

The Levels of CRP in Non-Complicated Patients With Total Laparoscopic Hysterectomy and its Role in Predicting Vaginal Cuff Hematoma

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ABSTRACT

We aimed to evaluate the mean C-reactive protein (CRP) levels in the patients who did not have any complications other than cuff hematoma after total laparoscopic hysterectomy (TLH) in order to determine the CRP levels to predict the potential to develop postoperative cuff hematoma.

The study was designed prospectively. The CRP levels, white blood cell (WBC) count, and haemoglobin values (Hb) of 106 patients, who underwent TLH for benign reasons, were measured preoperatively and on the days 1,2 and 7 postoperatively. The laboratory parameters of the patients who developed postoperative cuff hematoma were compared to those of the patients, who did not have any complications.

Of a total of 106 patients who underwent a laparoscopic hysterectomy, there were no differences in the demographic characteristics between the groups. The duration of operation was significantly longer in the group of patients with cuff hematoma ($p<0.05$). In the hematoma group, the level of CRP was statistically significantly different on POD7 ($p<0.05$).

We are of the opinion that CRP levels below the cut-off value of 12.5 mg/L measured on the postoperative 7th day indicate tissue damage secondary to surgical trauma, while care should be exercised to detect any possible complications in the patients with higher CRP levels above this value. We suggest that routine follow-up of the CRP levels may provide a cautious approach after a laparoscopic hysterectomy, allowing for early diagnosis and treatment for potentially developing complications including cuff hematoma and postoperative infections.

Keywords: C-Reactive Protein, Laparoscopic Hysterectomy, Vaginal Cuff Hematoma, White Blood Cell

Introduction

Laparoscopic surgery has well-known advantages such as shorter length of hospital stay, low-intensity postoperative pain, a shorter time required to return to normal activities of the daily life, low rates of infection at the surgical site, and low quantities of blood loss. Although minimally invasive approaches reduce the risk of systemic complications, postoperative infections and cuff hematoma remain to be the major ones. It is difficult to predict the timing of such complications; however, early diagnosis is important to improve the prognosis. Numerous studies support the correlation between the elevated levels of C-reactive protein (CRP) and the development of postoperative infectious complications, including intraabdominal abscess

(1,2).

Surgical procedures cause metabolic and inflammatory changes that correlate with the extent of tissue damage (3). The only objective method of assessing the extent of trauma is the quantification of acute-phase reactants (4). Surgical trauma alters the hemodynamic and metabolic states by activating neuroendocrine responses. Increments are observed in the levels of the inflammatory cytokines. The increase in cytokines activates a system for the production of acute-phase proteins and increases the levels of CRP (1,5). Numerous studies have investigated the effects of minimally invasive surgery and conventional open surgery on the acute-phase reactants (3). There are studies about hysterectomy, analyzing inflammatory responses caused by surgical trauma associated with different

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surgical approaches. It is suggested that both vaginal and laparoscopic approaches achieve superior outcomes compared to abdominal hysterectomy (2).

Early diagnosis and timely management of postoperative complications after laparoscopic hysterectomy are of great importance for the prognosis. CRP is a sensitive systemic marker of inflammation and tissue damage but it is not specific for infection (6,7). However, CRP levels remain as an infection monitoring tool in the perioperative period (8). The level of CRP peaks at the range from 36 to 50 hours after the release of bacterial endotoxins (6). There are no studies evaluating the timing of the peak levels of CRP in the postoperative period and determining the value of this finding after trauma due to gynaecologic surgical procedures. The aim of this study was to determine normal CRP levels in uncomplicated total laparoscopic hysterectomy (TLH) and to determine a cut-off value for CRP levels to predict a developing cuff hematoma in the early postoperative period.

Material and Methods

This prospective study was conducted in the period from January 2017 to January 2018. It included patients, who underwent TLH for benign reasons in the Gynaecology and Obstetrics Clinic of Istanbul Kanuni Sultan Suleyman Training and Research Hospital. The patients were followed up clinically and with the results of the laboratory tests. The clinical findings and the results of the laboratory tests were recorded prospectively. The study protocol was approved by the institution's Istanbul Taksim Health Practices and Research Central Ethics Committee at Health Sciences University in 2017 (TEAH-78/20.09.2017) and registered to ClinicalTrials.gov (NCT03879499). After the ethics committee approval was obtained, 136 female patients were included in the study after they provided their consents to participate in the study. Informed consent was obtained from the patients included in the study. The patients underwent TLH in our hospital due to benign gynaecological indications. The article was prepared in accordance with the Helsinki declaration principles.

