Effect of naloxone on intravenous fentanyl patient-controlled analgesia after laparoscopic cholecystectomy

Jun Zheng, MD\textsuperscript{a,b}, Wen Han, MD\textsuperscript{c}, Xiao-Dong Han, MD\textsuperscript{b}, Xiao-Yuan Ma, MD\textsuperscript{d}, Pengbo Zhang\textsuperscript{a,*}

Abstract
This study aims to evaluate the effect of naloxone on intravenous fentanyl patient-controlled analgesia after laparoscopic cholecystectomy under total intravenous anesthesia.

A total of 90 patients, who underwent intravenous fentanyl patient-controlled analgesia after laparoscopic cholecystectomy under total intravenous anesthesia, were included into this study. All patients were randomly divided into 3 groups (each group, n=30): naloxone group (naloxone+fentanyl), tropisetron group (tropisetron+fentanyl), and fentanyl group (fentanyl). Patients in each group were given a corresponding dose of naloxone. Postoperative analgesic effect and the incidence of side effects such as nausea and vomiting were observed.

Small doses of naloxone or tropisetron combined with fentanyl used for intravenous patient-controlled analgesia can significantly reduce the incidence of nausea and vomiting. Six hours after surgery, visual analogue scale (VAS) scores were significantly lower in patients that underwent intravenous patient-controlled analgesia using low-dose naloxone combined with fentanyl compared with patients who received fentanyl alone; however, the postoperative analgesic effect of tropisetron was not observed. Compared with the combination of tropisetron and fentanyl, low-dose naloxone combined with fentanyl can obviously reduce the incidence of nausea and vomiting in patients who underwent intravenous patient-controlled analgesia after laparoscopic cholecystectomy, and enhance the analgesic effect of fentanyl 6 hours after surgery.

Low-dose naloxone can reduce the incidence of nausea and vomiting in patients who underwent laparoscopic cholecystectomy under total intravenous anesthesia, and exhibits a certain synergic analgesic effect.

Abbreviations: ASA = American Society of Anesthesiologists, VAS = visual analogue scale.

Keywords: fentanyl, naloxone, nausea, patient-controlled analgesia after surgery, tropisetron, vomiting

1. Introduction
Pain is an unpleasant sense and emotional feeling, and is accompanied by substantial or potential tissue injury. Furthermore, it is a kind of subjective feeling.\cite{1} As the most common acute pain in surgery,\cite{2} postoperative pain has been thought to be one of the leading causes of anxiety and fear in patients\cite{3} and is a key issue for medical staff in the Department of Anesthesiology.\cite{4} Due to constraints on the level of understanding and professional technical development, pain after surgery has been considered to be a reasonable feeling; and adverse consequences brought about by the pain are often neglected.\cite{5}

Patient-controlled analgesia is a kind of analgesic method, which can realize on-demand analgesia by means of infusion devices, time devices, and self-medication. This is a new analgesic technique that has been widely used in recent years.\cite{6} Opioids are the main drugs for clinical analgesia, and fentanyl and sufentanil have been widely used in postoperative analgesia. However, opioids cause adverse reactions such as nausea, vomiting, dizziness, sleepiness, and respiratory depression. As a specific opioid receptor antagonist, nalmefene can be used to fully or partially reverse the effect of opioids.\cite{7} Studies have revealed that the concurrent administration of small doses of this opioid receptor antagonist combined with opioids can reduce adverse reactions.\cite{8,9} However, reports on patient-controlled intravenous analgesia combined with the application of nalmefene, sufentanil, and dezocine are rare. In this study, tropisetron was used as a control, in order to evaluate the effects of using a small dose of nalmefene in postoperative intravenous patient-controlled analgesia in elderly patients with hip fracture, providing reference for clinical practice.

2. Materials
This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of our hospital. Written informed consent was obtained from all participants.

