

〈Regular Article〉

Postoperative nausea and vomiting in benign gynecological laparoscopic surgery when acetaminophen is combined with non-opioid analgesic management

Soichiro SUZUKI¹⁾, Rikiya SANO¹⁾, Yumiko MORIMOTO¹⁾
Yoshiaki OTA¹⁾, Koichiro SHIMOYA²⁾, Mitsuru SHIOTA¹⁾

1) Department of Gynecologic Oncology,

2) Department of Obstetrics and Gynecology, Kawasaki Medical School

ABSTRACT Non-opioid analgesic management using intravenous acetaminophen has been reported to reduce pain and postoperative nausea and vomiting (PONV). This study aimed to assess the incidence rate and risk factors for PONV following benign gynecological laparoscopic surgery with non-opioid analgesic management, when using intravenous acetaminophen to achieve appropriate perioperative management. We conducted a retrospective observational study comprising 53 patients who underwent five types of laparoscopic surgical procedures for benign diseases. The patients were administered a single dose of intravenous acetaminophen at the conclusion of the operation, after which pain relief was induced with non-steroidal anti-inflammatory drugs and pentazocine. We analyzed patient characteristics, surgical outcomes, and numbers of analgesics and antiemetics administered postoperatively. Onset of PONV developed by postoperative day one. The incidence rate of PONV in patients who underwent surgery that included total hysterectomy was 94%, which was significantly higher than in those who underwent other procedures ($p = 0.020$). From the perspective of PONV, current postoperative pain management for laparoscopic surgery, including total hysterectomy, needs to be modified.

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Key words : Acetaminophen, Analgesics, Antiemetics, Hysterectomy, Laparoscopic surgery,
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INTRODUCTION

With recent advances in surgical techniques and methods, many gynecological operations are currently performed laparoscopically. Although

laparoscopy causes less postoperative pain than traditional surgical approaches¹⁾, the incidence of postoperative nausea and vomiting (PONV) is reportedly higher²⁻⁸⁾. Additionally, female sex is

Corresponding author
Soichiro Suzuki
Department of Gynecologic Oncology, Kawasaki
Medical School, 577 Matsushima, Kurashiki, 701-0192,
Japan

Phone : 81 86 464 1137
Fax : 81 86 464 1137
E-mail: soichi731@med.kawasaki-m.ac.jp

also a risk factor for PONV^{4, 6, 9, 10}. Therefore, gynecological laparoscopic surgery requires perioperative management recognizing PONV.

Pain itself is commonly believed to be a risk factor for PONV¹¹. To reduce the risk of developing PONV, pain management with non-narcotic analgesics is recommended¹². Among them, analgesic protocols using acetaminophen, which has few side effects, are attracting attention¹³. Acetaminophen has analgesic effects and has another potential mechanism that could be a direct antiemetic effect¹⁴.

Pain management using acetaminophen was also reported to reduce PONV in gynecological laparoscopic surgery^{15, 16}. However, few studies have evaluated the efficacy of acetaminophen for PONV in a completely non-narcotic postoperative analgesia protocol. In addition, previous studies have not investigated which of the gynecological laparoscopic surgeries has the highest incidence of PONV.

In the present study, we evaluated the incidence rate and risk factors for PONV in benign gynecological laparoscopic surgery utilizing non-opioid analgesic management using intravenous acetaminophen. We aimed to improve the postoperative analgesic protocol.

MATERIALS AND METHODS

Patients

This was a retrospective observational study of 53 patients who underwent minimally invasive surgery for benign gynecological disorders between April 2020 and June 2020 in Kawasaki Medical School Hospital. The procedures included laparoscopic myomectomy (LM), laparoscopic sacrocolpopexy (LSC), laparoscopic adnexal surgery (cystectomy and salpingo-oophorectomy), total laparoscopic hysterectomy (TLH), and robot-assisted simple hysterectomy (RSH). Notably, our standard LSC procedure requires the insertion of a mesh to

provide support following vaginal hysterectomy.

