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Original Research

A retrospective comparative analysis of systemic inflammatory response after laparoscopic, vaginal, and abdominal hysterectomy

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Abstract

Background: Lymphocyte to neutrophil ratio (NLR) is a rapid and simple marker for systemic inflammation and stress after major surgery. In this study, we aimed to compare NLR changes according to surgical methods of hysterectomy. **Methods**: A retrospective chart review for all patients who underwent hysterectomy for benign uterine disease from 2016 to 2020 was performed. A total of 1549 women were assigned to total laparoscopic hysterectomy (TLH) (n = 419), vaginal hysterectomy (VH) (n = 608), and total abdominal hysterectomy (TAH) (n = 522) groups. Patient characteristics, surgical outcomes, and NLR changes were compared among women who underwent TLH, VH, and TAH. **Results**: Preoperative mean NLR was similar among three groups ($p = 0.056$). However, mean NLR on postoperative day 1 ($p < 0.0001$) and day 3 ($p = 0.011$) was significantly lower in TLH group than others. Also, mean NLR change on postoperative day 1 was significantly lesser in TLH group than others (1.9 in TLH vs. 5.4 in VH vs. 4.7 in TAH; $p < 0.0001$). Mean NLR change on postoperative day 3 was greater in TAH group than others, although there were no statistically significant differences (0.2 in TLH vs. 0.3 in VH vs. 0.7 in TAH; $p = 0.354$). Multivariate analysis revealed that massive NLR change (>5.0) on postoperative day 1 was significantly associated with types of hysterectomy ($p < 0.0001$). **Conclusion**: Our data showed that acute NLR change was lesser in TLH group comparing to VH and TAH group, which suggests that TLH might be associated with less systemic inflammation and tissue trauma after surgery.

Keywords: Neutrophil-to-lymphocyte ratio; Systemic inflammatory response; Hysterectomy

1. Introduction

Hysterectomy is a major gynecologic surgery, which is the most commonly performed procedure worldwide for the treatment of benign uterine disease. With the advent of minimal invasive surgical techniques, the proportion of total laparoscopic hysterectomy (TLH) and total vaginal hysterectomy (VH) represents approximately half of all hysterectomies, whereas the proportion of total abdominal hysterectomy (TAH) is decreasing [1,2]. Although minimal invasive surgical approaches are considered to be associated with cosmetic advantage, less pain, early recovery, and cost effectiveness compared to TAH, which minimal invasive procedure should be preferred is still in debates [3–6].

It is well established that the systemic inflammatory response is related to alterations in circulating white blood cells, specifically the presence of neutrophilia with a relative lymphocytopenia [7,8]. In that respect, lymphocyte to neutrophil ratio (NLR) can be a rapid and simple marker for systemic inflammation [8]. Several reports suggested that NLR can be a useful marker for the prediction of cancer prognosis, risk of hypertension, and cystic fibrosis prognosis, which is highly relevant to systemic inflammatory response [9–13]. However, there have been no reports comparing systematic inflammation after TAH, VH, and TLH, which might be associated with tissue trauma and stress during surgery [4,5,14,15].

Therefore, in this study, we aimed to quantify surgical inflammatory response and tissue trauma after hysterectomy, by comparing postoperative NLR changes after TAH, TLH, and VH.

2. Materials and methods

This study includes all women undergoing hysterectomy (total abdominal hysterectomy (TAH), total laparoscopic hysterectomy (TLH), and vaginal hysterectomy (VH)) for the treatment of benign uterine disease (adenomyosis, uterine myoma, and dysfunctional uterine bleeding) or cervical precancerous lesions (CIN and CIS) at Hallym University hospital between 2016 and 2020. Women with prolapsed uterus or co-existent malignancy were excluded. Data was collected from a retrospective chart review.

