—Original—

Evaluation of Postoperative Pain Control and Quality of Recovery in Patients Using Intravenous Patient-Controlled Analgesia with Fentanyl: A Prospective Randomized Study

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Aim: Opioids are increasingly used to control postoperative pain via intravenous patient-controlled analgesia, with several advantages. The present study evaluated the effects of intravenous patient-controlled analgesia with different doses of fentanyl on postoperative pain and on the quality of physical/emotional recovery from surgery and anesthesia.

Methods: We retrospectively reviewed data from 288 patients, and evaluated whether intravenous patient-controlled analgesia with fentanyl correlated with the degree of postoperative pain. We then prospectively studied 47 patients who underwent elective laparoscopic cholecystectomy. The patients were randomized into 2 groups (15 or 30 μg/mL of fentanyl), and postoperative pain control was compared using a visual analog scale score. Furthermore, the Japanese 40-item quality of recovery (QoR-40J) score (*global* and *dimensional*) and Hospital Anxiety and Depression Scale (HADS) were used to assess the quality of recovery from surgery and anesthesia.

Results: Of 288 patients, 20% complained of intolerable pain and 18% experienced postoperative nausea and vomiting. In the prospective study, the visual analog scale pain score was lower in the Fentanyl 30 group than in the Fentanyl 15 group ($p<0.05$) on postoperative day 1. *Dimensional* QoR-40J pain subscales correlated with both the emotional state subscales (postoperative day 1, $p<0.05$; day 2, $p<0.05$) and *global* QoR-40 scores on both postoperative days (day 1, $p<0.05$; day 2, $p<0.05$).

Conclusion: The postoperative pain as well as the physical and emotional quality of recovery in the patients who underwent laparoscopic cholecystectomy could be alleviated by sufficient doses of opioids.

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Key words: 40-item quality of recovery score, fentanyl, laparoscopic surgery, patient-controlled analgesia, postoperative pain

Introduction

Opioids are most frequently used to control postoperative pain. Several routes, including general, epidural, spinal, and local analgesia, have been applied for controlling postoperative pain[1–5]. Opioids administered via intravenous patient-controlled analgesia (IVPCA) have the potential to be used increasingly, with several advantages: IVPCA has fewer side effects, including nerve damage, epidural hematoma, etc[6]. IVPCA can be administered to patients receiving anticoagulant medication and can achieve pain control equal to those of patient-controlled epidural analgesia. However, no basic guidelines or protocols for preventing side effects have been established, and an optimal method of pain control has not yet been determined.

Advances in anesthetic management and widespread use of minimally invasive surgery, such as laparoscopic cholecystectomy, have reduced morbidity, enhanced recovery, and allowed an earlier resumption of daily activities[7–9]. However, postoperative analgesia is still required

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Table 1 Retrospective data about postoperative pain and antiemetics

Department	Total	Intolerable pain	Manageable pain	No pain	Using anti-emetic during surgery	PONV[a]	Cessation of IVPCA[b]
Urology	11	1	8	2	2	1	0
Gynecology	71	8	59	4	38	18	5
Plastic surgery	32	6	23	3	12	7	2
Thoracic surgery	1	0	0	1	0	0	0
Otolaryngology	5	0	4	1	1	0	0
Gastrointestinal surgery	87	29	54	4	26	10	8
Cardiovascular surgery	18	4	12	2	0	4	1
Orthopedics	34	11	23	0	9	8	5
Emergency center	16	0	16	0	3	0	0
Endocrine surgery	1	0	1	0	0	0	0
Breast surgery	3	0	3	0	2	1	0
Neuro surgery	9	0	7	2	0	2	2
Total	288	59	210	19	94	52	23

[a]PONV, postoperative vomiting and nausea
[b]IVPCA, intravenous patient-controlled analgesia

in laparoscopic surgery, as postoperative pain could be associated with prolonged hospitalization and increased morbidity[1,10].

It has been reported that the majority of patients receiving only periodic oral NSAID treatment after laparoscopic surgery claimed to experience a moderate-to-high level of pain, and continued to report pain even after 1 week postoperatively, indicating a requirement of opioid administration[11]. Taking all into consideration, the optimal regimen of the opioid administration for postoperative analgesia remains to be elucidated.

