Effect of oxycodone hydrochloride combined with flurbiprofen axetil for intravenous patient-controlled analgesia in lower abdominal patients

A randomized trial

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Abstract

Background: Problems like postoperative pain are still common phenomena after general anesthesia. Oxycodone hydrochloride is a semisynthetic opioid with a safe and excellent therapeutic effect on visceral pain. Flurbiprofen axetil has the efficacy of targeted analgesia. We hypothesize that different doses of oxycodone hydrochloride combined with flurbiprofen axetil would generate great results on postoperative intravenous analgesia in lower abdominal patients.

Methods: In the clinical trial, 90 American Society of Anesthesiologists I or II patients scheduled for elective general anesthesia were randomly divided into 3 groups, 30 cases in each group. Group I: oxycodone hydrochloride 0.5 mg/kg + flurbiprofen axetil 150 mg, group II: oxycodone hydrochloride 0.75 mg/kg + flurbiprofen axetil 150 mg, group III: oxycodone hydrochloride 1.0 mg/kg + flurbiprofen axetil 150 mg. Dilute them with 0.9% saline to 150 mL, respectively, with the background dose of 2 mL/h, patient-controlled analgesia 2 mL per time, with an interval of 10 min, and the loading dose of 0.1 mL/kg. Record the preoperative situation, 24 h (T_0) before surgery, postoperative situation, 1 h (T_1), 4 h (T_2), 8 h (T_3), 12 h (T_4), 24 h (T_5), 48 h (T_6), 72 h (T_7) after the surgery, including the mean arterial pressure, heart rate, saturation of pulse oximetry, static and dynamic pain rating (NRS) and Ramsay sedation score, effective pressing and total pressing ratio (referred to as the pressing ratio), patient satisfaction, and occurrence of adverse reactions.

Results: There was no significant statistic difference in mean arterial blood pressure, heart rate, arterial oxygen saturation, and adverse reactions among the 2 groups at each time point ($P > .05$). Compared with group I, the static NRS rating in group II and group III were significantly lower than that in group I ($P < .05$) from T_1 to T_5. The dynamic NRS rating of group II from T_1 to T_4 and that of group III from T_1 to T_5 were significantly lower ($P < .05$). The effective pressing and total pressing ratio was significantly higher ($P < .05$). There was no significant statistic difference between group II and group III in NRS rating and the effective pressing and total pressing ratio ($P > .05$). Compared with group III, the Ramsay sedation scores of group I and group II were significantly lower from T_1 to T_4 ($P < .05$).

Conclusion: The dose of 0.75 mg/kg oxycodone hydrochloride combined with flurbiprofen axetil can provide safe and effective postoperative analgesia for lower abdominal patients, with fewer adverse reactions.

Abbreviations: ASA = American Society of Anesthesiologists, BMI = body mass index, MAP = mean arterial pressure, NRS = numerical rating scale, SpO_2 = peripheral oxygen saturation, TOF = train of 4 stimulation.

Keywords: analgesia, flurbiprofen, oxycodone, patient-controlled

1. Introduction

Postoperative analgesia and clinical anesthesia are an integral whole. Postoperative analgesia is an important step in improving the quality of patients' life during perioperative period. Proper handling of postoperative pain can reduce the incidence of complications. Oxycodone is currently the only double receptor agonists of pure opioid μ and κ, featuring rapid onset, strong analgesic effect, and small effect on hemodynamics. It is suitable for patient-controlled intravenous analgesia, especially effective on visceral pain and neuropathic pain,[1] but over dosage can lead to drowsiness, nausea, vomiting, and other adverse reactions. Flurbiprofen axetil is a nonsteroidal antiinflammatory drug with lipid microspheres as a carrier, with targeted analgesic effect.[2] Oxycodone hydrochloride combined with flurbiprofen axetil is safe and effective for postoperative multimodal analgesia.[3] This study was to observe the efficacy and safety of different doses of oxycodone hydrochloride combined with flurbiprofen axetil in postoperative abdominal surgeries, providing references for further clinical application.

