Effectiveness of Postoperative Pain Management By Multimodal Analgesia Without Epidural Analgesia After Laparoscopic Colon Cancer Surgery: A Prospective Cohort Study

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Abstract

Background:

Although epidural analgesia has been recommended for its strong analgesic effect for postoperative analgesia management, the increasing number of patients undergoing anticoagulant or antiplatelet therapy to treat cerebrocardiovascular diseases cannot receive epidural analgesia given the risk of serious complications, including epidural hematoma. We aimed to evaluate the analgesic effects of multimodal analgesia involving intravenous patient-controlled analgesia (IV-PCA), and repeated scheduled acetaminophen administration, and block as local anesthesia, to establish postoperative analgesia management method replacing epidural analgesia in laparoscopic colectomy.

Methods:

We enrolled patients undergoing laparoscopic surgery for colorectal cancer at our hospital. The primary outcome was days of postoperative hospital stay. The efficacies of multimodal and epidural analgesia were compared. The secondary outcomes were the pain assessment and safety.

Results:

We registered 48 patients; among them, 40 patients were eligible. The mean postoperative hospital stay was 9.00 days (95% CI = 8.19 to 9.39, $p < 0.0001$). There were relatively high pain scores from postoperative day (POD) 0-1, which subsequently decreased and reach their lowest value at POD 4-5.

Conclusions:

Multimodal analgesia with IV-PCA and repeated scheduled acetaminophen administration could provide a safe and effective analgesic effect after laparoscopic colectomy and may be a postoperative analgesia management alternative to epidural analgesia.

Background

Open surgery is conventionally applied for colon cancer surgery with Jacobs reporting the first case of laparoscopic colorectal resection in 1991 [1]. In Japan, there has been an increase in the use of the laparoscopic approach since its first report in 1992 [2]. The advantages of laparoscopic surgery include early post-surgery recovery with reports indicating it involves fewer postoperative hospitalization days compared to open surgery [1]. Further, there have been efforts to achieve early recovery at several facilities through enhanced recovery after surgery (ERAS), which is an evidence-based multidisciplinary program that integrates elements necessary for early recovery. ERAS protocol has significant advantages in open colectomy; moreover, continuous epidural analgesia is recommended for its strong analgesic effect and early bowel functional recovery [3]. Postoperative pain management is an important factor for early postoperative ambulation and recovery; however, epidural analgesia requires catheter placement and could negatively affect early postoperative ambulation. In addition, epidural analgesia requires an

invasive procedure where a thick needle is punctured into the epidural space under local anesthesia, which could cause fear among patients. Furthermore, patients undergoing anticoagulant or antiplatelet therapy to treat cerebrocardiovascular diseases, which has recently been increasing, cannot receive epidural analgesia given the risk of serious complications, including epidural hematoma.

Intravenous patient-controlled analgesia (IV-PCA) with opioids is a method of pain management that allows postoperative patients to easily secure the administration route. Moreover, it can be used even in patients unable to receive epidural analgesia. However, it has an inadequate analgesic effect during coughing and body movement [4, 5]. Furthermore, additional bolus opioid administration could be required in uncontrolled patients, which might induce opioid-related side effects [6]. Therefore, there is a need for a rational approach involving various treatment modalities to obtain optimal pain control and minimize opioid use. Multimodal analgesia, which combines different analgesic drug classes, is recommended for postoperative pain treatment since its synergistic effect on pain relief at lower analgesic doses [7].

Unlike open surgery, laparoscopic surgery has a high risk of mild pain and often requires alternative pain management to epidural analgesia. Given the increasing adoption of laparoscopic surgery for colorectal cancers, there is a need to establish postoperative pain management for replacing epidural analgesia. We aimed to evaluate the feasibility of IV-PCA and repeated scheduled acetaminophen administration to establish an alternative postoperative analgesia management protocol to epidural analgesia in laparoscopic colectomy.

Methods

Patients and eligible criteria

The inclusion criteria were as follows: patients aged 20-85 years old; having histologically confirmed colorectal cancer located at the colon or rectosigmoid junction; undergone laparoscopic colectomy at our hospital; having adequate critical organ function; and having an Eastern Cooperative Oncology Group performance status 0 or 1. We obtained written informed consent from all patients at study enrollment. The exclusion criteria were as follows: having rectal cancer and distant metastases; being allergic to any drugs used in this study; and having an active infectious disease, as well as uncontrolled diabetes mellitus, hypertension, and urinary disorder. The study was conducted in accordance with the Helsinki declaration on experimentation on human subjects. Further, this study was approved by the Institutional Ethical Review Boards of Kindai University (approval no. 29-033) and registered at the UMIN Clinical Trials Registry as UMIN000028240, 14/07/2017 (http://www.umin.ac.jp/ctr/index-j.htm).

