olması, hemoglobin düzeyinin normal olması, hastada oksidatif stresi azaltan medikal tedavinin (anjiyotensin dönüştürücü enzim inhibitörü ve anjiyotensin reseptör blokeri kullanımı) bulunması gibi sebeplerin sonuçları etkilediği ve renal hipoksiyi iyileştirdiği varsayılmıştır.

Anahtar Kelimeler: Hypoxia-inducible factor-1 alfa, erken dönem böbrek yetmezliği, renal hipoksi

Introduction

Chronic renal failure is a disease in which various etiologies cause irreversible nephron loss in the kidneys and its frequency increases in the world. The oxygen distribution in the kidney is heterogeneous in parallel with the blood distribution and plays a role in many physiological and pathological events of the kidney. Hypoxia-inducible factor-1 (HIF-1) alpha is a transcription regulator of metabolic processes such as angiogenesis, erythropoesis, iron and glucose metabolism of the kidney.

HIF-1 alpha gene protein, which activates the genes that are induced by hypoxia in humans, is one of the most well-known elements of the HIF-1 gene family. HIF-1 is a heterodimeric protein and consists of HIF-1 alpha (HIF-2 alpha and HIF-3 alpha are homologous) and HIF-1β (which is in nucleus) subunits. The stability and activity of the alpha subunit of HIF-1 is provided by post-transcriptional modifications such as hydroxylation, ubiquitination, acetylation and phosphorylation (2). In hypoxic conditions, non- hydroxylated HIF-1 alpha subunit becomes stable and activates with coactivators such as cAMP, protein/p300 and passes to the nucleus. It combines with the HIF-1β subunit to regulate the expression of the hypoxia response genes. HIF-1 was first described as a transcription complex that causes increase in erythropoietin (EPO) in response to hypoxia (3,4). In recent studies, it was found that HIF-1 proteins were the key regulator of the transcriptional activation responses to hypoxia of many genes related to adaptation to low oxygen pressure in cells and tissues, cell survival and proliferation, angiogenesis, erythropoesis, glucose intake and iron metabolism (5,6). Therefore, HIF-1 alpha is accepted as an adaptive response to pathophysiological processes in early chronic kidney disease (CKD).

In this study, HIF-1 alpha level in patients with early CKD with glomerular filtration rate (GFR) 60-90 mL/min/1.73m² were compared with healthy volunteers and the relationship between HIF-1 alpha level and biochemical and inflammatory parameters was discussed.

Methods

The study was approved by the ethics committee of İstanbul Training and Research Hospital (date: 15.12.2017 no: 1149). Twenty five patients with CKD with GFR between 60-90 mL/min/1.73m² (male/female: 11/14, mean age: 70±8.2 years) who were followed up in the outpatient clinic and 22 healthy volunteers (male/female: 8/14, mean age: 67.3±7.3 years) were included in the study.

In the patient group, 14 patients had diabetes mellitus (DM) (for 20 years and longer), 5 patients had hypertension (regulated with treatment) and 6 patients had no etiology. In patients with DM, 1 patient was using sulphonylurea (gliclazide 30 mg) and 13 were using insulin. All patients were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. All patients were normotansive. Patients with active malignancy or history of malignancy, cardiac failure, acute cardiac ischemia (within last 6 months), chronic obstructive pulmonary disease, high blood pressure or a history of irregular blood pressure and smokers or ex-smokers were exluded from the study. Non-high density lipoprotein cholesterol levels were normal in all patients.

Oral and written informed consents were obtained from all participants. Blood pressure measurements performed twice in the morning visits while the participants were in the sitting position were normal. Venous blood samples were taken from the antecubital vein following 10 hours of fasting in the sitting position in the morning. Serum HIF-1 alpha, fasting blood glucose, urea, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and C-reactive protein (CRP) levels and hemogram were measured.

HIF-1 alpha level was measured with ELISA (enzym linked immunosorbent assay) method in the Synergy HT device. Other parameters were measured at one time with spectrophotometric method in the Beckman Coulter AU 2700 plus (Beckman Coulter, Inc., Fullerton, USA) autoanalyzer.

Statistical Analysis

Descriptive statistics of the data were expressed as mean, standard deviation, median, lowest value, highest value, frequency and ratio. Distribution of the variables was checked by the Kolmogorov-Simirnov test. In the analysis of quantitative independent data, independent t-test and Mann-Whitney U test were used. In the analysis of qualitative independent data, the chi-square test was used. In correlation analysis, the Spearman correlation analysis was used. In the analysis of the data, SPSS 22.0 package program was used.

Results

There was no difference between groups in terms of mean age and gender distribution ($p>0.05$). There was no difference between groups in terms of HIF-1 alpha, fasting blood glucose, AST, ALT and GGT levels, platelet (PLT) count, mean platelet volume (MPV), plateletcrit (PCT) and platelet distribution width (PDW) values ($p>0.05$) (Table 1).

Urea, creatinine, uric acid and CRP levels and neutrophil/lymphocyte (N/L) ratio were significantly higher in the patient group than in the control group ($p<0.05$). Hemoglobin level was significantly lower in the patient group than in the control group ($p<0.05$) (Table 1).

Table 1. Comparison of the charecteristics and laboratory data in patient and control groups

		Patient group				Control group				p	
		Mean ± SD/n-%			Median	Mean ± SD/n-%			Median		
Age (years)		70.2	±	8.2	72.0	67.3	±	7.3	68.5	0.227	[m]
Gender	Female	14		56.0%	-	14		63.6%	-	0.595	X^2
	Male	11		44.0%	-	8		36.4%	-		
HIF 1 A (ng/mL)		1.59	±	1.54	1.28	2.04	±	1.78	1.45	0.359	[m]
Glucose (mg/dL)		143.8	±	71.6	107.0	104.5	±	16.8	104.0	0.053	[m]
Urea (mg/dL)		58.5	±	20.9	51.0	33.4	±	8.5	34.5	0.000	[m]
Creatinine (mg/dL)		1.28	±	0.27	1.26	0.75	±	0.14	0.72	0.000	[m]
Üric acide (mg/dL)		7.14	±	1.12	7.20	4.79	±	1.25	4.50	0.000	[m]
AST (U/L)		21.0	±	8.6	19.0	25.4	±	16.2	21.0	0.123	[m]
ALT (U/L)		17.5	±	9.9	15.5	22.6	±	10.9	21.5	0.050	[m]
GGT (U/L)		22.9	±	10.3	20.0	25.5	±	12.0	22.0	0.328	[m]
CRP (mg/L)		0.9	±	0.9	0.5	0.2	±	0.3	0.2	0.000	[m]
HGB (g/dL)		12.5	±	1.6	12.3	13.6	±	1,6	13.7	0.015	[m]
N/L		2.2	±	0.7	2.1	1.6	±	0.4	1.4	0.001	[t]
PLT (10^9/L)		257.0	±	85.3	258.0	252.2	±	57,3	254.0	0.831	[t]
MPV (fL)		10.7	±	0.8	10.6	10.7	±	0.9	10.7	0.947	[t]
PCT (%)		0.27	±	0.09	0.27	0.27	±	0.06	0.27	0.987	[t]
PDW (%)		13.0	±	1.6	12.9	13.2	±	1.8	13.0	0.692	[t]

[t]T test/[m]Mann-Whitney U test /[x2]chi-square test, HIF: hypoxia-inducible factor, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, CRP: c-reactive protein, HGB: hemoglobin, N/L: neutrophil/lymphocyte, PLT: platelet, MPV: mean platelet volume, SD: standard deviation

Table 2. Correlation between hypoxia-inducible factor-1 A level and other paramethers

		Glucose	Urea	Creatinine	Uric acide	AST
HIF 1 A	r	0.049	-0.268	-0.281	-0.310	0.183
	p	0.745	0.069	0.056	**0.048**	0.225
		ALT	**GGT**	**CRP**	**HGB**	**N/L**
HIF 1 A	r	0.367	0.032	-0.054	0.361	-0.143
	p	**0.012**	0.832	0.732	**0.015**	0.354
		PLT	**MPV**	**PCT**	**PDW**	**D VİT**
HIF 1 A	r	-0.181	0.157	-0.052	-0.088	0.156
	p	0.235	0.302	0.734	0.564	0.342
Spearman correlation						

HIF: hypoxia-inducible factor, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, CRP: c-reactive protein, HGB: hemoglobin, N/L: neutrophil/lymphocyte, AST: aspartate aminotransferase, PLT: platelet, MPV: mean platelet volume, PCT: plateletcrit, PDW: platelet distribution width, D VİT: vitamin D

There was no significant correlation between HIF-1 alpha level and fasting blood glucose, urea, creatinine, AST, GGT, CRP levels, N/L ratio, PLT count, MPV, PCT, PDW values ($p>0.05$) (Table 2).

There was a significant negative correlation between HIF-1 alpha and uric acide levels ($p<0.05$). There was a significant positive correlation between HIF-1 alpha, ALT and hemoglobin levels (Table 2).

Discussion

Increase in HIF-1 alpha is the primary defense mechanism of kidneys against hypoxia. In this study, no significant difference was found between healthy individuals and patients with early CKD in terms of HIF-1 alpha level. Normal hemoglobin levels in the patients and positive effects of the medications could explain this finding.

It is known that chronic hypoxia is an important factor in the progression of CKD regardless of underlying cause (7). It was shown that oxygen demand-supply mismatch occurs before visible damage occurs in kidneys in kidney diseases (8). Direct regulative effect of transforming growth factor (TGF) beta 1, a powerful profibrotic factor, on fibrogenic factors and the role of inflammation are the mechanisms of the development of renal fibrosis with the increase of HIF.

In contrast to the potential profibrotic role, there are studies showing that HIF-1 alpha may have a protective function with pro-angiogenic and cytoprotective effects under some CKD conditions (9-11). HIF-1 alpha can be found in the kidney in physiological conditions, and also it has been shown to increase in all cases (anemia, tumor, etc.) causing hypoxia in kidneys. Although kidney is an organ with high blood flow, the oxygen tension of the tissue in the parenchyma is lower than in other organs (12). This is due to the parallel placement of arterial and venous pre and post glomerular vessels (13). This array allows oxygen to pass through the arteries to the veins via the shunt, and cause the medullar region of kidney to be prone to hypoxia in case of the breakdown of blood flow to the kidney.

