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Impact of basal infusion on postoperative nausea and vomiting in fentanyl-based intravenous patient-controlled analgesia

A randomized controlled trial

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Abstract

Background: Fentanyl-based intravenous patient-controlled analgesia (IV PCA) is widely prescribed postoperatively. Basal infusion of fentanyl through IV PCA is associated with postoperative nausea and vomiting. However, the role of basal infusion in fentanyl-based IV PCA is not well-established.

Methods: This parallel-group, randomized controlled trial was conducted at a tertiary university medical center in the Republic of Korea from September 2022 to April 2023. Patient inclusion criteria were: age 20 to 65 years, intraperitoneal laparoscopic gynecologic surgery, patient-controlled analgesia (PCA) request from the surgical department, and written informed consent for PCA. Patients were allocated to basal infusion (BAS group) and bolus-only (BOL group) groups in a 1:1 ratio.

A sum of 100 mL of analgesic mixture containing fentanyl 18.5 μg/kg, nefopam 120 mg, and ramosetron 0.3 mg was mixed in PCA pumps of both groups. For BAS group, basal infusion rate, bolus volume, and lock-out interval were 2 mL/hour, 1 mL, and 15 minutes, respectively. BOL group received no basal infusion; bolus volume and lock-out interval were 1 mL and 6 minutes, respectively.

The primary outcome was postoperative nausea, measured using a self-response questionnaire 24 hours after operation and expressed as a 100-mm visual analog scale score. We also determined frequency of postoperative vomiting, quality of postoperative recovery (using Korean version of 15-item Quality of Recovery [QoR-15K] scale), and overall patient satisfaction with anesthetic service.

Results: A sum of 82 of the 88 patients enrolled were included. The visual analog scale score for postoperative nausea was 31.4 ± 31.3 mm; the condition was more severe in the BAS group than in the BOL group (95% confidence interval of difference: 2.1–28.9 mm, $P = .024$). The QoR-15K score, patient satisfaction, and rescue opioid doses used were similar across groups.

Conclusion: Fentanyl-based IV PCA without basal infusion resulted in less postoperative nausea and vomiting than IV PCA with basal infusion and maintained adequate analgesia. Basal infusion can be omitted to reduce postoperative nausea using IV PCA by applying an appropriate lock-out interval. Further research comparing variable PCA settings is warranted.

Abbreviations: BAS group = basal infusion group, BOL group = bolus-only group, ERAS = early recovery after surgery, IV = intravenous, IV PCA = intravenous patient-controlled analgesia, PACU = postanesthetic care unit, PCA = patient-controlled analgesia, PONV = postoperative nausea and vomiting, QoR-15K = Korean version of the 15-item Quality of Recovery scale, VAS = visual analog scale.

Keywords: analgesia, fentanyl, pain, patient-controlled analgesia, postoperative nausea and vomiting, postoperative pain

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study was reviewed and approved by the Institutional Review Board of Wonju Severance Christian Hospital (CR322072, approval date: August 24, 2022) and registered with the Clinical Research Information Service of Korea (KCT0007739) on September 26, 2022. Written informed consent was submitted by all subjects when they were enrolled, and all methods were carried out in accordance with relevant guidelines and regulations.

Trial registration: KCT0007739, Clinical Research Information Service, Republic of Korea. Registration date: September 26, 2022.

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1. Introduction

Intravenous patient-controlled analgesia (IV PCA) is prescribed in more than 1 million surgical cases annually in the Republic of Korea, and its prescription is increasing continuously.[1] Opioids are the main analgesics administered through IV PCA, and fentanyl is the most common opioid drug for IV PCA; it is mixed in two-thirds of all IV PCA regimens.[2]

Previous studies using morphine as the main opioid drug in IV PCA regimens reported that basal infusion, or background infusion, was not recommended.[3] Nie et al[4] reported that basal infusion can reduce early postoperative pain with sufentanil IV PCA without side effects, despite increased opioid consumption.