Intraoperative pain management

General anesthesia induction was performed using propofol, remifentanil, and rocuronium. Further, intraoperative anesthesia management was performed using desflurane or sevoflurane, remifentanil, and additional rocuronium. Additionally, at the time of closure before surgery end, 20 mL of 0.375%

ropivacaine (Anapeine®️ Injection; AstraZeneca, Osaka, Japan) was administered onto the fascia of each wound as local anesthesia.

Postoperative pain management

At the end of surgery, a solution of fentanyl (25 μg/mL) and droperidol (0.042 mg/mL) was administered at a rate of 1 ml/h using portable infusing devices (Syrinjector®️) until the morning of POD2. A 1 mL bolus was allowed at a lockout interval of 30 minutes if the patients wanted more analgesia. Furthermore, 1000 mg of acetaminophen intravenous solution (Acelio® Intravenous Injection; Terumo Corporation, Tokyo, Japan) was administered at the end of the surgery and subsequently at 6-h intervals until POD 3. In addition, the use of rescue analgesic drugs, including 50 mg flurbiprofen axetil (i.v.; Ropion®️; Kaken Phamaceutical, Tokyo, Japan) were permitted as needed.

Outcome measures

The primary endpoint was days of postoperative hospital stay. The secondary endpoints included the numerical rating scale (NRS) scores, prince Henry pain scale (PRS) scores, and safety. A nurse performed pain evaluation using the NRS and PRS at 8-hour intervals from 6 hours after surgery until POD5, as well as at first ambulation. Further, the frequency of the use of PCA (bolus administration) and rescue analgesic drugs was documented.

The NRS is an 11-point scale with “0” representing “no pain” and “10” representing “most severe pain imaginable”. The PRS is a 0-4 scale with 0, 1, 2, 3, and 4 indicating no pain at coughing, pain at coughing but not at deep breathing, pain at deep breathing but not at rest, pain at rest not requiring analgesics, and pain at rest requiring analgesics, respectively. Adverse events were evaluated using Common Terminology Criteria for Adverse Events (CTCAE) Ver.4.0. Postoperative complications were evaluated based on the evaluation classification of Clavian-Dindo.

Statistical analysis

The primary endpoint was days of postoperative hospital stay. There were 531 patients who underwent epidural analgesia for laparoscopic colectomy at our hospital between 2005 and 2015. The distribution of hospital days was skewed to the right, which indicates a long hospital stay. Subsequently, we analyzed the data on a log scale. The mean postoperative hospital stay was 2.310 (standard deviation [SD] = 0.378) on the log scale, where exp (2.310) = 10.073 days. Based on the aforementioned findings, we assumed that the expected postoperative hospital stay using multimodal analgesia was 2.303 (SD = 0.4) on the log scale, where exp (2.303) = 10 days. Based on these assumptions, this study was designed to examine the non-inferiority of multimodal analgesia compared with epidural analgesia using a 2-day margin. Based on a significance level of 0.025 (one-sided) and power of 0.8, a one-sample t-test showed that 40 patients were required. To account for patients ineligible for analysis, we enrolled 45 patients with the analysis set being patients with available records during the days of postoperative hospital stay. The results were presented after converting the mean and calculating the 95% confidence interval (CI) on the log scale to the exponential scale, with the one-sided p-value.

The secondary endpoints were the NRS score, PRS score, and safety. The NRS and PRS scores were summarized using box-whisker plots; moreover, the frequency of adverse events was determined.

All statistical analysis was performed using JMP pro15 (SAS Institute Inc., Cary, NC, USA).

Results

Demographics

Between September 2017 and August 2018, we performed 73 laparoscopic colectomies with 48 patients being registered and 40 of them being eligible. The 8 excluded patients included 3 with rectum lesions, 2 with resection of other organs, 2 with inappropriate intraoperative drug usage, and 1 who could not undergo postoperative evaluation due to dementia (Figure 1).