The preoperative demographic data of the patients including the age, gravidity, parity, and body mass index were recorded. A total of 30 patients who underwent an intraoperative conversion to laparotomy, who underwent laparotomy due to postoperative complications, who developed

infection due to causes other than surgery (such as urinary tract and pulmonary infections), who received blood transfusion after TLH, who had rheumatologic diseases, and who had prolonged length of hospital stay due to surgical wound infection were excluded from the study. A total of 106 patients, who were included in the study, were discharged on the second day after hysterectomy.

Venous peripheral blood samples to test the CRP levels and the white blood cell counts were taken on the first, second, and seventh postoperative days to evaluate tissue trauma and surgical inflammatory responses. CRP levels were quantified with turbidimetry under standardized conditions. The patients were invited to an outpatient follow-up visit on day 7 after the hysterectomy. The patients underwent a gynaecological examination in order to check out the presence of cuff hematoma and a transvaginal ultrasound examination so that the vaginal length was determined. In the ultrasound examination, cuff hematoma was defined as a hypoechoic area adjacent to the terminal vaginal cuff, being limited to the bladder anteriorly and to the intestines posteriorly. Hypoechoic areas displaying intestinal peristalsis were excluded. Only two longest distances in the area of interest were included in the measurements. Then, the presence or absence of hematoma in the cuff was checked out with transvaginal ultrasonography. Organized formations larger than 3 cm with thin septations were considered as cuff hematoma. Disorganized scattered mobile hypoechoic formations below 3 cm were considered as fluid collections and not considered as hematoma. The patients diagnosed with cuff hematoma were given antibiotherapy and they were invited to an outpatient follow-up visit on the 15th day after hysterectomy.

The length of the vagina was measured by taking the C-point as the reference from the Pelvic Organ Prolapse Quantification System (POP-Q) measurement performed without administering anaesthesia. During the abdominal ultrasonography in the follow-up visit, a rigid Hegar dilator was sensitively advanced through the vagina until it reaches the point, where it could not be moved further. Then, the part of the Hegar dilator at the level of the hymenal caruncle was marked to be measured when it was taken out. This value was recorded as the vaginal length after the hysterectomy. The Female Sexual Function Index (FSFI) scores of the patients were obtained preoperatively and on the postoperative 3rd and 6th months.

The data were analyzed using the IBM SPSS

Table 1. Comparison of demographic features and operative datas of patients with and without cuff hematoma after TLH

	Patients with Hematoma	Patients without Hematoma	p value
	(n : 16) Mean± SD	(n : 90) Mean± SD	
Age (years)	51.3±5.2	49.7±4.3	0.877
BMI (kg/m2)	27.1±2.1	28.3±3.2	0.453
Gravida	4.2±2.3	4.98±2.3	0.548
Parite	3.5±1.6	3.8±2.0	0.912
Uterine weight (g)	365±260	340±245	0.823
Uterus size (cm)	12.1±5.8	11.2±5.3	0.432
Operation time (min)	126±27	107±18	0.001

Sd: Standart deviation, TLH: Total laparoscopic hysterectomy, BMI: Body Mass Index, Student-t test, $p < 0.05$

Statistics v.20 software package for Macintosh. The Kolmogorov Smirnov test was used to analyze whether the distribution of the continuous variables was close to normal. The continuous variables were expressed as mean \pm standard deviation, and the nominal variables were expressed as numbers and percentages. The significance of the difference in the mean values between the groups was evaluated with the Student's t-test. Compare percentage values were evaluated with the Chi-Square test. The cut-off value for CRP was calculated using the receiver operating characteristic (ROC) curve analysis in a 95% confidence interval (CI). A p-value of < 0.05 was considered statistically significant.