The administration of basal infusion in fentanyl-based IV PCA is frequently adopted in clinical practice.[2,5–7] However, the role of basal infusion in fentanyl-based IV PCA remains controversial.[8] Basal infusion of fentanyl through IV PCA is associated with postoperative nausea and vomiting (PONV), the frequency of which is the highest in the first 24 hours after surgery.[9] PONV is one of the most undesirable side effects, and PONV prevention is associated with a lower cost of care and staff burden.[10]

PONV risk is increased by various factors such as female sex, laparoscopic procedures, and gynecological surgery.[10,11] Because of these risk factors, patients undergoing laparoscopic gynecologic surgery frequently experience PONV, and the incidence is reported to be 40% to 80%.[12] A retrospective study by Jung et al[8] reported comparable analgesia using IV PCA without basal infusion, which resulted in less opioid consumption and fewer side effects. Hence, in this randomized controlled trial, the authors compared IV PCA with basal infusion to IV PCA without basal infusion in terms of PONV among female patients undergoing laparoscopic gynecological surgery.

2. Materials and methods

2.1. Study design and setting

This parallel-group randomized controlled trial was approved by the institutional review board of Wonju Severance Christian Hospital (CR322072, date of approval: August 24, 2022). The trial was conducted at a tertiary care university medical center in Wonju, South Korea, and prospectively registered with the Clinical Research Information Service of Korea (KCT0007739, registration date September 26, 2022). The trial is reported in accordance with the Consolidated Standards of Reporting Trials guidelines.

2.2. Participants

All consecutive patients who underwent gynecologic surgery between September 7, 2022, and April 27, 2023, were screened for eligibility. The inclusion criteria were as follows: age of 20 to 65 years, receipt of intraperitoneal laparoscopic surgery, a consultation for patient-controlled analgesia (PCA) via electronic health record system from the gynecologic department and written informed consent of the patient for PCA. The following patients were excluded from the study: non-opioid-naïve patients who were prescribed opioids within 30 days after surgery, patients with a body mass index of ≥30, patients with an American Society of Anesthesiology physical status of ≥ IV, pregnant or breastfeeding patients, cognitively impaired patients who were incapable of independently responding to the postoperative questionnaire, or patients registered with other clinical trials. Furthermore, participants were excluded from the trial if they expressed a desire to quit or were incapable of independently completing the postoperative questionnaire 24 hours after surgery.

2.3. Study protocol

Patients were screened and enrolled before the day of surgery by the corresponding author. After they provided signed written informed consent for participation in the trial, the patients were randomly assigned to the basal infusion group (BAS group) or bolus-only group (BOL group) in a 1:1 ratio in accordance with a random allocation sequence by one of the authors (YHC). The random allocation sequence was generated with a permuted block system and the block size used was 8. The allocation sequences were generated each time a new block of patients was enrolled, by one of the authors (JHP), by using R statistics 4.2.0 (R Core Team, Vienna, Austria). The attending anesthesiologist was notified about the group allocation on the morning of the day of the surgery.

Patients received general anesthesia using desflurane or sevoflurane with 0.7 to 0.9 minimum alveolar concentration adjusted by age, and remifentanil 0.05 to 0.20 μg/kg·minute was administered as an intraoperative analgesic. The bispectral index was monitored to guide the depth of anesthesia, and the anesthetic agents used were titrated to maintain the bispectral index in the range of 40 to 60.

Fentanyl 18.5 μg/kg, nefopam 120 mg, and ramosetron 0.3 mg were mixed with normal saline to obtain 100 mL of the analgesic mixture.[7] The elastomeric PCA pumps used were made by the same manufacturer (Innotech Co., Goyang, Gyeonggi-do, Republic of Korea). Both types of PCA pumps were morphologically identical, except for the administration scheme (bolus volume, lock-out interval, and rate of basal infusion), which was printed in small letters. The rate of basal infusion and lock-out interval in the BAS group were 2 mL/hour and 15 minutes, respectively, which is frequently applied for IV PCA with basal infusion.[7,8] The BOL group did not receive a basal infusion, and the lock-out interval was 6 minutes. The bolus volume was 1 mL in both groups. No additional regional anesthesia was administered to either group.

Fentanyl 1 μg/kg was administered intravenously for immediate postoperative pain along with ramosetron 0.3 mg as PONV prophylaxis at the time of subcutaneous suture initiation. PCA was connected to the IV line at the conclusion of surgery. If a patient complained about PONV in the postanesthetic care unit (PACU), metoclopramide 10 mg mixed in 100 mL of normal saline was administered for 10 minutes. The rescue analgesics used in the PACU were acetaminophen 1 g and fentanyl 1 μg when the pain numeric rating scale (0–10) scores were <4 and ≥4, respectively. Patients were observed for at least 30 minutes in the PACU and discharged if their postoperative Aldrete Recovery Score was 9 or 10.

