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Comparison of tissue trauma after abdominal, vaginal and total laparoscopic hysterectomy

Porównanie urazu tkanek podczas brzusznej, pochwowej i laparoskopowej histerektomii

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Abstract

Objective: *The aim of the study was to compare the extent of tissue trauma after abdominal hysterectomy(AH), vaginal hysterectomy (VH), and total laparoscopic hysterectomy (TLH) using biochemical markers.*

Material and methods: *Seventy-one patients requiring hysterectomy for benign uterine diseases were enrolled in the study and divided into three treatment groups: AH (n=24), VH (n=23), and TLH (n=24). Blood samples for assay of interleukin-6 (IL-6) and creatine phosphokinase (CPK) were collected pre-, intra-operatively, and 2, 6 and 24 h after surgery.*

Results: *Serum levels of IL-6, and CPK were significantly elevated over basal values after surgery in all groups. IL-6 and CPK levels were significantly higher after AH as compared to VH and TLH. IL-6 concentrations were significantly higher in the VH group than the TLH group (p=0.001). There were no significant differences in CPK levels between the VH and TLH groups (p=0.824). TLH group had the smallest decrease in blood hemoglobin concentration and the shortest hospital stay.*

Conclusions: *AH causes more tissue trauma as compared to VH and TLH. Owing to the fact that TLH is associated with less tissue trauma and offers significant clinical benefits, including less blood loss and shorter hospital stay, it should be considered in women with benign gynecologic conditions, especially in experienced centers.*

Key words: **tissue trauma** / **hysterectomy** / **laparoscopy** / **IL-6** / **CPK** /

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Streszczenie

Cel pracy: *Celem badania było porównanie rozległości urazu tkanek podczas brzusznej histerektomii (AH), pochwowej (VH) i laparoskopowej (TLH) przy pomocy biochemicznych markerów.*

Materiał i metoda: *Do badania włączono siedemdziesiąt jeden pacjentek wymagających usunięcia macicy z powodu niezłośliwej patologii, które podzielono na trzy grupy badane: AH (n=24), VH (n=23), i TLH (n=24). Próbki krwi do badania w kierunku interleukiny 6 i kinazy fosfokreatynowej (CPK) pobierano przed-, podczas operacji, I 2,6 oraz 24 godziny po zabiegu.*

Wyniki: *Poziom Il-6 i CPK w surowicy po operacji był istotnie podwyższony w porównaniu do poziomu wyjściowego we wszystkich grupach badanych. Poziom IL-6 i CPK były istotnie wyższe po AH niż po VH i TLH. Stężenie IL-6 było istotnie wyższe w grupie VH niż w grupie TLH (p=0.001). Nie stwierdzono istotnych różnic w poziomie CPK pomiędzy grupą VH i TLH (p=0.824). W grupie TLH odnotowano najmniejszy spadek hemoglobin I najkrótszy pobyt w szpitalu.*

Wnioski: *AH powoduje większy uraz tkanek niż VH i TLH. Dzięki temu, że TLH jest związane z mniejszym urazem tkanek i daje istotne klinicznie korzyści, między innymi mniejszą utratę krwi i krótszy pobyt w szpitalu, powinno być rozważane u kobiet z niezłośliwą patologią, zwłaszcza w doświadczonych ośrodkach.*

Słowa kluczowe: **uraz tkanek** / **histerektomia** / **laparoskopia** / **IL-6** / **CPK** /

Introduction

Hysterectomy is the most common major gynecologic operation performed worldwide, with three main approaches for benign uterine diseases: abdominal hysterectomy (AH), vaginal hysterectomy (VH), and laparoscopic hysterectomy (LH). Laparotomy remains the procedure of choice in the majority of hysterectomies [1]. However, randomized studies demonstrate improved outcomes after the vaginal approach as compared to AH. Thus, it should be the preferred method of hysterectomy, if appropriate [2].

