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Original Article

Influence of butorphanol on the postoperative remifentanil hyperalgesia

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Abstract: Objective: To evaluate the influence of butorphanol on the postoperative remifentanil hyperalgesia. Methods: A total of 120 cases of patients undergoing laparoscopic resection of uterine fibroids were involved into the research work, which were divided into two groups: study group (n=60) and control group (n=60). About 10 min before the ending of the operation, 20 μg/kg butorphanol in tartaric acid injection were given to the patients in study group, while the equivalent normal saline was given to those in control group. The analgesic and sedative effects within 30 min, 1 h, and 4 h after analepsia were evaluated by visual analogue scale (VAS) and Ramsay sedation score, respectively. The remifentanil and propofol dosages during the operation and the tramadol dosages within 4 h after analepsia between the two groups were compared. The differences of operation duration, recovery time, extubation time, as well as adverse reactions within 4 h after analepsia were compared. Results: According to the intention to treat (ITT) principle; the final cases of study group and control group for evaluation were 58 and 59, respectively. Differences of the remifentanil and propofol dosages during the operation between the two groups were no statistical significance (P>0.05), while the tramadol dosages within 4 h after analepsia had statistically significant difference (P<0.05). The differences of operation duration, recovery time, and extubation time between two groups were not statistically significant (*P*>0.05). The VAS scores of study group within 30 min, 1 h, and 4 h after analepsia were all lower than those of control group, and the differences were statistically significant (P<0.05). There was no statistically significant difference between the Ramsay scores from two groups within 30 min, 1 h, and 4 h after analepsia (P>0.05). The incidences of nausea and vomiting, shivering, somnolence and dizziness within 4 h after analepsia between two groups were statistically significant (P<0.05). Conclusions: Butorphanol could safely and effectively prevent the postoperative remifentanil hyperalgesia.

Keywords: Butorphanol, remifentanil, hyperalgesia, analgesia

Introduction

Remifentanil is an ultra short acting μ opioid receptor agonist, which has been widely applied in clinical anesthesia due to its characterization of quickly operation, quickly metabolism, no enrichment in vivo, and without influence on the postoperative recovery. However, in recent years, many research works [1, 2] show that after large doses or long-term use of remifentanil, the postoperative pain would be earlier occurred and aggravated in case of drug withdrawal. The dosage increasing of opioid drugs may prone to opioid tolerance and hypersensitivity, i.e. opioids induced hyperalgesia (OIH) [3]. OIH may cause great clinical harm, such as mania and arrhythmia, requiring other analgesic drugs in advance. Butorphanol is a morphinan-type synthetic opioid analgesic developed by Bristol-Myers, which has been shown effectively inhibition effect on the remifentanil OIH according to the current research works [4, 5]. Butorphanol exhibits partial agonist and antagonist activity at the μ opioid receptor, as well as competitive antagonist activity and partial agonist activity at the κ opioid receptor. Stimulation of these receptors on central nervous system neurons causes an intracellular inhibition of adenylate cyclase, closing of influx membrane calcium channels, and opening of membrane potassium channels. This leads to hyperpolarization of the cell membrane potential and suppression of action potential transmission of ascending pain pathways. Because of its

κ-agonist activity, at analgesic doses butorphanol increases pulmonary arterial pressure and cardiac work. Up to now, there is rare contribution devote to the prevention effect of butorphanol on OIH. In this paper, the preventive effect of butorphanol before surgery on the remifentanil OIH was evaluated.

Materials and methods

General data

The study was approved by the ethics committee of our hospital, and all patients were approved and signed the informed consent. This work was designed as prospective, randomized, open, controlled study. By using the table of random number generated by computer, the patients were assigned to the two groups with the ratio of 1:1: butorphanol group (Study Group) and blank group (control group). All patients had no severe liver and kidney dysfunction, no history of drug allergy, and no neurological diseases. A total of 120 cases of patients undergoing laparoscopic resection of uterine fibroids from Jan. 2013 to Aug. 2014 were involved into the research work.