Patients were informed about how to use the PCA pump, bolus volume, lock-out time, and the rate of basal infusion right before transfer by a registered nurse in the PACU. The anesthesiologist delivering and retrieving the questionnaire was blinded to the group allocation. Analgesic medication in the ward was prescribed by the department of gynecology; dexibuprofen 400 mg was administered twice a day routinely, and the PRN analgesic use was IV tramadol 50 mg or intramuscular pethidine 50 mg.

2.4. Variables and assessments

The primary outcome was postoperative nausea within 24 hours after surgery, which was reported using the 100-mm visual analog scale (VAS) in a self-response written questionnaire.[13] The questionnaire also inquired about the presence and number of episodes of postoperative vomiting within 24 hours after surgery, and satisfaction (measured using a 5-point [0–4] satisfaction scale) with the overall anesthetic service. Furthermore, postoperative quality of recovery was measured using the Korean version of the 15-item Quality of Recovery (QoR-15K) scale previously validated by Yoon et al,[14] which was also self-reported in this study.

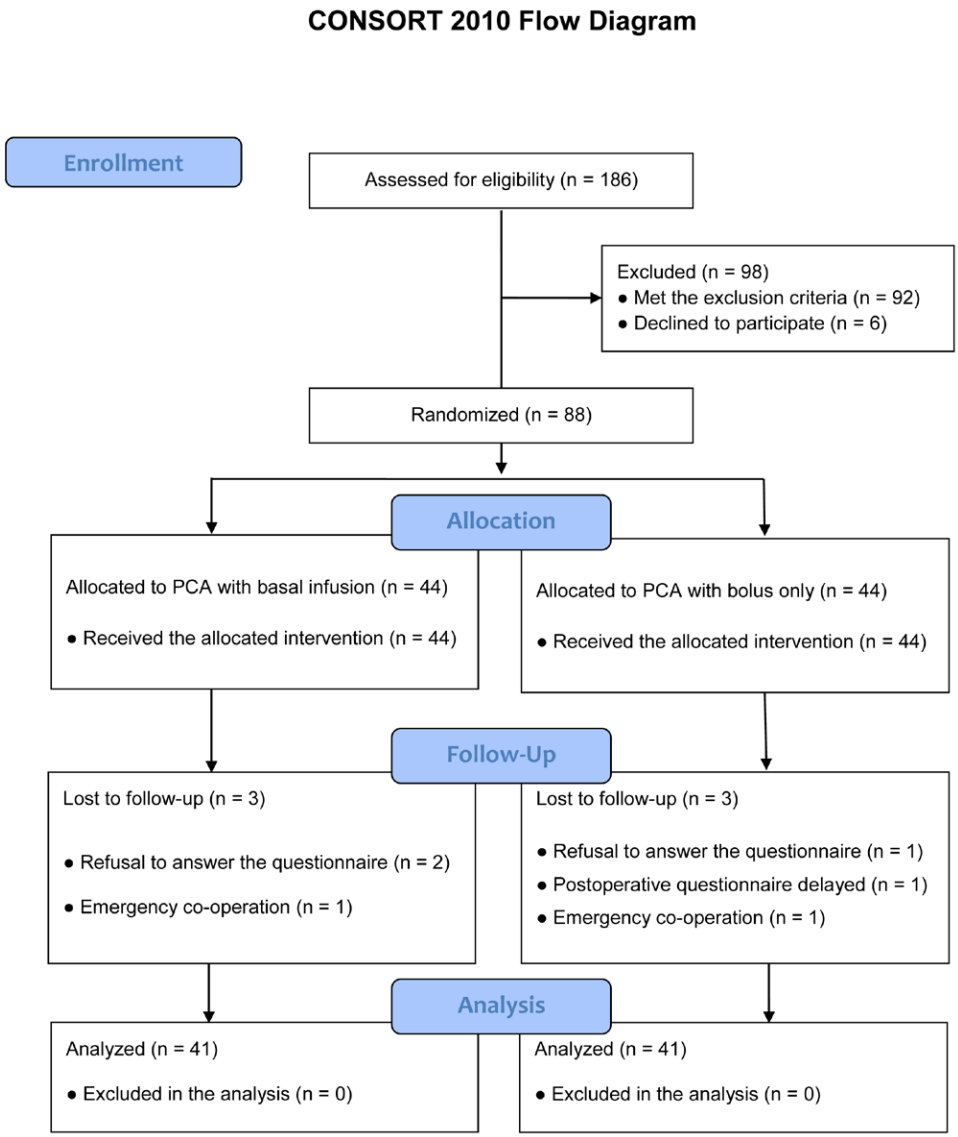

Figure 1. CONSORT flow diagram. PCA = patient-controlled analgesia.