Since the first documented procedure in 1989, laparoscopic hysterectomy has gradually become a popular alternative to the abdominal procedure [3]. Laparoscopic hysterectomy has been established as a safe and reliable procedure in routine clinical practice [4, 5]. Laparoscopic approach is either used to facilitate the ease of vaginal delivery of the uterus as in laparoscopy-assisted vaginal hysterectomy (LAVH), or all the steps of hysterectomy are done laparoscopically (total laparoscopic hysterectomy: TLH). Although LH takes more time, it is associated with less intraoperative blood loss, reduced hospital stay, and earlier return to normal activities as compared to abdominal hysterectomy [6, 7]. There are no specific criteria to determine the route of hysterectomy. The technique of hysterectomy can be selected on the basis of indication for surgery, experience of the surgeon, and patient preference.

Operative procedures stimulate a cascade of events that cause metabolic and inflammatory changes. Interleukin-6 (IL-6) is the major cytokine secreted from surgically damaged tissues and it triggers hepatic secretion of acute phase proteins such as C-reactive protein (CRP), fibrinogen, and haptoglobin. IL-6 is a sensitive and early marker of tissue damage [8, 9]. Also, a marked rise in the activity of serum creatine phosphokinase (CPK) has been observed as an indicator of muscle injury in relation to various surgical procedures [10]. The expression of these markers correlates with the extent of surgical trauma [8, 10].

Several studies have evaluated the degree of tissue damage using biochemical markers for two alternative methods of hysterectomy: AH and VH or LH. Numerous authors have found that tissue trauma and metabolic changes are more marked after AH than VH or LH [11-17]. However, limited number of studies have compared the extent of tissue damage after the three main types of hysterectomy [18-20], and found that AH caused more surgical trauma than VH and LH.

On the other hand, data on VH and LH are often contradictory. Some reports indicate less surgical trauma after VH [18], while others report no obvious differences between these two techniques [19, 20]. Therefore, in our study we examined the differences in tissue trauma between the three surgical techniques, i.e. abdominal, vaginal and total laparoscopic hysterectomy, by measuring IL-6 and CPK levels.

Material and methods

This prospective clinical study was carried out at the gynecology clinic of Zekai Tahir Burak Women's Health Education and Research Hospital, between January 2009 and May 2011. Women scheduled to undergo hysterectomy for benign uterine diseases were enrolled in the study. Local Ethics Committee approved of the study and written informed consent was obtained from all study participants.

The minimum sample size (necessary to detect statistical differences between the groups) was established using previously published study data [19]. We calculated that at least 15 women in each group would be needed for 90% study power and for a differentiation of 60 pg/mL between the means of IL-6 at 12h after surgery when type 1 error is 0.05.

Complete medical history was taken before enrollment. Detailed physical and sonographic examinations were performed. All patients underwent a preoperative endometrial biopsy to rule out malignancy. Patients with medical diseases or systemic infections that might result in altered metabolic and inflammatory responses to surgery were excluded.

Other exclusion criteria were: body mass index >30 kg/m², size of the uterus >12 weeks of gestation, history of several previous pelvic surgeries, pelvic inflammatory disease, moderate or severe endometriosis, suspicion of malignancy, total uterine prolapse, and the necessity of another concomitant surgery.

Patients were enrolled in three groups: abdominal hysterectomy (AH group), vaginal hysterectomy(VH group), or total laparoscopic hysterectomy (TLH group). The treatment was determined by the performing consultant physician. All of the abdominal and vaginal hysterectomies were carried out by consultant gynecological surgeons. Laparoscopic hysterectomies were performed by the same surgeon experienced in this kind of surgery. All operations were carried out under general anesthesia with endotracheal intubation. Preoperatively, all patients received antibiotic prophylaxis with 1 g of Cephazolin sodium intravenously (Cefamezin®, 1 g, Zentiva, Istanbul-Turkey).

In the AH group, following a Pfannenstiel incision, extra-fascial total hysterectomy was performed. Diathermy was used only for hemostasis, visceral peritoneum was left open, but parietal peritoneum was closed surgically. In the VH group, the incision was made in the cervicovesical junction, the bladder was pushed up and the pouch of Douglas was opened. Uterine ligaments and vessels were clamped, cut and ligated. The uterosacral ligaments were fixed to the cuff. In the TLH group, bipolar coagulation and scissors were used to cut the uterosacral and cardinal ligaments and the uterine vessels. The uterus was cut at the vault with the aid of a uterine manipulator. After the uterus was removed vaginally, the vaginal vault was closed by vaginal interference.