The route of hysterectomy was selected on the surgeon's discretion. Generally, VH was preferred to TLH for a mobile uterus with vaginal accessibility, regardless of the size of uterus. Uterine mobility was determined on pelvic examination using a tenaculum. If the cervix descended adequately (to more than the lower half of the vagina), the sur-

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geon opted for VH rather than laparoscopic or abdominal hysterectomies. TAH was opted for women with large size uterus (more than 12 weeks of size) and highly suspected severe pelvic adhesion. Each procedure was performed by one of the three senior surgeons in the conventional manner.

All patients had their complete blood count checked three times: on 1 day before surgery; postoperative 1 day; and postoperative 3 day. Patient characteristics included: age; parity; body mass index (BMI); and indications for surgery. Surgical outcomes included: estimated blood loss (EBL; estimated by anesthesiologist during surgery); surgery time (from skin incision to closure); uterine weight; and neutrophil to lymphocyte ratio (NLR).

Also fever (temperature >38 °C on two occasions six hours apart), hemorrhage (postoperative bleeding which leads to re-operation), infection, ileus, stump cellulitis or disruption, fistula, deep venous thrombosis, pulmonary embolus, urinary problems (urgency, incontinence), and adjacent organ injury (bowel, ureter, and bladder) were included as postoperative complications. We obtained approval from local institutional review board for this study.

Statistical analysis was performed using SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA). Dichotomous variables were compared by Fisher's exact test or the chi-square test. Continuous variables were compared by the *t*-test. Multivariate analysis was performed using binary logistic regression. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated. For all statistical tests, $p < 0.05$ was considered significant. The study protocol was approved by the Institutional Review Board of Hallym University Hospital (IRB file No. 2021-09-004-001).

3. Results

Total 1549 women underwent hysterectomy for benign uterine disease or cervical precancerous lesions (TLH = 419, VH = 608, TAH = 522) during the study period. 31 cases of TAH were conversion from 30 cases of TLH and 1 case of VH due to unexpected severe pelvic adhesion. Except for younger age in TLH group, patient characteristics including parity and BMI were similar among three groups (Table 1). In surgical outcomes, TAH was associated with the largest EBL and uterine weight. Other two groups showed similar EBL and uterine weight. Surgery time was the shortest in VH group (Table 1).

Indications for surgery were listed in Table 1. Uterine myoma was most frequently observed in all groups. CIN or CIS was the most highly associated with TAH group.

Preoperative mean NLR was similar among three groups ($p = 0.056$). However, mean NLR on postoperative day 1 ($p < 0.0001$) and day 3 ($p = 0.011$) was significantly lower in TLH group than others. Also, mean NLR change from preoperative to postoperative day 1 was significantly lesser in TLH group than others (1.9 in TLH vs. 5.4 in VH vs. 4.7 in TAH; $p < 0.0001$). Although mean NLR change from preoperative to postoperative day 3 was greater in TAH group than others, there were no statistically significant differences among three groups (0.2 in TLH vs. 0.3 in VH vs. 0.7 in TAH; $p = 0.354$) (Table 2). NLR changes from pre- to postoperative 1 and 3 day among three groups were described in Fig. 1.

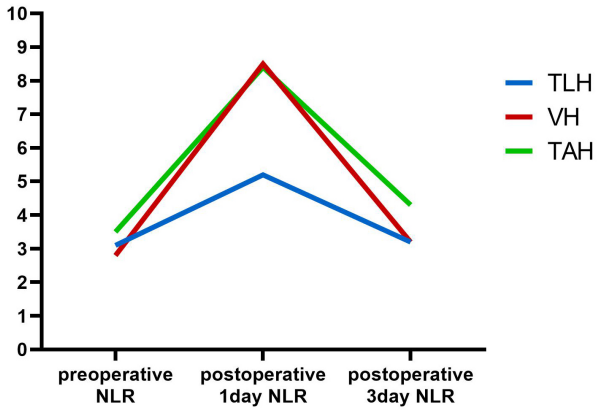

Fig. 1. NLR changes from pre- to postoperative 1 and 3 day.