Anemia is one of the leading causes of hypoxia in the kidney. Anemia is a common condition in CKD. In addition to the lack of EPO, functional iron deficiency contributes to the development of this condition. Kidney acts as the most important physiological oxygen sensor in the regulation of erythropoesis. EPO is a hematopoietic growth factor and regulates the production of red blood cells. EPO mRNA levels have been shown to increase 1000 times or more in kidney and liver cells in severe hypoxic conditions and HIF-1 alpha has been defined as the main transcriptional mediator of this process (1). In recent studies, it was shown that inhibition of HIF-1 alpha hydroxylase not only increased serum EPO levels but also improved iron intake and metabolism. The transferrin and its receptor were previously shown to be the direct transcriptional targets of HIF (14,15). The lack of EPO is the main cause of anemia in CKD and anemia accelerates the decrease in kidney function by inducing tubulointerstitial hypoxia (16). In this study, normal hemoglobin level (mean 12.5 mg) in the patient group was considered as protective against hypoxic conditions in the kidney. A number of genes that play a role in pathophysiological changes in the arteries and kidneys in hypertension are activated by HIF. Many genes (EPO, endothelin-1, vascular endothelial growth factor, tumor necrosis factor, TGF, collagen-1) are activated by HIF, which plays a role in the negative pathophysiological changes in blood vessels and kidneys in hereditary hypertension (17,18). Normotension prevents the increase in HIF levels. The blockage of the renin angiotensin system protects the blood flow to the peritubular capillary. The increase of angiotensin II in renal diseases increases renal oxidative stress by stimulating the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH). This prevents the efficient use of oxygen in tubular cells. Increased oxidative stress products lead to decreased nitric oxide (NO). Adler and Huang (3) showed that reduced NO increased energy consumption by two times by stimulating mitochondrial respiration and resulted in tissue hypoxia. Another experimental study showed that perfusion of low dose ang-2 increased NADPH oxidase activity in renal cortex, caused renal vasoconstriction, induced ang-2, and induced cortical hypoxia due to inadequate utilisation of oxygen for tubular sodium transport (19). CKD is associated with oxidative stress. Renal anemia is a condition that also increases oxidative stress. Norman et al. (20) showed that blockade of RAS protected peritubular blood flow and tissue oxygenation. Manotham et al. (21) showed improved peritubular capillary blood flow and oxygenation with angiotensin blocker olmesartan in the remnant renal model.

RAS inhibitors also act as antioxidants and play a healing role in mitochondrial uncoupling, lead to more efficient use of oxygen and improve mitochondrial respiration. They lead to more efficient use of oxygen which is necessary for sodium transport (22). In this study, all of the patients were using ARB or ACE inhibitors. This treatment decreases ang-2 levels and leads to renal recovery which were considered to affect HIF-1 alpha level in this study. Also, in this study, there was no difference between groups in terms of thrombocyte count and its parameters. As known, PLT parameters have prognostic and diagnostic significance in many diseases. Exposure of PLTs to uremic toxins causes functional and numerical changes which increase complications, especially cardiovascular complications in CKD (23). We did not find difference between groups which could be explained by the presence of early CKD and consequent short-term exposure to uremic toxins in the patients. In our study, inflammatory parameters (CRP, N/L) were found to be significantly higher in the patient group but no correlation was found between these parameters and HIF-1 alpha level. This could be explained by the positive contribution of the above mentioned healing factors.

Conclusion

As a result, HIF-1 alpha is in the center of the cellular response to hypoxia and activates transcription of genes that encode proteins that mediate adaptive responses to decreased oxygen presence in tissue. In the early stages of CKD, HIF-1 alpha increases due to the effects of lack of EPO, hypokalemia, anemia, increased ang-2 and other oxidative stress factors increase and contributes to the progression of the disease. Supportive studies will help us better understand the role of HIF-1 alpha, and in the future, HIF-1 alpha may become the target of treatments that slow down the progression of disease.

Ethics Committee Approval: This study was approved by the İstanbul Training and Research Hospital Ethics Committee in 15.12.2017 (no: 1149).

Informed Consent: Oral and written informed consents were obtained from all participants.

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Correlation Between Psoas Muscle Area and Clinical Frailty Score in Patients with Transcatheter Aortic Valve Replacement

Transkateter Aort Valve Replasmanı Yapılan Hastalarda Kırılganlığın Kantitatif Göstergesi Olan Psoas Kas Alanının Klinik Kırılganlık Skoru ile Korelasyonu

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ABSTRACT

Introduction: Transcatheter aortic valve implantation (TAVI) has been widely used in patients with high-risk aortic valve stenosis. Frailty is a parameter that significantly affects prognosis in cardiovascular diseases. In the clinic, the identification and validation of simple and inexpensive frailty evaluation methods are important. Our aim is to determine the importance of a simple and inexpensive clinical evaluation tool that can be used in patients with TAVI by examining the correlation between the "clinical frailty scale (CFS)" and "the psoas muscle area (PMA)", which is a quantitative indicator of fraility.

Methods: CFS was determined by clinical evaluation of 61 patients who underwent TAVI and PMA was calculated by computed tomography scan.

Results: A significant correlation was found between the CFS and PMA values of the patients in the correlation analysis (r=-0.970, p<0.001). Patients with early poor outcome had higher CFS values (6.0±0.9 vs 3.79±1.4; p<0.000) and lower PMA values (3.03±0.3 vs. 6.48±1.2; p<0.000).

Conclusion: In short and long term prognosis of all cardiovascular diseases, frailty is an important guidance. CFS, which is clinically simple, easy-to-apply and inexpensive, is highly correlated with PMA, which is a quantitative indicator of fraility and closely related to prognosis in TAVI.

Keywords: Transcatheter aortic valve implantation, frailty, prognosis

ÖZ

Amaç: Transkateter aort kapak replasmanı (TAVR) yüksek riskli aort kapak stenozu hastalarında yaygın şekilde kullanılmaya başlanmıştır. Kırılganlık kardiyovasküler hastalıklarda prognozu önemli düzeyde etkileyen bir parametredir. Klinikte basit ve masrafsız kırılganlık değerlendirme yöntemlerinin tespiti ve validasyonu önem taşımaktadır. Amacımız kırılganlığın kantitatif bir göstergesi olan "psoas kas alanı (PKA)" ile "klinik kırılganlık skorunun (KKS)" korelasyonunu inceleyerek TAVR hastalarında kullanılabilecek KKS gibi basit ve ucuz bir klinik değerlendirme aracının prognostik önemini tespit etmektir.

Yöntemler: TAVR uygulanan 61 hastanın klinik değerlendirme ile KKS'leri ve bilgisayarlı tomografi aracılığıyla PKA'ları hesaplandı.

Bulgular: Yapılan korelasyon analizi sonucunda hastaların KKS ve PKA değerleri arasında önemli düzeyde ilişki saptandı (r=-0,970, p<0,001). Erken kötü sonlanım gelişen hastalarda KKS değerleri daha yüksek iken (6,0±0,9 vs 3,79±1,4; p<0,000), PKA değerleri daha düşüktü (3,03±0,3 vs 6,48±1,2; p<0,000).

Sonuç: Tüm kardiyovasküler hastalıkların kısa ve uzun dönem prognozunda kırılganlık önemli bir yön gösterici olmaktadır. Klinik olarak basit, kolay uygulanabilir ve masrafsız olan KKS, kırılganlığın kantitatif göstergesi olan ve TAVR'de prognozla yakın ilişkisi tespit edilen PKA ile ileri düzeyde korele gözükmektedir.

Anahtar Kelimeler: Transkateter aort kapak replasmanı, kırılganlık, prognoz

Introduction

Cardiovascular diseases are the leading causes of hospitalization and mortality all over the world. The number of elderly people in the society is increasing due to both prolongation in life expectancy and advances in medical and percutaneous treatments. As a result, the number of patients with cardiovascular diseases who need intervention is increasing rapidly in the society. Although there is no universal definition, frailty is the inability to maintain homeostasis by not responding adequately to biological stressors due to decrease in reserve in multiple organ systems (1). Frailty is closely related to poor endpoints such as disability,

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longer hospitalization and mortality (2-4). In the evaluation of fragility, single parameters and scales consisting of combinations of multiple parameters are used. The clinical frailty score (CFS) is a simple and fast method for assessing fragility and is closely related to poor outcome (5). The CFS score is rated between 1 and 9, and the higher the rating, the higher the risk of poor outcome. Sarkopenia is progressive and generalized loss of skeletal muscle mass and strength in sarcopenia and is associated with mortality and reduction in the quality of life. The Psoas muscle is one of the main muscles and the psoas muscle area (PMA) reflects the skeletal muscle state of the entire body.

PMA is a predictor of early negative results in patients with transcatheter aortic valve implantation (TAVI). Shimura et al. (6) found CFS to be closely related to late-term mortality in patients with TAVI. Our aim is to investigate the correlation between PMA which is a quantitative scale and CFS which is semiquantitative scale and to reinforce the use of a simple and easy clinical scoring such as CFS with a quantitative tool in patients with TAVI.

Methods

Sixty one patients who underwent TAVI between 2014 and 2017 in our clinic were included in the study, retrospectively. CFS scores which we routinely added to the anamnesis of the patients and PMA values were calculated using computed tomography (CT) which was performed to evaluate peripheral arteries in patients with TAVI. The status of the patients at the end of the first month was learned in visits or by phone.

