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Department of Anesthesiology and Reanimation, Gulhane Training and Research Hospital, University of Health Sciences, Ankara, Türkiye Anesthetic Management in Post-Chemotherapy Retroperitoneal Lymph Node Dissection: Insights from Our Clinical Experience

Kemoterapi Sonrası Retroperitoneal Lenf Nodu Diseksiyonunda Anestezi Deneyimimiz

ABSTRACT Objective:

Testicular tumors, of which 95% are germ cell tumors, are generally solid tumors seen in men under the age of 35. Testicular tumors are primarily treated with orchiectomy. Following orchiectomy and chemotherapy, retroperitoneal lymph node dissection (RPLND) is an important surgical procedure in uro-oncology. In our study, we aimed to share our experiences by discussing our anesthesia management in RPLND operations conducted after chemotherapy at our hospital in light of current literature.

Material and Methods:

This study investigates cases of Retroperitoneal Lymph Node Dissection (RPLND) performed after chemotherapy at a tertiary education and research hospital between 2017 and 2023. After obtaining approval from the Ethics Committee (No: 2023/305), data including patients' ages, operation durations, perioperative blood gas and fraction of inspired oxygen (FiO2) values, and the amount of fluid administered during the procedure were retrospectively reviewed from patient records and anesthesia monitoring forms. Patients with incomplete information were excluded from the study. Blood gas samples obtained immediately after anesthesia induction were compared with those taken upon admission to the intensive care unit. In our clinic, routine consultations with chest diseases and medical oncology are obtained prior to this procedure.

Results:

In our study, data from 34 out of 37 RPLND cases conducted over a four-year period were included. ASA III patients constituted 35% (n=12), while ASA II patients made up 65% (n=22), with an average age of 28 years (range: 17 to 47). The average anesthesia duration from the time patients entered the operating room to their admission to the ICU was recorded as 340.7 minutes, and the average extubation time from ICU admission was 125.6 minutes. While there were no significant changes in the average pH, pO2, and pCO2 values in blood gases of patients a significant increase in lactate levels was observed. It was noted that the perioperative (FiO2) was maintained below 40% and the crystalloids administered in the first 2 hours were kept below 4 mL/kg/hour. All patients were discharged home after the operation.

Conclusion:

RPLND requires a multidisciplinary approach. Measures taken against perioperative hypoxia and hyperoxia, as well as fluid management, may be crucial in preventing major complications that can arise during both the intraoperative and postoperative periods.

Key Words:

Germcell tumors, Hiperoksi, Multidisciplinary approach, Pulmonary toxicity, Retroperitoneal Lymph Node Dissection

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ÖZ Ame

Amaç:

Genel olarak 35 yaş altı erkeklerde görülen testis tümörlerinin %95'i germ hücreli olup solid tümörlerdir. Öncelikle orşiektomi ile tedavi edilen testis tümörlerinde kemoterapiyi takiben retroperitoneal lenf nodu diseksiyonu (RPLND) önemli bir cerrahi uygulamadır. Çalışmamızda, RPLND operasyonlarındaki anestezi yönetimimizi güncel literatür ile tartışarak deneyimlerimizi paylaşmak istedik.

Gereç ve Yöntemler:

Çalışmada bir eğitim araştırma hastanesinde 2017-2023 yılları arasında gerçekleştirilen kemoterapi sonrası RPLND olguları incelendi. Etik kurulundan (No: 2023/305) onay alındıktan sonra, hastaların yaşı, operasyon süresi, peroperatif kan gazı ve işlem esnasında verilen sıvı miktarı hastaların eve taburculuk durumu, hasta dosyalarından ve anestezi takip formlarından retrospektif olarak incelendi. Bilgileri eksik olan hastalar çalışmaya dahil edilmedi. Anestezi indüksiyonundan hemen sonra alınan kan gazı örnekleri, yoğun bakım ünitesine kabul sırasında alınan örneklerle karşılaştırıldı. Kliniğimizde RPLND vakalarında rutin olarak peroperatif alınan havanın oksijen yüzdesi (FiO2) değeri %40 ve altında tutulmakta olup preoperatif multidisipliner değerlendirme yapılmaktadır.