The aim of the present study was 1) to elucidate the optimal dose of the fentanyl IVPCA and 2) to evaluate the association between postoperative pain relief and the patient's satisfaction.

Materials and Methods

Patients and Study Design

The study protocol was approved by the Institutional Review Board of Nippon Medical School Hospital (Tokyo, Japan).

First, we retrospectively collected and reviewed data of the medical records of patients who received IVPCA (Coopdech Syrinjector®; Daikeniki Co., Ltd., Sendai, Japan) for postoperative analgesia from January 2012 to June 2012 (**Table 1**). All patients (n=288) applied IVPCA as follows: fentanyl (15 μg/mL) at a basal rate of 1.0 mL/h and a 1.0 mL bolus dose, with a lockout time of 10 min. This cohort included patients from several departments as follows: urology, gynecology, plastic surgery, thoracic surgery, otolaryngology, gastrointestinal surgery, cardiovascular surgery, orthopedics, emergency center, endocrine surgery, breast surgery, and neurosurgery.

The achievement of pain relief and the degree of postoperative nausea and vomiting (PONV) were analyzed as follows. Pain scores were assessed on a 3-point scale (0: no pain, 1: manageable pain, and 2: intolerable pain). The use of anti-emetic drugs during surgery, the incidence of PONV, the requirement for nonsteroidal anti-inflammatory drugs (NSAIDs) for postoperative pain, and the cessation of IVPCA were also analyzed. Moreover, the relationship between the use of anti-emetic drugs during surgery and PONV/cessation of IVPCA was analyzed. Respiratory depression was defined as <10 breaths/min or oxygen saturation value via pulse oximeter (SpO_2) <90%.

Second, we further attempted to elucidate the optimal opioid doses of IVPCA analgesia in a prospective study. This study was registered at the University Hospital Medical Information Network Clinical Trials Registry (No. 000010661). Written informed consent was obtained from all subjects. We prospectively collected patients who underwent laparoscopic cholecystectomy from June 2013 to March 2015. Patients (n=47) were randomized into two groups (F15 group: fentanyl with 15 μg/mL; F30 group: fentanyl with 30 μg/mL, see below) using sealed envelopes; patients were blinded to their assignments. Operating room pharmacists prepared medication in IVPCA

pumps labeled with the patient's name. The inclusion criteria for this study were elective laparoscopic cholecystectomy and age 20–79 years. The exclusion criteria were concomitant disease, including Parkinson's disease; chronic pain requiring opioid treatment; history of allergy to any medication used in the study; severe renal (*i.e.*, serum creatinine >1.6 mg/dL) or liver disease (*i.e.*, liver enzymes >2-fold normal value); pregnancy; poor comprehension of Japanese; or psychiatric/central nervous system disturbances that would preclude completion of the IVPCA and questionnaires. Patients whose surgical procedure was transferred to open surgery and in whom the IVPCA was discontinued because of severe nausea or vomiting that could not be managed with anti-emetics were also excluded.

We set the primary endpoint as "pain control", and the secondary endpoint as "quality of recovery after anesthesia and surgery". To evaluate the primary endpoint, a visual analog scale (VAS) was scored from 0 to 100 mm: 0, no pain; 100, the worst pain imaginable. Both VAS *at rest* and VAS *with movement* were scored. The incidence of nausea and vomiting were also recorded at the end of surgery and on postoperative days 1 and 2. In addition, dizziness, headache, and the patient's impression of the use of IVPCA were evaluated on postoperative days 1 and 2. These variables were evaluated as follows: vomiting as presence (Y) or absence (N); nausea, dizziness, and headache on a 4-point ordinal scale (0=none, 1=mild, 2=moderate, 3=severe). The IVPCA button-hit counts, fentanyl consumption, and pain rescue (50 mg flurbiprofen), and anti-emetic drug requirements (10 mg metoclopramide) were also recorded.