Protocol of perioperative management for pain and nausea

All surgical procedures were performed under general anesthesia. At the end of the operation, 10 mL of 0.25% levobupivacaine was locally injected at the skin incision site, and acetaminophen was administered intravenously. The dose was 1000mg once. However, for patient weighing less than 50kg, acetaminophen was administered up to 15mg per 1kg of body weight. If the patient experienced breakthrough pain after returning to the ward, diclofenac sodium (50 mg) was administered rectally. If additional breakthrough pain occurred within 6 h of diclofenac sodium administration, pentazocine (15 mg) was injected intramuscularly. Swallowing and walking tests were conducted on the morning of postoperative day (POD) 1, and if no issues were evident, the intravenous route and catheter balloon were withdrawn. If the patient experienced pain after starting oral fluids, they were administered one tablet of loxoprofen sodium (60 mg). If they complained of pain again within 6 h of administration, pentazocine (15 mg) was injected intramuscularly. If they complained of PONV, metoclopramide (10 mg) was administered intravenously. Patients were excluded from the study if epidural anesthesia or patient-controlled analgesia were also used during the perioperative period, or if they received intravenous acetaminophen more than once.

Factors investigated for study endpoints

The patient characteristics evaluated included age, body mass index, operating time, hemorrhage, duration of postoperative hospital stay, and uterine weight (in cases of TLH, RSH, and LSC procedures) as an index of surgical outcome, and the number of times analgesics and antiemetics were used postoperatively. The number of analgesics

Table 1. Patient characteristics and perioperative data

	Operation method				
	LM (N = 5)	LSC (N = 9)	TL-SO/S/C (N = 10)	RSH (N = 11)	TLH (N = 18)
Age (years)	39 (32 - 44)	73 (56 - 85)	38.5 (12 - 78)	45 (32 - 52)	48 (32 - 57)
BMI (%)	21 (20 - 35)	25 (22 - 29)	22 (17 - 26)	24 (19 - 32)	23 (17 - 28)
Operating time (min)	118 (91 - 218)	169 (145 - 189)	74.5 (43 - 125)	145 (100 - 170)	138.5 (72 - 182)
Days of postoperative hospitalization	3 (3 - 5)	3 (3 - 6)	3 (2 - 4)	3 (3 - 3)	3 (3 - 3)
Blood loss (mL)	100 (60 - 800)	50 (10 - 125)	10 (10 - 200)	15 (10 - 250)	150 (10 - 380)
Weight of the removed uterus (g)	—	60 (40 - 79)	—	240 (100 - 730)	279 (96 - 990)

BMI, body mass index; LM, laparoscopic myomectomy; LSC, laparoscopic sacrocolpopexy; TLH, total laparoscopic hysterectomy; TL-SO/S/C, total laparoscopic (salpingo-oophorectomy/salpingectomy/cystectomy); RSH, robot-assisted simple hysterectomy.

used was determined from the total number of times that loxoprofen sodium and pentazocine were administered. In this study, we considered PONV to be present when antiemetics were used. The number of times the antiemetics were used for patients who underwent each type of procedure and the number of times they were used on each POD were evaluated. Additionally, we classified patients into those who underwent surgery that included total hysterectomy (TLH, RSH, and LSC) and those who underwent other procedures. Subsequently, we compared the surgical outcome and the number of times analgesics and antiemetics were used in both groups.

Statistical analysis

We used JMP statistical software (SAS, NC, USA) for all analyses. A Chi-squared test or Fisher's exact test was used to compare categorical variables. Wilcoxon's rank-sum test was used to compare continuous variables between two groups, and the Kruskal-Wallis test was used for three or more groups. Values of $p < 0.05$ were considered statistically significant.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kawasaki Medical School Hospital (approval number 5023-00). Appropriate informed consent was obtained from each patient.

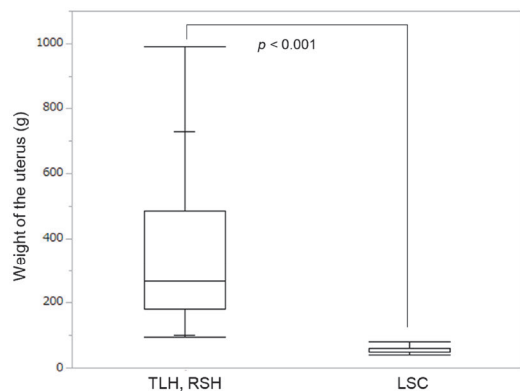


Fig. 1. Comparison of removed uterine weight. Data are shown as box-and-whisker plots with median, quartiles, and range.