Clinical characteristics

Table 1 presents the clinical characteristics of the patients. There were 22 males and 18 females. The median age was 73.5 years (range: 55-85 years). The median body mass index was 23.2 kg/m^2 (range: 15.0-30.1 kg/m^2). Eight (20%) patients had a history of diabetes mellitus while six (15%) patients had perioperative heparin substitution. The tumor location was the sigmoid colon in 16 (40%) patients, the ascending colon in 8 (20%) patients, the cecum in 7 (17.5%) patients, the rectosigmoid in 5 (12.5%) patients, the transverse colon in 3 (7.5%) patients, and the descending colon in 1 (2.5%) patient. Table 2 presents the surgical procedures and short-term outcomes. Among the patients with colorectal cancers, 6, 10, 3, 13, and 8 patients underwent ileocecal resection, right hemicolectomy, left hemicolectomy, sigmoidectomy, and high anterior resection, respectively. D3 and D2 lymph node dissections were performed in 35 (87.5%) and 5 (12.5%) patients, respectively. Functional end-to-end anastomosis was performed in 18 patients (45.0%) while the double stapling technique was performed in 22 (55.0%) patients. The median surgery duration, bleeding volume, induction time, and time spent in the operation room were 202 minutes (range: 139-317 minutes), 10 ml (range: 10-300 ml), 48 minutes (range: 35-89 minutes), and 289.5 minutes (range: 211-424 minutes), respectively.

Table 1
Clinical characteristics of the patients

	Total(n=40)
Age(years), median(range)	73.5(55~85)
Sex, n(%)	
Male	22(55)
Female	18(45)
BMI(kg/m^2), median(range)	23.2(15.0~30.1)
Diabetes mellitus, n(%)	8(20)
Heparin substitution, n(%)	6(15)
Location of the tumor, n(%)	
Cecum	7(17.5)
Ascending	8(20)
Transverse	3(7.5)
Descending	1(2.5)
Sigmoid	16(40)
Rectosigmoid	5(12.5)
BMI, body mass index	

Table 2
Surgical procedures and outcomes

	Total(n=40)
Surgical procedures, n(%)	
Ileocecal resection	6(15)
Right hemicolectomy	10(25)
Left hemicolectomy	3(7.5)
Sigmoidectomy	13(32.5)
High anterior resection	8(20)
Lymph node dissection, n(%)	
D2	5(12.5)
D3	35(87.5)
Anastomosis method, n(%)	
Functional end-to-end anastomosis	18(45)
Double stapling technique anastomosis	22(55)
Surgical outcomes	
Surgery duration, minutes, median(range)	202(139-317)
Bleeding volume, ml, median(range)	10(10-300)
Anesthesia induction time, minutes, median(range)	48(35-89)
Operation room time, minutes, median(range)	289.5(211-424)
Postoperative complications, n(%)	
Nausea	17(42.5)
Vomiting	12(30)
Liver dysfunction	7(17.5)
Lower gastrointestinal bleeding	1(2.5)

Postoperative hospital stay and pain evaluation

The mean postoperative hospital stay was 9.00 days (95% CI = 8.19 to 9.39, $p < 0.0001$), which indicates that the primary endpoint was met.

Postoperative pain was evaluated between POD0 and POD5 using the NRS and PRS (Fig. 2). There were relatively high NRS and PRS scores from POD0-1, which subsequently decreased and reached their

lowest values from POD4-5. During the observation period, 10 (25%) patients used PCA while 2 (5%) patients used adjuvant analgesics.

Postoperative ambulation and oral intake

The median time to ambulation and first oral intake was 1 day (range: 1-3 days) and 4 days (range: 4-5 days), respectively.

Short-term complications

Table 1 shows the postoperative complications. Nausea and vomiting occurred in 17 (42.5%) and 12 (30.0%) patients, respectively. Three (7.5%) patients discontinued IV-PCA due to nausea and vomiting. Liver dysfunction occurred in 7 (17.5%) patients with increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels (CTCAE v4.0 ≥ Grade 1) with all of them recovering rapidly. One (2.5%) patient presented with lower gastrointestinal bleeding (Clavien-Dindo classification ≥ Grade 2). There were no serious postoperative complications, including dysuria, respiratory depression, hypotension, allergic reactions, and asthma attacks.

Discussion

Our findings indicated that IV-PCA and repeated scheduled acetaminophen administration has an efficient analgesic effect as postoperative analgesia after laparoscopic colectomy. The IV-PCA and acetaminophen combination maintained a low pain score and did not affect the postoperative hospital stay. In addition, repeated scheduled acetaminophen administration exerted a persistent analgesic effect and reduced the frequency of the fentanyl bolus dose and unnecessary additional opioid administration. Furthermore, only two patients required additional use of non-opioid analgesics.