2.1. Study subjects
A total of 90 patients who underwent elective laparoscopic cholecystectomy under total intravenous anesthesia were en-
rolled into this study. Based on the American Society of Anesthesiologists (ASA) Physical Status Classification System, these patients were classified as grade I-II, and the age of these patients ranged from 18 to 55 years old. Exclusion criteria: (1) patients with endocrine diseases such as diabetes and hyperthyroidism; (2) patients with diseases in the heart, lungs, brain, liver, spleen, kidneys, and other important viscera; (3) patients with history of smoking; (4) patients with history of acute gastrointestinal diseases such as gastric ulcer and duodenal ulcer within the last 6 months; (5) patients with a history of abdominal surgery within 3 years; (6) patients with history of abnormal diseases with trauma or other acute and chronic pain; (7) patients need to change the operation mode or operation time is prolonged due to the patient’s special conditions; (8) patients who had operative accidents or anesthesia accidents during an operation. Before surgery, the patients and their family were informed of the protocol, and a signed informed consent was obtained. After surgery, an intravenous patient-controlled analgesia pump was fitted. The patients and their family members were instructed and guided on how to master the methods of using the pump.

Experimental groups: all patients were randomly divided into 3 groups (each group, n=30): naloxone group (naloxone + fentanyl), tropisetron group (tropisetron + fentanyl), and fentanyl group (fentanyl).

2.2. Research methods
2.2.1. The proportion of drugs used in postoperative patient-controlled analgesia.

(1) Naloxone group: 2 µg/kg of body weight of Naloxone and 16 µg/kg of body weight of fentanyl were diluted to 100 mL with 0.9% normal saline.

(2) Tropisetron group: 0.2 mg/kg of body weight of tropisetron (the highest dose was not more than 5 mg/d) and 16 µg/kg of body weight of fentanyl were diluted to 100 mL with 0.9% normal saline.

(3) Fentanyl group: 16 µg/kg of body weight of fentanyl was diluted to 100 mL with 0.9% normal saline.

2.2.2. General anesthesia-induced administration. A venous channel was established, and clinical parameters of the breathing machine were set. All patients used the same type of anesthesia and the same breathing pattern. Items included tidal volume (8–12 mL/kg), breathing frequency (8–14 times/minute), inspiratory-to-expiratory ratio (1:2), and oxygen flow rate (0.8 L/minute). Patients were instructed to breathe deeply while the oxygen flow rate was set at 6 L/minute. Patients were injected with the following drugs: 0.06 mg/kg of midazolam, 6 µg/kg of fentanyl, 0.06 mg/kg of cisatracurium, and 0.2 mg/kg of propofol. When muscles were relaxed, pressurized oxygen supply was performed with a mask, and assisted breathing was manually controlled. At an appropriate time, endotracheal intubation was conducted, and intubation response was minimized. After the trachea was fixed, the machine was started to control the breathing.

2.2.3. Intraoperative and postoperative measures. During surgery, anesthesia was maintained using an intravenous infusion pump, and these operations were conducted by the same anesthetist. The names and doses of the drugs that were administered before, during and after surgery were recorded in detail, and symptomatic treatments were performed for the specific events that appeared during the operation period. Drugs and their doses were as follows: propofol, 4–6 mg/kg h; remifentanil, 7 to 15 µg/kg h. Stable hemodynamics should be kept during the operation. Propofol and remifentanil infusion should be timely stopped according to the operation process. After surgery, the analgesia pump was connected. The pump rate was set at 2 mL/h when the following circumstances appeared: patients began to have spontaneous breathing and tidal volume was >6 mL/kg, swallowing reflex appeared, patients had basic consciousness, muscle strength recovered to normal, and blood oxygen saturation was >90%. A 2.0-mL injection was performed by pushing a button, and lock time was 15 minutes. Then, tracheal extubation was performed. Patients were sent back to the ward when they became fully awake.