Results

A total of 106 patients, who underwent TLH, were evaluated. Of these patients, 16 had cuff hematoma and 90 didn't have. There were no differences in the demographic characteristics and clinical outcomes (blood loss, complications, length of hospital stay) between the two groups of patients; namely, the group of patients with cuff-hematoma and the group of patients without a cuff hematoma ($p > 0.05$). The duration of the operative procedure was significantly longer in the hematoma group ($p < 0.05$) (Table 1). The complaints requiring admission to hospital, findings from the physical and ultrasonographic examinations, the results from the endometrial biopsy, the indications for the procedure, and the findings from the postoperative pathological examination were similar between the groups ($p > 0.05$) (Table 2).

There was an explicit increase in the postoperative CRP concentrations. For all TLH patients, the mean level of CRP was 31.96 ± 19.76 mg/L on

postoperative day 1 (POD 1), it was 47.43 ± 52.29 mg/L on POD 2, and it was 14.6 ± 10.1 mg/L on POD 7. The mean levels of CRP on POD 1 and 2 were high in both the hematoma patients and in the patients without cuff hematoma. While the CRP levels on POD1 and 2 were not significantly different between the groups, the CRP level on POD 7 was 20.79 ± 11.7 mg/L in the cuff hematoma group, which was significantly higher compared to the group of patients without hematoma ($p < 0.05$).

Because a significant difference in the levels of CRP on POD 7 was detected between the groups, the cut-off value was calculated using the ROC curve analysis. The sensitivity was 78.2% and the specificity was 71.3% for the CRP threshold value of 12.5 mg/L on POD 7 in order to predict postoperative cuff hematoma (Figure 1).

The white blood cell (WBC) count was elevated in the patients with and without cuff hematoma on POD 1 and POD 2, and then the counts were gradually decreased. The WBC counts on POD 1 and 2 were significantly higher in the cuff hematoma group compared to the non-hematoma group ($p < 0.05$). There were no significant differences between the groups in the postoperative follow-up haemoglobin and hematocrit values (Table 3).

The mean preoperative and postoperative vaginal length difference (Δ VL) of 106 TLH patients was 1.74 ± 0.91 cm. There was not a significant difference in Δ VL (1.82 ± 0.97 , 1.69 ± 0.88) between the groups with and without hematoma ($p > 0.05$). For all 106 patients included in the study, the mean preoperative FSFI score was 28.4 ± 4.3 , it was 25.1 ± 4.2 in the postoperative month 3, and it was 26.3 ± 3.8 in the postoperative month 6. While there was not a significant

Table 2. Comparison of preoperative period examination and pathologic findings of patients with and without cuff hematoma after total laparoscopic hysterectomy

	Patients with Hematoma (n: 16) Mean± SD	Patients without Hematoma (n: 90) Mean± SD	P value
Application complaint			
Vaginal bleeding	11(78.6 %)	80(87%)	0.87
Inguinal / abdominal pain	2(14.3%)	9(9.8%)	0.75
Routine control	1(7.1%)	3(7.1%)	0.69
Ultrasonography findings			
Normal	2(14.2%)	12(13%)	0.13
Myoma uteri	8(57.1%)	42(45.7%)	0.29
Endometrial polyp	2(14.3%)	20(21.7%)	0.78
Adenomyosis	1(7.1%)	10(10.9%)	0.19
Adnexial mass	1(7.1%)	5(5.4%)	0.66
Endometrial hyperplasia	0(0%)	3(3.3%)	NS
History of operation			
Yes (caesarean section, appendectomy, .vs)	4(28.6%)	29(31.5%)	0.32
No	10(71.4%)	63(68.5%)	0.44
Indications for hysterectomy			
Therapy resistant menometrorraphy	5(35.7%)	41(44.6%)	0.34
Myoma uteri	7(50%)	47(51.2%)	0.65
Endometrial hyperplasia	1(7.1%)	1(1.1%)	0.79
Adenomyosis	1(7.1%)	3(3.3%)	0.88
Pipelle biopsy results			
Endometrial polyp	1(7.1%)	12(13.0%)	0.76
Progesterone-influenced endometrium	6(42.9%)	47(51.0%)	0.82
Hyperplasia without complex atypia	2(14.3%)	7(7.6%)	0.23
Endometrial fragments	5(35.7%)	26 (28.2%)	0.47

Chi- square test; p<0.05

difference in the preoperative FSFI scores between the hematoma and non-hematoma groups of patients ($p>0.05$), it was observed that they were lower in the hematoma group compared to the non-hematoma group when the month-3 and month-6 FSFI scores were compared ($p <0.05$) (Table 4).

