The optimizing background infusion mode decreases intravenous patient-controlled analgesic volume compared to fixed-rate background infusion in patients undergoing laparoscopic cholecystectomy: a prospective, randomized, controlled, double-blind study

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Abstract: Background and objectives: Traditional intravenous, patient-controlled analgesia (PCA) uses a fixed-rate continuous background infusion mode. However, some patients suffer from inadequate analgesia or opioid-related adverse effects due to the biphasic pattern of postoperative pain. Therefore, we investigated the postoperative analgesic efficacy of PCA using an optimizing background infusion mode (OBIM), where the background injection rate varies depending on the patient’s bolus demand. Materials and Methods: We prospectively enrolled 204 patients who underwent laparoscopic cholecystectomy in a randomized, controlled, double-blind study. Patients were allocated into either the optimizing (group OBIM) or the traditional background infusion group (group TBIM). The numeric rating scale (NRS) score for pain was evaluated at admission to and discharge from the recovery room, as well as at the 6th, 24th, and 48th postoperative hours. Data of bolus demand count, total infused volume, and background infusion rate was downloaded from the PCA device at 30-min intervals until the 48th postoperative hour. Results: The NRS score was not significantly different between groups throughout the postoperative period (P = 0.621), decreasing with time in both groups (P < 0.001). The bolus demand count was not significantly different between groups throughout (P = 0.756). The mean cumulative infused PCA volume was lower in group OBIM [84.0 (95% confidence interval: 78.9–89.1) mL] than in group TBIM [102 (97.8–106.0) mL] (P < 0.001). The background infusion rate was significantly different between groups throughout (P < 0.001); it was higher in group OBIM than in group TBIM before the 12th postoperative hour, and lower from the 18th to the 48th postoperative hours. Conclusions: The OBIM combined with bolus dosing is useful in that it reduces the cumulative PCA volume compared to the TBIM combined with bolus dosing, while yielding comparable postoperative analgesia and bolus demand in patients undergoing laparoscopic cholecystectomy.

Keywords: background infusion; intravenous infusions; laparoscopic cholecystectomy; opioid analgesics; patient-controlled analgesia; postoperative pain

1. Introduction

Intravenous patient-controlled analgesia (PCA) is a common modality to immediately deliver analgesics as required by the patient via an infusion pump [1]. Its main benefit is the provision of appropriate analgesia on patient demand, ultimately increasing patient satisfaction [2,3]. The most
common PCA modes are intermittent, fixed demand dosing (self-administering) with or without continuous background infusion for postoperative analgesia [4,5]. Other variable parameters of PCA include loading dose, bolus dose, lockout interval (time lag between bolus doses), and continuous background-infusion rate [1].

However, despite using PCA devices, some patients experience inadequate analgesia due to the biphasic pattern of postoperative pain; it is more intense immediately after surgery and less intense from the day after surgery, than we expect [6,7]. Hence, patients may suffer from insufficient analgesia immediately after surgery, and may ultimately require frequent additional rescue analgesics because of the lockout interval and the fixed rate of continuous background infusion [6,7]. They may also experience postoperative opioid-related related adverse effects due to the combination of self-administered bolus and fixed-rate continuous background infusion [8,9].

To compensate for these shortcomings, the PAINSTOP medicine-injection pump (PS-1000, Unimedics Co., Ltd., Seoul, Republic of Korea) was introduced as a new device for PCA, providing an “optimizing background infusion mode” (OBIM) defined by the manufacturer [10]. The OBIM, also termed the “variable-rate feedback infusion mode” (VFIM), refers to the background injection rate that varies depending on bolus demand over a predefined time [1]. However, this mode is yet to be applied in clinical practice for postoperative pain control, and there is a lack of evidence of its usefulness [1,10,11].

We hypothesized that the OBIM would provide better postoperative analgesia, a lower cumulative opioid consumption, and fewer adverse effects compared with the traditional (fixed-rate) background infusion mode (TBIM). Therefore, we investigated the efficacy of PCA using bolus dosing and either the OBIM or the TBIM for postoperative analgesia in patients undergoing laparoscopic cholecystectomy.