Epidural analgesia is considered as a very useful postoperative analgesic method for postoperative recovery [6, 8–10]. However, as an epidural block, it involves potential technical and analgesic risks, including epidural hematoma, hypotension, postoperative urination disorder, limb paresthesia, and limb movement disorder. Moreover, it involves some risks associated with epidural opioids, including nausea, vomiting, and pruritus [8, 11–15]. Specifically, epidural hematoma has become a common severe adverse effect given the recent increase in the number of patients receiving anticoagulant therapy [16].

The single administration or patient-controlled analgesia (IV-PCA) with fentanyl is widely used as a postoperative analgesia alternative to epidural analgesia. However, compared to epidural analgesia, IV-PCA is considered to have an insufficient analgesic effect, especially during coughing and body movement [4, 5]. Patients using IV-PCA with postoperative uncontrollable pain could require additional bolus administration, as well as develop opioid side effects; specifically, postoperative nausea and vomiting (PONV), which is dose dependent [17]. Compared with placebo, repeated scheduled acetaminophen administration, i.e., 2 doses of intravenous acetaminophen (1000 mg q6h and 650 mg q4h), has been shown to have a significant analgesic effect after abdominal laparoscopic surgery [18].

Consequently, we speculated that IV-PCA and repeated scheduled acetaminophen administration could provide a sufficient analgesic effect and opioid side effects could be relieved by reducing the opioid dose.

Regarding the adverse effects of analgesics, PONV is among the major adverse effects and could cause extreme distress to postoperative patients. PONV is associated with prolonged length of postoperative hospital stay given the delayed first oral intake, which concomitantly leads to high medical costs [19]. PONV is usually caused by intraoperative volatile anesthetics and postoperative opioids [20]. Postoperative opioids increase the risk of PONV in a dose-dependent manner with the effect remaining throughout the opioid usage period for pain control in the postoperative periods [17, 21]. The volatile anesthetic effect on PONV is specifically prominent during the first 2-6 postoperative hours [20]. There are some risk factors for PONV, including female gender, non-smoking status, a history of PONV, a history of motion sickness, young age, laparoscopic surgery, and gynecological surgery [22]. Several drugs can be used for PONV, including 5-hydroxytryptamine and neurokinin-1 receptor antagonists, corticosteroids, butyrophenones, antihistamines, anticholinergics, etc. [22]. In our study, 17 (42.5%) patients (12 were women) presented with fentanyl-caused PONV after postoperative day 1 even with droperidol interfusion in IV-PCA. Future studies should discuss PONV prevention and treatment after laparoscopic colectomy.

Compared with epidural anesthesia, IV-PCA could induce other adverse effects, including respiratory depression [23] and delayed bowel movement [4, 8, 24]. Although properly applied IV-PCA is safe in most postoperative patients, some patients experience severe respiratory depression due to frequent additional bolus fentanyl, which requires opioid antagonists. We did not observe any cases of respiratory depression. Repeated scheduled acetaminophen administration could reduce the fentanyl dose and significantly contributes to reduced adverse events.

We preferred using acetaminophen, rather than NSAIDs, as a postoperative analgesic since NSAIDs increase the risk of gastrointestinal ulcers, renal toxicity, and anastomotic leakage [25, 26]. There is no association of short-term therapeutic use of acetaminophen with adverse effects, including bleeding, renal toxicity, and gastrointestinal disorders [27, 28]. This indicates that repeated acetaminophen administration is safer than repeated NSAID administration. Acetaminophen is a relatively safe drug; however, it could cause several adverse effects with liver dysfunction being the most adverse side effects [29]. In our study, 7 patients presented with liver dysfunction characterized by elevated AST or ALT levels (CTCAE Grade 1), which subsequently rapidly improved. Therefore, repeated acetaminophen administration is feasible in most patients without chronic liver damage.

Epidural analgesia has some potential disadvantages other than the aforementioned technical risks. The analgesic effect of epidural analgesia could be significantly dependent on the anesthesiologist’s skill. Moreover, even with proper insertion, an analgesic effect may not be attained. Furthermore, the epidural technique can be technically difficult and time consuming even when properly performed [15]. Contrastingly, IV-PCA lacks technical difficulties cannot be safely performed by non-experts. Moreover, it reduces the operating room time.

This study has several limitations. First, it analyzed a small sample size. In addition, we did not directly compare the outcomes between epidural and multimodal analgesia. Instead, we compared the outcomes between the study group and a previously analyzed historical group as the epidural analgesia group. There were some clinical between-group differences, including the period backgrounds.