Properly measured blood pressure >140/90 mmHg or use of antihypertensive medication was defined as hypertension. Diabetes mellitus was defined as fasting blood glucose >126 mg/dL or HbA1c ≥6.5%, or oral antidiabetic or insulin use. Kidney functions were evaluated using The Chronic Kidney Disease Epidemiology Collaboration equation. The presence of coronary artery disease was determined using medical records. Smoking was defined as smoking at least one cigarette per day for the last 1 year. The CFS score was first described by Rockwood et al. (3,7) and then it was modified. Meanings of 1-9 scores were as follows: 1 very fit (people who exercise daily, are energetic and are active compared with their cotemporaries), 2 well (people who have no active disease symptoms but are less fit than category 1), 3 managing well (people with comorbid diseases whose symptoms are less than category 4 under treatment), 4 vulnerable (people who have complaints despite medical problems are well controlled, but they are not dependent on others), 5 mildly frail (people depend mildly on others in daily activities), 6 moderately frail (people depend on others in daily activities and in non-daily activities such as climbing stairs), 7 severely frail (people depend on others in all forms of activity but are stable and risk of death is not high), 8 very severely frail (people who are so frail and have a high risk of death, even there is a minor disease), 9 terminally ill (people with a life expectancy <6 months) (7).

PMA measurements were obtained by dividing the sum of right and left PMAs obtained from single axial CT images at L3 vertebra level by the body surface area.

For biochemical analysis, blood samples were taken after 12 hours of fasting and analyzed in the first two hours. Our study was retrospective, so no informed consent from patients and Ethics Committee approval were taken.

Statistical Analysis

Statistical analyses were done with the Statistical Package for the Social Sciences version 17.0 (SPSS, Chicago, Illinois) program. Continuous variables with normal distribution were expressed as mean ± standard deviation and continuous variables without normal distribution were expressed as median (interquartile range). Categorical variables were expressed as percentages. Categorical variables are compared between groups by chi-square test. Kolmogorov-Smirnov test was used to determine whether continuous variables have normal distribution. Continuous variables with normal distribution were compared between groups by Student t-test and without normal distribution by Mann-Whitney U test. Correlation between two variables was calculated by Pearson correlation test. The results were evaluated in 95% confidence interval and $p<0.05$ was considered statistically significant.

Results

Sixty one patients with TAVI were included in the study. The mean age was 76.2±8.3 years and 34 (55.7%) of them were male. Other demographic and laboratory data were summarized in Table 1.

Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as n (%).

Death in 30 days as early poor outcome was encountered in 2 (3.3%) patients, 3 had (4.9%) stroke and 7 (11.5%) had vascular complications in the site of intervention. CFS was higher in patients with early poor outcome than in patients without early poor outcome (6.0±0.9 vs

Table 1. Baseline characteristics of the patients

Variables	
Age (years)	76.2±8.3
Male (n, %)	34 (55.7)
Hypertension (n, %)	15 (24.6)
Diabetes mellitus (n, %)	16 (26.2)
Hyperlipidemia (n, %)	19 (31.1)
Smoking (n, %)	12 (20.7)
Stroke (n, %)	3 (4.9)
PAD (n, %)	1 (1.6)
Cardiac failure (n, %)	20 (32.8)
Glucose (mg/dL)	112 (35.2)
Creatinin (mg/dL)	1.2±0.4
Total cholesterol (mg/dL)	192 (62.7)
LDL (mg/dL)	122±49
GFR (mL/min)	62.6 (37.2)
Hemoglobin (g/dL)	11.1±1.7
Hematocrit (%)	34±4,6
Platelet ($\times 10^9$/L)	205±77
WBC (mm^{-3})	8337±4607.5

PAD: peripheral artery disease, GFR: plomerular filtration rate, WBC: white blood cell count, LDL: low density lipoprotein, min: minimum

Table 2. Comparing of clinical and laboratory parameters between groups with poor outcome and without poor outcome

Variables	Early poor outcome (+) n=12	Early poor outcame (-) n=49	p
Age (years)	73.1±13.2	74.9±6.8	0.523
Male (n,%)	8 (66.7%)	26 (53.1%)	0.395
Hypertensiyon (n, %)	3 (25.0%)	12 (24.5%)	0.971
DM (n,%)	3 (25.0%)	13 (26.5%)	0.914
KAD (n, %)	10 (83.3%)	39 (79.6%)	0.770
CFS	6.0±0.9	3.79±1.4	**<0.000**
Smoking (n,%)	2 (16.7%)	10 (24.1%)	0.770
Glucose (mg/dL)	110.4 (36.0)	121.2 (38.3)	0.350*
Creatinin (mg/dL)	1.02±0.4	1.12±0.6	0.490
TC (mg/dL)	200.7 (51.2)	190.9 (45.2)	0.709*
LDL-C (mg/dL)	125.0±24.7	122.0±51.1	0.890
GFR (mL/min)	69.6 (24.3)	64.5 (29.3)	0.504*
Hemoglobin (g/dL)	10.9±1.8	11.2±1.7	0.585
Hematocrit (%)	33.9±4.3	34.1±4.7	0.628
WBC (mm^{-3})	9644.2±3858.2	8678.7±3573.3	0.340
PMA (cm^2/m^2)	3.03±0.3	6.48±1.2	**<0.000**

Continuous variables were expressed as mean ± standard deviation and categorical variables as n (%).

*Singed ones were analyzed by Mann-Whitney U test and other ones were analyzed by Student t-test.

DM: diabetes mellitus, KAD: koronary arter disease, CFS: clinical fraility score, TC: total cholesterol, LDL: low density cholesterol, GFR: glomerular filtration rate, WBC: white blood cell, PMA: psoas muscle area

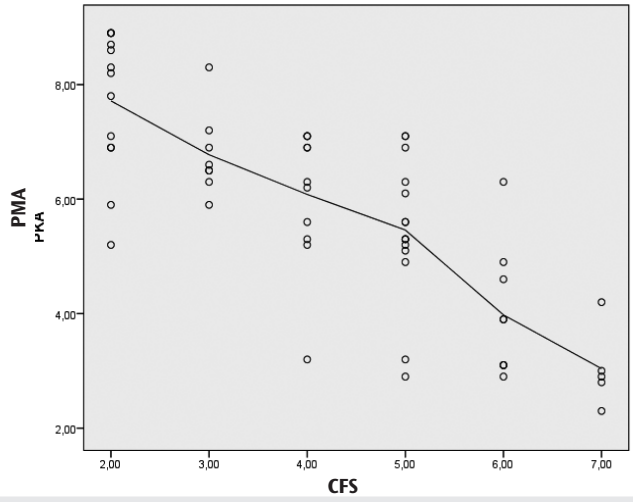

Figure 1. Correlation graph between psoas muscle area and clinical fraility score

PMA: psoas muscle area CFS: clinical fraility score

3.79±1.4; p<0.000), PMA was lower in patients with early poor outcome than in patients without early poor outcome (3.03±0.3 vs 6.48±1.2; p<0.000) (Table 2).

There was a strong and negative correlation between CFS and PMA values (r=-0.794, p<0.000) (Figure 1).

Discussion

Significant correlation between the PMA, which is the quantitive indicator of TAVI, and CFS, suggests that CFS can be used to predict prognosis in patients with TAVI.

Fraility is characterized by increased sensitivity to stressors due to decrease in physiological reserve and functional capacity and is closely related to hospitalization and mortality. It is associated with increased postoperative complication frequency in general surgery operations (8). Factors such as lipoprotein accumulation and chronic inflammation in the pathogenesis of aortic valve calcification play a role. Although it has a relationship with aging, we cannot provide adequate information for the prognosis of aortic valve patients only with age. In heart surgery, EuroScore and Society of Thoracic Surgeons scores are the most frequently used scores to determine operative mortality. However, these models have been developed for heart surgery and also have suboptimal predictability in high-risk patient groups.

Fraility is an important parameter in determining short-term complications and prognosis in patients with TAVI whose frequency is increasing nowadays. The most common method for assessing fraility is eye-balling, but it is weak in terms of objectivity and reproducibility. Although there are many fraility scores and scales, they are not only time consuming and complex, but also are not objective methods. Although the parameters based on daily life activity measurement and exercise capacity such as 5-minute walking test show morbidity and mortality, there is not enough measurement performed due to orthopedic problems in the elderly population (9,10). Rodes-Cabau et al. (11) found fraility as a predictor of 2-year mortality rate, regardless of other risk factors. However, eye-balling method was used in this study. Green et al. (12) showed a close relationship between parameters including albumin, daily life activities and walking speed and 1-year mortality rate in 159 patients with TAVI. Therefore, we used PMA in our study to determine fraility more accurately and quantitatively. However, since PMA is not a parameter that can be obtained in every patient,

we examined the relationship between CFS and PMA and found a close correlation between them. Thus, we showed that a cheap variable that can be obtained easily in anamnesis can be valuable in predicting prognosis in patients with TAVI.

Study Limitations

This study was performed in one center with relatively small sample size, which were the limitations of the study. Also, other fraility scores, 5-minute walking test, handgrip maneuver and cognitive function tests were not used in this study.

Conlusion

In short and long term prognosis of all cardiovascular diseases, frailty is an important guidance. CFS, which is clinically simple, easy-to-apply and inexpensive, is highly correlated with PMA, which is a quantitative indicator of frailty and closely related to prognosis in TAVI.

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.D.; Design - M.M.C.; Supervision - E.B.; Resources - İ.A.; Data Collection and/or Processing - G.D., F.E.G.; Analysis and/or Interpretation - G.D.; Literature Search - G.D.; Writing Manuscript - G.D.; Critical Review - E.B., M.M.C.

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The Importance of Computerized Drug Interaction Checker Programs Used in Community Pharmacies to Avoid Potential Drug Interactions: A Preliminary Study with Clarithromycin

Potansiyel İlaç Etkileşimlerinin Önlenmesinde Serbest Eczanelerde Kullanılan Bilgisayarlı İlaç Etkileşimi Kontrol Programlarının Önemi: Klaritromisin ile Yapılan Bir Ön Çalışma

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ABSTRACT

Introduction: Drug-drug interactions (DDI) due to multiple drug use are the most important cause of adverse drug reactions. DDIs are among medication errors that can be prevented. The integrated computerized drug interaction checker programs, which medical professionals use in addition to their medical and practical knowledge, can help medical staff to reduce potential DDIs (PDDIs), although they are not sufficient alone. The aim of this study was to investigate the role of computerized drug interaction checker programs in the identification and prevention of PDDIs in clarithromycin prescribed pediatric outpatients.