LSC, laparoscopic sacrocolpopexy; TLH, total laparoscopic hysterectomy; RSH, robot-assisted simple hysterectomy

RESULTS

Patient characteristics and surgical procedures

Table 1 describes the patient characteristics and surgical outcomes. Five patients underwent LM, nine underwent LSC, ten underwent laparoscopic adnexal surgery, ten underwent TLH, and 11 underwent RSH. Patients who underwent LSC were significantly older than the others ($p < 0.001$). The operating time for adnexal surgery was significantly shorter than the other procedures ($p < 0.001$). In procedures that included hysterectomy, the uteruses removed by LSC were significantly lighter in weight than those removed by laparoscopic hysterectomy (TLH, or RSH) (60 vs. 268 g, Fig. 1).

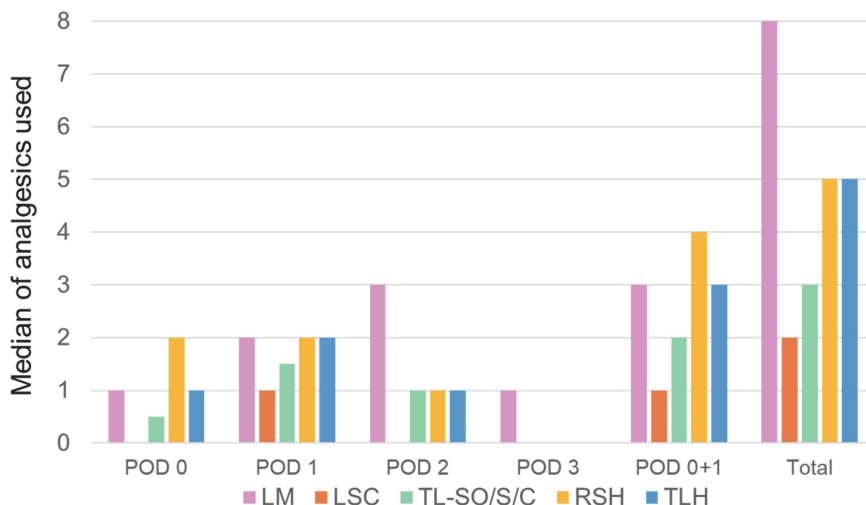


Fig. 2. Frequency of analgesic use on each postoperative day. LM, laparoscopic myomectomy; LSC, laparoscopic sacrocolpopexy; POD, postoperative day; TLH, total laparoscopic hysterectomy; TL-SO/S/C, total laparoscopic (salpingo-oophorectomy/salpingectomy/cystectomy); RSH, robot-assisted simple hysterectomy

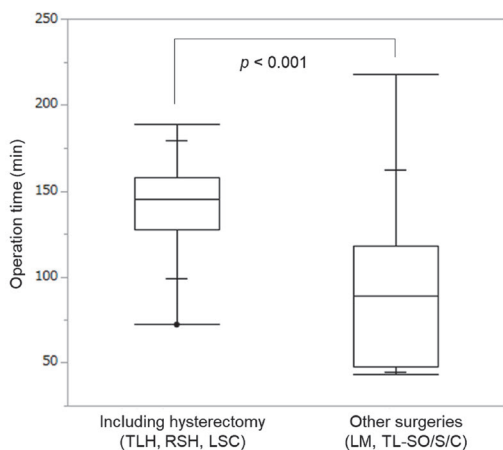


Fig. 3. Operation time with and without hysterectomy. Data are shown as box-and-whisker plots with median, quartiles, and range.

LM, laparoscopic myomectomy; LSC, laparoscopic sacrocolpopexy; POD, postoperative day; TLH, total laparoscopic hysterectomy; TL-SO/S/C, total laparoscopic (salpingo-oophorectomy/salpingectomy/cystectomy); RSH, robot-assisted simple hysterectomy

Analgesic use according to surgical procedure

The median number of times analgesics were used was four throughout the patient’s hospitalization and three until POD 1 (Fig. 2). The procedures in which analgesics were used more than four times were

TLH, RSH, and LM. The use of analgesics peaked on POD 1 after TLH, RSH, LSC, and TL-SO/S/C, and on POD 2 after LM. For surgical procedures that included total hysterectomy (namely, TLH, RSH, or LSC), the operation time was significantly longer than for procedures that did not include total hysterectomy (146 vs. 89 minutes, Fig. 3).