Conclusions

Our findings suggest that continuous intravenous fentanyl administration and repeated scheduled acetaminophen administration could provide a safe and efficient analgesic effect in laparoscopic colectomy. There is a need for future prospective comparative studies to compare between epidural and multimodal analgesia.

Declarations

Ethics approval:

All authors comply that this research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Further, this study was approved by the Institutional Ethical Review Boards of Kindai University (approval no. 29-033) and registered at the UMIN Clinical Trials Registry as UMIN000028240, 14/07/2017 (http://www.umin.ac.jp/ctr/index-j.htm). Written informed consent were obtained from all patients at study enrollment.

Consent to participate:

Written informed consent was obtained from all individual participants included in the study.

Consent for publication:

All authors have approved the final version of the manuscript and agree with submission to *BMC Anesthesiology.*

Data Availability Statement:

The data that support the findings of this study are available from the corresponding author, YY, upon reasonable request.

Conflicts of interests/ Competing interests:

The authors have no conflicts interest to disclose.

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Author Contributions:

All authors contributed to the study conception and design. Material preparation and data collection were performed by YY and KD. Analysis and interpretation of data were performed by YY, YC, and JK. The first draft of the manuscript was written by YY. KD, TS, JH, KU, SNand JK commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Code availability: Not applicable

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Figures

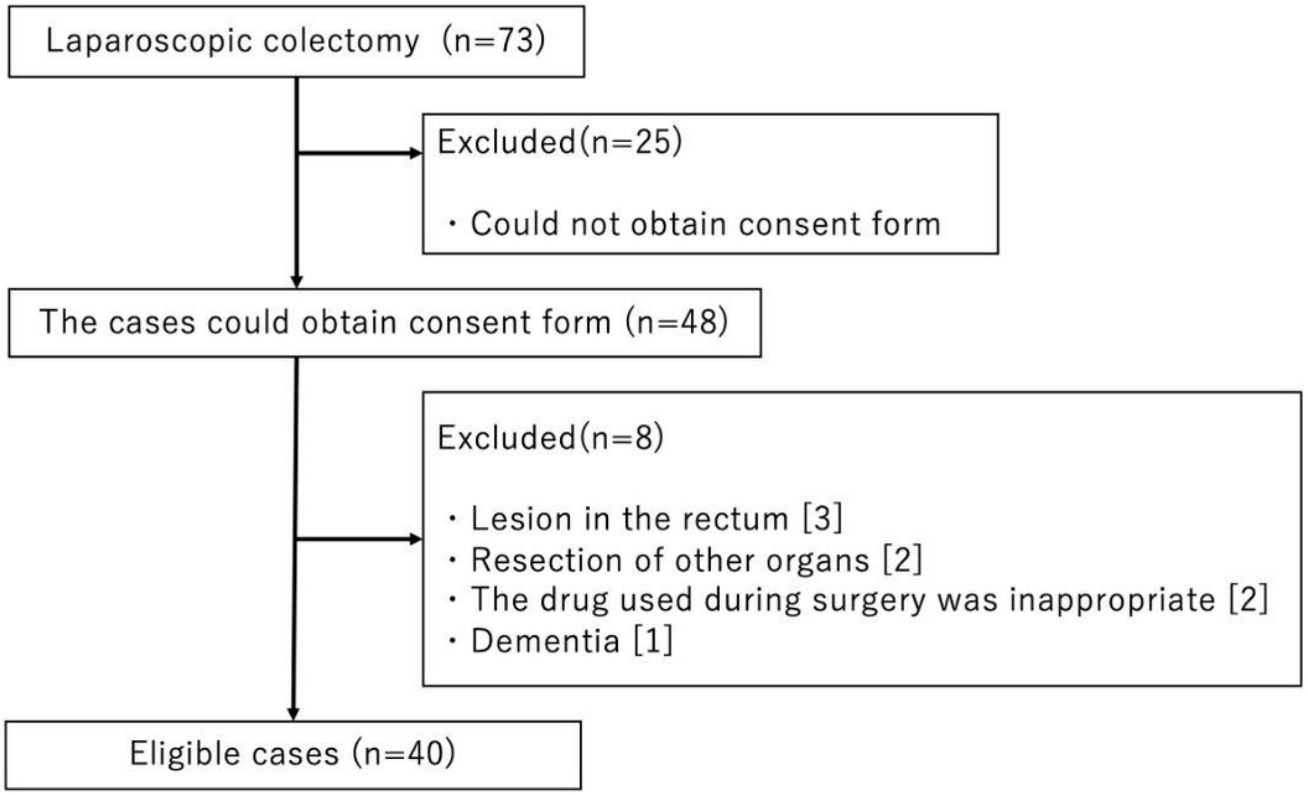

Figure 1

Selection of Study Patients.