Methods: The study was a retrospective observational prescription analysis held in three community pharmacies operating in the province of Üsküdar-İstanbul during 12-month period. The prescriptions with oral clarithromycin medication were selected and PDDIs were analyzed using the R_xMediaPharma® software on an active substance base.

Results: During the 12-month period, 100 prescriptions containing 266 medicines were prescribed by 52 different physicians. The mean number of medicines per prescription was 2.66±1.11. Of the 16 PDDIs detected, five were clarithromycin-related (31.25%) and 11 were non-clarithromycin-related (68.75%). When PDDIs were categorized by severity, 10 out of 16 (62.5%) were high-risk, two (12.5%) were moderate and four (25%) were low-risk. Clarithromycin interactions were moderate with lidocaine and low with both metronidazole and sultamicillin (ampicillin/sulbactam).

Conclusion: Although evidence based computerized drug interaction checker programs that provide rapid access is not sufficient alone, they can help health care professionals in preventing PDDIs. The use of this program in the community pharmacies could minimize PDDIs during the dispensing of medicine.

Keywords: Adverse drug reactions, computerized drug interaction checker program, drug interactions

ÖZ

Amaç: Çoklu ilaç kullanımına bağlı olarak gelişen ilaç-ilaç etkileşimleri (DDI) advers ilaç reaksiyonlarının en önemli nedenidir. İlaç hatalarından bir tanesi olarak sayılan DDI önlenebilir. Sağlık profesyonellerinin tıbbi ve pratik bilgilerinin yanında kullanacakları entegre bilgisayarlı ilaç etkileşimi kontrol sistemleri, tek başlarına yeterli olmamakla beraber olası etkileşimlerin azaltılması için sağlık personeline yardımcı olabilir. Bu çalışmada ayaktan pediatri hastalarına reçete edilen klaritromisin ile potansiyel DDI'ların (PDDI) belirlenmesi ve önlenmesinde bilgisayarlı ilaç etkileşimi kontrol sistemlerinin rolünün araştırılması amaçlanmıştır.

Yöntemler: Retrospektif gözlemsel reçete analizi niteliğinde olan bu çalışmada, 12 aylık periyotta (Ocak-Aralık 2016) pediatrik ayaktan hastalara solunum yolu enfeksiyonu tanısı ile oral klaritromisin yazılan reçeteler İstanbul ili Üsküdar ilçesinde faaliyet gösteren ve çalışmaya katılmayı kabul eden, üç serbest eczaneden toplanarak müstahzar isim ve sayıları ile hasta demografik verileri (yaş, cinsiyet) kayıt edildi. PDDI'lar etkin madde bazında R_xMediaPharma® programı ile tespit analiz edildi.

Bulgular: On iki aylık periyotta 52 farklı hekim tarafından 266 adet müstahzarın reçetelendiği 100 adet reçete toplanmış olup, reçete başına ortalama müstahzar sayısı 2,66±1,11 idi. Tespit edilen 16 PDDI'nın 5'i klaritromisin (%31,25) ve 11 tanesi klaritromisin dışı (%68,75) idi. PDDI'lar şiddet bazında kategorize edildiğinde, toplam 16 etkileşimden 10 tanesi (%62,5) yüksek, 2 tanesi (%12,5) orta ve 4'ü (%25) düşük idi. Klaritromisin etkileşimleri ise: Lidokain ile orta; metronidazol ve sultamisin (ampisilin/sulbaktam) ile ise minör kategorisinde idi.

Sonuç: Hızlı erişim imkanı sağlayan bilgisayarlı ilaç etkileşimi kontrol sistemleri tek başlarına yeterli olmamakla beraber PDDI'ların önlenmesinde sağlık personeline yardımcı olabilir. Bu sistemlerin serbest eczanelerde kullanımı ilacın hastaya verilmesi esnasında yaşanacak olan DDI'ların önlenmesinde oldukça önem taşımaktadır.

Anahtar Kelimeler: İlaç etkileşimi, bilgisayarlı ilaç etkileşimi kontrol programı, advers ilaç reaksiyonları

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Introduction

Although there is no definite consensus on its definition, polypharmacy is basically defined as the use of multiple drugs at the same time for more than one indication (1). The main problem with multi-drug use is drug-drug interactions (DDIs). DDIs can be described as a change in the effect of a drug when used in combination with another drug. DDIs may cause an increase or decrease both in the effectiveness and efficacy of the drugs used together, or it may lead to the development of adverse drug reactions (ADRs) (2). Studies show that DDIs account for 3 to 5% of treatment errors in the hospitals. ADRs as a result of DDIs have been reported as the main cause of hospitalizations with rates of 10-20% (3), and between the fourth and sixth leading cause of death in hospitalized patients (4). It is, therefore, important to prevent harmful potential DDIs (PDDIs) to prevent drug-related morbidity and mortality and to ensure drug safety during outpatient treatment.

Among drug medications, DDIs can easily be prevented (5). However, each year, a large number of medications are offered to the market, and as a result, interactions between medications are gradually increasing. For this reason, it is no longer practical for physicians to trust only to their knowledge in the prevention of PDDIs (6). Additionally, especially due to large number of patients visiting the primary health care facilities, limited examination time is allocated to each patient and consequently, the physicians are not adequately informed about the medication used by the patients. Thus, this leads to duplicated prescriptions and DDIs (7). To prevent this, there are certain computerized drug interaction checker programs; however, these are not sufficient alone since they can aid health professionals to reduce potential interactions only if they are integrated into the medical and practical knowledge of health professionals (6).

Although the importance of increased ADR risk caused by pediatric polypharmacy induced PDDI is widely accepted as in adult patients, research in this area is quite rare. The information obtained from such research will help physicians develop drug use habits for pediatric patients and will enable the design of safer systems for drug prescription ordering or subsequent drug follow-up (8,9).

Non-steroidal anti-inflammatory drugs and antibiotics are the most frequently prescribed drug groups in primary care practices (6). Clarithromycin, a member of macrolide group, is a widely preferred antibiotic in the treatment of respiratory tract infections in children with a broad spectrum of antimicrobial activity, a relatively low rate of adverse events, and ease of dosing twice daily (10).

The aim of this study was to investigate the role of computerized drug interaction checker programs in the identification and prevention of PDDIs in clarithromycin prescribed pediatric outpatients.

Methods

This study was a retrospective observational prescription analysis held in Üsküdar-İstanbul for a period of 12-month from January to December 2016. Pediatric outpatient clarithromycin prescriptions with a diagnosis of respiratory tract infection were collected from three different community pharmacies located around three different family medicine clinics.

The prescriptions were analyzed with respect to the medication (name and number) and the patient demographic data (gender and age). The active ingredients of the prescribed medications were determined and PDDIs were checked via R_xMediaPharma® database (GEMAŞ Corp., İzmir, Turkey) (11). For medications containing more than one active substance (for example combined cold medications), the analysis was performed for each active substance. The severity of PDDIs was classified according to Table 1 by the software program.

The local ethical committee approval was obtained for the study (İstanbul Medipol University Ethical Committee for Non-Interventional Clinical Investigations, dated: 18.01.2017, number: 01). Informed consent was not obtained in this study.

Statistical Analysis

Data were analyzed descriptively and presented as frequencies and percentages using SPSS version 21 (SPSS Inc., Chicago, IL, USA).

Results

A total of 100 prescriptions were examined and 51 of the prescriptions were written for patients between 0-2 years of age, 48 for 2-6 years of age and one for 6-18 years of age. The distribution of prescriptions by age and gender is shown in Table 2.

In a total of 100 prescriptions, 266 different medications were prescribed by 52 different physicians. The mean number of medications per prescription was 2.66±1.11. In 44 of the prescriptions, there were more than 3 medications prescribed (Figure 1). The number of prescription-based medications was higher in the 0-2 age group. From the prescriptions examined, a total of 16 PDDIs were identified, five of

Table 1. Classification of interaction by R_xMediaPharma® program

Severity	Explanation
High	The interaction between these drugs can be life threatening or cause permanently damage. These drugs are not usually used together, they require medical intervention. An alternative medicine should be used
Moderate	The clinical impact of interaction is limited, but can be disturbing. Patient should be monitored for the findings of interaction
Low	Interaction may occur depending on the mechanism of action of co-administered drugs. Caution should be taken with regard to the reduced or increased efficacy related to the combined drugs

Table 2. Distribution of prescriptions by age and gender

Age, years	Number of prescription (n)		
	Female	Male	Total
0-2	23 (45%)	28 (55%)	51
3-6	17 (35%)	31 (65%)	48
7-18	0 (0.0)	1 (100%)	1

which were clarithromycin-related (31.25%) and 11 of them were non-clarithromycin-related (68.75%). Of the PDDIs identified, 72.3% were in the same prescription and 27.7% were in different prescriptions. The active substances that were found to interact with clarithromycin in the R_xMediaPharma® program were lidocaine, metronidazole and sultamicillin. Of the total 5 prescriptions, 3 were lidocaine and 1 was metronidazole and sultamicillin (Table 3).

When PDDIs were examined on a severity basis, 10 out of 16 (62.5%) were high-risk, two (12.5%) were moderate and four (25%) were low-risk. DDIs with clarithromycin were moderate with lidocaine, and low with metranidazole and sultamicillin (ampicillin/sulbactam) (Table 4).

