

Comparison of the Tissue Trauma Markers Following Total Laparoscopic Hysterectomy vs Total Abdominal Hysterectomy

Laparoskopik ve Abdominal Histerektomide Doku Travma Belirteçlerinin Karşılaştırılması

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Abstract

Objective: To compare abdominal and laparoscopic techniques of hysterectomy in terms of the surgery-induced trauma with measuring serum Pentraxin-3 (PTX-3) level and neutrophil to lymphocyte ratio (NLR).

Materials and Methods: In this study, preoperative and postoperative blood samples were used to compare the change at the level of PTX-3 and NLR in order to evaluate the inflammatory response in 40 patients, of whom, 20 had experienced Total Laparoscopic Hysterectomy (TLH) + Bilateral Salpingo-Oophorectomy (BSO) and 20 had experienced Total Abdominal Hysterectomy (TAH + BSO).

Results: Based on our comparison, change in PTX-3 level in TLH+BSO group 4.5 ng/mL (0.3-18.6) was slightly higher than that of TAH+BSO group 3.0 ng/mL (0.0-18.1), but the difference was not statistically significant ($p=0.429$). Likewise, the increase in the NLR in TLH+BSO group 3.5 (1.2-19.4) was slightly higher than that of TAH+BSO group 2.8 (-0.3-8.8), but not to a statistically significant extent ($p=0.114$).

Conclusion: When we use the inflammatory markers of PTX-3 and NLR, there was no significant difference between the two surgery techniques in terms of degree of tissue trauma. Further studies conducted with inflammatory markers other than PTX-3 and NLR are required to elucidate the choice of surgery technique in similar patients.

Keywords: Pentraxin; neutrophil to lymphocyte ratio; hysterectomy; tissue trauma

Öz

Amaç: Pentraxin-3 (PTX-3) seviyesi ve nötrofil/lenfosit oranını ölçerek, cerrahi işlemin neden olduğu doku travması bakımından abdominal ve laparoskopik histerektominin karşılaştırılması.

Materyal ve Metod: 20 Total laparoskopikhisterektomi + bilateral salpingo-ooferektomi (TLH+BSO) ve 20 total abdominal histerektomi + bilateral salpingo-ooferektomi (TAH + BSO) olmak üzere toplam 40 hasta çalışmaya dahil edildi. Tüm hastalardan operasyon öncesi ve sonrası dönemde kan örnekleri toplanarak Pentraxin-3 (PTX-3) seviyesi ve nötrofil/ lenfosit oranı belirlendi. Elde edilen veriler ile iki grup arasında karşılaştırmalı analizler yapıldı.

Bulgular: Yaptığımız analizlerin sonucunda, PTX-3 seviyesindeki değişim TLH+BSO grubunda (4.5 ng/mL (0.3-18.6)) TAH+BSO grubuna göre (3.0 ng/mL (0.0-18.1)) istatistiksel anlam olmamasına rağmen hafif yüksek bulunmuştur ($p=0.429$). Benzer şekilde, nötrofil/ lenfosit oranındaki artış TLH+BSO grubunda (3.5 (1.2-19.4)) TAH+BSO grubuna göre (2.8 (-0.3-8.8)) istatistiksel anlam olmamasına rağmen hafif yüksek bulunmuştur ($p=0.114$).

Sonuç: İnflamatuvar belirteçler olan PTX-3 ve nötrofil/ lenfosit oranı incelendiğinde, iki cerrahi teknik arasında doku travma dereceleri bakımından anlamlı fark gözlenmemiştir. İleride yapılacak olan PTX-3 ve nötrofil/ lenfosit oranı dışındaki inflamatuvar belirteçlerin değerlendirilmesi benzer hastalarda cerrahi teknik seçimini aydınlatmaya katkı sağlayacaktır.