Major complications after hysterectomy were listed in Table 3. There were 1 case of stump disruption, 1 case of fever, and 1 case of hemorrhage after TLH, 1 case of fever after VH, and 4 cases of adjacent organ injury (2 bowel injury, 1 ureteral injury, and 1 bladder injury) after TAH.

Multivariate analysis revealed that massive NLR change (>5.0) on postoperative day 1 was significantly associated with types of hysterectomy (TLH; HR 0.241 (95% CI 0.174–0.333), VH; HR 1.430 (95% CI 1.129–1.810)), irrespective of BMI, surgery time, or EBL (Table 4).

4. Discussion

Hysterectomy is a major gynecologic procedure, which can be performed via several approaches, such as transabdominal, transvaginal, laparoscopic-assisted, and robotic techniques. With the advent of surgical techniques, minimal invasive surgery including VH, TLH, LAVH, and robotic hysterectomy is preferred to conventional TAH. Although which minimal invasive procedure should be preferred is still in debates, several reports suggested that VH should be standard for the treatment of benign uterine disease and TLH should be reserved for women who cannot be a candidate for VH. VH showed several advantages comparing to TLH, such as no abdominal scar, shorter surgery time, and cost effectiveness [3,16]. However, there have been no reports comparing systemic inflammation and tissue trauma between two minimal invasive techniques, which might be associated with adhesion making, postoperative pain, and recovery after surgery.

In our data, TLH was associated with less postoperative 1 day change of NLR comparing to VH, and TAH. On postoperative 3 day, NLR resumed approximately similar

Table 1. Patient characteristic, surgical outcomes and indications.

	TLH (N = 419)	VH (N = 608)	TAH (N = 522)	*p* value
Patient characteristics				
Age, years	45.9 (±5.47)	46.7 (±5.14)	47.4 (±7.85)	0.001
Parity	1.9 (±0.75)	1.9 (±0.65)	1.9 (±0.99)	0.305
BMI, kg/m^2	23.7 (±3.59)	23.7 (±3.04)	24.1 (±3.74)	0.070
Surgical outcomes				
EBL, mL	326.2 (±96.88)	353.7 (±109.34)	480.7 (±158.88)	<0.0001
Surgery time, min	132.7 (±33.69)	95.0 (±45.45)	128.6 (±34.97)	<0.0001
Uterine weight, g	235.5 (±119.46)	236.9 (±114.72)	355.4 (±315.64)	<0.0001
Indications				
Uterine myoma	265 (63%)	416 (68%)	323 (61%)	
Adenomyosis	45 (11%)	42 (7%)	30 (6%)	
Uterine myoma & Adenomyosis	69 (16%)	112 (18%)	72 (14%)	
CIN or CIS	37 (9%)	37 (6%)	95 (18%)	
Dysfunctional uterine bleeding	3 (1%)	1 (1%)	2 (1%)	

BMI, body mass index; EBL, estimated blood loss; CIN, Cervical Intraepithelial Neoplasia; CIS, Carcinoma *In Situ*; TLH, total laparoscopic hysterectomy; VH, vaginal hysterectomy; TAH, total abdominal hysterectomy.

Table 2. Neutrophil to lymphocyte ratio (NLR) changes.

	TLH (N = 419)	VH (N = 608)	TAH (N = 522)	*p* value
Preoperative NLR	3.2 (±4.19)	2.9 (±3.47)	3.5 (±3.71)	0.056
Postoperative day 1 NLR	5.2 (±5.08)	8.4 (±4.95)	8.3 (±5.81)	<0.0001
Postoperative day 3 NLR	3.3 (±10.41)	3.3 (±2.32)	4.3 (±3.80)	0.011
NLR changes from preoperative to postoperative day 1	1.9 (±6.41)	5.4 (±5.98)	4.7 (±6.62)	<0.0001
NLR changes from preoperative to postoperative day 3	0.2 (±11.19)	0.3 (±4.04)	0.7 (±6.84)	0.354

NLR, neutrophil-to-lymphocyte ratio; TLH, total laparoscopic hysterectomy; VH, vaginal hysterectomy; TAH, total abdominal hysterectomy.