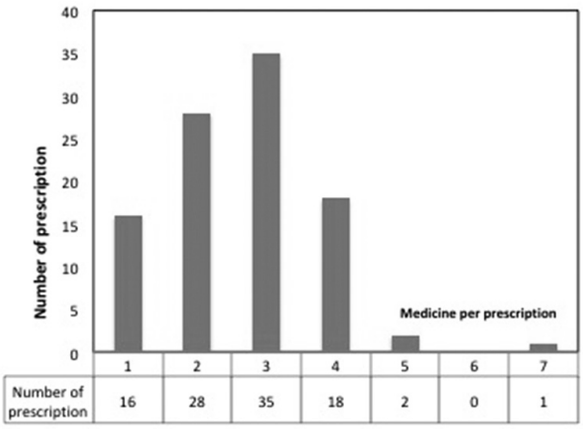

Figure 1. Distribution of medicines per prescription

Table 3. Classification of interaction with clarithromycin by R_xMediaPharma®

Active substance	Number of prescription	Severity	Possible result
Lidocaine	3	High	Prolongation of QT interval, Myocardial depression
Metronidazole	1	Low	Risk on the prolongation of QT interval
Sultamicillin	1	Low	Risk on reduction in pharmacological effect

Table 4. Distribution of potential drug-drug interactions according to the severity

Severity	Age, years			Total
	0-2	3-6	7-18	
Low	2	2	0	4
Moderate	2	0	0	2
High	6	4	0	10
Total	10	6	0	16

Discussion

Drug interactions in multidrug use are a potential concern. Although comprehensive drug evaluations are effective, they are very labor intensive and costly. It is possible to avoid interaction and dose-related errors with integrated drug systems that health professionals could use in conjunction with medical and practical knowledge.

This study investigated the efficacy of drug interaction checker programs in the prevention of PDDIs with prescribed clarithromycin in pediatric patients. This group of patients was chosen for several reasons. First of all, this group of patients is more susceptible to medication errors. Additionally, the medical management of the pediatric patients presents unique challenges throughout the medication use process. Furthermore, studies with this group of patients are few in number (12). Macrolide group antibiotics is the most commonly prescribed group after penicillin in pediatric patients, and clarithromycin, one of the group members, is the most frequently prescribed active substance following erythromycin (13). DDIs induced Q-T prolongation with clarithromycin is the major concern despite the relatively low rate of adverse events (10). Although there are several checker programs (Micromedex®, Lexicomp®, Medscape®, R_xMediaPharma® etc.) for the evaluation of PDDIs, owing to the price advantage, R_xMediaPharma® is the most widely preferred program in the community pharmacies.

In this study, of the detected 16 PDDIs, five were clarithromycin-related (31.25%) and 11 were non-clarithromycin-related (68.75%). In the literature, the reported PDDI rate widely ranges between 19% and 90% (14-16). This difference might be due to the difficulties in conducting standardized prevalence studies in the area (17). The 16% rate reported in this study can be explained by the fact that the prescriptions were collected from a limited number of pharmacies that were relatively close in locations.

Studies show that PDDI rates vary depending on the healthcare centers that the patients refer to. While PDDI rate is 16% in emergency services, it is 70% in family medicine policlinics (18). Unlike previous study, however, the PPDI rate was found to be 16% in the present study. We should note here that although the prescriptions were collected from pharmacies located around the family medicine policlinics, they were collected only from three community pharmacies.

It is known that DDIs are proportional to the number of medications used concomitantly. Karas (19) reported a PPDI incidence of 5.6% in patients using two different medications, 56% in patients using five different medications and 100% in patients using seven different medications. Similarly, Goldberg et al. (20) reported a PDDI prevalence of 13% for two medications and 80% for seven and above drug use. We also found that 72.3% of the interactions in our study were of the same prescription and that the incidence of PDDI increased with the increased number of medications per prescription. Among the prescriptions collected, there were more prescriptions for 0-2 age group patients, and the number of medications per prescription was high. We believe that physicians tend to prescribe more medications in this age group since these patients are unable to express themselves and parents are more prone to direct the physicians in assessing the symptoms.

In our study, the majority of detected PDDIs (n=10, 62.5%) were in high-risk category. It should be emphasized once again that the findings we obtained identify only PDDIs, because the database used in our study was insufficient to determine the clinical ADR (21). Similar previous studies showed that PDDI prevalence that may cause clinically significant ADRs is low despite the high prevalence of PDDI (22). According to Peng et al. (23), among the 2% PDDIs identified by sophisticated DDI checker program, only 0.04% of the total prescriptions were clinically relevant DDIs which were identified by the combination of DDI checker program and clinical pharmacist review. On the other hand, it should be noted that ADRs may result in significant morbidity and mortality, and that the level of evidence for the severity of 62% of PDDIs is based on clinical practice (24,25).

It is noteworthy that three of the five-clarithromycin-related interactions detected in our study were with lidocaine prescribed by different physicians. Both pharmacokinetics and pharmacodynamics interaction are seen with lidocaine. When given in combination with lidocaine, clarithromycin causes an increase the risk of ventricular arrhythmia by QT prolongation, on the other hand enhances the lidocaine effect/level by inhibiting the CYP3A4 enzyme (26). For this reason, patients should be monitored with electrocardiogram during treatment and motorization of serum lidocaine levels is suggested.

In our study, although the clarithromycin-to-metronidazole interaction was indicated as a low risk by the checker program, there are a few studies suggesting the prolongation of QT interval by metronidazole (27). Theoretically, co-administration of medications that can prolong QT interval may lead to an increased risk of ventricular arrhythmia, including torsade de pointes and sudden death. Although QT prolongation and ventricular arrhythmia were reported in patients treated with metronidazole in isolated studies, a causal relationship has not been established due to underlying conditions involved and concomitant medications in these studies (27).

The interaction with clarithromycin and sultamicillin (ampicillin/sulbactam) was also classified as "low" in our study. Although some *in vitro* data indicate synergism between macrolides and penicillin, there are also some *in vitro* studies showing antagonism. Although data is available for erythromycin, this interaction may theoretically occur with other macrolides. According to the literature, there is no need to take any special precaution other than monitoring the effectiveness of treatment for this interaction (28-30).

Surveys show that 39% of medical errors occur during the prescribing process and 11% during the dispensing process (31). Tightening the control steps can significantly reduce DDIs and ARDs, which are important part of drug errors experienced during the prescribing procedure. Two important tools developed for this purpose are hospital information system and e-order system (32). With these systems, the physician can observe PDDIs and ADRs during prescribing procedure (33,34). Still, the main problem with these systems is that patients do not always take their medical care from the same healthcare providers (35). Especially, in the Eastern cultures, it is common for patients to visit multiple hospitals with the same or similar conditions, and to change their doctors and/or hospitals (36,37). There are studies showing that patients who receive medical care from different healthcare providers are more likely to suffer ADRs (36,38). These systems are often designed for use in a single hospital or one managed care organization settings, and they do not have a common infrastructure for sharing the patient's medication history (34). For this reason, PDDI controls with these systems cannot go beyond hospital boundaries (39). Even though the computerized drug support and drug interaction checker programs have been developed to close this gap, the main issue with these programs is that they are stand-alone programs, which cannot be integrated into patient management systems. Therefore, for each check, physician should transfer data from the patient management system into DDI database and repeat this process for each prescribed medication (34). Especially in healthcare facilities with large number of outpatients, limited examination times of physicians is the biggest obstacle for the effective use of these programs. Consequently, prior to the initiation of treatment, the pharmacist, as the last ring of the healthcare chain in contact with the patient, is the final line of defense against harmful PDDIs (7).

Routine use of drug interaction checker programs in community pharmacies, which provide fast access, can help pharmacist for the prevention of vital malfunctions such as PDDIs. The use of these programs in combination with the medical and practical knowledge of health professionals could increase the quality and ensure the safety of the healthcare services offered.

Study Limitations

The basic limitation we should note here is that the prescriptions were collected from a limited number of community pharmacies. Despite the fact that 12 pharmacies were invited to take part in the study, six pharmacies did not agree to participate due to workload. What is more, during data collection process, three pharmacies that did not regularly provide prescriptions were excluded from the study. Therefore, a generalizability of the findings may be a limiting factor.

Conclusion

Computerized drug interaction checker programs with rapid access are not sufficient alone, but can help health professionals to prevent of PDDIs. The use of these programs, especially in community pharmacies, can serve for the identification of DDIs during delivery of the medicine to the patient. To ensure the effective use of the programs by health professionals, they need to be standardized to provide clinically relevant ADRs in line with evidence-based information, along with their integration into e-order systems. Hence, DDIs and ADRs caused by DDI during both prescribing and dispensing will be prevented more effectively.

Ethics Committee Approval: The local ethical committee approval was obtained for the study (İstanbul Medipol University Ethical Committee for Non-Interventional Clinical Investigations, dated: 18.01.2017, number: 01).

Informed Consent: Informed consent was not obtained in this study.

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A Rare Cause of Colon Perforation; Intrauterin Device

Nadir Görülen Bir Kolon Perforasyon Nedeni; Rahim İçi Araç

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ABSTRACT

Intrauterin device (IUD) is one of the most common used contraseptive methods in the world. Migration of IUD to sigmoid colon is a rare and serious complication. This report represents a case with an acute abdominal condition due to a migrating IUD which perforated the uterus and migrated to and perforated the sigmoid colon. IUD was removed from the abdomen laparoscopically and at the same session, laparoscopic repair of the sigmoid colon and uterus were performed. Laparoscopy is a reliable method for patients with lost intra-abdominal IUD which migrates by perforating the uterus. It enables repair of organ perforations at the same session and provides less tissue damage by minimal incision, less postoperative pain and decreased risk of intra-abdominal adhesion and therefore, facilitating the patient's comfort and decreasing duration of hospitalization.

Keywords: Sigmoid colon perforation, uterus perforation, intrauterin device, laparoscopy

ÖZ

Rahim içi araç (RİA) dünyada en sık kullanılan kontraseptif yöntemlerinden biridir. RİA'nın sigmoid kolona migrasyonu nadir görülen ciddi bir komplikasyondur. Bu çalışmamızda uterusu perfore ederek sigmoid kolona migrasyon yapan ve kolon perforasyonu oluşturarak akut batın kliniği veren hastamızda, RİA'nın laparoskopik olarak batın dışına çıkarılmasını ve aynı seansta laparoskopik sigmoid kolon ve uterus onarımının yapılmasını sunduk. Uterus perforasyonu oluşturarak migrasyon yapmış kayıp batın içi RİA olgularında laparoskopi güvenilir bir yöntem olup, aynı seansta organ perforasyonlarının tamirine de olanak sağlamakta ve minimal insizyonla daha az doku travması, daha az postoperatif ağrı ve azalmış intra-abdominal adezyon riski sağlayarak hasta konforu ve yatış süresinin kısalmasına olanak tanımaktadır.