The QoR-15K questionnaire includes items inquiring about moderate and severe postoperative pain within last 24 hours; a score of "0" indicates "Always" and "10" suggests "Never." The doses of the rescue opioid analgesics used after 24 hours of surgery were converted into morphine milligram equivalents.[15,16] Due to the inherent characteristics of elastomeric PCA pumps, it was not feasible to accurately quantify the exact volume administered at specific time points. Severe adverse events, such as respiratory depression, cardiac arrest, and in-hospital mortality, were recorded. There was no missing data.

2.5. Statistical analysis

Intention-to-treat analysis was performed. Numerical values were analyzed with the t-test unless otherwise mentioned. Categorical values were analyzed with a chi-square test. The number of episodes of postoperative vomiting and the length of PACU stay were analyzed with the Wilcoxon rank-sum test. Statistical significance and statistical power were set at 0.05 and 0.80, respectively. The R statistics program version 4.2.2 was used for statistical analysis, and the "ggplot2" package of the program was used for visualization.

2.6. Sample size

The minimal clinically significant change in nausea measured using the 100-mm VAS was 15 mm, and the standard deviation was 23.5.[13,17] With a statistical significance of 0.05 and statistical power of 0.80, 40 participants were required in each group. Finally, 88 patients were enrolled, reserving 10% of the withdrawal.

3. Results

Overall, 82 patients, 41 in each group, were included in the analysis (Fig. 1). Two patients in the BAS group and 1 patient in the BOL group were withdrawn from the trial because they refused to answer the postoperative questionnaire. One patient in each group was withdrawn owing to emergency co-operation with other surgical departments. One patient answered the postoperative questionnaire on postoperative day 2 and was thus withdrawn.

Table 1

Patient demographics and characteristics.

Variable	BAS group (n = 41)	BOL group (n = 41)	*P* value
Age*	50.1 ± 7.9	46.5 ± 7.1	.033
Weight	59.8 ± 6.6	60.1 ± 7.4	.625
BMI	24.1 ± 2.6	24.1 ± 2.8	.999
ASA physical status classification, n			.591
ASA I	19	18	
ASA II	21	20	
ASA III	1	3	
Apfel score, n			.314
2	5	3	
3	35	34	
4	1	4	
Surgical duration (min)	105.0 ± 36.7	110.2 ± 42.9	.554
Anesthesia duration (min)	145.0 ± 36.2	153.8 ± 46.5	.343
Robotic surgery, n (%)	18 (43.9)	15 (36.6)	.652
Fluid intake (mL/h)	230.2 ± 83.9	247.3 ± 98.0	.398

ASA = American Society of Anesthesiologists, BAS group = basal infusion group, BMI = body mass index, BOL group = bolus-only group.

*$P < .05$.

Table 2

Postoperative nausea and vomiting within 24 hours after surgery.

Variable	BAS group (n = 41)	BOL group (n = 41)	*P* value
VAS score for postoperative nausea, mean ± SD*	39.1 ± 30.9	23.7 ± 30.1	.024
VAS score for nausea = 0, n (%)*	9 (22.0)	19 (46.3)	.036
Episodes of postoperative vomiting, median (IQR)	0 (0–1)	0 (0–0)	.104
Did not experience postoperative vomiting, n (%)	27 (65.9)	33 (80.5)	.213

BAS group = basal infusion group, BOL group = bolus-only group, IQR = interquartile range, SD = standard deviation; VAS = visual analog scale.

*$P < .05$.

The mean age of the patients was 48.3 ± 7.7 years, and the BOL group was younger (Table 1). Other baseline characteristics were similar between the groups. Robotic surgery accounted for 40.2% of surgical cases. The VAS score for postoperative nausea was 31.4 ± 31.3 mm for the entire cohort. No postoperative nausea or a VAS score of 0 for nausea was reported in 28 patients (34.1%, Table 2). Postoperative nausea was less severe in the BOL group than in the BAS group and the 95% confidence interval of difference was 2.1 to 28.9 mm (Fig. 2).