Decline in hemoglobin levels, duration of anesthesia, operation, and the hospital stay, as well as perioperative and early postoperative morbidity such as the need of blood transfusion, febrile morbidity, and infection were recorded for each patient. The length of the operation was calculated as the time from the first incision to the last suture.

Venous blood samples of all patients were drawn at the following times: a baseline sample before surgery, intraoperatively (on peritoneal closure), and on postoperative hour 2, 6 and 24 for the measurement of serum IL-6 and CPK levels. The sera were separated and stored at -20°C until analysis. Interleukin-6 (IL-6) levels were examined using electrochemiluminescence immunoassay (Elecsys IL-6 kit, Roche Diagnostics GmbH Mannheim, Germany). The assay detects IL-6 concentrations as low as 1.5 pg/mL and has an intra- and inter-assay variation coefficient of 6.0% and 8.5%, respectively. Serum creatine phosphokinase (CPK) was measured by Roche CK-NAC liquid assay (Roche Diagnostics GmbH, IN, USA) with a detection limit of 7 U/L, and has an intra- and inter-assay variation coefficient of 0.6% and 1.4%, respectively.

Data analysis was performed using SPSS for Windows version 11.5 statistical package software (SPSS, Inc., Chicago, IL, USA). Continuous data were expressed as the means ± standard deviation (SD) or median with range, according to data distribution. Categorical data were analyzed by chi-square test. Changes in the markers between the groups were analyzed using the analysis of variance (one-way ANOVA) and Bonferroni test for normal distribution, and Kruskal-Wallis test for non-normal distribution.

Comparison of variables overtime were analyzed with paired-*t* test for normal distribution and Wilcoxon test for non-normal distribution. Statistical significance was defined as $p < 0.05$.

Results

Seventy-five patients were initially recruited into the study; 25 were operated on abdominally, 25 vaginally and 25 laparoscopically. In the AH group, one woman had severe pelvic adhesions and extensive adhesiolysis was required. In the VH group, one woman had postoperative blood transfusion due to vaginal hematoma and another patient developed a febrile episode, whereas bladder injury occurred in one woman from the TLH group. Therefore, a total of 71 patients were enrolled for tissue trauma analysis: 24 in the AH group, 23 in the VH group and 24 in the TLH group.

Mean age was 51.2±6.3 years (range 37-70 years). The TLH group had lower mean age than AH and VH groups (47.9±4.2 vs. 51.4±5.4 and 54.2±7.5, respectively; p=0.002). The groups were found to be similar with regard to parity and indications for hysterectomy. Myoma uteri was the most common indication in all groups (60.6% cases), followed by abnormal uterine bleeding and adenomyosis. Group characteristics are summarized in Table I.

A significantly smaller decrease in blood hemoglobin concentration was observed in the TLH group as compared to the VH and the AH groups at 24 h after surgery (1.3±0.9 g/dL vs. 2.1±0.9 g/dL and 1.5±0.7 g/dL, respectively; p=0.024) (Figure 1). The TLH group had longer anesthesia and operation time than both, AH and VH groups (p<0.001), but the average hospital stay for the TLH group was shorter than for the other two groups (p<0.001). Operative characteristics of the groups are shown in Table II. No major intraoperative and postoperative complications occurred in the study groups. There was only one case of a febrile episode (over 37.5°C) in the VH group.

No differences were observed in median preoperative serum IL-6 and CPK levels between the groups. Serum levels of IL-6 and CPK were significantly elevated over basal values after surgery in all groups. Table III shows the levels of biochemical markers at various time points in the three groups.

Median serum concentrations of IL-6 were significantly higher following AH as compared to VH and TLH, and reached the peak at 6 h after surgery (39.2 pg/mL vs. 34.1 pg/mL and 11.5 pg/mL, respectively; p=0.001). When the VH and TLH groups were compared, the levels of IL-6 were significantly higher in the VH group (p=0.001) (Figure 2).

CPK concentration reached the highest level at 24 h post-operatively in all groups. In the AH group, median serum CPK activity at 24 h after operation was significantly higher than in the VH and TLH groups (199 U/L vs. 110 U/L, and 127 U/L, respectively; p<0.001); whereas there was no significant difference between the VH and TLH groups (p=0.824) (Figure 3).