Treatment methods

The patients were intramuscular injected by 0.5 mg atropine and 100 mg phenobarbital 30 min before surgery. After entering the operating room, vein channel were established, routine monitoring of electrocardiogram (ECG), blood pressure (BP), heart rate (HR), oxygen saturation of blood (SpO_2) and partial pressure of carbon dioxide in end expiratory gas ($P_{ET}CO_2$). A total of 0.05 mg/k midazolam, 1.5 mg/kg propofol, 4 μg/kg fentanyl, and 0.5 mg/kg vecuronium bromide were applied for Induction of anesthesia. After the action of the muscle relaxants, the mechanical ventilation was performed, maintaining the $P_{ET}CO_2$ at 30~40 mmHg (1 mmHg=0.133 kPa). For the maintenance of anesthesia, 0.15 μg/(kg·min) remifentanil and 4~6 mg/(kg·h) propofol were given to patients with intermittent injection of vecuronium bromide. During the surgical operation, muscle relaxants were given if HR<55/min for 1 min. The depth of anesthesia was maintained in BIS 40~60 by adjusting the anesthetic drugs. About 10 min before the ending of the operation muscle relaxants was stopped. A total of 20 μg/kg butorphanol in tartaric acid injection (trade name Noyon; Jiangsu Hengrui Medicine Co., Ltd.; specifications 1 ml:1 mg; Chinese medicine quasi word H20020454) were given to the patients in study group, while the normal saline was given to those in control group with equivalent dosage and similar usage of study group. The propofol was stopped when suture of skin and remifentanil was stopped after surgery. When the patients recovered spontaneous breathing, they were waked to open the eyes. When HR>12/min and tidal volume >6 ml/kg, the patients were extubated and sent to anesthesia recovery room. No other analgesic drug was given to patients. When the VAS score for moderate of severe, additional intravenous tramadol with 50 mg each time was given, maximum daily dose lower than 400 mg.

Evaluation methods

Postoperative pain: The postoperative pain was evaluated by using visual analogue scale (VAS) with the range of 0~10: 0 for painless, 10 for intolerable pain, 0~3 for slight pain, 4~6 for tolerable moderate pain influencing sleep, and 7~10 for intolerable severe pain. The evaluation times were 30 min, 1 h, and 4 h after analepsia.

Ramsay sedation score: The sedative results within 30 min, 1 h, and 4 h after analepsia were evaluated by Ramsay score with range of 1~6, 1 for poor sedation effect, 2~4 for satisfied sedation effect, 5~6 for over sedation.

Drug dosage: The remifentanil and propofol dosages during the operation and the tramadol dosages within 4 h after analepsia between the two groups were compared.

Postoperative recovery status: The differences of operation duration, recovery time, and extubation time between two groups were compared.

The occurrence of adverse reactions: The occurrences of adverse reactions within 4 h after analepsia between the two groups were compared. According to the relationship with the drugs, the symptoms divided into 5 levels absolutely related, related, probably related, unrelated, and absolutely unrelated. The first three were considered as adverse reactions. The evaluation included respiratory depression, dizziness, nausea and vomiting, hypotension, shivering, somnolence, etc.

Table 1. Comparison of the general data between two groups

Group	Cases	Age (Year)	Myoma diameter (cm)	ASA classification (I/II)	Weight (kg)	Height (cm)
Study group	58	40.1±4.2*	3.6±0.6*	24/34*	62.2±6.4*	163.4±5.3*
Control group	59	39.6±4.6	3.5±0.6	27/32	61.7±6.3	163.6±4.8

Note: *P>0.05, compared with the control group.

Table 2. Comparison of anesthesia and analgesic drugs dosages between two groups (x±s)

Group	Cases	Remifentanil (μg)	Propofol (mg)	Tramadol (mg)
Study group	58	1078.5±126.3*	513.2±62.3*	7.8±2.1#
Control group	59	1104.1±133.8	532.1±65.2	27.1±6.8

Note: *P>0.05, #P<0.05, compared with the control group.

Table 3. Comparison of postoperative recovery between two groups (x±s)

Group	Cases	Operation duration (min)	Recovery time (min)	Extubation time (min)
Study group	58	115.6±13.8*	10.2±1.8*	14.8±2.0*
Control group	59	119.3±12.7	9.9±1.9	14.6±1.9

Note: *P>0.05, compared with the control group.