Postoperative vomiting within 24 hours of surgery occurred in 22 patients (26.8%), with 3 being the maximum number of episodes. The rescue antiemetic administered to 17 patients (20.7%) in the ward was metoclopramide 10 mg by the order of the department of gynecology (Table 3). Metoclopramide was administered once to 13 patients and twice to 4 patients in the ward. IV PCA was terminated early in 1 patient in the BAS group at 25th hour of application due to nausea. The quality of recovery measured with the QoR-15K and opioid administration other than the PCA regimen were comparable between the groups.

There was no difference in scores representing moderate and severe postoperative pain measured using the QoR-15K (Fig. 3). Patient satisfaction was similar in both groups (Table 4; $\chi^2 = 2.926$, $P = .570$). No severe adverse events other than postoperative pain and PONV were observed.

4. Discussion

Opioids stimulate the vestibular apparatus and chemoreceptor trigger zone and inhibit gut motility.[18] PONV, which is increased by postoperative administration of opioids, are common but distressing symptoms for patients and are increasingly being focused on as important issues.[11] In some patients, PONV can be worse than postoperative pain.[19] PCA is widely prescribed by anesthesiologists, and measures to minimize PONV induced by PCA should be adopted while reducing pain appropriately. For example, non-opioid adjuvants have been reported to be beneficial in PCA regimens, enhancing analgesia and reducing PONV.[7,20] 5-Hydroxytryptamine (5-HT_3) receptor antagonists, such as ramosetron, in PCA regimens can reduce PONV induced by PCA.[21]

In this study, we found that omitting basal infusion with an appropriate lock-out interval results in less postoperative nausea. Approximately 2-fold patients who used the PCA pump without basal infusion were free of nausea 24 hours postoperatively than those who were administered basal infusion. Basal infusion increases serum fentanyl concentration, and increased opioid concentration is reportedly directly associated with nausea.[22] According to Chae et al,[20] increasing the basal infusion to 0.1 μg/kg·hour was associated with an odds ratio of 1.20 for PONV within 48 hours after the operation. A retrospective study compared IV PCA without basal infusion versus IV PCA with basal infusion among 1317 patients showed that opioid-related side effects and postoperative fentanyl consumption were reduced in the patients who used IV PCA without basal infusion than in those who used IV PCA with basal infusion.[8]

As seen in a previous study by Jung et al,[8] there was no difference in postoperative pain between those who used IV PCA with or without basal infusion in this study and the doses of rescue analgesics were similar between both groups. Thus, higher serum opioid concentration does not result in better pain control and patient satisfaction. Andreassen et al[23] reported that serum concentrations of oxycodone and its metabolites were not associated with pain intensity. Pain thresholds are influenced by the environmental and genetic features of patients. Moreover, pain is a subjective symptom and not specific to opioid treatment.[23]

This was widely known in the case of morphine-based IV PCA, and the same seems true for fentanyl-based IV PCA.[3,24] Therefore, the authors suggest using fentanyl-based IV PCA without basal infusion as one of the measures to minimize PONV and providing adequate pain control in those undergoing laparoscopic gynecologic surgery. This could also be a useful way to reduce PONV in other surgeries with a higher risk of PONV, such as cholecystectomy, bariatric surgery, or other laparoscopic procedures.[11]

Reducing PONV is also important for early recovery after surgery (ERAS) and reducing the cost of care.[25–27] PONV were reported to prolong hospital stay by 2 more days in patients who underwent elective colorectal surgery at an ERAS® center recognized by the ERAS® Society.[25] PONV reportedly delays resuming solid food intake by 2 days and requires additional hospital stay. Postoperative nausea has been reported to be associated with a high cost of care, which can be reduced in surgical patients by omitting basal infusion using IV PCA, as PONV is reduced through this regimen[26]; no additional cost is required for a PCA device without basal infusion.

Despite random allocation, the mean age differed between the groups, with patients in the BOL group being on average 3.6 years younger than those in the BAS group (95% confidence interval 0.3–6.9 years). The younger a surgical patient is, the higher the risk of PONV.[11,28,29] Sinclair et al[29] reported a 13% decrease of the PONV risk with 10 years of senescence.