Incidence and risk factors for PONV

PONV occurred in 17 (32%) patients, and all experienced PONV until POD 1 (Fig. 4). Over half of the patients who underwent RSH or LSC experienced PONV (Fig. 5). Of the 17 patients who developed PONV, 16 (94%) had a procedure that included total hysterectomy (TLH, RSH, or LSC). The incidence of PONV was significantly higher in patients who underwent a procedure that included total hysterectomy than in those who underwent other procedures ($p < 0.020$, Table 2). There was no significant difference in the total number of times analgesics were used during hospitalization ($p = 0.406$) or the number of times they were used until POD 1 ($p = 0.882$) between patients who developed PONV and those who did not.

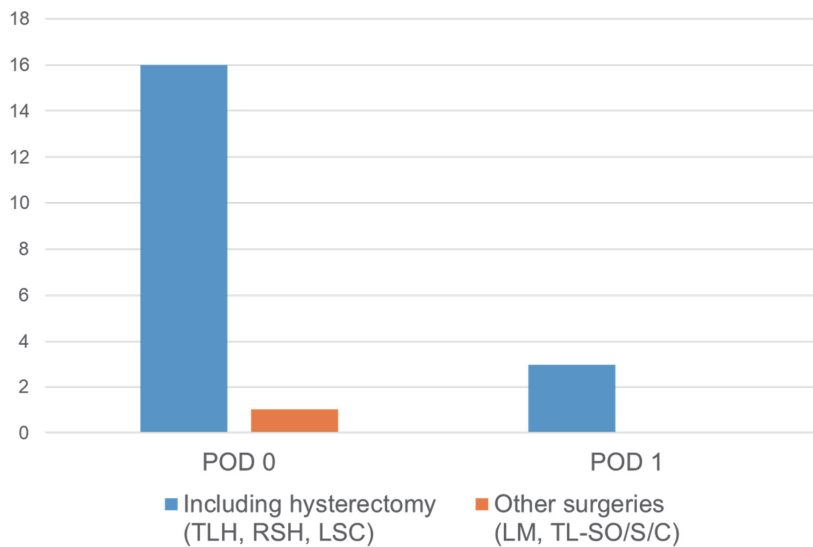


Fig. 4. Incidence rate of PONV by surgical procedure.

LM, laparoscopic myomectomy; LSC, laparoscopic sacrocolpopexy; POD, postoperative day; TLH, total laparoscopic hysterectomy; TL-SO/S/C total laparoscopic (salpingo-oophorectomy/salpingectomy/cystectomy); RSH, robot-assisted simple hysterectomy

* All patients who developed PONV in POD 1 overlap with those who developed POD 0.

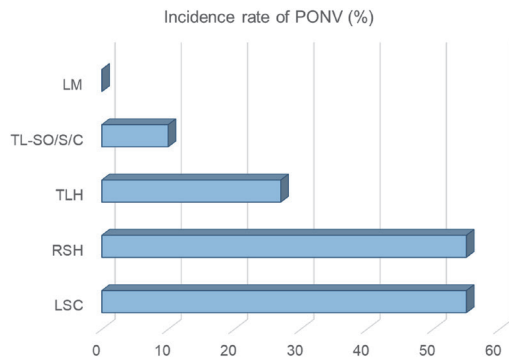


Fig. 5. Incidence number of PONV by surgical procedure with and without hysterectomy

LM, laparoscopic myomectomy; LSC, laparoscopic sacrocolpopexy; POD, postoperative day; TLH, total laparoscopic hysterectomy; TL-SO/S/C total laparoscopic (salpingo-oophorectomy/salpingectomy/cystectomy); RSH, robot-assisted simple hysterectomy

All patients who developed PONV in POD 1 overlap with those who developed POD 0.

DISCUSSION

We found that if PONV is present, it appears by POD 1, and the incidence rate of PONV is higher after surgical procedures that include total

hysterectomy than after other procedures, when non-narcotic pain management and intravenous acetaminophen is given. In this study, the incidence rate of PONV was 32%, and 94% of those who experienced PONV had undergone a procedure that included total hysterectomy.