Anahtar Kelimeler: Pentraxin; nötrofillenfositoranı; histerektomi, dokutravması

Introduction

Hysterectomy is among the most widespread surgeries applied in the United States (USA) where each year an average of 600,000 hysterectomies are performed¹. Although no definite overall figures are available in our country, Turkey, it is known that hysterectomy is a frequently applied gynecological procedure². The most common indications for hysterectomy include symptomatic leiomyoma (40.7%), endometriosis (17.7%), and uterine prolapse (14.5%)¹.

Different techniques might be applied during a hysterectomy surgery and the choice of which depends on the pelvic anatomy, surgical indication, cost, patient preference, any medical comorbidities, adnexial pathologies of the patient, and surgeon's experience³. Currently, Total Abdominal Hysterectomy (TAH) stands for more than 60% of the hysterectomy surgeries applied in USA³. Total Laparoscopic Hysterectomy (TLH) offers a number of advantages compared to TAH in patients for whom vaginal hysterectomy (VH) is not applicable. However, it is controversial due to disadvantages such as extended duration of surgery and increased risk of urinary tract damage⁴. VH results in fewer complications than other techniques do. VH is favorable over TAH as it shortens both the hospital stay and the time until return to daily activity, and it also takes shorter than a TLH surgery⁴. Although VH is often the first choice, TLH is reported superior to VH from the viewpoint that it causes less blood loss, milder postoperative pain, shorter hospital stay following hysterectomy, and allows to treat any additional pathologies during the surgery⁵.

Acute trauma and major surgeries activate a series of cascades to evoke systemic inflammatory response. The magnitude of the resulting inflammatory response is proportional to the severity of the tissue trauma. Pentraxin-3 (PTX-3) is an acute phase reactant, but, unlike other acute phase reactants such as CRP and IL-6, it is secreted both locally and systematically⁶. Alterations in the level of PTX-3 is directly associated with the size of systemic inflammatory response and tissue trauma⁷.

The neutrophil/lymphocyte ratio (NLR) has been reported as a sensitive serum marker to evaluate the inflammatory status of the human immune system in different conditions, such as malignancy, cerebrovascular and cardiovascular diseases⁸. Recent studies have also showed that NLR is increased at tissue injury associated with brain⁹.

In this study, the severity of the inflammatory response resulting from the tissue trauma due to the techniques of TLH+BSO and TAH+BSO applied in our department were compared based on the PTX-3 molecule as well as NLR.

Materials and Methods

This prospective study included patients between 43-60 years of age who visited the Department of Gynecology and Obstetrics, Muğla Sıtkı Koçman University, School of Medicine and experienced TLH+Bilateral Salpingo-Oophorectomy (BSO) or TAH+BSO due to benign reasons between the time period of January 2015 and December 2015. TLH+BSO or TAH+BSO was applied for the patients and these two techniques were compared regarding the PTX-3 levels as well as change in NLR.

A total of 40 patients, composed of 20 TLH+BSO patients and 20 TAH+BSO patients were included into the study and randomly grouped. Firstly, approval of Medical Ethics Committee was obtained for the study (Ethics Committee Decision No:19.03.2015-58-56). It is necessary to mention that this study tried to comply with Helsinki declaration principles. The patients to be included to the study were informed verbally and in written and each of whom then signed a consent form.

I. Exclusion criteria for the study were established as follows:

History of a chronic disease (coronary artery disease, diabetes mellitus, hypertension, coronary liver failures, chronic kidney disease, chronic respiratory diseases, connective tissue disorders) which may affect levels of PTX-3 and other inflammatory markers.