Anahtar Kelimeler: Sigmoid kolon perforasyonu, uterus perforasyonu, rahim içi araç, laparoskopi

Introduction

Intrauterine device (IUD) is one of the most common and reversible contraception methods (1). Although the long-term and systematic side effects of IUD are minimal, it can cause mortality due to migration of the device to neighboring organs. The rate of uterine perforation due to IUD is reported as 0.05-13/1000 in the literature (2). As a result of the migration of IUD; ischemia, perforation, obstruction and mesenteric injury may occur in the small and large intestines. Complications such as migration to luminal organs, adhesions and infection in peritonial cavity have also been reported (3). After perforation, IUD migrates to adjacent organs such as appendix, peritoneum, omentum and bladder, and sigmoid colon perforation was rarely presented as a case report (4). Laparoscopy can be used in cases in whom IUD is lost in abdomen by migrating outside the uterus for both diagnostic purpose and for therapeutical purpose to repair organ damage. In this study, we showed the removal of IUD, which migrated to sigmoid colon and caused perforation, outside abdomen and repairing of sigmoid colon and uterus by laparoscopy.

Case Report

A 31-year-old female was admitted to emergency service with left-lower quadrant pain. The patient had a history of IUD placement 1 year ago. She had left-lower quadrant pain for 10 days and it worsened for 1 day. The nullipara patient had no other feature in medical history, her hemodynamics were stable and body her temperature was normal. In examination, she had tenderness in the left-lower quadrant of abdomen and systemic examinations were normal. Leucocyte count was 11.13/mm^3 in hemogram and other parameters were normal.

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In gynaecological examination, it was thought that IUD had left the myometrium of uterus and went out of the serosa, when the tail of IUD was not observed and the transvaginal ultrasonography did not show the echogenicity of IUD. Laparoscopic exploration was planned for the patient with acute abdomen findings. Laparoscopic surgery was performed under general anesthesia. In exploration, the sigmoid colon was attached to the posterior wall of the uterus. Uterus was perforated by the IUD and half of the IUD was in the sigmoid colon (perforation). Laparoscopic surgery was continued with 3 trocars and the colon adhesions on the back wall of the uterus were opened. In the sigmoid column, IUD was removed from the 0.5 cm perforation area and taken out of the abdomen (Figure 1). This defect was repaired with 2/0 silk suture (Dogsan, İstanbul, Turkey). Colporrhapy was performed (Figure 2) and the defect in the posterior wall of the uterus was repaired primarily. The abdomen was washed with saline and then was aspirated. Following hemostasis control, the operation was laparoscopically completed by placing 1 drain into the neighbourhood of colon repair area. She was discharged without complications in the postoperative 5th day. The patient was followed up in the outpatient clinic after discharge. There were no complications requiring surgical or medical treatment in the control of the patient. Informed consent was obtained from the patient to use her data in this study.

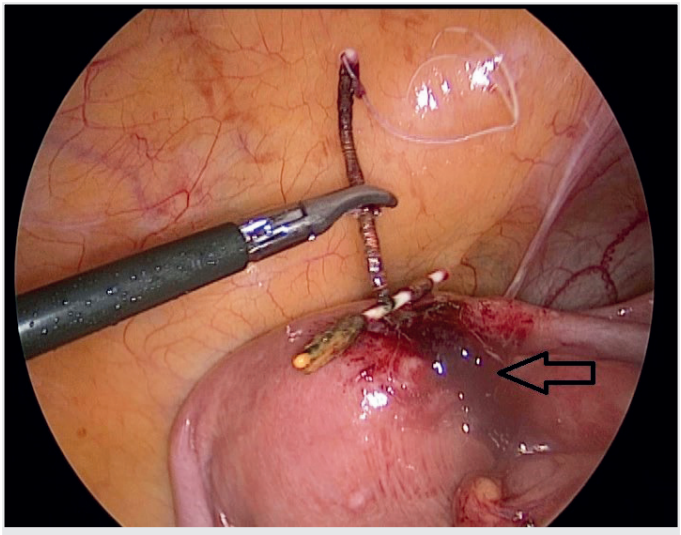

Figure 1. Removal of intrauterine device from uterus and sigmoid colon, laparoscopically; the site of perforation in uterus (Black arrow)

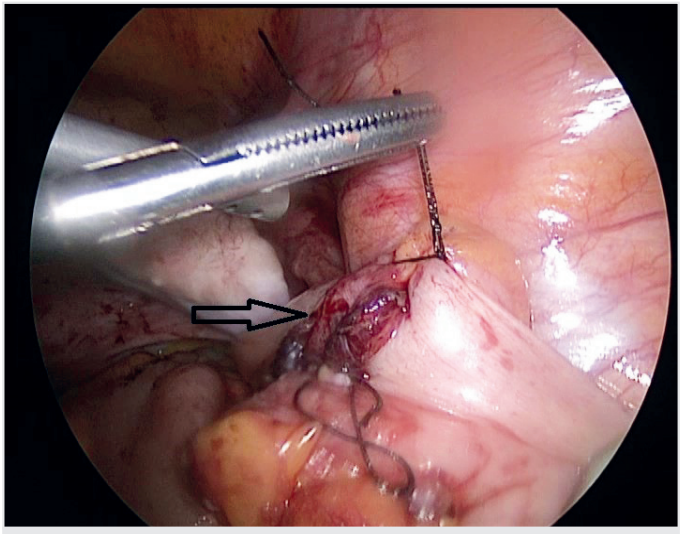

Figure 2. Laparoscopic repair of sigmoid colon which was perforated by intrauterine device

Discussion

The using rate of IUD as a contraceptive method in developed countries is 9.4% and 16.4% in undeveloped countries (5). In recent years, use of IUD has decreased with the belief that it increases the risk of infection (6). In addition to the experience of the health personnel performing IUD, anatomic position of uterus is a risk factor for perforation and organ injury. Although perforations are usually from the posterior or fundal wall of uterus, these perforations are often thought to occur during the insertion process (7,8). The time between migration of IUD to abdomen and adjacent organ injury was reported as 17 months on average (9). In our case, this time was 12 months. Perforation may not be noticed immediately after the placement of IUD. Abdominal pain and uterine bleeding may be seen and also some patients may be asymptomatic. Among intestinal segments, IUD migrates mostly to the rectum, sigmoid colon and small intestines (10). In our case, IUD migrated to sigmoid colon and the patient was clinically asymptomatic for 1 year after IUD placement.

In order to determine the localization of IUD which is lost, ultrasonography, direct graphy, hysteroscopy, computed tomography and surgery may be performed (11). The perforation of the sigmoid colon can be detected insidentally and also it can present with pain and lower gastrointestinal system bleeding (12).

Andersson et al. (13) reported that patients admitted in the late period were mostly asymptomatic and the most common finding in patients admitting in the early period (first one month) was left-lower quadrant pain.

In our case with left-lower quadrant tenderness, diagnostic laparoscopy was performed due to suspected dislocation of the uterus based on the findings that the tail of IUD was not seen in vaginal examination and IUD was not detected in the uterine cavity in ultrasonography.

In diagnostic laparoscopy, uterus and sigmoid colon were attached to each other and formed an inflamed appearence and laparoscopic exploration was continued. In our case, half of the IUD was observed in sigmoid colon and the other half in uterus myometrium. IUD was taken out of uterus and sigmoid colon. The perforation of the sigmoid colon and uterus was repaired laparoscopically and the operation was completed. In the literature, although IUD's migration to sigmoid colon was rarely reported, laparoscopy was used in the diagnosis of similar organ migration cases, but laparotomy was often chosen for organ repair.

Laparoscopic surgery procedures are procedures that require experience and training. Laparoscopy was associated with less postoperative pain, increased quality of life after discharge, early return to normal physical activity, decreased intraabdominal adhesion risk, early discharge and decreased risk of incisional hernia in the long-term period compared with conventional surgery (14).

Intrauterin device migrated to abdominal cavity can cause recurrent pain, intestinal obstruction, and infertility by forming adhesions. Therefore, IUD should be removed if not seen in the uterine cavity, even if the patient does not have symptoms (15).

Conclusion

The fact that we used laparoscopy for both diagnosis and repair of sigmoid colon and uterus makes our case different from similar cases in the literature. The use of laparoscopy in cases with IUD located outside the uterin cavity for both diagnosis and repairing the organs contributes to the improvement in postoperative quality of life of the patients.

Informed Consent: Informed consent was obtained from the patient to use her data in this study.

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Spontaneous Intramuscular Hematoma due to Subcutaneous Enoxaparın

Subkütan Enoksaparine Bağlı Spontan Kas İçi Hematom

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ABSTRACT

Low molecular weight heparins (LMWH) are generally used for acute coronary syndrome (ACS) treatment. Although bleeding is the most common complication associated with the use of LMWH, it that can lead to hemodynamic disorder is rare. Here we present a case of rectus abdominis intramuscular hematoma (RAIH) after use of subcutaneous LMWH. A 73 -year-old female patient was hospitalized with a diagnosis of ACS and pneumonia. Due to ACS, LMWH was started as anticoagulant therapy. When follow up in the service, the patient developed sudden abdominal pain. Immediately, abdominal ultrasonography and computed tomography were performed and left RAIH was detected. Emergency surgery was not intended and supportive therapy (fluid, erythrocyte suspension, analgesics) was given to the patient. Hemodynamic parameters of the patient were followed up closely. Hematoma declined in follow up and reducing the patient's symptoms. Coronary angiography was performed when patient stabilizied hemodynamically and stent was placed to obtuse marginal artery which is a branch of the circumflex artery. After the procedure, the patient without symptoms was discharged with the recommendations. Patients who LMWH administered subcutaneously and was performed suddenly abdominal pain with a palpable mass in physical examination, RAIH should be considered in the differential diagnosis. In patients with predisposing factors to reduce the risk of fatal RAIH, lower dose of LMWH should be used and care should be taken to make the injection under the skin. When RAIH develops, early diagnosis and a multidisciplinary approach and not be delayed treatment are the most important factor in combating these complications.