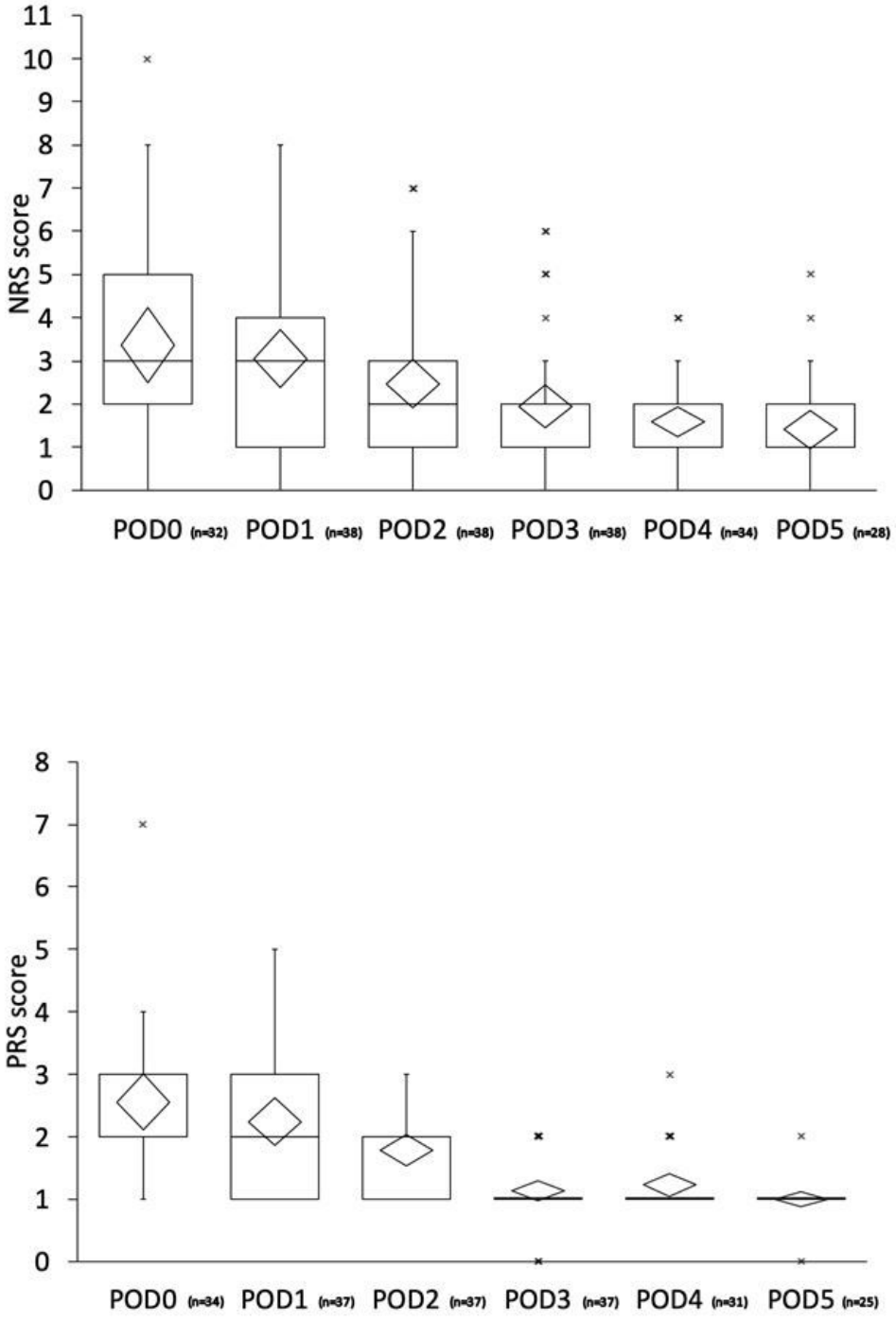

Figure 2

Postoperative pain assessment with NRS score (A) and PRS score (B). NRS score were used 11-points scale and PRS score were used 5-points scale. These scales were observed every 8 hours from 6 hour after surgery to POD5. The box plots show the median, the inter-quartile range, and the confidence interval.

Supplementary Files

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