To evaluate the secondary endpoint of "quality of recovery after anesthesia and surgery", 2 questionnaires, viz. the QoR-40J and Hospital Anxiety and Depression Scale (HADS), were preoperatively submitted to the enrolled patients. Briefly, the QoR-40J is a Japanese version of a 40-item questionnaire intended to evaluate the quality of recovery after anesthesia and surgery, where each item is scored on a 5-point Likert scale: the *global* QoR-40J ranges from 40 (extremely poor quality of recovery) to 200 (excellent quality of recovery). The items are grouped according to the following subscales (*dimensions*): 9 items on emotional state, 12 on physical comfort, 7 on patient support, 5 on physical independence, and 7 on pain[12]. The score of the HADS ranged from 0 to 21, and assesses whether the symptoms of anxiety/depression are absent (0–7), possible (8–10), or severe (11–21)[13].

Anesthetic and Surgical Management

Standard monitoring was applied to patients upon arrival in the operating room. Anesthesia was induced with propofol (2.0–2.5 mg/kg), rocuronium (0.6 mg/kg), and remifentanil (0.2–0.3 μg・kg^{-1}min^{-1}). Anesthesia was maintained with remifentanil, rocuronium (7 μg・kg^{-1} min^{-1}), and sevoflurane (1.5%–2.5%), which were titrated to a bispectral index of 40–60 and a mean arterial blood pressure value within 20% of the baseline measures. Ventilation was controlled mechanically using a 45% oxygen-air gas mixture to maintain an end-tidal carbon dioxide concentration of 35–40 mmHg. After tracheal intubation, a gastric tube was inserted via the nose or mouth and removed immediately before or after tracheal extubation. Lactated Ringer's solution was used for fluid resuscitation at a rate of 6–8 mL/kg. Approximately 30 min before surgery was completed, fentanyl (200 μg) and droperidol (0.5 mg) were injected; then, a disposable IVPCA device was connected to the intravenous line to begin the infusion. Neuromuscular blockade was reversed with (2–4 mg/kg) before tracheal extubation.

The IVPCA was applied during the first 24 h after the completion of surgery. The amount of fentanyl used in this study was determined in reference to previous reports[14–19]. Fentanyl at either 15 μg/mL (F15 group) or 30 μg/mL (F30 group) was administered into each pump. As mentioned above, the IVPCA device was initially programmed to deliver fentanyl at a basal rate of 1.0 mL/h and a bolus dose of 1.0 mL, with a lockout time of 10 min. Patients were instructed to push the button for IVPCA whenever they felt pain. In both groups, NSAIDs (flurbiprofen, 50 mg) were administered for inadequate pain control, and the use of anti-emetics (metoclopramide, 10 mg) was recorded. After the patients started drinking on postoperative day 1, 200 mg of celecoxib was initially prescribed, followed by a dosage of 100 mg twice daily. Laparoscopic cholecystectomy with a conventional port setting was performed by a surgeon (Y.M.) or by other surgeons under supervision of Y.M.

Statistical Analysis

The χ^2 test and Fisher's exact test was used to compare the categorical variables. An unpaired *t*-test and Mann-Whitney test were used to compare the difference in distribution between two groups. Pearson's correlation test was used to compare the correlation of the two variables. For the prospective study, a power calculation based on VAS scores from a previous study[14], with a statistical power of 80% and $\alpha<0.05$, identified that a minimum

Table 2 Relationship between antiemetic use during surgery and symptoms

	No antiemetic (n=194)	Droperidol (n=65)	Metoclopramide (n=18)	Droperidol and metoclopramide (n=11)
PONV[a, c]	36	11	4	1
No PONV	158	54	14	10
Cessation of IVPCA[b]	14	6	3	1

[a]χ^2 test for PONV independence, p=0.83
[b]χ^2 test for IVPCA cessation independence, p=0.56
[c]PONV, postoperative vomiting and nausea
IVPCA, intravenous patient-controlled analgesia

Table 3 Demographic, preoperative, and intraoperative parameters

	F15 (n=21)[a]	F30 (n=22)[a]	p value
Sex (M/F)[b]	11/10[c]	8/14	0.466
Age (year)	57.7±13.1	60.1±8.5	0.467
Weight (kg)	61.1±13.8	63.7±12.3	0.507
Height (cm)	161.5±9.1	164.0±9.2	0.373
Anesthesia time (min)	211.7±51.5	199.09±35.4	0.354
Surgical time (min)	134.1±40.6	133.6±41.2	0.974
Crystalloid (mL)	1,353.3±634.1	1,109.1±260.3	0.103
Sevoflurane dose (mL)	101.6±27.1	95.8±20.9	0.432
Remifentanil consumption (mg)	1.8±0.8	1.6±0.6	0.317