The first reason why PONV is high in surgical procedures that included hysterectomy is hypothesized to be associated with postoperative pain⁸). There was no difference in the onset of PONV and the number of analgesics used in pain management with our protocol. However, the onset of PONV and frequency of analgesics used peaked by POD 1. The possibility that PONV is caused by pain cannot be ruled out, and we believe postoperative pain management is important in controlling the onset of PONV.

The most common pain experienced after total hysterectomy is one of visceral intensity¹⁷⁻¹⁹). The uterus receives primary innervation from the uterosacral plexus, which is located near the lateral

Table 2. Risk factor for PONV

	PONV (-) N = 36	PONV (+) N = 17	p-value
Age (years)	46 (38.25 - 52)	50 (45 - 71.5)	0.057
BMI (%)	23 (21 - 25)	24 (21 - 25.5)	0.438
Operation time (min)	129 (92 - 147)	147 (113 - 165)	0.081
Blood loss (mL)	50 (10 - 150)	50 (10 - 175)	0.679
Postoperative hospitalization (days)	3 (3 - 3)	3 (3 - 3)	0.854
Number of analgesics until POD 1	3 (2 - 4)	3 (2 - 4)	0.882
Total number of analgesics	4 (3 - 5.75)	4 (2 - 5)	0.406
Surgery type			
Including hysterectomy(TLH, RSH, LSC)	22	16	
Not including hysterectomy(TL-SO/S/C, LM)	14	1	0.020

PONV, postoperative nausea and vomiting

Values are expressed as median (interquartile range) and number (percentages)

side of the uterine cervix, within the uterosacral ligament. This plexus is derived from the hypogastric plexus. The uterosacral ligament is not cut by any procedure other than total hysterectomy. Furthermore, ligation of part of the sacral uterine ligament when suturing the vaginal stump is also considered to be a cause of pain²⁰⁾.

The reason why analgesics were used less frequently in LSC than in RSH and TLH is that total hysterectomy is performed transvaginally in LSC. From our results, the uterus requiring LSC was smaller than those removed by TLH and RSH. If the uterus is small, we can minimize the area we cut. Also, we do not need to detach the ureter and cut off the uterine artery near the hypogastric nerve, affecting postoperative pain.

LM most frequently required analgesia during hospitalization, but the incidence rate of PONV for the LM procedure was low. Similar to the present study, Nasu *et al.* reported that LM used more postoperative analgesics than did TLH²¹⁾. They argued that the pain of TLH is predominantly in the low abdomen, while the pain of LM is predominantly in the umbilical region. In our study, LM had a slower peak in analgesic use compared to hysterectomy. Considering these facts, the pain of LM and hysterectomy may be different. This may have contributed to the low incidence of PONV in

LM.

Besides pain, operation time and age are also risk factors for PONV^{5, 9)}. If the incidence rate of PONV increases in surgeries for gynecological malignancy where hysterectomy is included in the standard procedure and the operation time is longer than for benign surgery, our conclusions may be substantiated. However, there are no studies comparing benign and malignant surgical procedures, and there are no reports comparing PONV with or without total hysterectomy, as with our study. Future studies should be conducted to prove our study result.

PONV occurred by POD 1. The median number of times analgesics, excluding acetaminophen, were used until POD 1 was three times. If these analgesics were substituted with continuous intermittent acetaminophen, would the incidence of PONV be reduced? Previous studies reported that the scheduled continuous administration of acetaminophen is more analgesic than as-needed in patients undergoing cesarean section²²⁾. Similar results following traditional total hysterectomy methods have been reported²³⁾. Reducing pain can be expected to reduce the incidence rate of PONV. Until POD 1, which requires bed rest and movement restrictions, an intravenous infusion certainly causes less discomfort than a rectal suppository or

intramuscular injection. Multiple administration of acetaminophen may be useful in procedures requiring hysterectomy with a high incidence of PONV.

There are some limitations to be considered in the interpretation of our results. Cases in which the drug was not used, despite pain and nausea, have not been examined. Since only the number of times the analgesic was used was evaluated, there are cases in which pain relief was sustainable even if the number of times of use was small. Moreover, considering that the observation period in this study was short, more cases should be considered to improve the generalizability of the study findings.

Our results showed that the incidence rate of PONV was higher in patients who underwent total hysterectomy than in those who underwent other procedures. From the perspective of PONV, current pain management needs to be modified for laparoscopic surgery, including hysterectomy.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose

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