2. Subjects and methods

2.1. Subjects

This study was approved by the Human Research Ethics Board of Zhejiang Cancer Hospital, Hangzhou, with the patients or family members' signing of the written consent form prior to participation.

The inclusion criteria were American Society of Anesthesiologists physical status I and II patients, aged between 18 and 64 years old, weighing from 50 to 75 kg, scheduled for lower abdomen general anesthesia surgeries. Exclusion criteria included patients who had hepatitis and renal failure, existence of severe blood system dysfunction, chronic respiratory disease or psychiatric history, and long-term use of opioids or nonsteroidal antiinflammatory analgesics. Patients who were allergic to oxycodone hydrochloride, or flurbiprofen axetil or other drugs were also excluded from this study. This study included surgeries of colorectal cancer, cervical cancer, ovarian cancer, and prostate cancer.

Using random number table method, subjects were divided into 3 groups, 30 cases in each group. Group I: oxycodone hydrochloride 0.5 mg/kg + flurbiprofen axetil 150 mg; group II: oxycodone hydrochloride 0.75 mg/kg + flurbiprofen axetil 150 mg; and group III: oxycodone hydrochloride 1.0 mg/kg + flurbiprofen axetil 150 mg. Dilute them with 0.9% saline to 150 mL, respectively, with the background dose of 2 mL/h, patient-controlled analgesia 2 mL per time, with an interval of 10 min, and the loading dose of 0.1 mL/kg.

2.2. Methods

On the first day of this study, demographic and medical data, including the patients' age, body mass index (BMI), and history of diseases were collected. The subjects were not given any sedative, analgesic, or antiemetic drugs 24 h before the operation. Solids and liquids were fasted in patients 8 h before the operation.

On the second day, all selected patients were under monitoring of arterial blood pressure (by way of invasive automated sphygmomanometer), heart rate (by way of electrocardiography), and arterial oxygen saturation (by way of pulse oximetry) before anesthesia induction and after the operation, as well as the recovery period, recording operation types and time. Infusion of compound sodium lactate 300 to 500 mL was applied, through internal jugular vein. Intravenous injection of midazolam 0.05 mg/kg, sufentanil 4 μg/kg, propofol 1.0 to 2.0 mg/kg, and rocuronium 0.6 mg/kg administered through the induction of anesthesia in the operation room. Tracheal intubation or laryngeal mask placement was administered 3 min later, and then mechanical ventilation was administered, tidal volume 8 mL/kg, respiration rate 12 beats/min. During the operation, remifentanil 0.15 to 0.30 μg/kg per min and propofol 4 to 8 mg/kg per h were delivered to maintain the depth of anesthesia, with discontinuous injection of cisatracurium to keep muscle-relaxing. The doses of drugs were adjusted according to different intraoperative blood pressure (basical value ±20%): rapid rehydration or intravenous injection of ephedrine 6 to 10 mg/time was administered if mean arterial pressure (MAP) was lower than 60 mm Hg; atropine 0.3 to 0.5 mg was administered if heart rate was fewer than 50 times/min; 30 min before the end of surgery, cisatracurium was discontinued and azasetron 10 mg was injected intravenously. Upon closing up the peritoneal cavity, patient-controlled intravenous analgesic pump was started and the loading dose of 0.1 mL/kg was given. The propofol and remifentanil was stopped after the surgery. The TOF value (train of 4 stimulation) was observed with a nerve monitor during the whole operation. When the patient regained consciousness and spontaneous breathing, and TOF value reached 90%, muscle-relaxing antagonist was injected, then the tracheal tube was pulled out. The patient was transferred into the anesthesia recovery room after observation for 3 to 5 min in the operation room.