[a]F15, fentanyl 15 μg/mL at a basal rate of 1 mL/h
and F30, 30 μg/mL at a basal rate of 1 mL/h
[b]M, male; F, female
[c]Data are shown as mean±standard deviation or number of patients

sample size of 17 was necessary. A p-value<0.05 was considered statistically significant. All data were performed using IBM SPSS statistical software 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Firstly, we sought to overview the usage and feasibility of IVPCA after surgery under general anesthesia. From the review of the medical records that we retrospectively collected (n=288), 18% and 20% of patients that complained of intolerable pain and PONV, respectively, were identified (**Table 1**). IVPCA was most frequently used for gastrointestinal surgery, including laparoscopic cholecystectomy, in our institute (n=87), where 33% (n=29) of patients complained of intolerable pain, while postoperative pain could be controlled in 67% of patients (**Table 1**). No patient developed respiratory depression in this cohort. Among patients who were administrated anti-emetic drugs, including droperidol and/or metoclopramide, during surgery, 17% (16/94) patients experienced PONV (**Table 2**). No significant difference in the incidence of PONV (p=0.83) or cessation of IVPCA was noted among the administered drugs (p=0.53; **Table 2**).

From the observations mentioned above, we further sought to elucidate the optimal regimen for IVPCA in a prospective study. The demographic data of the patients are shown in **Table 3**. In this prospective study, 43 patients (F15, n=21; F30, n=22) completed the study protocol. Four patients were excluded from the study because of IVPCA cessation due to severe nausea or vomiting (F15, n=2; F30, n=2). There were no significant differences in baseline variables between the groups (**Table 3**).

In terms of the VAS score (**Table 4**), the VAS score *with movement* was lower in the F30 group than in the F15 group on postoperative day 1, (F15: 52.4 ± 23.7, F30: 38.2 ± 24.0, p≤0.05). Although the VAS score analysis showed a tendency for the F30 group to have a lower score in general, there was no significant difference between the groups with respect to other points (**Table 4**).

Fentanyl use via IVPCA, button-hit counts, and the requirements for NSAIDs and antiemetic drugs are listed in **Table 5**. Increased fentanyl consumption was observed

Table 4 Visual analogue scale (VAS) scores

	F15 (n=21)[a]	F30 (n=22)[a]	p value
at rest			
end of surgery	36.4±29.2[b]	37.2±21.6	0.91
postoperative day 1	42.9±24.2	31.1±22.9	0.11
postoperative day 2	30.0±21.7	24.1±21.5	0.37
with movement			
end of surgery	52.62±36.9	40.5±24.2	0.21
postoperative day1	52.4±23.7	38.2±24.0	0.05
postoperative day 2	37.8±19.8	31.3±22.3	0.31

[a]F15, fentanyl 15 μg/mL at a basal rate of 1 mL/h and F30, 30 μg/mL at a basal rate of 1 mL/h

[b]Data are shown as mean±standard deviation or number of patients

Table 5 Postoperative data

	F15 (n=21)[c]	F30 (n=22)[c]	p value
Fentanyl (μg)	874.8±156.8	1,553.3±208.4	<0.001
BHC[a]	22±26.9	13±13.9	0.195
NSAID[b] requirement	6 (30.0%)	6 (27.2%)	0.927
Antiemetic requirement	6 (30%)	3 (14%)	0.239

[a]BHC, button hit counts

[b]NSAID, non-steroidal anti-inflammatory drug

[c]F15, fentanyl 15 μg/mL at a basal rate of 1 mL/h and F30, 30 μg/mL at a basal rate of 1 mL/h

[d]Data are shown as means±standard deviations or %.

in the F30 group compared to the F15 group, whereas there were no significant differences in the other variables.