Bulgular:

Çalışmamıza altı yıllık bir süre boyunca yürütülen kemoterapi sonrası 37 RPLND vakasından verileri eksiksiz olan preoperatif multidisipliner ekip tarafından değerlendirilen 34 hasta çalışmaya dahil edildi. ASA III hasta %35 (n:12), ASA II hasta %65(n:22) olup ortalama yaşları 28 (en az 17-en fazla 47)'idi. Hastaların ameliyathaneye giriş anından yoğun bakım ünitesine yatış süresine kadar geçen süre ortalama 340,7 dakika, yoğun bakım ünitesine yatıştan itibaren ortalama ekstübasyon süresi 125,6 dakika olarak kaydedildi. Hastaların kan gazlarında ortalama pH, pO2 ve pCO2 değerlerinde anlamlı bir değişiklik olmazken, laktat seviyelerinde anlamlı bir artış gözlendi. Peroperatif FiO2 %40'ın ve kristaloid sıvı ilk 2 saate 4 mL-1 kg-1 saat 'in altında tutulmaya çalışıldığı görüldü. Peroperatif ve postoperatif kardiyak pulmoner majör komplikasyon gelişmeyen hastalar eve taburcu edildiler.

Sonuc:

RPLND multidisipliner bir yaklaşım gerektirir. Perioperatif hipoksi ve hiperoksiye karşı alınan önlemler ve sıvı yönetimi, hem intraoperatif hem de postoperatif dönemde ortaya çıkabilecek majör komplikasyonların önlenmesinde önemli olabilir.

Anahtar Kelimeler:

Germ hücre tümörü, Hiperoksi, Multidisipliner yaklaşım, Pulmoner toksisite, Retroperitoneal lenf nodu diseksiyonu

INTRODUCTION

Testicular tumors are predominantly solid tumors seen in men under the age of 35, and their incidence has been increasing in recent years due to unexplained factors (1, 2). Ninety-five percent of these tumors are germ cell tumors; there are two types, seminomatous and non-seminomatous germ cell tumors (NSGCTs). Their lymphatic spread is often seen along the periaortic lymph nodes. Testicular tumors, which require a multidisciplinary approach, are primarily treated with orchiectomy. Following orchiectomy and chemotherapy, the possibility of residual tissue remaining in the retroperitoneal area for NSGCTs is approximately 20-50% (3). Even in advanced-stage testicular tumor cases, current multidisciplinary approaches result in a 10-year survival rate of approximately 98% (4). Retroperitoneal lymph node dissection (RPLND) offers a survival rate of 90% and above (5). This operation, typically performed through a broad abdominal incision extending up to the sternum, is particularly demanding and involves a fragile patient group, hence it requires special attention in the preoperative, intraoperative, and postoperative periods in terms of anesthesia.

Since the 1970s, platinum-based chemotherapeutic agents employed in the treatment of testicular tumors have significantly reduced mortality rates, though they are also associated with severe side effects that may persist throughout life. The most commonly preferred chemotherapy regimen for the treatment of testicular tumors is the bleomycin, etoposide, and cisplatin (BEP) procedure. Bleomycin, first isolated in 1966 by Umezawa et al., is an antitumor antibiotic that causes DNA damage, particularly leading to endothelial damage in the lungs (4, 6). Bleomycin is specifically associated with acute pulmonary toxicity. Factors known to increase the risk of acute pulmonary toxicity include a cumulative bleomycin dose exceeding 300 U, impaired renal function, smoking, and advanced age (7). Cisplatin, a platinum-based other chemotherapeutic used in this protocol, is known for its most common side effect, acute kidney damage and hypomagnesemia, which reportedly affect about 90% of patients (8). In addition to these side effects, cardiotoxicity, cisplatin-induced peripheral neuropathy (CIPN), and ototoxicity are serious side effects associated with this agent and are related to the cumulative doses used (9). In a review by Cameron et al., which examines the relationship between chemotherapeutic agents and vascular damage, acute and chronic vascular complications associated with cisplatin were detailed. The review emphasizes the association of cumulative doses with increased hypertension, myocardial ischemia/infarction, thromboembolism, and cerebrovascular events (10).

Etoposide, another chemotherapeutic agent used in the BEP protocol, is associated with myelosuppression developed during treatment (4).

Retroperitoneal lymph node dissection is a technically challenging surgery due to the risk of invasion of major vessels and the need for nephrectomy in the same session in about 11% of cases (11). Despite their young age, patients face significant cardiovascular and respiratory system risks due to exposure to platinum-based chemotherapeutic agents. RPLND requires specialized anesthesia management due to the complexity of the operation technique and anatomy, the duration of the surgery, and the management of potential complications for the patient. There is evidence in the literature suggesting that maintaining the FiO2 value carefully below 30% plays a role in preventing bleomycin-associated pulmonary complications (12). This operation is performed in selected centers worldwide, including in our country. In our study, we aimed to examine the anesthesia management in RPLND operations following chemotherapy in light of current literature data.

