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

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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 analgesia 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.[1] As the most common acute pain in surgery,[2] postoperative pain has been thought to be one of the leading causes of anxiety and fear in patients;[3] and is a key issue for medical staff in the Department of Anesthesiology.[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.[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.[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.[7] Studies have revealed that the concurrent administration of small doses of this opioid receptor antagonist combined with opioids can reduce adverse reactions.[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-

Editor: Kazuo Hanaoka.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2016) 95:48(e5074)

Received: 11 July 2016 / Received in final form: 11 September 2016 / Accepted: 13 September 2016

http://dx.doi.org/10.1097/MD.0000000000005074

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 machine 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 l6.0. Measurement data was expressed as mean ± standard deviation ($x \pm SD$). 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

Table 1

VAS score comparisons among groups.

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

* $P < 0.05$.

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 clinic.[1–3] 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 times of that of morphine. This is the reason for the use of fentanyl in postoperative analgesia. One of the inducing factors of postoperative nausea and vomiting is the use of opioids in the process of anesthesia. Basbaum and Fields and Watcha and White[4–6] found that the main analgesic mechanism of fentanyl was that opioid receptors distributed in the central nervous system are blocked. Hence, pain signals could not be transmitted upwards. In addition to analgesia, fentanyl can also excite the medulla oblongata center, and increase the sensitivity of the vomiting center by stimulating the vestibular nerve system, causing nausea, vomiting, and other discomforts. Bamigbude and Langford considered that the disorder of gastric and duodenal motility caused by opioid receptor agonists was one of the main causes of nausea and vomiting.[7–10] Therefore, on the basis of not reducing the analgesic effect, the prophylactic use of antiemetic drugs or drugs that can reduce the adverse reactions of opioids can improve the postoperative satisfaction rate of analgesia in patients.

Anti-nausea drugs that are commonly used in clinic include 5-HT_3 receptor antagonist, dexamethasone and droperidol. Furthermore, Weren M has previously reported in recent years that a small amount of naloxone can also prevent nausea and vomiting. Related studies have revealed that there was a certain equivalence relation in the prevention of nausea and vomiting among 5-HT_3 receptor antagonists such as granisetron and tropisetron.[11–14] Therefore, there is scientific basis that in this experiment, 2 antiemetic drugs, tropisetron (a 5-HT_3 receptor antagonist) and naloxone, were used for clinical comparisons. Tropisetron is an antinausea drug commonly used in clinical practice, which plays an important role in the prevention and treatment of nausea and vomiting caused by patient-control analgesia.[15–18] Tropisetron mainly exerts on 5-HT_3 receptors in the central nervous system.

The incidences of nausea, vomiting, and very severe nausea and vomiting were compared between the tropisetron and fentanyl groups, and the differences were statistically significant. These experimental results confirm that the effect of tropisetron in the prevention of nausea and vomiting was satisfactory. Furthermore, some scholars have considered that nausea and vomiting were most serious at 6 hours after surgery, and the probability of the occurrence was also the greatest. Therefore, if a certain amount of tropisetron was administered before the end of the 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 2

Comparison of incidences of nausea and vomiting among the 3 groups.

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

* $P < 0.05$.

Table 3

Comparison of very severe (could not be tolerated by the patient) nausea and vomiting incidences among groups ($P < 0.05$).

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

* $P < 0.05$.

differences were statistically significant compared with the tropisetron and fentanyl groups. Furthermore, this was consistent with results reported in literature.[4,5] In addition, a literature[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.

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