2.2.4. Postoperative observation. Patients were graded based on the classification of nausea and vomiting of the World Health Organization (WHO; no distinction of nausea and vomiting): grade 0, no vomiting; grade I, mild vomiting (1–2 times/day); grade II, moderate vomiting (3–5 times/day); grade III, severe vomiting (>5 times/day). If several vomiting incidences occurs within 1 minute, these are regarded as one incidence. If the interval between 2 vomiting incidences is larger than 1 minute, these should be calculated as 2 vomiting incidences. Pain degrees at postoperative hour 2, 6, 12, 24, and 48 were observed and recorded, and visual analogue scale (VAS) scoring was performed. VAS scoring was performed as follows. A vernier of ~10 cm in length was used, in which one side was marked with 10 scales. The 2 ends of this scale were labeled as the “0” end and the “10” end, respectively. The “0” end represents painless, whereas the “10” end represents the most intense and intolerable pain. Clinical scores of 0 to 2 were regarded as excellent, clinical scores of 3 to 5 were regarded as good, clinical scores of 6 to 8 are regarded as acceptable, and clinical scores of >8 were regarded as poor.

2.3. Statistical analysis
Data were analyzed using statistical software SPSS 16.0. Measurement data was expressed as mean ± standard deviation (x±SD). First, the variates underwent a normal test and a homogeneity test of variance. Measurement data were compared using t-test and analysis of variance (ANOVA). P<0.05 was considered statistically significant.

3. Results
3.1. VAS score comparisons among groups
VAS scores in each period were lower in the naloxone group than in the tropisetron and fentanyl groups. Furthermore, differences in mean VAS score in each period between the naloxone and tropisetron groups, as well as between the tropisetron and fentanyl groups, were all not statistically significant (P>0.05). However, 6 hours after surgery, the difference in VAS scores between the naloxone and fentanyl groups was statistically significant (P<0.05). Details are shown in Table 1.

3.2. Comparison of incidences of nausea and vomiting among the 3 groups
Inter-group comparison of the overall incidence of nausea and vomiting: the difference between the naloxone and fentanyl groups was statistically significant (P<0.05), and the incidence of nausea and vomiting was lower in the naloxone group than in
the fentanyl group. Furthermore, the incidence of nausea and vomiting was lower in the tropisetron group than in the fentanyl group, and the difference was statistically significant \( P < 0.05 \). Moreover, the incidence of nausea and vomiting was lower in the naloxone group than in the tropisetron group, and the difference was statistically significant \( P < 0.05 \). Details are shown in Table 2.

### 3.3. Comparison of very severe (could not be tolerated by the patient) nausea and vomiting incidences among groups

Inter-group comparison: the incidence of severe nausea and vomiting was lower in the naloxone group than in the tropisetron group, but the difference between these 2 groups was not statistically significant \( P > 0.05 \). Furthermore, the incidence of severe nausea and vomiting was lower in the naloxone group than in the fentanyl group, and the difference was statistically significant \( P < 0.05 \). Moreover, the incidence of severe nausea and vomiting was lower in the tropisetron group than in the fentanyl group, and the difference was statistically significant \( P < 0.05 \). Details are shown in Table 3.

### 4. Discussion

At present, opioids such as morphine and fentanyl are the main analgesic drugs used in clinics.\(^{13-19}\) Fentanyl has a short time of taking effect, a short maintenance time, relatively few side effects, and a stronger analgesic effect. Its analgesic effect is 80 to 120 minutes after taking effect, a short maintenance time, relatively few side effects, and a stronger analgesic effect. Moreover, some scholars have once set the dose of tropisetron before the end of surgery, and the probability of occurrence was also the greatest. Therefore, if a certain amount of tropisetron was administered before the end of surgery, the occurrence of nausea and vomiting could be prevented to a considerable degree. For the loading of tropisetron, some scholars have once set the fluid infusion rate of the analgesia pump at 2 to 3 mL/hour,\(^{11}\) and good results were achieved.\(^{19}\) In order to form a contrast with the naloxone group and ensure that the lowest effective intravenous concentration of tropisetron was 100 µg/L, the postoperative infusion volume in this experiment was set at 0.1 mL/kg. In addition, the difference in the VAS scores of patients between the tropisetron and fentanyl groups was not statistically significant, which was also consistent with the study results of Derbent.\(^{20}\)