MATERIAL and METHODS

In our study, cases of Retroperitoneal Lymph Node Dissection (RPLND) performed at a hospital between 2017 and 2023 were examined. After obtaining approval from the Ethics Committee (No: 2023/305), data including patients' ages were collected. Preoperative chemotherapy dosages, operation durations, perioperative blood gas and FiO2 values, and the amount of fluid administered during the procedure were retrospectively reviewed from patient records and anesthesia monitoring forms. Patients with incomplete information were excluded from the study. Blood gas samples obtained immediately after anesthesia induction were compared with those taken upon admission to the intensive care unit.

Following multidisiplinary pre-operative evaluation, all RPLND cases were electively performed under general anesthesia. The routine anesthesia practices in our clinic for RPLND operations are as follows. Patients are provided standard monitoring according to American Society of Anesthesiologists (ASA) standards, including electrocardiogram (ECG), non-invasive arterial pressure, and pulse oximetry. Difficult peripheral venous access due to chemotherapy history is established using 20G - 22G angiocatheters. Standard general anesthesia induction and endotracheal intubation were followed by an Allen test on the non-dominant extremities, then invasive arterial cannulation and central venous catheterization (CVC) under ultrasound guidance were performed. In patients assessed as having a high risk of vascular injury, an internal jugular venous sheath catheter is additionally placed under ultrasound guidance. To prevent gastric distension, a nasogastric tube is inserted for drainage. During surgery, which is performed through a large abdominal incision extending to the sternum, heat loss is prevented by placing heating pads and fluid warmers under the patients, and close temperature monitoring is ensured with an oropharyngeal temperature probe. Anesthesia maintenance is provided with an air/oxygen mixture containing 1-2% sevoflurane and a remifentanil infusion at a dose of 0.1-0.2 mcg kg-1 min-1. The patients' FiO2 levels are maintained at 40% or below through blood gas and saturation monitoring. Train of four (TOF) monitoring is applied to all patients to evaluate neuromuscular block response and reduce the risk of injury during delicate dissection around major vessels by preventing involuntary movements. Rocuronium doses of 0.1 mg kg-1 are intermittently applied to maintain the TOF value within the optimal range. In patients with a predisposition for peripheral neuropathy due to a history of cisplatin exposure, both arms are drawn close to the body to facilitate optimal surgical access and prevent potential peripheral nerve damage; the arms are wrapped and secured beneath the patient using a drape and gel pads. At the end of the operation, patients are transferred to our intensive care unit while intubated and on remifentanil infusion. Postoperative analgesia is provided with a patient-controlled analgesia (PCA) device, starting after skin suturing, and continuing until extubation, with morphine infusion and additionally a bilateral Transversus Abdominis Plane (TAP) Block performed under ultrasound at the end of the operation. Patients actively warmed in the ICU are electively extubated on the same day once hemodynamic stability was achieved and TOF>0.9.

RESULTS

Our study included data from 37 RPLND cases conducted over a six -year period. Three patients with incomplete data were excluded, and the demographic data for 34 patients are shown in Table I.

 Table I. Demographic data, duration of anesthesia and time until extubation in intensive care unit (after surgery) was given in terms of median values.

	Median (Min-Max)
Age (year)	28 (17- 47)
Height cm	174,9 (169- 185)
Weight kg	81,6 (65- 105)
Duration of Anesthesia (minute)	340,7 (240-440)
Time until extubation in	125,6 (35-295)
intensive care unit (minute)	Maria magina

Min: minimum Max : maximum

Blood gas samples taken immediately after anesthesia induction were compared with those taken upon admission to the intensive care unit. While there were no significant changes in average pH, pO_{2s}, and pCO₂ values, a significant increase in lactate levels was observed (Table II).