Comparisons of the following aspects among the 3 groups were recorded, at the time of 24 h before surgery, 1, 4, 8, 12, 24, 48 and 72 h after surgery: the mean arterial blood pressure, heart rate, arterial oxygen saturation, static numerical rating scale (NRS) scores (the degree of pain when lying still) and dynamic NRS scores (the degree of pain when coughing, turning over and moving the body) (0: pain free; 1–3: mild pain, does not affect sleep; 4–6: moderate pain; 7–9: severe pain, cannot sleep or wake up from pain; and 10: sharp pain), Ramsay sedation scores (1: anxious, restless, irritable; 2: cooperative, oriented, tranquil; 3: only responsive to instructions; 4: asleep, with a brisk response to stimulus; 5: asleep, with a sluggish response to stimulus; and 6: asleep, with no response), the pressing ratio (the ratio of effective pressing times, which can reduce the pain, to the total pressing times, which is the sum of effective pressing times and noneffective pressing times), patient satisfaction, and occurrence of adverse reactions.

Adverse reactions include somnolence (defined as not easily wake up), respiratory depression (defined as respiratory rate <8 breaths/min), nausea, and vomiting. A score from 0 to 10 was given for the level of nausea and vomiting. If the patient had no nausea or vomiting, a score of 0 was given; and if the patient had severe nausea and vomiting, a score of 10 was given.

2.3. Statistical analysis

Statistical analysis SPSS 17.0 was adopted. A sample size of 30 in each group was determined to be required for a power of 0.80 and an a-value of 0.05. The measurement data were expressed as mean ± standard deviation ($\overline{x} \pm s$), using single factor analysis of variance. The t test was adopted among group comparisons, and categorical data were assessed with the chi-squared test. If P value was <.05, the difference was considered statistically significant.

Table 1

General data comparison among 3 groups.

Observation indexes	Group I	Group II	Group III
Age, y	48.7±4.9	49.6±5.3	46.8±4.2
BMI	19.9±1.8	20.3±2.0	19.2±1.6
Operation types (cases)	Colorectal Cancer (10) Cervical cancer (9) Ovarian cancer (5) Prostate cancer (6)	Colorectal Cancer (12) Cervical cancer (10) Ovarian cancer (3) Prostate cancer (5)	Colorectal cancer (9) Cervical cancer (11) Ovarian cancer (6) Prostate cancer (4)
Operation mean time, h	2.7±0.4	2.6±0.5	2.9±0.4

The data expressed as mean±standard deviation.
BMI=body mass index.

3. Results

The data of the enrolled subjects are shown in Tables 1 and 2. A total of 90 patients were enrolled between March 1, 2016 and December 31, 2016, and the study was finally finished with their data being analyzed for the final results (n=30 per group). There were no significant statistical differences in age, BMI, operation types and time, MAP, heart rate, and arterial oxygen saturation among the 3 groups at each time point ($P > .05$) (see Tables 1 and 2).

No additional postoperative analgesic drugs were used except for drugs in the analgesic pump. Compared with group I, the static NRS scores of group II and group III were significantly decreased from T_1 to T_5 ($P < .05$); and the dynamic NRS score of group II from T_1 to T_4 and that of group III from T_1 to T_5 were significantly lower ($P < .05$). Compared with group III, the Ramsay sedation scores of group I and group II from T_1 to T_4 were significantly lower ($P < .05$) (see Table 3).

Compared with group I, the pressing ratio of group II and group III were significantly higher, and patient satisfaction was significantly increased ($P < .05$) (see Table 4).

With the increasing doses of oxycodone, the incidence of somnolence in group III increased, but the difference was not statistically significant, and there was no respiratory depression in all 3 groups (see Table 5).

Table 2

Comparison of MAP, HR, and SpO$_2$ among 3 groups at each time point ($\overline{x} \pm s$).