II. Diagnosis of any type of malignancy prior to surgery.

III. History of an intra-abdominal surgery, except for cesarean section.

IV. History of any disease which may lead to intra-abdominal adhesions (endometriosis, past pelvic infection).

Definition of the surgical procedures

All patients included in the study were operated under general anesthesia with endotracheal intubation. TAH was performed in patients at supine position and TLH at lithotomy position. During the TLH surgery, the team took their positions such that the surgeon stays on the left side, the first assistant on the left side and the second assistant between the legs of the patient. Prior to the surgery, antibiotic prophylaxis of 2 g cefazolin sodium (Cefozin 1 g IM for injection, Bilim Ilac San. ve Tic. A.S., Turkey) was administered to each patient. A 16F Foley catheter was inserted to each of the patients before the surgery which was removed on the first day after the surgery. No postoperative drain was placed to any of the patients.

In the entire set of TAHs, Pfannenstiell incision was made. Uterine ligaments and vessels were cut through the conventional grasp-ligate-cut method. Vaginal cuff was closed through abdominal route by continuous suture first placing the corner bites. The skin was subcutaneously stitched using absorbable suture. During the TLH+BSO surgeries, an intrauterine RUMI 2 SYSTEM manipulator (CooperSurgical Inc., USA) was used. Uterine ligaments and vessels were sealed and divided using LigaSure™. Covidien LigaSure™ 5 mm Blunt Tip 37 cm Laparoscopic Instrument (MEDTRONIC, Minneapolis, USA) were used for all surgeries. Uterus was removed using hook electrocauterization at the junction between uterus and vagina. Vaginal cuff was closed through vaginal route by continuous suture first placing the corner bites.

Collection of blood samples

From all patients who were hospitalized for a scheduled TLH or TAH, 6 cc of blood sample were collected for biochemical analysis preoperatively and drawn into an EDTA tube. These samples were centrifuged for 15 min at 1500 rpm and the sera were stored at -70°C.

An additional approximately 6 cc of blood sample was also collected from each patient during the time of routine follow-up at postoperative 24 hour and centrifuged in the same manner as described above and then stored at -70°C until all samples are prepared. Once samples from the entire patient cohort were ready, PTX-3 levels were measured using human PTX3 ELISA Kit 96 Tests/Box (Cat. No: CK-E90303) (Hangzhou EastbiopharmCo.,Ltd. PRC) and also read by an ELISA device matching with the kit. The kit has a detection range of 0.1ng/mL→30ng/mL and a sensitivity of 0.05ng/mL. For the purpose of measurement, microplate washer RT 2600 device and Rayto microplate reader RT 2100C device were used. Then, two surgical groups were compared by means of PTX-3 level from the preoperative baseline to the 24 hour after the surgery.

Moreover, complete blood counts (CBC) of each patient were taken and used to calculate the NLRs to compare the change in NLRs between the two techniques at both preoperative and postoperative time.

Age, body weight, height, and body mass index (BMI) of the patients were recorded.

Statistical analysis

Statistical analysis of the data was made using the SPSS 21.0 (SPSS Inc., Chicago, IL, USA) package program. Shapiro Wilk test was applied to check whether the data has a normal distribution. Continues variables were presented with mean value and standard deviation (SD) if they have a normal distribution, otherwise they were presented with median value (minimum-maximum). Categorical variables were presented as number and percentage. When comparing two techniques, Mann Whitney U test was applied for independent samples, and Wilcoxon signed-rank test was applied for dependent samples. Correlation of PTX-3 with other parameters was assessed by Spearman correlation test. Values of p<0.05 were accepted as statistically significant.

Results

A total of 40 patients were included into the study. Median age of the patients was 49 (40-60) years, mean BMI was 26.1±3.1 kg/m². BMI in TLH group was 25±3 kg/m² and BMI in TAH group was 27.1±3 kg/m², with no statistically significant difference between the groups. In our patient population, most common indications for surgery were uterine myoma 25 (62.5%) and simple endometrial hyperplasia without atypia 4 (10.0%), respectively. Distribution of patients by their indication for the surgery is given in Table 1. Of all the patients, 20 (50.0%) patients underwent TAH and the other 20 (50.0%) patients underwent TLH.