Discussion

Our findings demonstrate that three different routes of hysterectomy (AH, VH, and TLH) are associated with significant stress response in terms of objective parameters of surgical trauma. This response is more prominent following AH than VH and TLH. On the other hand, no significant difference was observed between the VH and the TLH groups concerning CPK levels, but IL-6 levels were significantly higher in the VH group than TLH group.

Surgery is a major trauma leading to tissue damage and surgical trauma is followed by a release of cytokines from

Table I. Characteristics of patients undergoing abdominal, vaginal and total laparoscopic hysterectomy.

	AH (n=24)	VH (n=23)	TLH (n=24)	*p*-value
Age (years)	51.4±5.4[a]	54.2±7.5	47.9±4.2	0.002*
Parity	3 (0-8)[b]	3 (2-9)	3 (1-5)	0.492
Indications				
Myoma uteri	14 (58.3%)[c]	16 (69.6%)	13 (54,2%)	0.843
Dysfunctional uterine bleeding	6 (25%)	6 (26.1%)	8 (33.3%)	
Adenomyosis	3 (12.5%)	1 (4.3%)	2 (8.3%)	
Postmenopausal uterine bleeding	1 (4.2%)	0 (0%)	1 (4.2%)	

AH – Abdominal hysterectomy, VH – Vaginal hysterectomy, TLH – Total laparoscopic hysterectomy;
[a] mean±standard deviation, [b] median and (range), [c] number with(percentage), * statistically significant by ANOVA test

Table II. Comparison of treatment groups in terms of operative characteristics.

	AH (n=24)	VH (n=23)	TLH (n=24)	*p*-value
Duration of anesthesia (min.)	100±17.8	109.7±18.6	137.5±33.4	<0.001*
Operation time (min.)	90.3±16.7	101.3±17.2	128.1±32.6	<0.001*
Decline in hemoglobin level (g/dL)	1.5±0.7	2.1±0.9	1.3±0.9	0.024*
Hospital stay (day)	3.2±0.5	3.2±0.5	2.5±0.5	<0.001*

Values are given as mean±standard deviation; * statistically significant by ANOVA test

Table III. Serum levels of biochemical markers in the groups.

Time	AH (n=24)	VH (n=23)	TLH (n=24)	*p*-value
IL-6 (pg/mL)				
Preoperative	2.1 (2-60.3)	2 (2-16.2)	4.1 (2-20)	0.43
Intraoperative	6.6 (2-141)	2.7 (2-28.2)	7.8 (2-21.4)	0.049*
2h postoperative	22.7 (2-109)	19.7 (2-74.2)	12.8 (2-23.8)	0.012*
6h postoperative	39.2 (2-120)	34.1 (5.6-247)	11.5 (3.5-27)	0.001*
				(VH vs. TLH p=0.001)
24h postoperative	35 (2-100)	21.6 (5.4-78)	15 (6.2-58)	0.001*
CPK (U/L)				
Preoperative	63.5 (18-310)	57.0 (15-311)	64 (12-84)	0.284
Intraoperative	71.5 (15-385)	73 (17-347)	74 (14-123)	0.069
2h postoperative	99 (42-250)	65 (15-327)	80 (7-146)	0.155
6h postoperative	126 (25-368)	85 (13-278)	102 (9-187)	0.022*
24h postoperative	199 (70-732)	110 (7-310)	127 (19-221)	<0.001*
				(VH vs. TLH p=0.824)

Values are given as median and (range); *AH vs. VH and TLH, statistically significant by ANOVA test