2. Materials and Methods

2.1. Study Design and Ethical Statement

This prospective, randomized, controlled, double-blind study was approved by the Institutional Review Board of Chosun University Hospital (Chosun 2018-02-011) on March 6, 2018, and was prospectively registered with the Clinical Research Information Service (CRIS: https://cris.nih.go.kr/, ref: KCT0002777) on April 5, 2018. It was conducted according to the Declaration of Helsinki of 1964 and all its subsequent revisions.

2.2. Selection of Study Population

The subjects included patients aged 20 to 70 years with an American Society of Anesthesiologists (ASA) physical status of I-III, and who were scheduled to undergo elective laparoscopic cholecystectomy under general anesthesia from September 3, 2018 to February 14, 2020. Written informed consent was obtained from all participants after a thorough explanation of the purpose of this study. Participants were instructed to push the “demand” button of the PAINSTOP device whenever they experience pain of >4 points on the numeric rating scale (NRS: 0=no pain, 10=worst pain imaginable). We excluded patients with severe cardiopulmonary disease, renal or hepatic functional abnormalities, neuromuscular disorders, or a history of opioid-related complications.

2.3. Randomization and Masking

Two hundred four patients were randomly assigned to two groups that used a PCA device applying either the fixed-rate background infusion mode (group TBIM, n=102) or the optimizing background infusion mode (group OBIM, n=102). In addition, in each group, the enrolled patients were randomly assigned to two groups, receiving either fentanyl or sufentanil. Randomization was performed using a computer-generated table of random numbers via the permuted block method (a 1:1 allocation ratio and a block size of 2). This randomization was performed using PASS 15 Power Analysis and Sample Size Software (2017) (NCSS, LLC., Kaysville, Utah, USA).
The researcher who managed the anesthesia (RA) was responsible for obtaining informed consent from participants, as well as gathering and recording data from participants and PCA devices. The researcher who managed PCA (RP) was responsible for assigning the correct drugs to each PCA device according to the randomization scheme. For blinding, RP recorded the drug assignment on anesthesia record paper after the anesthesia was completely finished, and RA finally collated the data of patient medical records and that generated in the trial. Neither RA nor RP participated in the statistical analysis.

2.4. Interventions

After premedication with intramuscular midazolam (0.05 mg/kg), the patients were transported to an operating room. AA anesthetized the patients using total intravenous anesthesia with propofol and remifentanil, and maintained the optimal neuromuscular paralysis with rocuronium. Ten minutes before the end of surgery, RP started the PCA device according to the group allocation after administration of a bolus dose (2 mL; fentanyl: 0.29 μg/kg or sufentanil 0.04 μg/kg) from the PCA device and ramosetron (0.3 mg).

The total PCA volume was 140 mL, comprised of normal saline, fentanyl (20 μg/kg) or sufentanil (3 μg/kg), nefopam (160 mg), and ramosetron (1.2 mg). All PCA devices were initially set to administer a bolus of 2 mL (fentanyl: 0.29 μg/kg or sufentanil: 0.04 μg/kg) with a lockout interval of 10 min and a background infusion rate of 2 mL/h. The background infusion rate of group OBIM was set to increase automatically by 0.4 mL/h (fentanyl: 0.06 μg/kg/h or sufentanil: 0.01 μg/kg/h) each time a bolus dose was required, and decrease by 0.2 mL/h (fentanyl: 0.029 μg/kg/h or sufentanil: 0.004 μg/kg/h) when a bolus dose was not required for 1.5 h. The background infusion rate was limited to a maximum of 4.0 mL/h (fentanyl: 0.57 μg/kg/h or sufentanil: 0.09 μg/kg/h) and a minimum of 1 mL/h (fentanyl: 0.14 μg/kg/h or sufentanil: 0.02 μg/kg/h). All drug doses were based on the ideal body weight of patients.