Table 1. Distribution of the cases by indication for surgery

	Number (n)	%
SIMPLE ENDOMETRIAL HYPERPLASIA W/O ATYPIA	4	10.0
CIN3	1	2.5
H-SIL	1	2.5
COMPLEX ATYPICAL ENDOMETRIAL HYPERPLASIA	1	2.5
MENOMETRORRHAGIA	3	7.5
UTERINE MYOMA	25	62.5
OVARIAN CYST	2	5.0
PELVIC MASS	1	2.5
POST-MENAUPOUSAL BLEEDING	2	5.0
Total	40	100.0

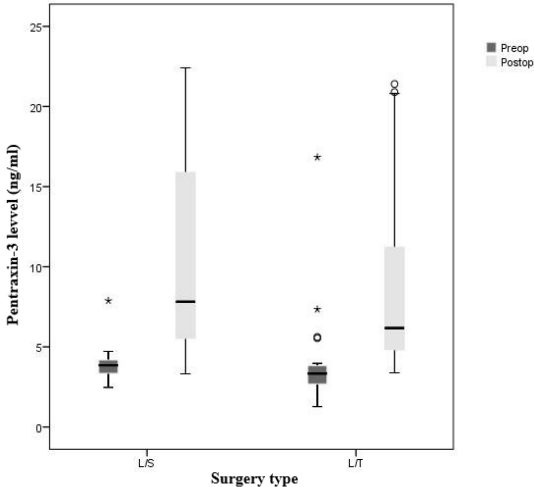
The analysis within the TAH and TLH groups revealed PTX-3 levels have significantly increased after the surgery in both groups relative to the baseline ($p<0.001$ and $p<0.001$, respectively). When the two groups were compared, on the other hand, neither preoperative and postoperative PTX-3 levels nor the change in between them were found to have any significant difference ($p=0.091$, $p=0.429$, and $p=0.429$, respectively) (Table 2) (Figure-1).

Table 2. Preoperative and postoperative PTX-3 and hemoglobin values by surgery type

Surgery	Preop PTX-3 (ng/mL) Mean ± SD	Postop PTX-3 (ng/mL) Mean ± SD	Change in PTX-3 level (ng/mL) Mean ± SD	<i>p</i>
TLH (n=20)	3.9 (2.5-7.9)	7.8 (3.3-22.4)	4.5 (0.3-18.6)	<0.001
TAH (n=20)	3.3 (1.3-16.8)	6.2 (3.4-21.4)	3.0 (0.0-18.1)	<0,001
<i>P</i>	0.091	0.429	0.429	
Surgery	Preop Hemoglobin	Postop Hemoglobin	Change in Hemoglobin	<i>p</i>
TLH (n=20)	12.0 (9.2-14.4)	10.8 (7.8-12.6)	-1.4 (-3.1-0.9)	<0.001
TAH (n=20)	12.3 (9.2-13.4)	10.8 (7.6-12.6)	-1.7 (-3.6-1.1)	<0.001
<i>P</i>	0.738	0.799	0.925	

$p<0.05$ indicates a statistically significant difference.
PTX-3: Pentraxin 3, TLH: Total Laparoscopic Hysterectomy, Total Abdominal Hysterectomy

Figure1. Comparison of PTX-3 values in two grou



Intra-group hemoglobin levels were significantly lower after the surgery in comparison to the baseline level prior to the surgery, both in TAH and TLH groups ($p<0.001$ and $p<0.001$, respectively). When the two groups were compared, on the other hand, neither preoperative and postoperative hemoglobin levels nor the change in hemoglobin levels were found to have any significant difference ($p=0.738$, $p=0.799$, and $p=0.925$, respectively) (Table 2).

Table 2. Preoperative and postoperative PTX-3 and hemoglobin values by surgery type.