Index	Group	T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_7
					After using PCA pump, h				
MAP, mm Hg	Group I	82±7	80±9	79±7	80±9	78±10	79±9	81±8	78±8
	Group II	82±8	81±8	78±9	79±10	80±9	83±8	81±10	79±9
	Group III	82±7	79±9	80±8	78±9	79±8	80±9	78±9	77±8
HR, times/min	Group I	76±12	74±11	73±10	72±9	73±9	71±10	73±10	70±9
	Group II	74±11	73±9	69±10	70±9	68±8	71±7	73±9	71±10
	Group III	75±11	72±10	70±9	69±8	69±9	71±8	72±8	69±8
SpO$_2$, %	Group I	99.2±0.7	99.3±0.6	99.1±0.6	99.3±0.5	99.5±0.6	99.4±0.7	99.4±0.8	99.3±0.7
	Group II	99.3±0.6	99.2±0.6	99.3±0.5	99.4±0.6	99.3±0.5	99.4±0.6	99.5±0.6	99.4±0.7
	Group III	99.3±0.7	99.2±0.5	99.4±0.7	99.3±0.5	99.4±0.7	99.5±0.6	99.3±0.7	99.4±0.6

The data expressed as mean±standard deviation.
HR=heart rate, MAP=mean arterial pressure, PCA=patient-controlled analgesia, SpO$_2$=peripheral oxygen saturation, T_0=before surgery, (postoperative), T_1 = 1 h, T_2 = 4 h, T_3 = 8 h, T_4 = 12 h, T_5 = 24 h, T_6 = 48 h, T_7 = 72 h.

Table 3

Comparisons of NRS and Ramsay sedation scores among 3 groups (points, $\overline{x} \pm s$).

Index	Group	T_1	T_2	T_3	T_4	T_5	T_6	T_7
NRS (static)	Group I	3.9±0.8	3.9±0.7	3.8±0.9	3.7±0.7	3.5±0.7	2.6±0.5	2.5±0.5
	Group II	2.4±0.6*	2.3±0.6*	2.2±0.5*	2.1±0.5*	2.1±0.5*	2.3±0.6	2.2±0.7
	Group III	2.3±0.7*	2.3±0.6*	2.1±0.6*	2.0±0.6*	2.2±0.5*	2.2±0.6	2.3±0.5
NRS (dynamic)	Group I	5.0±0.9	4.9±1.0	4.8±0.8	4.5±0.7	3.8±0.7	3.7±0.8	3.6±0.9
	Group II	3.4±0.9*	3.3±0.9*	3.4±1.0*	3.3±1.0*	3.5±0.8	3.5±0.9	3.3±1.0
	Group III	3.3±1.0*	3.2±0.9*	3.4±1.0*	3.4±0.9*	3.3±0.9*	3.3±0.8	3.2±0.9
Ramsay sedation scores	Group I	1.6±0.7†	1.7±0.7†	1.5±0.8†	1.6±0.7†	1.7±0.5	1.9±0.7	1.6±0.6
	Group II	1.7±0.6†	1.8±0.6†	1.6±0.7†	1.6±0.8†	1.8±0.6	1.9±0.6	1.5±0.5
	Group III	3.0±0.9	3.1±0.7	3.1±0.8	3.0±0.9	2.2±0.7	2.0±0.8	1.7±0.6

The data expressed as mean±standard deviation.
NRS = numerical rating scale.
T_0=before surgery, (postoperative) T_1 = 1 h, T_2 = 4 h, T_3 = 8 h, T_4 = 12 h, T_5 = 24 h, T_6 = 48 h, T_7 = 72 h.
* $P < .05$; compared with group I.
† $P < .05$; compared with group III.

Group	Pressing ratio	Satisfaction, cases (%)
Group I	0.48±0.16	18 (60.0)
Group II	0.78±0.11[*]	28 (93.3)[*]
Group III	0.83±0.10[*]	29 (96.7)[*]

The data expressed as mean ± standard deviation. The numbers in the brackets stand for percentage.
[*] $P < .05$; compared with group I.

4. Discussion

Abdominal surgeries are prone to causing acute pain in patients after operation, causing heart rate increase, rising of blood pressure, irritability, sweating and other complications, accompanied by nausea and vomiting, and respiratory activity changes in the patients. The reason lies in the body's complex psychological and physiological responses to the tissue damage and repair process. Preventions and treatments should be timely carried out in clinical work. Therefore, reasonable and effective postoperative analgesia can reduce breathing, circulation, and endocrine dysfunction caused by pain, and can significantly reduce the patient's mental trauma.