The patients were transferred to the recovery room (RR) after the complete reversal of rocuronium-induced neuromuscular paralysis and being fully awake. When patients experienced pain of >4 points on the NRS in the RR, the RR nurse or the patient pushed the button for administration of a bolus dose. When patients required additional rescue analgesics within the lockout interval, the RR nurse intravenously administered either ketorolac (30 mg) or nefopam (20 mg). We also allowed the intravenous injection of opioids, nonsteroidal anti-inflammatory drugs, or tramadol as a rescue analgesic to treat pain of >4 points on the NRS in the ward. We treated postoperative nausea and vomiting (PONV) of >4 points on the NRS with intravenous injection of metoclopramide (10 mg). Our research staff decided whether to stop the PCA device or change its setting based on severity of signs and symptoms, and we excluded such cases from the final statistical analysis.

2.5. Outcomes

The primary outcome of this study was NRS score for pain at the 6th postoperative hour. We recorded NRS score for pain; PONV; and need of additional rescue analgesics and antiemetics at admission (RR1) to and discharge (RR2) from the RR, and at the 6th, 24th, and 48th postoperative hours. We downloaded the data from the PCA device (bolus demand count, total infused volume, background infusion rate), using its built-in Wi-Fi system, in 30-min intervals until the 48th postoperative hour. We recorded data regarding demographics, (age, sex, height, weight, ASA physical status, intraoperative remifentanil dose, operating time, anesthesia time, PCA composition), and perioperative complications, as well as the incidence of and causes for early termination of PCA.

2.6. Sample Size

To estimate the sample size for the primary outcome, we used G*Power software (ver. 3.1.9.1, Heinrich-Heine-Universität Düsseldorf, Germany). We set the two-tailed level of statistical significance as $\alpha = 0.05$, the power as 90%, and the medium effect size as 0.5 (defined by Cohen for
analyses using the Student t-test); the latter was an assumption, as there were no previous data with which to calculate the effect size [12].

The study required 172 patients in total; thus, we enrolled 204 patients, allowing for a dropout rate of approximately 15%.

2.7. Analysis
IBM SPSS Statistics for Windows, ver. 26.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. All data were analyzed as if their probability distributions were normal, based on the central limit theorem, and presented as means (95% confidence intervals [CI]), numbers (of patients (n), or numbers (percentage) of patients (n [%])). We analyzed continuous variables using the Student t-test and nominal variables with the χ² or Fisher’s exact test. For analysis of time-interval data that passed Mauchly’s sphericity test, we used repeated measures analysis of variance; we used Wilk’s lambda multivariate analysis of variance for data that did not pass Mauchly’s sphericity test. To compare two groups in a time interval, the Student t-test was employed. P values < 0.05 were considered statistically significant.

3. Results
3.1. Demographic Data
There were no important harms or unintended effects in either group in this study. Two hundred four patients were finally enrolled; however, 71 patients were excluded inform the final analysis, a 34.8% dropout rate (Table 1, Figure 1).

The number of excluded patients was significantly different between the groups (P < 0.001): 23 (22.5%) in group TBIM and 48 (47.1%) in group OBIM (Table 1). The causes of exclusion were data loss during collection in 38 patients, early PCA termination in 20 patients, and device setting errors in 13 patients (Table 1).

The causes of early PCA termination were postoperative nausea (2 patients in group OBIM) and patient request due to a lack of pain (7 in group TBIM, 11 in group OBIM). However, the number of early PCA terminations was not significantly different between the groups (P = 0.214) (Table 1).

No statistically significant differences were observed in demographic data, intraoperative variables, or PCA regimens after exclusion of the above patients (Table 2, Table 3).

Table 1. Incidences and causes for exclusion and early termination of PCA

| Variables                     | Group TBIM (n = 102) | Group OBIM (n = 102) | P value |
|-------------------------------|----------------------|----------------------|---------|
| Exclusion (No/Yes)            | 79 (77.5)/23 (22.5)  | 54 (52.9)/48 (47.1)  | <0.001  |
| Causes for Exclusion          |                      |                      |         |
| Data loss                     | 13 (12.7)            | 25 (24.5)            |         |
| Early PCA termination         | 7 (6.9)              | 13 (12.7)            |         |
| Setting error                 | 3 (2.9)              | 10 (9.8)             |         |
| Early PCA termination (No/Yes)| 95 (93.1)/7 (6.9)    | 89 (87.3)/13 (12.7)  | 0.214   |
| Causes for PCA termination    |                      |                      |         |
| Nausea                        | 0 (0.0)              | 2 (2.0)              |         |
| No pain                       | 7 (6.9)              | 11 (10.8)            |         |

Values are expressed as the number (percentage) of patients. PCA: patient-controlled analgesia, OBIM: optimizing background infusion mode, TBIM: traditional background infusion mode.
**Figure 1.** CONSORT diagram for patient recruitment. OBIM: optimizing background infusion mode, TBIM: traditional background infusion mode.