This experiment revealed that patients in the naloxone group had a reduced general incidence of nausea and vomiting, and the

### Table 1

| Groups | 2 h   | 6 h   | 12 h  | 24 h  | 48 h  |
|-------|------|------|------|------|------|
| N group | 2.5 ± 1.3 | 2.2 ± 1.0\( ^* \) | 2.0 ± 0.6 | 2.0 ± 0.6 | 0.9 ± 0.3 |
| T group | 2.7 ± 1.3 | 2.4 ± 1.1 | 2.2 ± 0.2 | 2.1 ± 0.8 | 1.4 ± 0.2 |
| C group | 2.5 ± 1.3 | 3.1 ± 1.3 | 2.2 ± 1.2 | 2.1 ± 0.8 | 1.3 ± 0.3 |

\( ^* P < 0.05 \).

### Table 2

| Groups | With nausea and vomiting (case) | Without nausea and vomiting (cases) | Total (cases) | Incidences of nausea and vomiting (%) |
|-------|---------------------------------|-------------------------------------|---------------|--------------------------------------|
| N group | 6                              | 24                                  | 30            | 20\( ^* \)                            |
| T group | 18                             | 12                                  | 30            | 60\( ^* \)                            |
| C group | 27                             | 3                                   | 30            | 90                                   |
| Total  | 51                             | 39                                  | 90            | 56.7                                  |

\( ^* P < 0.05 \).
differences were statistically significant compared with the tropisetron and fentanyl groups. Furthermore, this was consistent with results reported in literature.\cite{[14],[5]} In addition, a literature\cite{[21]} has revealed that small doses of naloxone can enhance the analgesic effect of the opioid receptor agonist. The results of this study suggests that the VAS scores of patients in each period were lower in naloxone group than in the other 2 groups, and at 6 hours after surgery, the difference in VAS scores between the fentanyl and naloxone groups was statistically significant. This suggests that naloxone enhanced the analgesic effect of fentanyl, and further illustrates that the analgesic effect of naloxone is dose-dependent. In addition, naloxone has a more satisfactory effect than tropisetron in reducing the total incidence of nausea and vomiting, and the difference was statistically significant. In the prevention of severe nausea and vomiting, naloxone did not exhibit any superiority; the difference was not statistically significant compared with tropisetron. Therefore, it could be concluded that the administration of naloxone did not give a satisfactory effect in dealing with patients with severe nausea and vomiting after surgery. The reason for this may be related to the dose of naloxone, which needs further studies.

As a result, small doses of naloxone can enhance the analgesic effect of the opioid receptor agonist. Since the dose of naloxone is small, it also has certain advantages in terms of drug costs. After laparoscopic cholecystectomy, the addition of small doses of naloxone and tropisetron into patient-controlled analgesia can obviously reduce the incidence of nausea and vomiting, and the effect of naloxone is better. Furthermore these can reduce gastrointestinal adverse reactions such as nausea and vomiting caused by opioids, and increase analgesic effect, which reduce the degree of pain after laparoscopic cholecystectomy. However, the analgesic effect of naloxone, and its effects on nausea and vomiting, when surgery is conducted in other parts of the body, needs to be investigated through further studies.