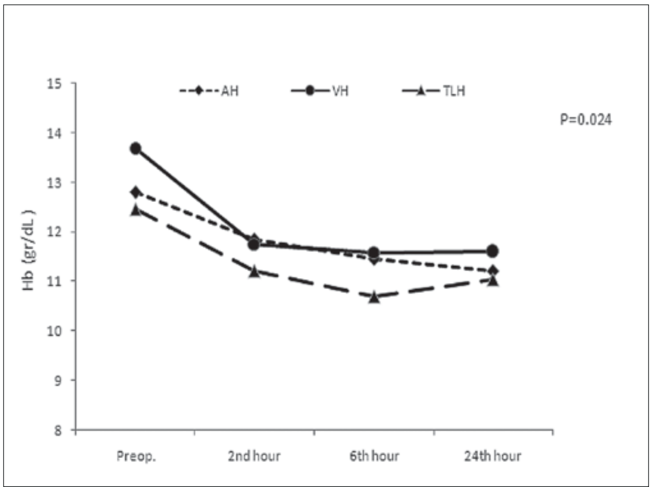

Figure 1. Changes in serum hemoglobin levels in the groups.
AH – Abdominal hysterectomy, VH – Vaginal hysterectomy, TLH – Total laparoscopic hysterectomy.

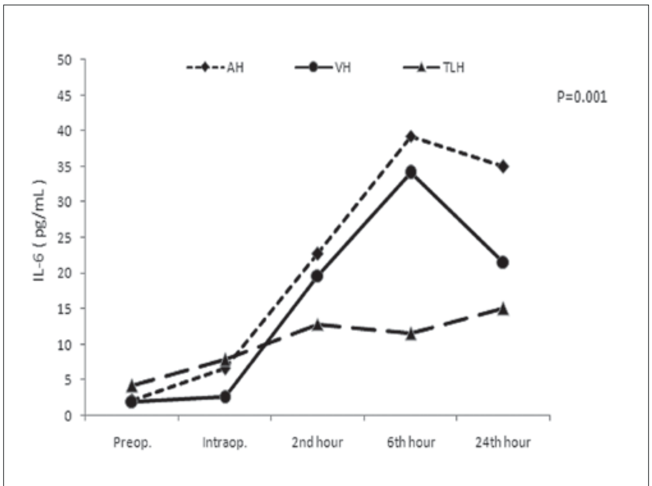

Figure 2. Changes in serum IL-6 levels in the groups.
AH – Abdominal hysterectomy, VH – Vaginal hysterectomy, TLH – Total laparoscopic hysterectomy. AH vs. VH and TLH, p=0.001. VH vs. TLH, p=0.001

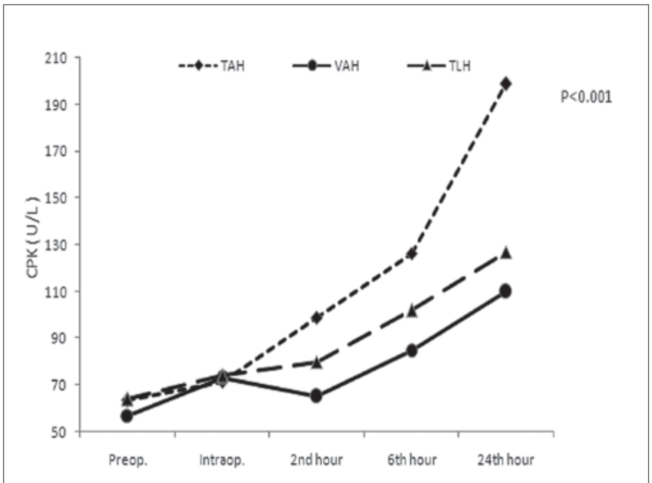

Figure 3. Changes in serum CPK levels in the groups.
AH – Abdominal hysterectomy, VH – Vaginal hysterectomy, TLH – Total laparoscopic hysterectomy. AH vs. VH and TLH, p<0.001, VH vs. TLH, p=0.824

lymphocytes, macrophages, and fibroblasts of the damaged tissues [15]. The markers of muscle and tissue trauma may change during the peri- and postoperative period. In the published reports, IL-6, CRP and CPK are the most commonly used biochemical markers for surgical tissue trauma [14, 16, 20, 21].

Of all the markers, IL-6 is the main acute phase protein that is released with surgical trauma, and the concentration of IL-6 entering the systemic circulation is correlated with the magnitude of tissue injury [8, 21]. It increases rapidly and peaks between 3 and 24 hours after surgery [22, 23]. Creatine phosphokinase, an enzyme found mainly in the heart, brain, and skeletal muscle, is another marker of tissue trauma. A marked rise in CPK activity, related to tissue trauma and injury, has been observed postoperatively, with the maximal level recorded at 24 to 48 hours after surgery, followed by a decline toward normal over the period of the next days [24]. Changes in both, total and isoenzyme activity (CK-MM and CK-MB) are consistent with the extent of soft tissue trauma [25]. Therefore, we measured total CPK levels to compare tissue trauma of different hysterectomy techniques.