**Table 2.** Demographic data and intraoperative variables

| Variables                  | Group TBIM (n = 79)       | Group OBIM (n = 54)       | P value |
|----------------------------|---------------------------|---------------------------|---------|
| Age (yr)                   | 49.7 (46.9-52.4)          | 49.1 (45.6-52.5)          | 0.795   |
| Sex (M/F)                  | 39/40                     | 34/20                     | 0.122   |
| Height (cm)                | 165.5 (163.7-167.4)       | 166.3 (164.1-168.6)       | 0.589   |
| Weight (kg)                | 68.7 (65.7-71.7)          | 68.4 (64.3-72.4)          | 0.888   |
| ASA-PS (I/II/III)          | 39/36/4                   | 31/23/0                   | 0.203   |
| Cumulative remifentanil (µg) | 397.9 (318.2-477.6)      | 369.9 (287.0-452.8)       | 0.638   |
| Operation time (min)       | 45.8 (35.8-55.9)          | 43.9 (34.7-53.1)          | 0.789   |
| Anesthesia time (min)      | 59.1 (48.7-69.5)          | 54.2 (45.0-63.3)          | 0.503   |

Values are expressed as the mean (95% confidence interval) or number of patients. ASA-PS: American Society of Anesthesiologists physical status, OBIM: optimizing background infusion mode, TBIM: traditional background infusion mode.

**Table 3.** PCA regimens

| Drugs                      | Group TBIM (n = 79)       | Group OBIM (n = 54)       | P value |
|----------------------------|---------------------------|---------------------------|---------|
| Drug               | Mean (95% CI)             | OBIM (mg) (95% CI) | TBIM (mg) (95% CI) | p-value |
|--------------------|---------------------------|--------------------|--------------------|---------|
| Fentanyl (μg)      | 665.8 (528.6-803.0)       | 543.7 (367.2-720.2)| 0.272              |
| Sufentanil (μg)    | 80.5 (59.6-101.5)         | 97.1 (72.9-121.3)  | 0.309              |
| Nefopam (mg)       | 160.0 (160.0-160.0)       | 160.0 (160.0-160.0)| 1.000              |
| Ramosetron (mg)    | 1.2 (1.2-1.2)             | 1.2 (1.2-1.2)      | 1.000              |

Values are expressed as means (95% confidence intervals). PCA: patient-controlled analgesia, OBIM: optimizing background infusion mode, TBIM: traditional background infusion mode.

3.2. NRS Scores
The NRS score was not significantly different between the groups throughout the postoperative period (P = 0.621), and it decreased with time in both groups (P < 0.001, Figure 2).

![Figure 2](image_url)

Figure 2. Time-sequential changes of numeric rating scale (NRS) scores. Data points and error bars represent means and 95% confidence intervals, respectively. OBIM: optimizing background infusion mode, TBIM: traditional background infusion mode, RR1: at admission from the recovery room, RR2: at discharge from the recovery room.

3.3. Bolus Demand Counts
The bolus demand count was not significantly different between groups throughout the postoperative period (P = 0.756, Figure 3).
3.4. Background Infusion Rate

The background infusion rate was significantly different between groups throughout the postoperative period (P < 0.001, Figure 4). The background infusion rate of group OBIM was significantly different from that of group TBIM for all time intervals except for the 12th postoperative hour (P < 0.001, Figure 4b). The background infusion rate was higher in group OBIM than in group TBIM before the 12th postoperative hour, and lower from the 18th to the 48th hours (Figure 4b). The maximum and minimum background infusion rates were 3.3 (3.2–3.5) and 1.1 (1.0–1.2) mL/h, respectively, in group OBIM, while the background infusion rate in group TBIM was constantly 2.0 mL/h.
3.5. Infused Volume