Table 3. Complications after hysterectomy.

	TLH (N = 419)	VH (N = 608)	TAH (N = 522)
Fever	1	1	0
Stump disruption	1	0	0
Hemorrhage	1	0	0
Bowel injury	0	0	2
Ureteral injury	0	0	1
Bladder injury	0	0	1

TLH, total laparoscopic hysterectomy; VH, vaginal hysterectomy; TAH, total abdominal hysterectomy.

Table 4. Mutivariate analysis for risk factors of massive NLR changes (>5.0) after hysterectomy.

Risk factors	Hazard ratio (95% CI)	*p*-value
BMI ≥30	0.431 (0.167–1.111)	0.081
Surgery time ≥120 min	1.273 (0.821–1.973)	0.280
EBL ≥500 mL	0.731 (0.352–1.515)	0.399
Hysterectomy type		<0.0001
TLH	0.241 (0.174–0.333)	<0.0001
VH	1.430 (1.129–1.810)	0.003
TAH	1.000	

BMI, body mass index; EBL, estimated blood loss; TLH, total laparoscopic hysterectomy; VH, vaginal hysterectomy; TAH, total abdominal hysterectomy.

to preoperative status in all procedures. In addition, massive changes in NLR (more than 5) on postoperative 1 day were significantly associated with type of surgery, regardless of BMI, surgery time, and EBL. We consider that less change in NLR following TLH might be stem from less manipulation of tissue during surgery and minimal incision. It is well-known that performing the least invasive method, which is associated with less tissue trauma and less systemic inflammation, is the key to decrease the risk of adhesion formation [17]. There are a number of trials supporting that laparoscopic hysterectomy is associated with less postoperative pain, less tissue manipulation, and earlier resumption to normal activity than vaginal or abdominal approaches. A small prospective, randomized, controlled study which includes 46 women who underwent TAH (n = 23) or LAVH (n = 23) reported that analgesic requirement is lower in the laparoscopy group than laparotomy group [18].

A meta-analysis which includes 34 trials comparing surgical outcomes of TAH, TLH/LAVH, and VH revealed that TLH/LAVH and VH were associated with earlier resumption to normal activities than TAH (VH vs. TAH, mean difference 9.5 days; TLH/LAVH vs. TAH, mean difference 13.6 days) [3]. A prospective, randomized study, which includes 125 women (40 VH, 44 laparoscopy-assisted vaginal hysterectomy (LAVH) and 41 TLH) who indicated to undergo hysterectomy for benign uterine disease, reported that LAVH and TLH group were associated with less consumption of analgesics comparing to VH group ($p = 0.012$) [19]. In a recent prospective, non-randomized trial which includes 164 women, TLH group consumed less opioid than VH group during the 20 hrs period after surgery (19.9 mg vs. 22.8 mg at postoperative 4 hr, $p = 0.040$; 23.5 mg vs. 27.4 mg at postoperative 6 hr, $p = 0.026$) [20]. Pain scores were also lower after TLH than VH ($p = 0.026$) [20].

Although there have been several reports regarding systemic inflammatory response after hysterectomies, which marker is specific for postoperative inflammatory response is still undetermined. The authors usually checked multiple inflammatory markers, such as C-reactive protein (CRP), creatine phosphokinase (CPK), and lactic dehydrogenase (LDH), interleukin-6, cortisol, cystatin C, serotonin and white blood cells count [18,21,22]. A prospective, randomized, controlled study comparing tissue trauma in TAH and LAVH showed that mean plasma levels of CRP and CPK were significantly higher in the TAH group on postoperative days 1 and 2 than in the LAVH group ($p < 0.05$) [18]. However, LDH increased only in TAH group on postoperative day 2, which is not similar pattern to other markers [14]. Another prospective study including 45 women undergoing hysterectomy (TLH = 15, TAH = 15, LAVH = 15) reported that plasma levels of CRP and IL-6, and VAS core at postoperative 24 hrs were significantly higher in TAH group compared to either laparoscopy groups [23]. In our study, we only checked postoperative changes of NLR. Although we did not consistently check other inflammatory markers such as CRP, our data supports that NLR simply and immediately reflects postoperative systemic inflammatory responses. It is not clear that NLR is the best marker for systemic inflammatory response. However, NLR is a relatively inexpensive and universally available method.