Keywords: Acute coronary syndrome, low molecular weight heparins, enoxaparin, hematom

ÖZ

Düşük molekül ağırlıklı heparinler (DMAH) akut koroner sendrom (AKS) tedavisinde sık kullanılmaktadır. DMAH kullanımına bağlı en sık görülen komplikasyon kanama olmakla birlikte hemodinamik bozukluğa yol açabilecek kanamalar nadiren görülmektedir. Burada subkütan DMAH kullanım sonrası rektus abdominis kas içi hematom (RKİH) gelişen bir olgu sunuldu. Yetmiş üç yaşında kadın hasta AKS ve pnömoni tanısı ile servise yatırıldı. AKS nedeni ile antikoagülan tedavi olarak DMAH başlandı. Takiplerde ani gelişen karın ağrısı olan hastanın yapılan batın ultrasonografi ve batın bilgisayarlı tomografide sol RKİH saptandı. Acil cerrahi düşünülmeyen hastaya destek tedavisi (eritrosit süspansiyon replasmanı, sıvı ve analjezik tedavi) verildi ve hemodinamik olarak yakın takip edildi. Takiplerde hematom geriledi, hastanın semptomları azaldı. Hemodinamik olarak stabilleşen hastaya yapılan koroner anjiyografi neticesinde sirkümfleks arter obtus marjinal yan dalına stent yerleştirildi. İşlem sonrası semptomu olmayan hasta önerilerle taburcu edildi. Subkütan DMAH uygulanan, ani gelişen karın ağrısı ve fizik muayenede ele gelen kitlesi olan hastalarda RKİH ayırıcı tanıda akla gelmelidir. Ölümle sonuçlanabilen RKİH riskini azaltmak için predispozan faktörü olan hastalarda daha düşük doz DMAH kullanılmalı ve enjeksiyonun deri altına yapılmasına dikkat edilmelidir. RKİH geliştiğinde erken tanı, multidisipliner yaklaşım ve tedavinin geciktirilmemesi bu komplikasyon ile mücadeledeki en önemli unsurlardır.

Anahtar Kelimeler: Akut koroner sendrom, düşük molekül ağırlıklı heparin, enoksaparin, hematom

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Introduction

Heparin is a routine agent used in the treatment of acute coronary syndrome (ACS). Low molecular weight heparin (LMWH) is a type of heparin commonly used in the treatment of ACS due to its ease of use. Although major bleeding complications due to LMWH are frequently observed, bleeding that causes severe hemodynamic impairment is rarely observed. In this article, we present a case of rectus intramuscular hematoma (RIMH) after subcutaneous LMWH use.

Case Report

A 73-year-old woman without a history of chronic disease was admitted to the emergency department with palpitations and shortness of breath. Her vitals were as follows: blood pressure: 136/84 mmHg, heart rate: 154 / min and arrhythmic, respiratory rate: 20/minute, oxygen saturation: 92% and body temperature: 37.4 °C. Electrocardiogram (ECG) was consistent with atrial fibrillation rhythm and sinus rhythm was achieved after 25 mg intravenous diltiazem. T wave negativity was seen in lateral leads in sinus rhythm ECG. Auscultation revealed crepitant rales at the base of the right lung. Chest X-ray showed findings in favor of pneumonia in the right lung. The patient's complete blood count (CBC) and biochemistry values were as follows: leukocyte: 19320/µL (n=4500-10500/µL), hemoglobin: 11.4 g/dL (n=11.5-15.5 g/dL), creatinine: 1.15 mg/dL (n=0-1.17 mg/dL), glucose: 222 mg/dL (n=82-115 mg/dL), sodium: 137 mmol/L (n=135-148 mmol/L), potassium: 4.2 mmol/L (n=3.5-5.5 mmol/L), aspartate aminotransferase: 48 U/L (n=0-40 U/L), alanine aminotransferase: 25 U/L (n=0-41 U/L), C-reactive protein: 173.2 mg/L (n=0-5 mg/L), D-Dimer: 3090 ug/L (n=0-500 ng/L) and troponin I: 1.04 ng/mL (n=0-0.06 ng/mL). The patient was hospitalized in the coronary intensive care unit with the diagnoses of atrial fibrillation, ACS and pneumonia. Anti-ischemic treatment (LMWH, clopidogrel, aspirin, ramipril, nitroglycerin, metoprolol, atorvastatin) was initiated for ACS, and antibiotherapy was started for pneumonia with the suggestion of department of infectious diseases. Coronary angiography was planned following infection control. Echocardiography showed moderate left ventricular systolic function (ejection fraction: 35%), left ventricular wall motion abnormalities, mild mitral and tricuspid regurgitation. During follow-up, the patient's symptoms decreased and acute phase reactants regressed. On the sixth day of admission, the patient had abdominal pain on the left lower quadrant that increases with movement. Physical examination revealed a palpable mass on the left lower quadrant of the abdomen. In the abdominal ultrasonography of the patient, a 65x30 mm lesion compatible with hematoma was found on the anterior surface of the left rectus muscle. Supportive treatment (fluid and analgesic treatment) was started. LMWH was discontinued in his treatment; but clopidogrel and aspirin in treatment were continued because of ACS. Serial CBC tests were performed. Emergency surgery was not considered by department of general surgery. Abdominal computed tomography of the patient that was performed one day later revealed a 97x55 mm hematoma at the left rectus abdominis muscle (Figure 1). On follow-up, hemoglobin levels decreased to 8.2 g/dL and 2 units of erythrocyte suspension were administered to the patient. The hemoglobin level after replacement was 10.4 g/dL. Coronary angiography was performed to the patient when hemodynamic stabilization was achieved. It revealed 70% stenosis in the obtuse marginal artery (Cx-OM), a branch of the circumflex artery, and a stent was placed successfully. The patient had no symptoms at the follow-up period and control abdominal ultrasound showed that the diameter of hematoma decreased to 60x32 mm. The patient, who was symptom free and had stable hemoglobin levels, was discharged with recommendations. Written informed consent was obtained from the patient for publication of this case report.

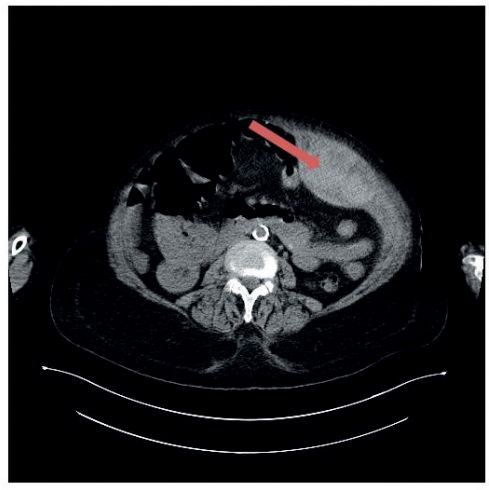

Figure 1. Left rectus abdominis intramuscular hematoma on computed tomography

Discussion

RIMH is an uncommon picture reported on case basis (1). It may cause a misdiagnosis with clinical similarity to acute abdomen and may be fatal if not noticed (2). RIMH can be caused by rupture of the rectus muscle due to strain and rupture of the inferior epigastric artery. The risk increases in elderly, chronic kidney and liver diseases, degenerative muscle diseases, collagen tissue diseases, hematological diseases, and chronic obstructive pulmonary disease (COPD) patients with frequent coughing that leads to increased intra-abdominal pressure (1,3).

The cases of LMWH-related RIMH are generally elderly female patients with COPD who have chronic cough (2). It is more common in women than in men (4,5). In one case series, 11 of 12 patients who received anticoagulant therapy and developed RIMH were female, and 7 had complaints of frequent cough (6). It is reported that its high prevalence in women may be due to deformation of the rectus abdominis muscle due to pregnancy (4). The fact that our patient was old and female and had frequent coughs due to pneumonia may have facilitated the development of RIMH.

LMWH has been widely used in the treatment of ACS, pulmonary thromboembolism and deep vein thrombosis. As it can be administered subcutaneously instead of infusion and follow-up activated partial thromboplastin time is not required, it has replaced unfractionated heparin (7-9). The most common complication of LMWH is associated with bleeding. In a study, enoxaparin-induced major bleeding was found to be 6.5% and minor bleeding was 18.5% (10). In another study, 14 major bleeding were observed in 554 patients using enoxaparin and 4 of them were reported as hematoma spreading in the anterior abdominal wall muscles (11).

It has been reported that intramuscular injection causes hematoma in the development of LMWH-associated RIMH, but that it is not sufficient to develop hematoma alone. It has also been reported that the rupture of inferior epigastric artery due to strain of the rectus abdominis muscle in case of cough that increases intra-abdominal pressure or local anticoagulant effect causes extensive hematoma (1,12). In our case, the presence of frequent cough episodes due to pneumonia may have facilitated the development of RIMH.

One of the most important bleeding complications that may occur due to subcutaneous LMWH is the anterior abdominal wall intramuscular hematoma. This complication can be seen mostly in injections applied to the abdomen. Changing the injection site reduces this complication development but does not completely eliminate it. As a matter of fact, no injection was made in the hematoma area in our patient. Although intramuscular hematomas may be self-limited, surgical intervention may be required in some cases and may cause death in rare cases (13). In our case, the RIMH was self-limited despite aspirin and clopidogrel treatment due to ACS, and the patient's symptoms regressed with supportive therapy (erythrocyte suspension replacement, fluid and analgesic treatment).

Conclusion

In patients who were administered subcutaneous LMWH and who had a sudden onset abdominal pain and a mass in the physical examination, RIMH should be considered in the differential diagnosis. The frequent use of LMWH in the treatment of ACS in cardiology practice, especially in the treatment of older female patients with predisposing factors, RIMH may be expected to occur more frequently. In patients with predisposing factors, a lower dose of LMWH should be used and the injection should be performed subcutaneously to reduce the risk of fatal RIMH. Early diagnosis, multidisciplinary approach and early initiation of treatment are the most important factors in the management of this complication.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Peer-review: Externally peer-reviewed.