Discussion

There are different techniques described for performing a hysterectomy in the gynaecology practice. They are abdominal hysterectomy (AH), vaginal hysterectomy (VH), laparoscopically assisted vaginal hysterectomy (LAVH), and total

laparoscopic hysterectomy (TLH) techniques. Numerous studies have compared the subjective parameters emerging secondary to surgical trauma associated with these techniques (9,10). Labib et al. compared acute-phase reactants as the objective parameters of surgical trauma caused by different surgical techniques. It was demonstrated that IL-6 and CRP levels were significantly elevated in the 24-36 hours after the operation in abdominal surgeries (11,12). Furthermore, it was reported that the duration of the operation had no effects on the IL-6 and CRP levels (12). It has been suggested that the reported increments were not significant due to the major tissue trauma occurring after laparotomy (13). Despite the

Table 3. Comparison of CRP, WBC and Hb values in patients with and without cuff hematoma after TLH

	Patients with Hematoma (n : 16) Mean± SD (Min-Max)	Patients without Hematoma (n : 90) Mean± SD (Min-Max)	p value
C- Reactive protein levels (mg / L)			
1st. day	37.43±23.6 (7-82)	31.13±19.1 (6-134)	0.987
2nd. day	61.29±59.9 (12-255)	45.3±51.0 (2-431)	0.235
7th. day*	20.79±11.7 (2-36)	13.68±13.4 (1-65)	0.004
White blood cell count (mm ³)			
1st. day*	11427.8±3173.5 (6400-20000)	9130.7±1923.2 (6000-14590)	0.002
2nd. day*	11624.2±5679.1 (6730-29240)	8155.9±1687.3 (5030-16550)	0.001
7th. day	8551.9±1687.3 (5140-13590)		0.239
Hemoglobin values (g/dl)			
Preoperative day	10.9±1.1 (7-12)	11.1±1.3 (8-13)	0.610
1st. day	10.5±1.2 (8-13)	10.7±1.6 (7-14)	0.187
2nd. day	10.7±1.5 (7-13)	10.5±1.6 (7-15)	0.853
7th. day	11.0±1.4 (9-15)	10.9±1.4 (8-15)	0.654

Sd: Standart deviation, CRP: C-Reaktif Protein, WBC: White Blood Cell, Hb: Hemoglobin, Student-test, *p <0,05

Table 4. Comparison of total FSFI scores of patients with and without cuff hematoma after TLH

Parameters	Patients with Hematoma (n : 16) Mean± SD	Patients without Hematoma (n : 90) Mean± SD	p value
Preoperative FSFI scores	27.6±4.4	28.1±4.3	0.41
Postoperative 3rd month FSFI scores	22.3±4.1	25.1±4.2	0.03
Postoperative 6th month FSFI scores	23.6±3.9	25.9±3.8	0.01

FSFI: Female Sexual Function Index; Sd: Standart deviation, TLH: Total laparoscopic hysterectomy, Student-t test, p<0.05

minimal tissue trauma in laparoscopic procedures in gynaecology, the studies evaluating the levels of CRP associated with this type of surgeries are limited. The aim of our study was to demonstrate the postoperative course of CRP levels and WBC counts in patients, who underwent TLH.

CRP is a serum acute-phase reactant synthesized in the liver and released by proinflammatory cytokines as a response to stimulation. Its synthesis occurs as a part of a non-specific acute-

phase reaction to most forms of tissue damage such as infection, inflammation, and malignant neoplastic changes. In healthy young adults, the mean CRP concentration is about 0.8 mg/L; however, after acute phase stimulation, the values may increase by more than 500 mg/L. De novo synthesis in the liver starts rapidly after a single stimulus and peaks within 48 hours. The plasma half-life of CRP is approximately 19 hours and is constant in any condition (11).