The findings of our study are consistent with results of previous studies showing that AH induces more biochemical and inflammatory responses than VH or LH [12-17]. It has been suggested that AH is associated with greater trauma because of a larger abdominal incision, intraoperative manipulation and desiccation of the exposed tissues [16].

In contrast to these previous reports, Ellström et al. [9], did not find significant differences in serum IL-6 and CRP levels in patients who underwent AH and LH. However, in that study subjects who underwent laparoscopic surgery had significantly longer operation time, which might have obscured the benefit of less tissue trauma. Similarly, in their case-control study, Rorarius et al. [26], compared AH and LAVH and found that CRP and IL-6 were the most sensitive markers of the systemic response and did not discriminate between the two types of surgery.

In a prospective randomized study, Drahonovsky et al.[27], assessed clinical results and tissue trauma of three minimally invasive hysterectomy techniques: VH, LAVH and TLH. They reported that the increase in inflammatory markers was significantly higher in the VH group as compared to the two other groups. On the other hand, VH had the shortest operation time and least blood loss.

In a limited number of studies comparing tissue trauma after abdominal, vaginal and laparoscopic hysterectomies, greater tissue damage was found to accompany AH [18-20]. Malik et al. [19], reported IL-6 levels to be significantly higher after AH than VH and LH, but there was no difference in the acute phase reaction provoked by VH or LH. In a randomized study by Ribeiro et al. [18], inflammatory response was substantially higher in AH, whereas no difference was noted between VH and LH.

Our findings are partially consistent with these studies. Similarly, we found that IL-6 concentrations and CPK activity were higher in the AH group than the VH and TLH groups. When the VH and TLH groups were compared, we observed that CPK activity was not different between the patients who underwent VH and TLH, whereas IL-6 concentrations were significantly higher in the VH group than the TLH group.

In our study, we also observed that operation time was longer in the laparoscopic hysterectomy group than the other two groups, what is consistent with other studies [27, 28]. Laparoscopic surgeries in our series were performed with the use of conventional bipolar instruments and scissors instead of advanced electrosurgical instruments due to our institutional conditions. It could be the reason why TLH surgeries had longer operating times. The extent of tissue damage due to surgical trauma may affect postoperative healing. Therefore, less tissue trauma may account for early mobilization and shorter hospital stay. In our study, the hospitalization period for the laparoscopy group was significantly shorter than the AH and VH groups. We also found minimum blood loss in the TLH group.

Our study is not without limitations. Even though the criteria for the enrollment in the study were clearly defined, a selection bias for the choice of the operative procedure could not be excluded completely. In our institute, treatment is determined according to the preference of the patient or the performing consultant physician. Therefore, randomization could not been performed. Another limitation is that we focused on comparing tissue trauma of different hysterectomy types. Although early postoperative morbidity such as a decline in hemoglobin levels, hospitalization duration, febrile morbidity, and infection were evaluated, we could not compare clinical outcomes of the groups due to a small number of cases with early postoperative morbidity.

Conclusions

As far as our results are concerned, surgical trauma provoked by AH is significantly greater than after VH and TLH. Owing to the fact that laparoscopic hysterectomy is associated with less tissue trauma concerning IL-6 levels and more rapid recovery, which is the indirect indicator of tissue damage, it should be the preferred technique for women with benign diseases of the uterus, especially in experienced centers.

Further prospective randomized studies with larger sample size are needed to compare the level of tissue trauma after different hysterectomy techniques with clinical outcome data.

Authors' contribution:

1. Aysegul Oksuzoglu – conception and study design, acquisition of data, article draft.
2. Berna Seckin – conception and study design, article draft, corresponding author.
3. Ayse Figen Turkcapar – conception and study design, article draft.
4. Sarp Ozcan – acquisition of data.
5. Tayfun Gungor – conception and study design.

Authors' statement

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