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

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Does Attenuated Mckittrick-Wheelock Syndrome Exists?

Hafif Mckittrick-Wheelock Sendromu Var Olabilir mi?

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ABSTRACT

McKittrick-Wheelock syndrome is caused by fluid and electrolyte hypersecretion from colorectal tumor. We present a patient with large villous adenoma who had hyponatremia and rectal bleeding and treated with laparoscopic surgery. A 52-year-old female patient presented with rectal bleeding and hyponatremia (117 mEq/lt sodium) in biochemistry. After electrolytic replacement therapy and preoperative colonoscopy and magnetic resonance imaging examinations, the patient underwent laparoscopic surgery and full postoperative recovery was achieved. This case raises the question whether there are mild forms of McKittrick-Wheelock syndrome.

Keywords: Villous adenoma, hyponatremia, McKittrick-Wheelock syndrome

ÖZ

McKittrick-Wheelock sendromu kolorektal bir tümörün yüksek miktarda sıvı ve elektrolit salgılamasıyla oluşur. Bu yazıda büyük bir villöz adenom nedeniyle hiponatremi ve rektal kanaması olan ve laparoskopik cerrahi ile tedavi edilen bir hastayı bildirmekteyiz. Elli iki yaşında kadın hasta rektal kanama ve hiponatremi (117 mEq/lt) ile başvurdu. Elektrolit replasman tedavisi ile preoperatif kolonoskopi ve manyetik rezonans görüntüleme ardından hastaya laparoskopik cerrahi uygulandı ve postoperatif tam iyileşme sağlandı. Bu olgu McKittrick-Wheelock sendromunun daha hafif formlarının olabileceği sorusunu akla getirmektedir.

Anahtar Kelimeler: Villöz adenom, hiponatremi, McKittrick-Wheelock sendromu

Introduction

Villous adenomas of colon might cause electrolyte and protein loss. This phenomenon was first described by McKittrick and Wheelock in 1954 (1) and then by Mckittrick et al. (2) in 1956. McKittrick and Wheelock syndrome is a complex clinical syndrome including fluid and electrolyte imbalance, hypovolemic shock and renal dysfunction due to colonic villous adenoma. Symptoms and findings of this syndrome are hyponatremia (headache, muscle cramps, lethargy etc.) and hypokalemia (paresthesia, ileus, hypotension, arrhythmia etc.) (3,4).

Case Report

Sixty-seven years old female patient was evaluated in our outpatient clinic for rectal bleeding and a mass was palpated in rectal examination. A detailed colonoscopy revealed a 6-7 cm villous adenoma occupying the rectal lumen at 8 cm from anal verge. The biopsy of the mass showed severe dysplasia. A computed tomography of the abdomen showed multilobular mass inside rectum (Figure 1). The patient was hospitalized for surgery, but her serum sodium level was 117 mEq/lt. Multidisciplinary intervention was undertaken to normalize intractable low serum sodium levels that could only be raised to 130 mEq/lt. The surgery was delayed for one week. Later, the patient had a laparoscopic low anterior resection. Serum sodium level on postoperative day 1 was 138 mEq/lt and it remained stable thereafter. Pathological examination of the resected mass revealed villous adenoma without any findings of malignancy. Written informed consent was obtained from the patient.

Discussion

Three percent of villous adenomas, particularly those larger than 7-18 cm, have secretory activity (5). These adenomas are mainly localized in the rectum, but also rarely in sigmoid colon (5-7). Not all of these adenomas present with Mckittrick-Wheelock syndrome (MWS), which has rather severe clinical symptoms. This was also true for our patient who only had intractable hyponatremia. In the context of complexity of MWS, single electrolyte deficiency of our case raises the question whether this is an attenuated form of the syndrome. In a case series involving 35 patients with MWS, hyponatremia is the second most common finding after hypokalemia and renal failure. These metabolic disarrangements in surgical patients adversely affect management of patients.

Villous adenoma and electrolyte disorders are also seen in Cronkhite-Canada syndrome, thalassemia, cirrhosis, deep venous thrombosis,

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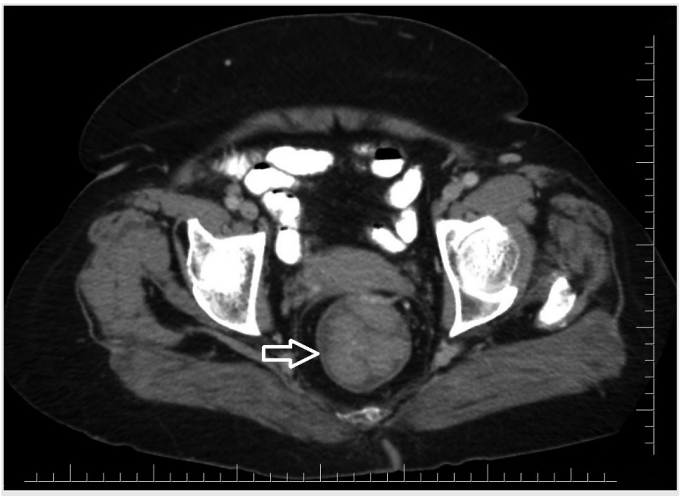

Figure 1. Arrow points the multilobular mass

dermatomyositis and diabetes (7). Our patient also had diabetes. As it is demonstrated in our case, the definitive treatment of these patient should be surgical, despite the presence of constellation of medical disorders (5). In the literature, endoscopic submucosal dissection has been reported to be feasible and useful for MWS treatment (8). In another study, it was reported that the symptoms of MWS may be reduced 48 hours after the start of indomethacin therapy (9). Transabdominal laparoscopic procedures are the most described methods in the treatment of MWS. Additionally, transanal minimally invasive surgery, has been reported as an alternative surgical approach (10).

Conclusion

Our case could be representing a mild form of MWS. Surgery should be undertaken in such cases, as there is high risk of malignancy and intractable nature of the electrolyte disorder.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept - S.E., B.C.Y.; Design - S.Ö., D.T.; Supervision - B.C.Y., B.D.Y.; Data Collection and/or Processing - S.Ö., D.T.; Analysis and/or Interpretation - S.Ö., D.T., M.T.; Literature Search - S.E., B.D.Y.; Writing Manuscript - S.E., B.D.Y., M.T.; Critical Review - B.C.Y., M.T.

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Disease Severity and The Effect of Disease Severity on Quality of Life in Patients with Acne Vulgaris

Akne Vulgarisli Hastalarda Hastalık Şiddeti ve Hastalık Şiddetinin Yaşam Kalitesi Üzerine Etkisi

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Keywords: Acne vulgaris, psychosocial aspects, quality of life

Anahtar Kelimeler: Akne vulgaris, psikososyal yönleri, yaşam kalitesi

Acne vulgaris is one of the most common diseases affecting the quality of life among skin diseases (1). Studies have shown that patients with acne have high rates of depression, anxiety, suicidal tendency, and negative effects on quality of life have generally been shown to increase with increased acne severity (2). Motley and Finlay (3) from Cardiff University developed "Cardiff Acne Disability Index" (CADI) specifically for patients with acne vulgaris. This index evaluates the findings of how the patient was affected physically, psychologically, emotionally, and socially due to illness. The Turkish version of the CADI form was used in our study (4).

Global Acne Grading System (GAGS), which is used to evaluate clinical severity, is one of the most commonly used scoring systems (5). The study was started following local ethics committee approval (dated 15/12/2016, number: 135).

A total of 202 patients (13-45 years old, 133 female and 69 male) with acne vulgaris were included in the study. Seventy-six patients were under 18 years old and 126 patients were 18 years or older. The mean value of CADI was 6.8±3.0 in all patients, 7.1±3.0 in females and 6.1±3.1 in males. These results showed that CADI was significantly higher in females than males (p=0.033). The mean overall CADI score was 6.3±3.0 in female patients under 18 years of age and 7.5±3.0 in female patients 18 years or older (p=0.035). The mean overall CADI score was 6.6±2.9 in male patients under 18 years of age and 5.7±3.1 in male patients 18 years and older (p=0.184).

The question indicating how the patient perceived his psychological condition had the lowest mean value with a score of 1.9±0.8 and the question asking discomfort due to the presence of acne vulgaris lesions had the lowest mean value with a score of 0.7±0.9. The mean score of question asking for the negative emotions and psychological status of the patient due to acne vulgaris was significantly higher in females (mean: 1.5) than in males (mean: 1.2) (p=0.017). Also, the mean score of the question showing how the patient perceived the disease was significantly higher in females (mean: 2.0) than in males (mean: 1.7) (p=0.028). These results showed that women perceived their illness as more severe. The mean score of the question on the negative effects of acne lesions on social life was significantly lower in females under 18 years of age than in females 18 years or older (0.7 vs. 1.1, respectively, p=0.017). There was no significant difference between individual questions in terms of gender and age.

There was no significant correlation between age and GAGS score in all patients and in only female patients (p=0.183, p=0.214, respectively). However, GAGS score was significantly higher in male patients under 18 years of age than those aged 18 years and older (p=0.045).

Men had more severe acne vulgaris than women. Regarding age, male patients under 18 years of age had more severe acne vulgaris lesions compared to male patients aged 18 years and older and female patients.

There was no significant correlation between GAGS score and overall CADI score and individual question scores (p=0.218).

Although the severity of acne vulgaris in females was less than in males in this study, it was found that their quality of life was negatively affected and that CADI scores were significantly higher than males. While CADI score was significantly lower in females under 18 years of age than in females 18 years and older, there was no difference in males in terms of age.

This study also presented as poster in 3. National Dermatology & Cosmetology Congress with International Participants on 14-17 March.

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Questionnaire score regarding the effects of acne vulgaris lesions in the body was found to be low in our study. Unlike other studies, the question asked in order to reveal how a person perceives his or her own disease psychologically has the highest mean value in all patients.

In conclusion, although the GAGS score was higher in male patients and males had more severe acne lesions clinically, it was found that female patients were more affected psychosocially and that this effect was more prominent especially in women aged 18 and over regarding CADI scores.

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