NLR is a noticeable systemic inflammatory marker, which is rapid, simple, and cheap. Recently, several reports suggested that NLR can be a useful prognostic marker for various types of cancer, hypertension, and cystic fibrosis, which is highly relevant to systemic inflammatory response [9–13]. Specifically, a lot of trials are on-going to evaluate the predictive value of NLR in cancer patients. In a retrospective study including 254 patients who underwent surgery for colorectal cancer, higher pre- and post-operative NLR was significantly related to lower overall survival rates ($p = 0.0388$, $p = 0.0006$) [9]. In a meta-analysis to determine the predictable value of NLR in the clinical outcome of colorectal cancer patients, elevated pretreatment NLR was associated with poorer overall survival (Hazard ratio (HR): 1.813, 95% confidence interval (CI): 1.499–2.193) and progression-free survival (HR: 2.102, 95% CI: 1.554–2.843) [10]. In addition, increased NLR is also significantly associated with the poorer differentiation of the tumor (Odds ratio (OR): 1.574, 95% CI: 1.226–2.022) and higher carcino-embryonie antigen (CEA) level (OR: 1.493, 95% CI: 1.308–1.705) [10]. Similarly, another meta-analysis including 12 prospective and retrospective trials was performed to demonstrate the prognostic value of NLR in non-small cell lung cancer [24]. The authors suggested that higher NLR (more than 5.0) appears to be associated with a worse survival as well as a worse response to treatments [24].

In our data, TLH was associated with the least changes in NLR, which is followed by VH, and TAH. Also, multivariate analysis revealed that massive changes in NLR (more than 5.0) after surgery were highly associated with the type of procedure. We consider that less change in NLR following TLH compared to VH, and TAH might be related to less tissue manipulation, less tissue trauma during the performance of TLH, which can be associated with less pain, less adhesion formation, and earlier recovery after surgery.

This study has some limitations: (1) Retrospective study. (2) No information of correlations among NLR changes, postoperative pain (VAS score, and consumption of NAIDs), and early recovery. (3) Biases derived from multiple surgeons. Thus, there is a possibility of potential biases associated with the type of hysterectomy selection and sureons' skill. (4) No information of long-term NRL changes. (5) Single medical center based medical records. Hence, we do not relflect a fairy diverse population. More well-designed prospective study will be required.

5. Conclusions

In conclusion, our data suggested that TLH could be preferred to VH and TAH for the treatment of benign uterine disease, because TLH was associated with less systemic inflammation and tissue trauma during surgery and showed equivocal surgical outcomes comparing to VH, except for longer surgery time.

Abbreviations

BMI, body mass index; EBL, estimated blood loss; Hb, hemoglobin; NRL, Lymphocyte to neutrophil ratio; LAVH, laparoscopy assisted vaginal hysterectomy; TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy; VH, vaginal hysterectomy.

Author contributions

SHP and STP conceived and designed the manuscript; SHP, SYJ and HYC performed the review and editing; STP,

SYJ and HSK analyzed the data; HYC and HSK wrote the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Waiver of Informed consent was obtained from all study participants and the study protocol was approved by the Institutional Review Board (IRB) at Hallym University Kangnam Sacred Heart Hospital (IRB file No. 2021-09-004-001).

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Conflict of interest

The authors declare no conflict of interest.

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