Surgery	Preop PTX-3 (ng/mL) Mean ± SD	Postop PTX-3 (ng/mL) Mean ± SD	Change in PTX-3 level (ng/mL) Mean ± SD	<i>p</i>
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Surgery	Preop Hemoglobin	Postop Hemoglobin	Change in Hemoglobin	<i>p</i>
TLH (n=20)	12.0 (9.2-14.4)	10.8 (7.8-12.6)	-1.4 (-3.1-0.9)	<0.001
TAH (n=20)	12.3 (9.2-13.4)	10.8 (7.6-12.6)	-1.7 (-3.6-1.1)	<0.001
<i>P</i>	0.738	0.799	0.925	

$p<0.05$ indicates a statistically significant difference.
PTX-3: Pentraxin 3, TLH: Total Laparoscopic Hysterectomy, Total Abdominal Hysterectomy

In both of the TAH and TLH groups NLR levels had significantly raised after the surgery compared to the respective prior levels ($p<0.001$ and $p<0.001$, respectively). Comparison of the two groups in terms of NLR levels showed no significant difference in preoperative or postoperative NLR measurements ($p=0.583$, $p=0.102$, and $p=0.114$, respectively) (Table 3) (Figure-2).

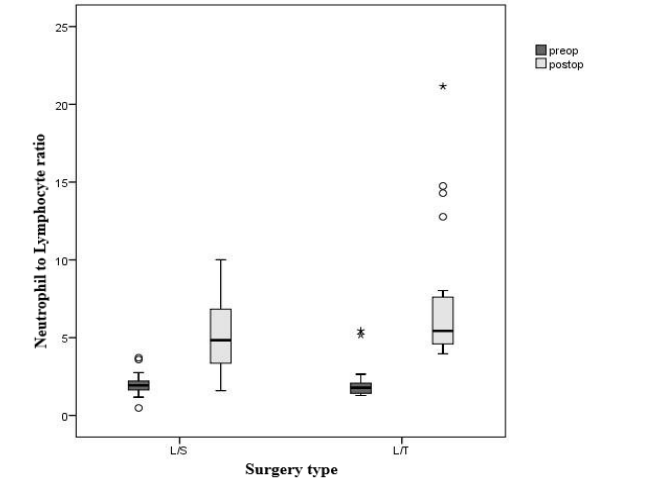
Table 3. Preoperative and postoperative NLR values by surgery type

Surgery	Preop PTX-3 (ng/mL) Mean ± SD	Postop PTX-3 (ng/mL) Mean ± SD	Change in PTX-3 level (ng/mL) Mean ± SD	p
TLH (n=20)	3.9 (2.5-7.9)	7.8 (3.3-22.4)	4.5 (0.3-18.6)	<0.001
TAH (n=20)	3.3 (1.3-16.8)	6.2 (3.4-21.4)	3.0 (0.0-18.1)	<0,001
P	0.091	0.429	0.429	

Surgery	Preop Hemoglobin	Postop Hemoglobin	Change in Hemoglobin	p
TLH (n=20)	12.0 (9.2-14.4)	10.8 (7.8-12.6)	-1.4 (-3.1-0.9)	<0.001
TAH (n=20)	12.3 (9.2-13.4)	10.8 (7.6-12.6)	-1.7 (-3.6-1.1)	<0.001
P	0.738	0.799	0.925	

p<0.05 indicates a statistically significant difference.
PTX-3: Pentraxin 3, TLH: Total Laparoscopic Hysterectomy, Total Abdominal Hysterectomy

Figure2. Comparison of NLR values in two groups300



Correlation analysis did not result in any significant correlation between preoperative and postoperative PTX-3 levels with age, height, weight, BMI, hemoglobin and NLR values (p>0.05). (Table 4).