The HADS and *global* and *dimensional* QoR-40J scores (see description in Materials and Methods) are presented in **Table 6**. The HADS scores and the preoperative *global* and *dimensional* QoR-40J scores showed no significant differences between the groups. On postoperative days 1 and 2, however, the *dimensional* QoR-40J scores of pain subscales were significantly better (higher) in the F30 group than in the F15 group (p=0.021, p=0.024, respectively). However, the scores at the other time points did not differ between the two groups. In addition, there was no statistically significant difference in the incidence of side effects between the two groups (**Table 7**).

Lastly, we analyzed the correlation among the scores of *global* and *dimensional* QoR-40J and VAS at each time point, to study the association of postoperative pain with physical/emotional status. The *global* QoR-40J (r=0.72, p< 0.05), *dimensional* QoR-40J of subscales of emotional state (r=0.77, p<0.05), and the subscales of pain (r=0.61, p< 0.05) scores on postoperative day 1 correlated significantly with those on day 2 (**Fig. 1**). For other variables, the results (day 1 vs. day 2) were as follows: physical comfort (r=0.43, p=0.08), physical independence (r=0.41, p<0.05), and psychological support (r=0.69, p<0.05).

On postoperative day 1, the VAS scores both *at rest* and *with movement* exhibited weak correlations with the HADS scores (at rest: r=0.37, p<0.05; with movement: r= 0.35, p<0.05). Other pain scores and side effects did not correlate with the HADS scores (day 2 at rest: r=−0.16, p =0.29; with movement: r=−0.14, p=0.36). *Dimensional* QoR-40J of subscales of pain correlated with both the subscales of the emotional state (postoperative day 1: r= 0.41, p<0.05; day 2: r=0.61, p<0.05) and *global* QoR-40 scores on both postoperative days (day 1: r=0.71, p<0.05; day 2: r=0.72, p<0.05; **Fig. 2**).

Discussion

Pain is one of the most common complications associated with patient discomfort during the early postoperative period[15]. Postoperative pain can increase the mortality rate and the risk of adverse effects on multiple organs, complication incidence, and the development of chronic

Table 6 HADS and QoR-40J scores

	F15 (n=21)[c]	F30 (n=22)[c]	p value
HADS[a]	3.95±3.9	4.41±4.1	0.712
QoR-40J[b] dimensions			
Emotional state			
preoperative	42 (23–45)	42 (32–45)	0.767
postoperative day 1	37 (16–45)	37 (24–45)	0.857
postoperative day 2	38 (9–45)	40 (27–45)	0.483
Physical comfort			
preoperative	58 (49–60)	57 (48–60)	0.593
postoperative day 1	43 (28–58)	46 (21–59)	0.843
postoperative day 2	52 (32–60)	52 (37–60)	0.96
Psychological support			
preoperative	33 (26–35)	32 (17–35)	0.661
postoperative day 1	29 (15–35)	30 (16–35)	0.67
postoperative day 2	29 (19–35)	31 (17–35)	0.319
Physical independence			
preoperative	24 (23–25)	24 (15–25)	0.537
postoperative day 1	18 (6–25)	18 (6–25)	0.962
postoperative day 2	22 (13–25)	21 (5–25)	0.596
Pain			
preoperative	34 (31–35)	34 (31–35)	0.615
postoperative day 1	27 (16–30)	31 (23–35)	0.021
postoperative day 2	29 (16–35)	32 (24–35)	0.024
Global QoR-40			
preoperative	192 (161–200)	190 (160–200)	0.794
postoperative day 1	160 (107–197)	162 (112–195)	0.775
postoperative day 2	173 (105–200)	175 (129–200)	0.794

[a]HADS, hospital anxiety and depression scale
[b]QoR-40J, Japanese version of the 40-item quality of recovery scoring system
[c]F15, fentanyl 15 μg/mL at a basal rate of 1 mL/h and F30, 30 μg/mL at a basal rate of 1 mL/h

Table 7 Side effects

	F15[a] (n=21)	F30[a] (n=22)	p value
vomiting (Y : N)	6 : 15	5 : 17	0.652
nausea	1.2 (0–3)	1.3 (0–3)	0.701
headache	1.3 (0–3)	0.79 (0–3)	0.92
dizziness	1.9 (0–3)	1.9 (0–3)	0.988

[a]F15, fentanyl 15 μg/mL at a basal rate of 1 mL/h and F30, 30 μg/mL at a basal rate of 1 mL/h

pain that affects a patient's quality of life[1]. In the present study, we demonstrated that pain control after elective laparoscopic cholecystectomy could be better achieved with 30 μg/mL fentanyl via IVPCA than with 15 μg/mL fentanyl IVPCA. In addition, we showed that reduced postoperative pain allowed a better comparison of the patient's physical and emotional states and could enhance patient satisfaction.