At present, the acute pain after abdominal surgeries is mainly manifested as mixed body aches and visceral pain. Opioids are currently commonly used drugs for acute pain after surgeries, among which oxycodone especially has a better effect of inhibiting visceral pain.[4] Compared with morphine, although oxycodone has lower intrinsic activity with respect to the μ-type receptor, it has a stronger analgesic effect.[5–8] This is due to the fact that the concentration of unbound oxycodone in the brain is 6 times higher compared with morphine, though concentrations in the blood of both opioid analgesics is comparable. Hence, the oxycodone has a higher safety and efficacy than other opioid analgesics, and minimal immunosuppressive activity.[9–11] But Amri and others' studies[12] found that oxycodone had caused dose-dependent respiratory depression. In order to achieve good analgesia effect while reducing adverse reactions, this study designed 3 different doses of oxycodone and observed the efficacy.

In this study, hemodynamics of the patients was relatively stable at each time point, indicating that oxycodone combined with flurbiprofen axetil had resulted in a good analgesic effect, which was related to the fact that oxycodone did not lead to histamine release, without inhibiting parasympathetic or leading to bradycardia.[13]

In this study, the NRS score was used to evaluate the analgesic effect of oxycodone. The study showed that 3 different doses of oxycodone had all relieved acute pain after surgeries to a certain degree. This is because oxycodone can achieve analgesic purposes via stimulation of the peripheral and central opioid receptors of the μ and κ types, it is reported that κ receptors play a crucial part in the analgesic mechanism of activity of oxycodone,[5] especially the κ2b receptor agonism.[14] The mechanisms of visceral pain

constitution involved opioid receptors of the κ type. Besides, by interacting with the G-protein, oxycodone promotes the potassium channels to open and hinders activation of voltage-dependent calcium channels. The described effects lead to the result of a decline of the excitability of nerve cells. Hence, it has a stronger analgesic effect on the visceral pain than other opioids.

Affected by different doses, the 3 groups exhibited different analgesic effects: compared with a dose of 0.5 mg/kg oxycodone, doses of 0.75 mg/kg and 1.0 mg/kg oxycodone significantly reduced the NRS scores, while the pressing ratios were significantly higher and patient satisfaction was improved, indicating that analgesic effect with a low dose of 0.5 mg/kg oxycodone was not ideal, which may be associated with hyperalgesia and central sensitization.[15]

In this study, the Ramsay score was used to evaluate the sedative effect of oxycodone. The study found that with the increase in the dose of oxycodone, the incidence of somnolence increased, most obviously in the 1 mg/kg group, which may be related to the larger dose of oxycodone achieving sedative effect through κ receptor agonism in the central nervous system.

No respiratory depression occurred in this experiment. This may be because oxycodone takes pharmacological effects mainly through the κ receptor, being less sensitive to the μ receptor agonism, thereby reducing respiratory depression while achieving the purpose of analgesia through the μ receptor agonism. Meanwhile, as the analgesic effect was good, the patient's respiration extent increased. In addition, opioid analgesics can lead to nausea, vomiting, and other adverse reactions, but this study showed that oxycodone did not increase the incidence of nausea or vomiting. Because a combination usage with NSAIDS drugs can reduce the amount of opioids and may mitigate the reaction of nausea and vomiting caused by μ-receptor agonism.[16]

In the treatment of the pain, oxycodone is featured with the most ideal pharmacokinetic characteristic and a high safety characteristic in patients simultaneously treated with other drugs. The interactions, which is caused by inhibition of CYP3A4 and CYP2D6 activity by other drugs, have practically no clinical implication.[17]

In summary, a dose of 0.75 mg/kg oxycodone hydrochloride combined with flurbiprofen axetil can provide safe and effective postoperative analgesia for lower abdominal patients, with fewer adverse reactions.

The results of this clinical trial are open to further discussion and more precise analysis in the future due to the study limitation of a moderate number of enrolled patients.

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Group	Cases	Somnolence	Respiratory depression	Nausea	Vomiting
Group I	30	1	0	1	0
Group II	30	2	0	1	0
Group III	30	4	0	2	0

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