Table 4. Relationship among demographic parameters, hemoglobin, PTX-3, and NLR

	HEIGHT	WEIGHT	BMI	AGE	PREO P HGB	POST OP HGB	PREOP NLR	POSTOP NLR
PRE PTX3	0.080	-0.009	-0.102	0.047	-0.261	-0.200	-0.124	0.100
	0.624	0.954	0.529	0.774	0.104	0.216	0.448	0.541
POST PTX3	-0.242	-0.281	-0.273	0.197	0.059	-0.146	-0.167	0.009
	0.133	0.079	0.088	0.222	0.718	0.368	0.304	0.957

p<0.05 indicates a statistically significant difference.
*Spearman correlation analysis

Discussion

TLH was first described by Reich in 1989 and since then a number of studies have demonstrated its superiority over abdominal technique from many aspects¹⁰⁻¹². Apparently, the technique to be applied changes from patient to patient. Nevertheless, there is also a lack of consensus on the technique to be applied in the similar patient populations. Available literature compares and discusses different techniques based on various parameters including duration of surgery, amount of intraoperative bleeding, severity of postoperative pain, length of hospital stay, and surgery-induced tissue trauma. In our literature survey, we did not find a study comparing PTX-3 levels, which are known to be indicative of tissue trauma in laparoscopic and abdominal hysterectomy patients. In our study, we investigated whether there was a difference between the two surgical techniques in terms of tissue trauma. To this end, we compared the PTX-3 and NLR levels and the changes in these measurements. According to the primary results of our study, we observed a significant increase in PTX-3 levels in TLH or TAH patients in the post-operative period compared to the preoperative period. However, there was no significant difference in PTX-3 levels between both surgical groups. According to the secondary results of our study, we observed a significant increase in NLR levels in patients with TLH or TAH in the post-operative period compared to the preoperative period. However, there was no significant difference in NLR levels between both surgical groups.

Techniques applied in hysterectomy surgeries have been compared from different points of view in various studies¹³. One aspect of comparison is the inflammatory response caused by the surgery-induced tissue trauma following TAH and TLH techniques. Such studies rely on acute phase reactants such as C-reactive protein (CRP), interleukin-6 (IL-6), and cortisol by comparing the inflammatory response during the postoperative period.

Some authors found a lesser extent of immune response development in patients who had undergone TLH compared to those who had undergone TAH whereas others have not identified any significant difference in systemic inflammatory response between the two groups¹⁴⁻¹⁶.

The first study to compare tissue trauma arising from TAH and TLH was carried out by Ellstöm *et al* in 1996. In that study, the authors have kept track of neutrophil count, IL-6, CRP, and cortisol levels along five different time points. Based on the increase in the levels of these parameters, they have compared the tissue trauma between the groups which found to be alike¹⁶.

Another study by Demir A. and colleagues was published in 2007 and compared postoperative tissue trauma caused by TAH and TLH. In their study, the investigators collected samples at three different time points (preoperative, postoperative, and postoperative 24-hour) to measure IL-6 and CRP values to compare tissue trauma induced by two techniques as indicated by the increase in these biomarker levels. As a result, they found significantly higher increase in CRP and IL-6 levels after TAH compared to TLH¹⁷.

In 1997, Labib M. *et al* compared tissue trauma after laparoscopically assisted vaginal hysterectomy (LAVH) and TAH and showed trauma-induced inflammatory response following LAVH is significantly lower than that of TAH¹⁸.

PTX-3 is produced in response to cytokines in an inflammatory event occurring anywhere in the body. PTX-3 is also an inflammatory protein involved in the immune system, takes role in fibrosis and matrix destruction^{19,20}. In their study, Ulkumen *et al* showed that the increase in PTX-3 levels in hysterectomized diabetic rats reflected the inflammatory process and fibrosis²¹. Liu *et al* compared PTX-3 levels in preoperative and postoperative periods in patients diagnosed as colorectal cancer whom they performed radical surgery²². They found significant increase in plasma PTX-3 levels during the postoperative period of patients. In parallel with the results of our study, a significant increase in PTX-3 levels during the post-operative period reveals the inflammatory events of the surgery and how effective the formation of fibrosis is in the patient. In the same study, they reported that PTX-3 ≥ 12.6 ng/mL could be indicative of a poor prognosis²². In our study, the mean PTX-3 values of our hysterectomy patients remained below this cut off value. This remarkable data may be guiding to show that extreme inflammatory response and tissue destruction persist in particularly complicated cases after surgery.