	After Anesthesia Induction Median (Min-Max)	ICU Admission Median (Min-Max)
рН	7,372 (7,266-7,48)	7,366(7,24-7,48)
pO ₂ (mmHg)	156,66 (68-234)	146,13(90-298)
pCO ₂ (mmHg)	37,92 (28,9-46,7)	37(21,6-57,9)
Hemoglobin (g/dL)	14,5 (10,9-17,7)	14,0 (10,6-16,8)
Hematocrit (%)	44,7 (33,6-52)	43,0 (32,6-51,4)
Lactate (mmol/L)	1,51(0,7-2,6)	1,9(0,5-3,6)

Table II. Parameters of blood gas from blood samples, were taken after anesthesia induction and at intensive care unit admission, were given as median values.

The mean FiO₂ level of patients' was 0.35. Patients monitored with arterial blood gases did not experience pulmonary complications during or after the operation. The average anesthesia duration from the time patients entered the operating room to their admission to the ICU was recorded as 340.7 minutes, and

the average extubation time from ICU admission was 125.6 minutes. A standard combination of crystalloids and colloids was used for intravenous fluid management. The distribution of fluids used during the intraoperative period is indicated in Table III.

Table III. The distribution of fluids used during the intraoperative period were given with the body temperature.

	Median (Min-Max)
Crystalloid (ml)	2500 (1000-4000)
Colloid (ml)	607,1 (500-100)
Body Temperature (C ⁰)	35,6 (34,5-37,5)

Only four patients (10.8%) required blood and blood product transfusions, with one unit of red blood cell suspension (ES) and one unit of fresh frozen plasma transfusion (TDP) being administered. No significant decreases in hemoglobin and hematocrit values were detected in the arterial blood gases taken at ICU admission compared to those taken at the start of the operation.

The preoperative patients had received 4 cycles of Bleomycin, Etoposide, and Cisplatin. Each cycle consisted of Bleomycin (30 units) administered on days 1, 5, and 8, and Etoposide (100 mg/m²) and Cisplatin (20 mg/m²) administered on days 1, 2, 3, 4, and 5. It was observed that patients with active lymph nodes larger than 1 cm underwent surgery 20 days after the last chemotherapy (Table IV).

Table IV. Bleomycin Etoposide and Cisplatin Cure Times

BEP Cure	Times
Bleomycin (30 unite) day 1, 8, 15	4
Etoposide (100mg/m²) day 1-5	4
Cisplatin (20mg/m ²) day 1-5	4

DISCUSSION

In our study, patients who underwent RPLND had received platinum-based chemotherapy prior to the procedure. Patients receiving chemotherapy were in a fragile condition despite being young and having no illnesses other than the accompanying cancer. A pulmonology consultation was requested to assess the patients' respiratory functions prior to surgery In a similar study, Jayakrishnan et al. emphasized the importance of preoperative multidisciplinary evaluation in these cases. They also highlighted the significance of maintaining controlled fluid balance while avoiding hyperoxia during general anesthesia (13). Patients reviewed in our article had routinely undergone the BEP procedure after orchiectomy, and none had a cumulative bleomycin dose exceeding 360 mg. We believe this factor played a significant role in ensuring none of our patients experienced pulmonary complications. While major pulmonary complications are rare after RPLND, the literature reports that pulmonary complications occur more frequently in patients exposed to bleomycin, approximately at a rate of 1-8% (14). These complications can range from pneumonia and pulmonary embolism to even acute respiratory distress syndrome (ARDS). The incidence of bleomycin-related pulmonary toxicity is directly proportional to the cumulative dose of the drug used. Literature has shown that high cumulative doses of bleomycin are associated with increased pulmonary toxicity (15). Jayakrishnan et al., published a case report on the successful anesthesia management of a patient diagnosed with bleomycin-related pulmonary fibrosis who remained under anesthesia for an extended period due to retroperitoneal surgery due to RPLND (13).

The literature suggests that both the inspired fractional oxygen level (FiO2) and the fluid resuscitation administered during the intraoperative period are associated with the risk of pulmonary toxicity (16, 17). These parameters have been the foundation of intraoperative management guidelines for years to prevent pulmonary complications. Various sources in the literature recommend maintaining the FiO2 level between 30-40% or keeping the minimum oxygen concentration where the partial pressure of oxygen (PaO2) in arterial blood gases is above 60 mmHg. It is also advised that intraoperative fluid maintenance be limited to 4 mL-1 kg-1 hr-1 for crystalloids and 2 mL-1 kg-1 hr-1 for colloids in the first 2 hours, and that blood transfusions be avoided unless clinically indicated (4, 18). In our study, it was observed that fluid management was close to these limits (Table III).