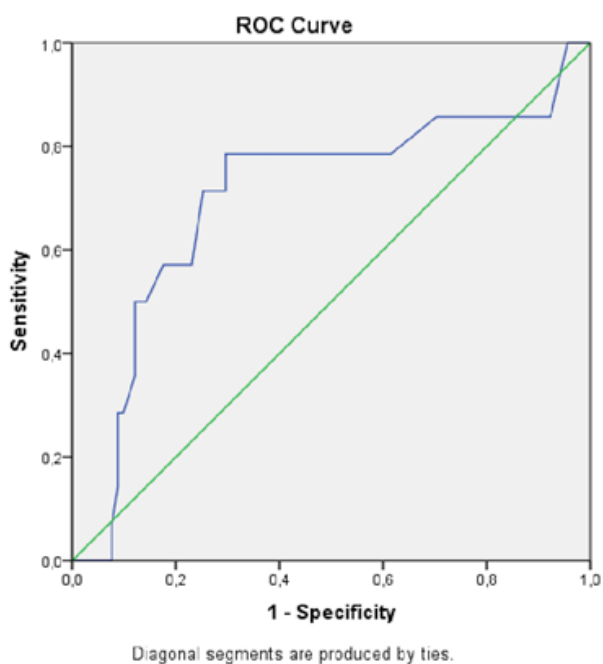


Fig. 1. ROC curve analysis of C-reactive protein levels on postoperative 7th day

Laparoscopic hysterectomy produces a low-grade inflammatory response compared to other techniques (14). There are studies available in the literature, evaluating the inflammatory response to determine whether there is a correlation between the clinical outcomes of minimally invasive surgery and the laboratory results (3,11,15). In the inflammatory response, each cytokine reaches its peak value at different time points. Therefore, we carried out a detailed evaluation by quantifying the CRP levels on postoperative days 1, 2, and 7. The highest CRP values after TLH were detected on POD 2 and increased to 431 mg/L at maximum. Although the values on POD 1 also tended to be high, the maximum value was 134 mg/L. Subsequently, it was observed that the POD 7 levels of CRP decreased nearly to the normal levels and they were 65 mg/L at maximum. It was found out that the CRP values were higher in 14 patients, who developed cuff hematoma compared to the levels detected in the patients in the non-hematoma group, and that the CRP levels on POD 7 might indicate a risk of developing a hematoma.

Early diagnosis of infectious complications is of importance in order to achieve better postoperative outcomes. It is necessary to find out a marker that can alert the surgeon about the development of a septic complication before it becomes clinically apparent. Evaluation of such a marker may be beneficial in making the decision whether the patient will be discharged or continue

staying at the hospital for further examinations (16). Many studies on colorectal surgery support the correlation between the increase in CRP and the development of postoperative infectious complications, including an anastomotic leakage or intraabdominal abscess (17). All these studies attempt to establish a cut-off value for CRP as an indicator of such complications. There is no determined CRP cut-off value after laparoscopic gynaecological operations.

An isolated increase in the levels of CRP is not sufficient to make a diagnosis of major complications because many patients may produce severe systemic inflammatory responses and have elevated CRP levels for a long period of time depending on other factors including surgical trauma, blood loss, and prolonged duration of the surgical procedure. However, some authors argue that the quantification of CRP levels on the postoperative 3rd or 4th day should be included in routine laboratory tests since the high negative predictive value of CRP levels excludes the possibility of septic complications (18). Multimodal rehabilitation programs and the use of laparoscopic surgery cause a low-grade systemic inflammatory response in patients (19). This low-grade systemic infection may increase the sensitivity and specificity of the CRP levels to detect infectious complications in the early postoperative period. However, the postoperative CRP levels did not significantly increase totally in our study. This finding can be explained by the laparoscopic approach applied to all patients. When the data of the patients, who developed cuff hematoma, were analyzed; it was found out that their CRP levels tended to increase in the early postoperative period and that these patients were diagnosed with hematoma during the outpatient follow-ups. Early diagnosis of a hematoma, initiation of prophylactic antibiotherapy, and a close follow-up to monitor the disease are important for preventing the development of an intraabdominal abscess, which may follow emergent cuff cellulite.