When we evaluate the hysterectomy patients in their own groups, we can say that there is a significant increase in post-operative tissue trauma. However, when we compared the laparoscopic and abdominal groups according to our data, we found that there was no significant difference. Today, laparoscopic surgery is thought to have many advantages over open surgery.

In their study, Chandler *et al* stated that as the usage time and power of the instruments used in laparoscopy increase, the undesirable mechanical tissue trauma increases²³. The fact that PTX-3 levels in our study were similar in both groups suggests that the use of thermogenic instruments used in laparoscopy showed similar effects to mechanical tissue trauma seen in open surgery. As can be understood from here, the suggestions for shortening the time of use of hand tools such as ligasure harmonic, which are used very often in laparoscopy, or using as low power as possible, are important in terms of reducing the effects of tissue trauma.

In previous studies, the NLR has been reported as a sensitive and useful biomarker to evaluate the inflammatory response of the human immunity system and tissue injury^{24,25}. Moldal *et al* compared the surgical stress caused by hysterectomy+ ooforectomy or ooforectomy by looking at CRP, glucose, and iron levels in their animal study of female rats²⁶. They did not see any difference between the two surgical techniques in terms of surgical stress. In the present study, NLR showed a statistically significant difference in intra-groups by means of preoperative and postoperative NLR values but it did not show a statistically significant difference between the two groups. According to this conclusion, we can say that there is no difference between laparoscopic and abdominal technique in patients undergoing hysterectomy and inflammatory response.

In several studies assessing intraoperative and perioperative blood loss, TLH was associated a lesser bleeding than TAH^{19,27}. In other studies, on contrary, no difference in blood loss was identified between the two techniques^{28,29}. In our cohort, hemoglobin levels significantly decreased after the surgery regardless the technique in comparison to the baseline level prior to the surgery ($p < 0.001$ and $p < 0.001$, respectively). But, when the techniques were compared, there was no significant difference in surgery-related blood loss.

We did not coincide any study that associates PTX-3 level with hysterectomy technique directly. Although it is difficult to generalize the findings of this study, due to its single-centre design, small sampling size and lack of follow up of patients by means of PTX-3 and NLR levels, the fact that increased levels of inflammatory markers following TLH+BSO and TAH+BSO may be an important factor for tissue trauma after these type of surgeries. However, our study did not reveal any significant difference between the two techniques in terms of PTX-3 and NLR levels.

Conclusion

Based on our results, two techniques have no difference with regards to PTX-3 level and NLR or intraoperative blood loss arising from tissue trauma. Choice of surgery technique must be contemplated taking account the surgeon's set of skills at the first place, and also other factors such as long-term morbidity following the surgery, cost, patient preference, and rates of major complications.

There has been no consensus about the choice of technique among the comparable patient populations. Therefore, there is an unmet need to conduct randomized studies with greater sample size to compare two techniques.

Author contributions

K.Hançer: Project development, data collection, manuscript writing, participate in surgery

E.Akbaba: Data collection, manuscript writing, editing, participate in surgery

B.Sezgin : Manuscript writing, data analysis, editing

N.Turhan: Project development,supervision, editing

Compliance with ethical standards**Conflict of interest**

K.Hançer, E.Akbaba, B.Sezgin, N.Turhan declare that they have no conflict of interests.

Ethical approval

All procedures performed in studies involving human participants were done with the ethical standards set by local ethics committee for clinical research of Mugla Sitki Kocman University, Faculty of Medicine, Mugla, Turkey, in accordance with the 1964 Helsinki declaration and its later amendments.

Informed consent

Informed consent was obtained from all individual participants.

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