Patients undergoing retroperitoneal lymph node dissection are often young, yet a majority have a history of exposure to cisplatin, a cardiotoxic chemotherapeutic agent. Therefore, even in young patients, an ECG must routinely be included in the preoperative evaluation. The incidence of cisplatin-associated cardiotoxicity has been increasingly reported in the literature over the past decade (9). While the most common cardiac pathology caused by cisplatin is sinus tachycardia, it can also prolong the QT interval leading to bradycardia and even Torsade de Pointes rhythms. In patients who have developed Long QT Syndrome (LQTS), it is necessary to avoid all drugs that can prolong the QT interval during the perioperative period, including agents such as propofol, fluoroquinolone and macrolide antibiotics, various proton pump inhibitors, and antiemetics. In patients diagnosed with LQTS in the preoperative period, the administration of a titrated midazolam-fentanyl combination is considered safe for anesthesia induction, and the avoidance of ketamine, which is specifically emphasized in the literature due to its potential to increase sympathetic discharge and cause arrhythmias, should be observed. Another important consideration for patients with LQTS during the perioperative period is the normalization of serum electrolyte levels (19). As previously mentioned, cisplatin can lead to hypomagnesemia, which may lower the threshold for malignant ventricular arrhythmias. Hypothermia that may develop during surgery with a long and extensive abdominal incision can prolong the QT interval, hence close temperature monitoring is crucial. In patients with developed LQTS and/or considered high risk, defibrillation pads should be placed where they can be easily accessed. In our study, routine cardiology evaluations were performed for each patient, and anesthesia procedures were carried out with consideration of the pulmonary and cardiac side effects of chemotherapy.

Patients with preoperative electrolyte levels monitored should also have their electrolyte levels assessed during intraoperative blood gas analyses. Monitoring electrolyte levels and kidney function tests will facilitate the early detection of nephrotoxicity, which is the most common side effect of cisplatin, and the resultant hypomagnesemia (9). While hypomagnesemia is a consequence of nephrotoxicity, it is also an underlying cause of cardiac pathologies. Any existing anemia and blood electrolyte abnormalities in patients should be corrected during the preoperative period. Easily administered replacements in the preoperative period play a significant role in reducing mortality and morbidity. None of the 34 patients mentioned in our article developed cardiac pathology or acute kidney injury during the perioperative period.

Retroperitoneal lymph node dissection is a high-risk surgical procedure performed through a wide abdominal incision, located near major vessels such as the aorta, inferior vena cava (IVC), and others supplying the spinal cord, requiring meticulous care. Due to its location, there is a very high risk of abundant bleeding during the surgery, and sudden, brief periods of hypotension can occur due to pressure on the IVC. For these reasons, blood pressure must be monitored using invasive methods. The potential need for massive blood transfusions in this high-bleeding-risk surgery should not be overlooked. In these patients, where post-chemotherapy peripheral venous access can be difficult, establishing wide vascular access following anesthesia induction is crucial for handling massive transfusion scenarios (20). At our clinic, we routinely perform a radial arterial cannulation and right internal jugular central venous catheterization under ultrasound guidance after the Allen test from the non-dominant upper extremity following anesthesia induction, unless contraindicated. After reviewing patients' tomography, in patients anticipated to have a high risk of major bleeding due to the location during dissection, a sheath catheter is additionally placed. In the 34 RPLND cases mentioned in our article, major vascular injuries occurred in two cases. RPLND surgeries at our hospital are performed in the cardiovascular surgery operating room. Immediate additional surgical interventions by the cardiovascular surgery team were applied to these patients with major vascular injuries, and the injuries were repaired with primary suturation.

One of the most serious complications that can occur after retroperitoneal lymph node dissection is spinal cord ischemia, which can result in paralysis of the lower extremities (13). Linz et al. reported a case of anterior spinal artery syndrome due to injury to the artery of Adamkiewicz during an RPLND in a published case report (18). Kesler et al. reported in their study involving 268 patients that paraplegia developed in 6 patients following retroperitoneal lymph node dissection (RPLND), with a neurological complication rate of 2.2% (21). In the 34 cases performed at our clinic, major vascular injuries occurred in two cases; however, these injuries were not arterial injuries that could lead to neurological complications. None of our cases resulted in neurological complications.