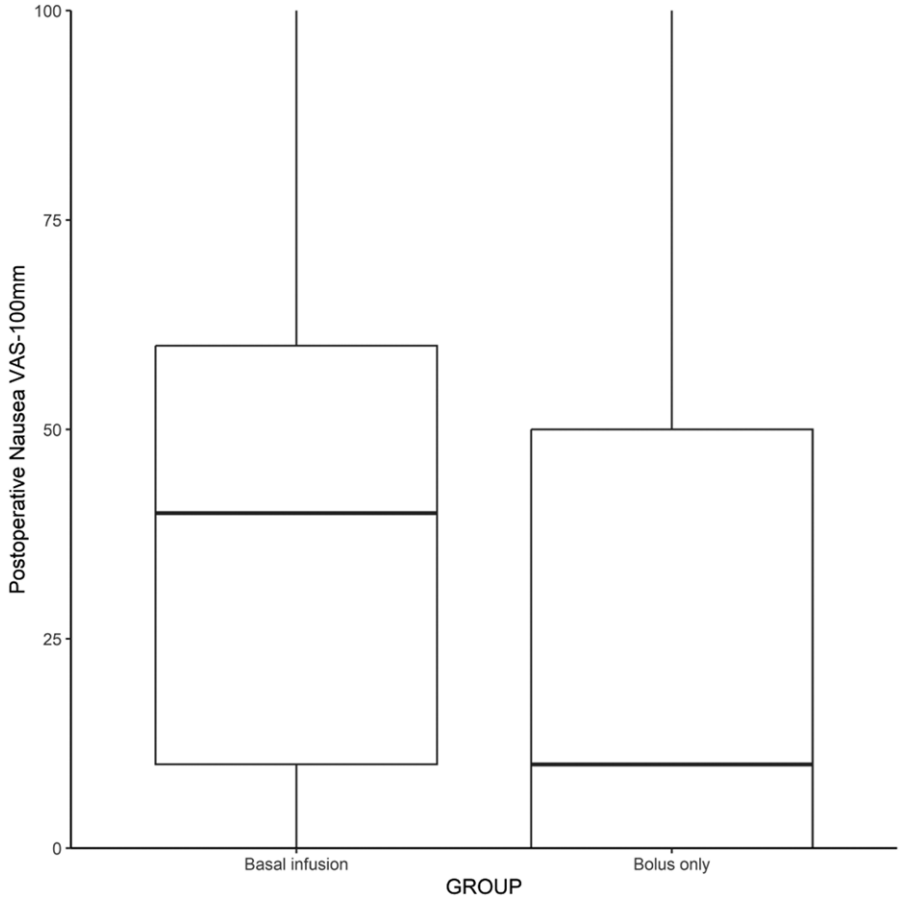

Figure 2. Postoperative nausea score in both groups. VAS = visual analog scale.

Table 3

Postoperative recovery profile.

Variable	BAS group (n = 41)	BOL group (n = 41)	*P* value
PACU stay, min (IQR)	30 (30–30)	30 (30–30)	.465
QoR-15K	99.8 ± 21.1	93.7 ± 24.7	.235
Administration of a rescue antiemetic in the PACU, n (%)	1 (2.4)	4 (9.8)	.356
Administration of a rescue antiemetic in the ward, n (%)	10 (24.4)	7 (17.1)	.586
Dose of rescue opioid analgesics, MME	14.0 ± 9.7	17.0 ± 11.3	.203

BAS group = basal infusion group, BOL group = bolus-only group, IQR = interquartile range, MME = morphine milligram equivalents, QoR-15K = The Korean version of the 15-item Quality of Recovery Scale, PACU = postanesthetic care unit, PCA = patient-controlled analgesia.

However, PONV was less severe in the BOL group despite the minimal additional risk of PONV.

The main limitation of this study is that the infusion scheme, which consists of basal infusion rate, bolus volume, and lock-out interval, was fixed in both groups. Additionally, only non-obese adults were included in this study. Further studies comparing long-term outcomes using PCA without basal infusion versus various infusion schemes are warranted.

5. Conclusion

Fentanyl-based IV PCA without basal infusion resulted in less PONV than IV PCA with basal infusion and provided adequate pain control in patients undergoing laparoscopic gynecologic surgery. Basal infusion can be omitted to reduce postoperative nausea using IV PCA, applying an appropriate lock-out interval. Thus, more research comparing variable PCA settings is required.