The cumulative infused PCA volume was significantly different throughout the postoperative period (P < 0.001) and at each measured interval (P ≤ 0.005) except at the 24th and 30th postoperative hours (Figure 5a). It was higher in group OBIM than in group TBIM until the 18th postoperative hour, and lower from the 38th to the 48th postoperative hour (Figure 5a). The final cumulative infused volume was lower in group OBIM [84.0 (78.9–89.1) mL] than in group TBIM [102 (97.8–106.0) mL] (P < 0.001, Figure 5a). The per-interval infused PCA volume was significantly different between groups throughout the postoperative period (P < 0.001, Figure 5b). It was higher in group OBIM than in group TBIM until the 12th postoperative hour, and lower from the 24th to the 48th hours (P ≤ 0.004, Figure 5b).

**Figure 4.** Time-sequential changes of background infusion rate at 30-min intervals (a) and at specific time points (b). Data points and error bars represent means and 95% confidence intervals, respectively. OBIM: optimizing background infusion mode, TBIM: traditional background infusion mode. *: P < 0.05 compared with group TBIM.
Figure 5. Time-sequential changes of cumulative (a) and per-interval (b) infused PCA volume. The gray boxes represent the intervals in which there were statistically significant differences between the groups. Data points and error bars represent means and 95% confidence intervals, respectively. OBIM: optimizing background infusion mode, PCA: patient-controlled analgesia, TBIM: traditional background infusion mode. *: P < 0.05 compared with group TBIM.

3.6. Rescue Drugs and Complications
The requirements of rescue analgesics and antiemetics were not significantly different between the groups throughout the recovery period (P = 0.165 and P = 0.686, respectively) (Table 4).
Although the VFIM was associated with more efficient postoperative analgesia following surgery, it is more efficient postoperative analgesia following surgery. However, we observed no significant differences in NRS score or bolus demand counts between groups OBIM and TBIM. This may be explained by the relatively high proportion of patients receiving additional rescue analgesics throughout the recovery period in group TBIM, and by the relatively low pain following laparoscopic cholecystectomy compared with that following spinal surgery. If we restricted the use of additional rescue analgesics and studied patients who underwent more painful surgeries, the results may have differed.

Considering the biphasic postoperative-pain pattern, opioid-related adverse effects are a major concern in patients using PCA. OBIM PCA may result in adverse effects because of an increased background infusion rate and an increased bolus demand due to high levels of pain experienced immediately after surgery. On the other hand, TBIM PCA may result in an unnecessary infusion of

| Variables | Groups | RR2 | 6 h | 24 h | 48 h | Total |
|-----------|--------|-----|-----|------|------|-------|
| Analgesics | Group TBIM (n = 79) | 1 (1.3) | 14 (17.7) | 8 (10.1) | 6 (7.6) | 23 (29.1) |
|          | Group OBIM (n = 54) | 1 (1.9) | 8 (14.8) | 4 (7.4) | 1 (1.9) | 10 (18.5) |
|          | P value | 1.000 | 0.658 | 0.761 | 0.240 | 0.165 |
| Antiemetics | Group TBIM (n = 79) | 0 (0) | 0 (0) | 3 (3.8) | 0 (0) | 3 (3.8) |
|           | Group OBIM (n = 54) | 0 (0) | 2 (3.7) | 1 (1.9) | 1 (1.9) | 3 (5.6) |
|           | P value | - | 0.163 | 0.646 | 0.406 | 0.686 |

Values are expressed as the number (percentage) of patients. OBIM: optimizing background infusion mode, TBIM: traditional background infusion mode.

4. Discussion

This prospective, double-blind, randomized, controlled study revealed that the NRS score and the bolus demand count did not differ between groups throughout the recovery period. Patients in group OBIM exhibited a higher background infusion rate before the 12th postoperative hour, and a lower rate from the 12th to the 48th postoperative hours, compared with those in group TBIM. The final cumulative infused volume was approximately 18 mL lower in group OBIM than in group TBIM.