Mustard et al. found that serial quantification of CRP levels in the postoperative period predicted the emergence of postoperative septic complications before the clinical diagnosis in patients, who underwent intraabdominal or intrathoracic procedures (20). The studies with variable designs and enrolling different patient populations have shown that the postoperative 3rd day provides values with a good diagnostic accuracy. Especially to predict anastomotic leakages and infectious complications associated

with bowel movements and passage obstruction and that the high CRP concentrations persist at this time point. In these studies, the clinical diagnosis of complications is made on the postoperative days from 5 to 9. Laboratory tests for CRP may, therefore, shorten the time until the diagnosis and the required period for the treatment of complications. For predicting postoperative infectious complications, the cut-off value of CRP has been shown to be 140 mg/L on the postoperative day 3 and 145 mg/L on POD 4. In another study, it was reported to be 125 mg/L on POD 4 (21). Moreover, the values in the range between 80-100 mg/L are used as the CRP threshold values to differentiate non-infectious SIRS from sepsis in internal medicine and in surgical intensive care unit patients (6,22). In our study, the best diagnostic accuracy for the postoperative CRP levels (area under the ROC curve) was obtained on postoperative day 7. CRP levels obtained on POD 7 were found to be significantly higher in the follow-up visits of the patients, who developed hematoma in the postoperative period.

A high WBC count is a non-specific marker of inflammation but it is one of the diagnostic criteria for systemic inflammatory response syndrome (SIRS). However, it has a poor diagnostic performance for detecting infection in the postoperative period (23,24). Some authors report a delayed increase in the WBC count, correlating with the clinical diagnosis of complications in patients developing infectious complications following surgery (6). In our study, the postoperative WBC counts performed in the follow-up visits were significantly higher in the cuff hematoma group on POD 1 and 2. But there was not a significant difference on POD 7. Therefore, the WBC count does not appear to be a very effective parameter in predicting cuff hematoma.

In our study, the vaginal length was measured conventionally. Regardless of the hysterectomy type, the postoperative vaginal length is shorter compared to the length of the vagina before the surgery (25). The difference in the preoperative and postoperative length of the vagina (Δ VL) showed that the vaginal length was shortened in our study. However, there was not a significant difference in Δ VL between the hematoma and non-hematoma groups.

There are numerous studies evaluating the effects of different types of hysterectomy on sexual functioning of women. A review of specific studies focusing on premenopausal women with

benign pathologies reveals variable results reported in the current literature. A reduction in the intensity of perceived sexual pleasure following a hysterectomy is likely to result in low FSFI scores. This type of findings can occur since the pelvic, hypogastric, and vagus nerves, innervating these organs may be damaged or ruptured during a hysterectomy (26). In this present study, the evaluation of the preoperative and postoperative total FSFI scores of the TLH patients revealed that a decrease occurred in the postoperative months 3 and 6. However, the FSFI scores in the postoperative months 3 and 6 were lower in the patients who developed postoperative vaginal cuff hematoma compared to the non-hematoma patients. This finding was associated with the negative effects of the complications on the sexual desire of the patients. Postoperative vaginal cuff hematoma may also be associated with sexual avoidance and low FSFI scores in the early period. The poor postoperative FSFI scores in some of our patients are consistent with the argument that pre-existing sexual problems due to benign gynaecological diseases may worsen after hysterectomy. Also, it may have a negative effect on sexual functions by causing vaginal dryness, pain, and bleeding in the postoperative period. Having undergone an operation like hysterectomy, negatively affecting the vagina and the surrounding tissues to a great extent, may be a troublesome condition that may impair sexual functions in the postoperative period over the short term. Therefore, we are of the opinion that the sexual functions of these women should be evaluated after a period longer than one year, allowing for the alleviation of the postoperative problems.

The main limitations of our study were the small sample size and the single-centred study design, as well as, the unavailability of the FSFI scores in the first year after the procedure. The absence of evaluations of a number of other inflammatory markers (procalcitonin, IL-6, etc.) is another limitation. There is a need for further large-scale studies contributing to our results to confirm the sensitivity of the cut-off values we determined. The prospective design and the serial testing of the CRP levels and the WBC counts as the indicators of infection are the strengths of our study.

We suggest that a routine follow up of the CRP levels after laparoscopic hysterectomies will be a cautious approach to predict the risk for developing cuff hematoma and postoperative infections and that such an approach will be

helpful in the early diagnosis and treatment before the emergence of overt clinical findings.

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