Author contributions

Conceptualization: Sujin Kim, Ji-Hyoung Park, Seung Woo Song.
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Formal analysis: Sujin Kim, Seung Woo Song.
Investigation: Sujin Kim, Yeong-Gwan Jeon, Seung Woo Song.
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Supervision: Yeong-Gwan Jeon, Seung Woo Song.
Validation: Seung Woo Song.
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Writing – review & editing: Sujin Kim, Ji-Hyoung Park, Yeong-Gwan Jeon, Yun Hyung Cho, Jung Hyun So, Seung Woo Song.

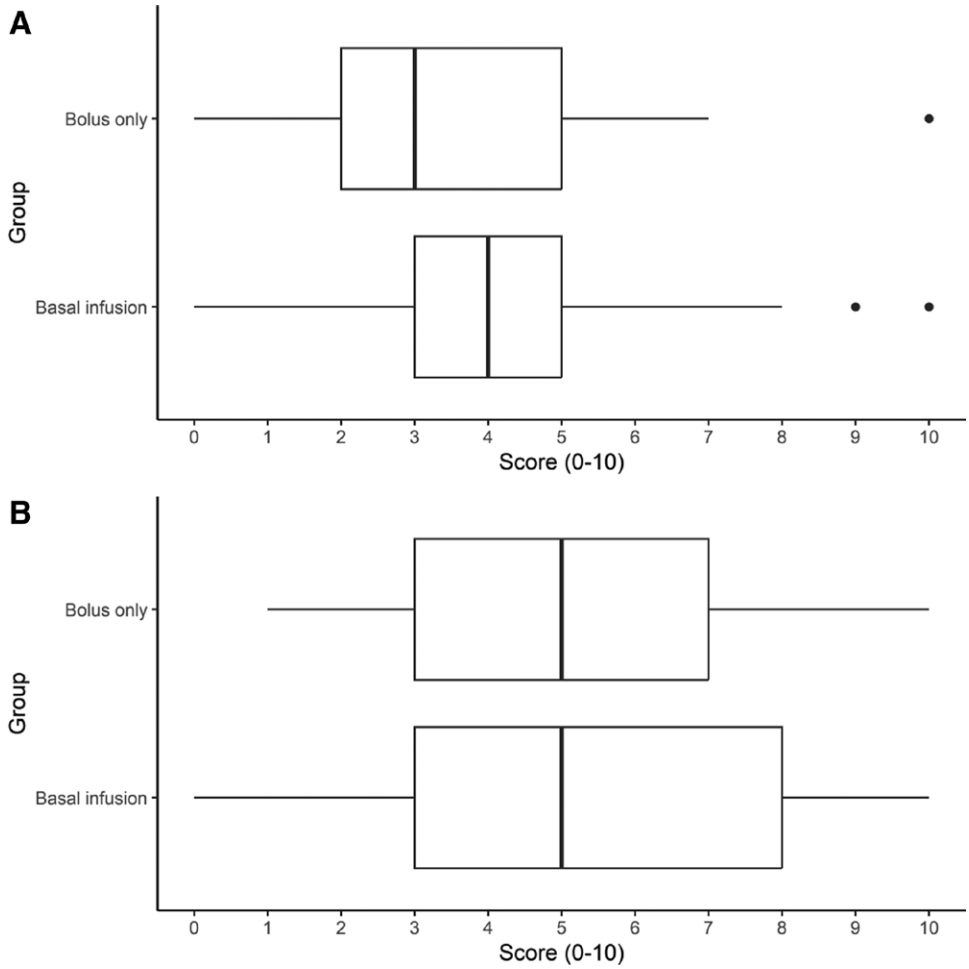

Figure 3. Response to the question addressing postoperative pain in the QoR-15K questionnaire. (A) Moderate pain. (B) Severe pain. QoR-15K = Korean version of 15-item Quality of Recovery Scale.

Table 4

Five-point scale (0–4) for measuring patient satisfaction with the overall anesthetic service.

Score	BAS group (n = 41)	BOL group (n = 41)
0 (very dissatisfied)	0	1
1 (dissatisfied)	1	0
2 (neutral)	4	2
3 (satisfied)	18	17
4 (very satisfied)	18	21

BAS group = basal infusion group, BOL group = bolus-only group.

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