Advances in the laparoscopic cholecystectomy have reduced many complications, including pain. Nonetheless, when compared to open surgery, laparoscopic cholecystectomy sometimes incurs intense pain at an early postoperative stage[2,16]. In addition, the pattern of pain after laparoscopic cholecystectomy is complex, and patients are unlikely to benefit from similar analgesic treatment of open surgery[17]. Moreover, Bisgaard et al. reported that 60% of patients receiving only periodic oral NSAID treatment claimed to experience a moderate-to-high level of pain and continued to report pain even 1 week postoperatively, supporting the requirement of opioid administration[11]. Consequently, as with open surgery, patients undergoing laparoscopic surgery still require optimal opioid administration to manage postoperative pain because of individual differences in pain thresholds[10].

PONV was the most frequent side effect of opioid administration with a reported incidence of 20%–30%[17,18]; the previously reported incidence was higher than that in our study (18%). This difference was possibly due to dis-

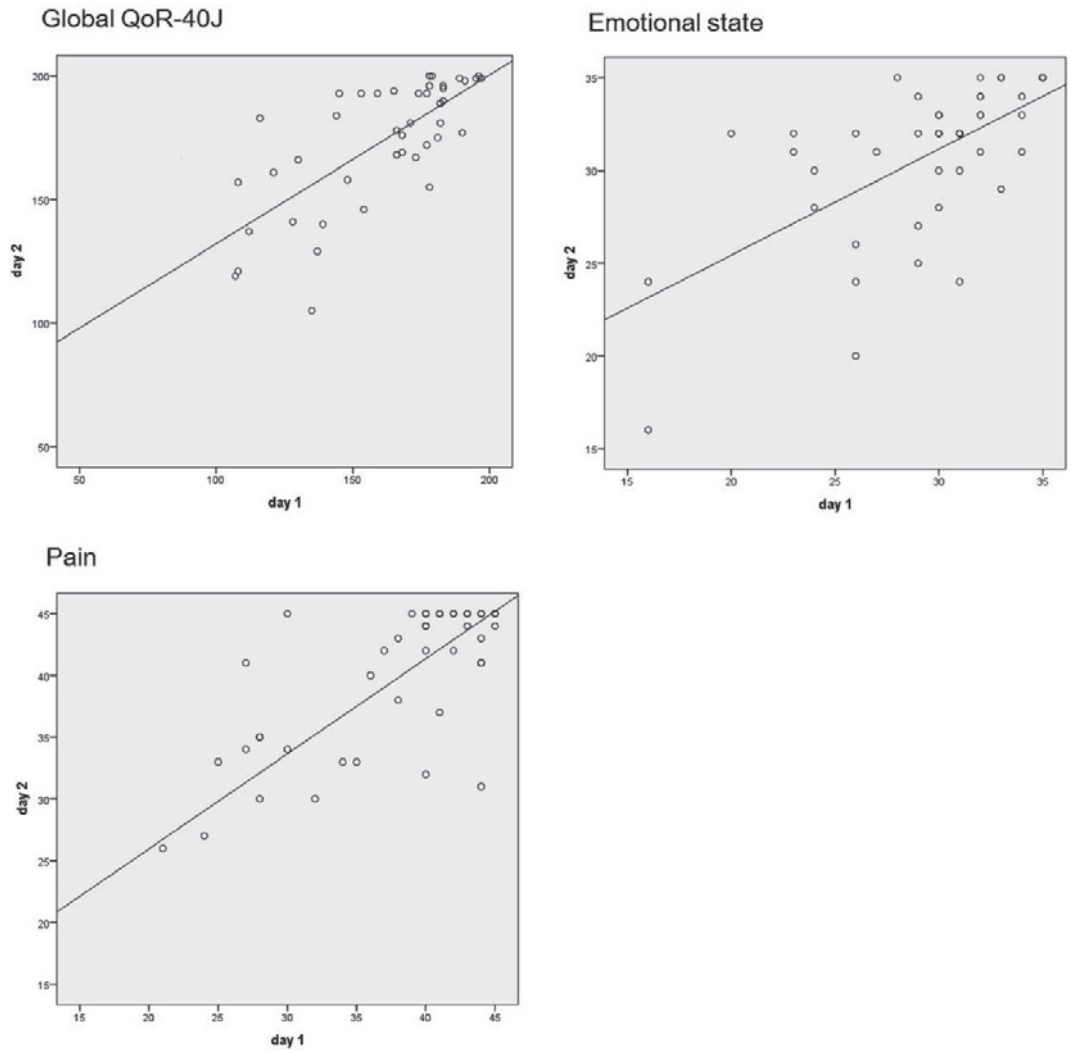

Fig. 1 Correlation of the *global*, emotional state, and pain QoR-40J scores between postoperative days 1 and 2. The *global* QoR-40 (r=0.72, p<0.05), emotional state (r=0.77, p<0.05), and pain (r=0.61, p<0.05) scores on postoperative day 1 correlated significantly with those on day 2.