To ensure an optimal view for the surgeon, RPLND is performed through a wide thoracoabdominal incision. Although the pain caused by this major incision can be managed with epidural analgesia, it should not be forgotten that during surgeries close to major vascular structures, such as potential vascular injuries, patients may need to be heparinized. Current ASRA (The American Society of Regional Anesthesia and Pain Medicine) guidelines recommend delaying the application of unfractionated heparin until 1 hour after neuraxial interventions when low-dose heparin is used and neuraxial blocks are applied (22). However, difficult or traumatic placement of an epidural catheter, advanced age, and coagulation disorders are serious risk factors for the development of epidural hematomas. During the repair of the two previously mentioned inferior vena cava injuries at our clinic, it was necessary to heparinize the patients. Linz et al. reported using epidural analgesia for postoperative analgesia in a morbidly obese patient undergoing RPLND, noting that the development of anterior spinal artery syndrome was masked due to the epidural analgesia (18). Considering these potential complications, we believe opting for neuraxial analgesia could be a risky approach. At our clinic, especially during the early postoperative period, we manage severe pain complaints by applying a TAP block under ultrasound guidance and using patient-controlled analgesia devices with intravenous morphine infusion. The ultrasound-guided TAP block method is defined as the application of a local anesthetic agent between the transversus abdominis and internal oblique muscles. This method, which has a very low complication rate and is highly effective when applied under ultrasound guidance, provides significant pain relief. In a recent study Stephens et al. reported achieving analgesia through intermittent local anesthetic injections via a rectus sheath catheter directly visualized and placed by the surgeon following the application of a rectus sheath block (RSB) at the start of the surgery (4). RSB is a regional anesthesia technique targeting the terminal branches of thoracic nerves, primarily indicated for vertical midline incisions, and can be applied under ultrasound guidance (23). However, according to the results of a recent meta-analysis, RSB did not demonstrate superiority over placebo in managing post-abdominal surgery pain and reducing opioid consumption (23). Further advanced randomized controlled trials are needed to examine the outcomes of other regional anesthesia techniques that could be applied for RPLND surgery.

Close monitoring of this patient group, which remains at risk for complications in the postoperative period, is crucial. Particularly for patients at high risk of pulmonary complications, close monitoring with pulse oximetry or arterial blood gases measuring PaO2 is recommended, and it is important to protect patients from both hypoxia and hyperoxia. Our goal in oxygen therapy is to maintain a PaO2 level above 60 mmHg, and the minimum oxygen support needed to achieve this level is recommended (4). Venous thromboembolism (VTE), whose incidence increases with exposure to cisplatin, is also a complication that requires close monitoring during the perioperative period. It has been reported in the literature that the use of compression devices during the intraoperative period to prevent VTE is contraindicated, as they can increase inferior vena cava pressure and thereby the risk of bleeding (4). At our clinic, we routinely prefer to use compression stockings for VTE prophylaxis throughout the operation. We also believe that the use

of low molecular weight heparin in the postoperative period is important in these patients, despite their young age, due to their predisposition to VTE.

The limitations of our retrospective study include the inability to obtain dosages of other chemotherapeutic agents aside from bleomycin and the number of chemotherapy cycles. Additionally, intraoperative and postoperative kidney function tests were not compared in terms of nephrotoxicity. There is a need for prospective studies that analyze a greater number of variables.

CONCLUSION

RPLND requires a multidisciplinary approach. Although patients are young after chemotherapy, they are fragile. While precautions should be taken against pulmonary and cardiac complications, measures must also be implemented to prevent major vascular injuries and deep vein thrombosis in the extensive surgical field. Postoperative pain management should be planned with consideration of potential complications. Measures addressing perioperative hypoxia and hyperoxia, along with fluid management and preoperative evaluation, can play a significant role in preventing major complications that may arise during both the intraoperative and postoperative periods.

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Ethics Committee Approval:

This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Declaration, and has been approved by the Gulhane Medical Faculty Ethical Committee, Healthy Science University University (approval number: 2023/305).

Informed Consent:

All the participants' rights were protected were obtained the procedures according to the Helsinki Declaration.Since the study is retrospective, informed consent was not obtained.

Author Contributions:

Concept - ; HZ., NY.; Design - H.Z., N.Y.; Supervision ., N.Y.; Resources – H.Z., N.Y. ; Materials – N.Y.; Data Collection and/or Processing – H.Z., F.Ç.; Analysis and/ or Interpretation – H.Z., N.Y.; Literature Search – H.Z.; Writing Manuscript -HZ., N.Y.; Critical Review - H.Z., N.Y.

Conflict of Interest:

The authors have no conflict of interest to declare.

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