### References

1. Chinese Pharmacopoeia Commission. Clinical Application Guidelines of Drugs Guidelines. 2005; Beijing: People’s Medical Publishing House, 101-104,109.
2. Bilgin H, Basagan Mogol E, Bekar A, et al. A comparison of effects of alfentanil, fentanyl, and remifentanil on hemodynamic and respiratory parameters during stereotactic brain biopsy. J Neurosurg Anesthesiol 2006;18:
3. Fritz HG, Holzmayr M, Walter B, et al. The effect of mild hypothermia on plasma fentanyl concentration and biotransformation in juvenile pigs. Anesth Analg 2005;100:986–1002.
4. Rasbaum AL, Fields HL. Endogenous pain control mechanisms: review and hypothesis. Ann Neurol 1978;4:451–62.
5. Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment and prevention. Anesthesiology 1992;77:162–84.
6. Natalini CC. Plasma and cerebrospinal fluid alfentanil, butorphanol, and morphine concentrations following caudal epidural administration in horses. Ciência Rural 2006;36:
7. Bamigbude TA, Langford MR. The clinical use of tramadol-hydrochloride. Pain Rev 1998;5:154–5.
8. Shipton EA. Pruritus—a side-effect of epidural fentanyl for postoperative analgesia. S Afr Med J 1984;66:61–2.
9. Petrova GI, Getov IN. Calculating the cost for drug treatment including the adverse drug reactions treatment cost (primer for fentanyl TTS in Bulgaria). Bolletino Chimico Farmaceutico 2002;141:150–3.
10. Topacoglu H, Karcioglu O, Camtin AH, et al. Respiratory arrest after low-dose fentanyl. Ann Saudi Med 2005;25:508–10.
11. Mannino MJ. Setting up an office anesthesia practice. CRNA 1999; 10:54–8.
12. Haj-Mirzaian A, Kordjazy N, Amir A, et al. Involvement of nitric oxide-cyclic guanosine monophosphate pathway in the antidepressant-like effect of tropisetron and ondansetron in mice forced swimming test and tail suspension test. Eur J Pharmacol 2016;780:71–81.
13. Herrstedt J, Sigsgaard TC, Nielsen HA, et al. Randomized, double-blind trial comparing the antiemetic effect of tropisetron plus metopimazine with tropisetron plus placebo in patients receiving multiple cycles of multiple-day cisplatin-based chemotherapy. Support Care Cancer 2007;15:417–26.
14. Hodge CW, Niehus JS, Samson HH. Morphine induced changes in ethanol-and water-intake are attenuated by the 5-HT 3/4 antagonist tropisetron (ICS 205-930). Psychopharmacology 1995;119:186–92.
15. Hudson S. Reentry using naloxone: one anesthesia department’s experience. AANA J 1998;66:360–4.
16. White LA, Vanarase M, Brockbank K, et al. Patient-controlled analgesia and postoperative nausea and vomiting: efficacy of a continuous infusion of ondansetron. Anesthesia 2001;56:365–9.
17. Sommers DK, Szyman JR, van Wyk M. Effects of metoclopramide and tropisetron on aldosterone secretion possibly due to agonism and antagonism at the 5-HT4 receptor. Eur J Clin Pharmacol 1996;50:371–3.
18. Khalifeh S, Fakhfouri G, Mehr SE, et al. Beyond the 5-HT3 receptors: a role for 5nACh receptors in neuroprotective aspects of tropisetron. Human Exp Toxicol 2015;34:922–31.
19. Yokoyama T, Yamashita K, Manabe M, et al. Tracheobronchomalacia-like lung collapse during three separate trials of general anesthesia. Anesth Analg 2006;103:1039–40.
20. Derbent A. Can anesthetics really relieve pain? Adv Ther 2005;22: 307–12.
21. Kim ES, Lee J, Choi JH. Optimal dose range of epidural naloxone to reduce nausea in patients receiving epidural morphine. Can J Anaesth 2004;51:1048–9.

| Groups | With nausea and vomiting (case) | Without nausea and vomiting (cases) | Incidences of nausea and vomiting (%) |
|--------|---------------------------------|------------------------------------|--------------------------------------|
| N group | 2                               | 28                                 | 5°                                   |
| T group | 9                               | 21                                 | 30°                                  |
| C group | 18                              | 12                                 | 60                                   |
| Total   | 29                              | 61                                 | 32.2                                  |

*P < 0.05.