similarities in the protocol. Using higher doses of opioids may increase the incidence of PONV. Thus, in our prospective study, we used an anti-emetic drug during surgery to prevent PONV. Unexpectedly, the postoperative onset of PONV was 25%, and the actual rate of IVPCA cessation due to the postsurgical use of antiemetic drugs was 8%, as was the IVPCA cessation rate in the retrospective study. Notably, a higher fentanyl concentration did not significantly increase the incidence of PONV, and no significant differences in any side effects were observed between the two groups, or in the retrospective study and the previous study.

It has been reported that the quality of recovery from anesthesia and surgery is one of the factors that is directly associated with patients' satisfaction[12,15,19,20]. Likewise, postoperative discomfort and complications could lead to later feeding, ambulation, and a prolonged hospital stay. The QoR-40 is the best instrument for assessing the recovery of patients who have undergone surgery or have undergone anesthesia[9]. Efforts towards precisely measuring and evaluating the QoR-40 could improve the overall quality of recovery and enhance patient satisfaction[9]. In our study, we used the Japanese version of the QoR-40 (QoR-40J), which has been tested for its validity, reliability, and feasibility in clinical evaluations of postoperative recovery[12]. The QoR-40J pain scores on postoperative days 1 and 2 tended to be better in the F30 than in the F15 group. In an investigation of each category on both postoperative days, we found that an improvement in the emotional state category on day 1 was also notable on day 2. The same result was observed for the *global* QoR-40J. As our treatment schedule included the use of