Many previous studies of PCA using the VFIM were conducted in patients using “computer-integrated” patient-controlled epidural analgesia (PCEA) during labor and delivery [13-16]. Their results suggested that patient satisfaction was greater in those using the computer-integrated PCEA than in those using traditional PCEA, but that the incidence of breakthrough pain and the cumulative local anesthetic consumption did not differ statistically significantly between groups [14,16]. However, we are aware of only one other study in which the effect of intravenous PCA was evaluated using a similar VFIM technique in combination with demand dosing, to that of our study, in patients that underwent spinal surgery [10]. In that study, the VFIM did not statistically significantly decrease the NRS score for postoperative pain compared with the TBIM, and the NRS score decreased over time in both groups [10]. The cumulative infused PCA volume was statistically significantly lower in the VFIM than in the TBIM group at the 24th and 48th postoperative hours. The authors assumed that it resulted from the corresponding lower bolus demand counts throughout the recovery period, with statistically significantly lower bolus demand counts in the VFIM than in the TBIM group at the 12th and 24th postoperative hours [10]. Hence, they suggested that the VFIM could provide more efficient postoperative analgesia and reduce the cumulative infused PCA volume than the TBIM [10]. This study also demonstrated that the OBIM contributed to a reduced cumulative infused PCA volume during the first 48 postoperative hours. However, we observed no significant differences in NRS score or bolus demand counts between groups OBIM and TBIM. This may be explained by the relatively high proportion of patients receiving additional rescue analgesics throughout the recovery period in group TBIM, and by the relatively low pain following laparoscopic cholecystectomy compared with that following spinal surgery. If we restricted the use of additional rescue analgesics and studied patients who underwent more painful surgeries, the results may have differed.
opioids in patients that do not require active pain control beyond the acute period of postoperative pain [10]. This study revealed that postoperative nausea mainly occurred before the 6th postoperative hour in the OBIM group (3.7%), and after the 6th postoperative hour in the TBIM group (3.8%). No other adverse effects were observed.

Lee et al. [10] documented that the overall incidence of PONV requiring antiemetics was lower in the OBIM group (18%) compared with the TBIM group (33%), whereas, in this study, it was higher in the OBIM group (5.6%) compared with the TBIM group (3.8%). This discrepancy has several possible explanations. First, Lee et al. [10] made use of PCA with opioids alone, while we made use of a combination of opioids and antiemetics. Our use of premixed antiemetics probably contributed to reducing the overall incidence of PONV in both groups compared with that of the study by Lee et al [10]. Second, we did not confirm whether the PONV was directly related with the administered opioid dose, as we did not record the incidence of PONV at each time interval. In this study, we enrolled patients who underwent laparoscopic surgery, a high risk factor of PONV. Even though the premixed antiemetics reduced the overall incidence of PONV, this risk factor was probably increased by the increased background infusion rate of opioids during the acute period in the OBIM group, resulting in a higher incidence of PONV in this group than in the TBIM group.

The major limitation of this study is the drop-out rate (34.8%), which was much higher than expected (15%). The causes were data loss when downloading from the device (18.2%), early termination of PCA (9.8%), and device-setting errors (6.4%). First, even though we allowed the RP an ample time for the RP to be trained in the setup of the PCA, we had to exclude 2.9% of patients in group TBIM and 9.8% in group OBIM due to setting errors. OBIM requires, in addition to the setup of TBIM, setting up conditions and sizes for the increase and decrease of the background infusion rate, as well as the maximum and minimum allowable background infusion rates. This complex setup, combined with unfamiliarity with the OBIM of the PCA device, requires ample training time to prepare and operate the device to reduce setup and operation errors [10]. Second, some patients who underwent laparoscopic surgeries were discharged early due to low levels postoperative pain and a quick recovery. Third, a part of the PCA data was lost, as we overlooked the fact that the data is erased when the device is powered down. Therefore, a more secure system should be implemented for downloading data from the device.

5. Conclusions

In conclusion, the OBIM of PCA is useful in that it reduces the cumulative administered opioid volume compared to the TBIM, while yielding comparable postoperative analgesia and bolus demand in patients undergoing laparoscopic cholecystectomy. In addition, further studies are required to determine the efficacy of the OBIM of PCA considering different types of surgery and degrees of postoperative pain.

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