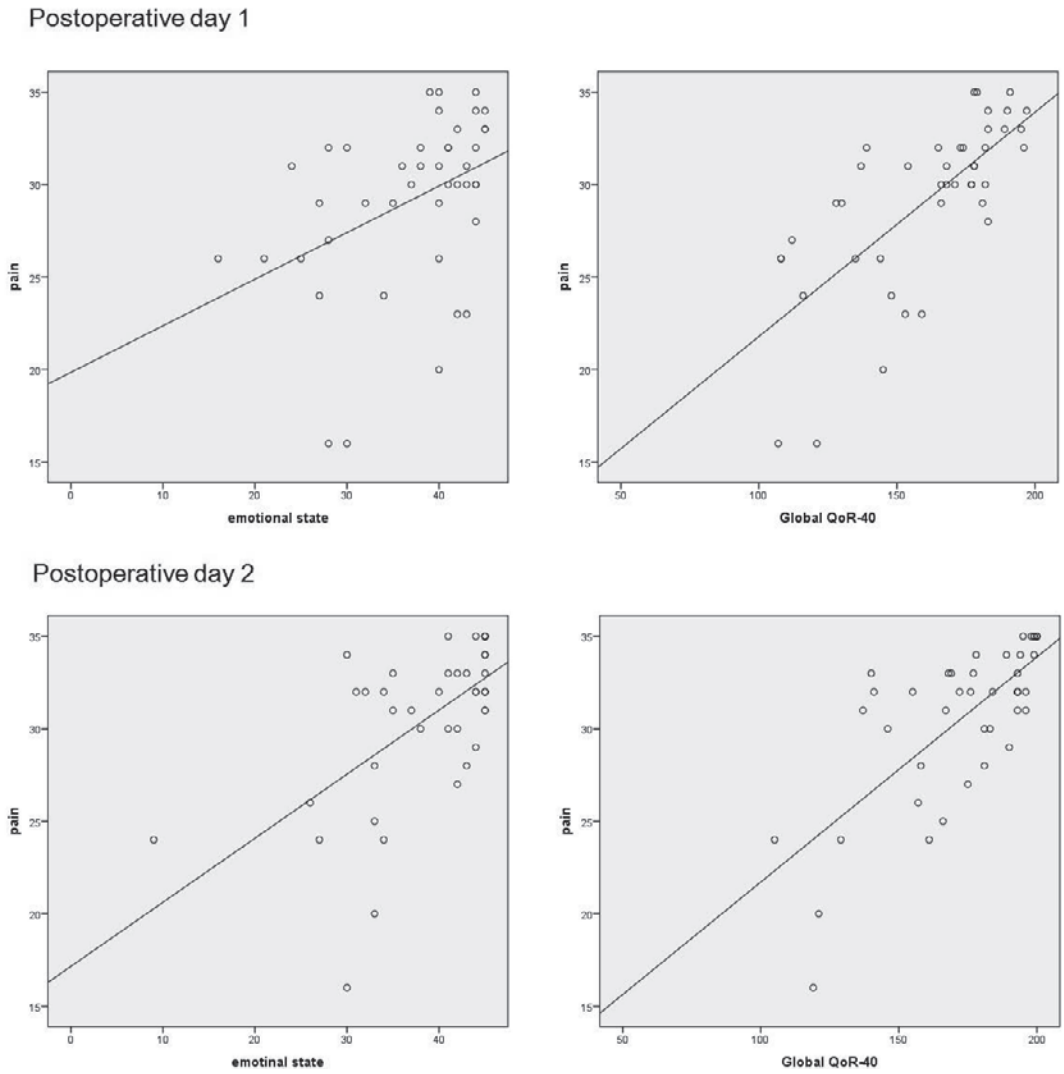

Fig. 2 Correlations among QoR-40J (the *global* and pain, and emotional state and pain). Each of the categories were compared among variables of the QoR-40J (the *global* and pain, emotional state, and pain scores) in postoperative day 1 and 2. The QoR-40 dimension of pain correlated with both the emotional state (postoperative day 1: r=0.41, p<0.05; day 2: r=0.61, p<0.05) and, *global* QoR-40 scores on both postoperative days (day 1: r=0.71, p<0.05; day 2: r=0.72, p<0.05)

IVPCA for 24 h after surgery and the internal use of the same NSAIDs in both groups, we concluded that early postoperative pain control influences the patient's pain for up to 2 days after surgery.

In this study, we have also evaluated the correlation between postoperative VAS and HADS scores. However, we were unable to identify clear correlations between the different methods and patients' postoperative conditions, indicating that preoperative fear did not have an important influence on postoperative pain relief.

This study has some limitations. This study was conducted to compare different fentanyl doses allocated to the 2 subject groups; therefore, a non-opioid treatment was not evaluated. The inclusion of a non-opioid group may have led to different results regarding pain, side effects, and patient satisfaction. Secondly, we could not evaluate pain conditions at a later time than postoperative day 2. Lastly, this study was conducted using a relatively small number of patients. Consequently, additional well-designed clinical studies with larger sample sizes are warranted to evaluate the efficacy and safety of this mode of analgesia.

Thus, in conclusion, the postoperative pain as well as the physical and emotional quality of recovery in patients who have undergone laparoscopic cholecystectomy can be alleviated by sufficient doses of opioids.

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Conflict of Interest: The authors declare no conflict of interest.

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