Table 4. Comparison of VAS scores within 30 min, 1 h, and 4 h after analepsia between two groups (x±s)

Group	Cases	30 min	1 h	4 h
Study group	58	2.5±0.6#	1.8±0.5#	0.9±0.3#
Control group	59	4.2±0.8	3.8±0.7	2.2±0.5

Note: #P<0.05, compared with the control group.

Table 5. Comparison of Ramsay scores within 30 min, 1 h, and 4 h after analepsia between two groups (x±s)

Group	Cases	30 min	1 h	4 h
Study group	58	2.7±0.5*	2.4±0.4*	2.1±0.4*
Control group	59	2.8±0.6	2.5±0.5	2.2±0.4

Note: *P>0.05, compared with the control group.

Statistical method

The results were statistical analyzed by using software SPSS 17.0 package. The VAS scores, Ramsay scores, drug dosages and postoperative recovery status were presented as mean ± standard deviation (x±s) and compared by using t test. The side effect rates were categorical data are presented as percentage and compared by chi-square test. A p value less than 0.05 was considered statistically significant.

Results

Comparison of the general data between two groups

There were two cases from the study group (one case referral and one case abdominal open operation because of refusing laparoscopic operation) and one case (referral) from the control group were withdrawn from the study before the surgery, and the final cases of study group and control group for evaluation were 58 and 59, respectively. The data were analyzed by using intention to treat (ITT) principle, shown in **Table 1**. As there was no statistically significant in general data between two groups (P>0.05), the evaluation results were comparable.

Comparison of anesthesia and analgesic drugs dosages between two groups

Differences of the remifentanil and propofol dosages during the operation between the two groups were no statistical significance (P>0.05), while the tramadol dosages within 4 h after analepsia had statistically significant difference (P<0.05). In the study group, a total of 8 cases were given tramadol, 50 mg for 7 cases and 100 mg for 1 case. For the control group, 24 cases were given tramadol, 50 mg for 19 cases, 100 mg for 3 cases and 150 mg for 1 case. The results were shown in **Table 2**.

Comparison of postoperative recovery status between two groups

The differences of operation duration, recovery time, and extubation time between two groups were not statistically significant (P>0.05), as shown in **Table 3**.

Comparison of VAS scores between two groups

It can be seen in **Table 4** that the VAS scores of study group within 30 min, 1 h, and 4 h after

Table 6. Comparison of adverse reactions between the two groups [cases (%)]

Group	Cases	Nausea and vomitting	shivering	somnolence	dizziness	hypotension
Study group	58	6 (10.3)#	3 (5.2)#	11 (19.0)#	15 (25.9)#	6 (10.3)*
Control group	59	22 (37.3)	10 (16.9)	18 (30.5)	24 (40.7)	2 (3.4)

Note: *P>0.05, #P<0.05, compared with the control group.

analepsia were all lower than those of control group, and the differences were statistically significant (P<0.05).

Comparison of Ramsay scores between two groups

There was no statistically significant difference between the Ramsay scores from two groups within 30 min, 1 h, and 4 h after analepsia (P>0.05), as shown in **Table 5**.

Comparison of adverse reactions between the two groups

The incidences of nausea and vomiting, shivering, somnolence and dizziness within 4 h after analepsia between two groups were statistically significant (P<0.05), while the difference of hypotension were no statistically significant (P>0.05), as shown in **Table 6**.

Discussions

As the females were more sensitive to pain than males [6, 7], the female patients after uterine leiomyoma removal were selected as research objects. At present, there are various controlling drugs for the comparison to butorphanol on the OIH treatment, leading to the diverse results. In order to more directly investigate the results, the blank saline was applied for the control group to butorphanol in this work. With the VAS score of moderate or severe, the tramadol was added for analgesia, meeting the requirements of medical ethics. The previous clinical study [8] has shown that 20 μg/kg of butorphanol was sufficient for effectively prevention the postoperative OIH. Combined with clinical experience and the Drug Manual, the dosage of butorphanol in this study was set as 20 μg/kg. Since all cases were in disposable drug delivery without analgesia pump, the tramadol was given in cases of moderate or severe pain. Therefore, the dosage of tramadol was involved in the evaluation index. The ITT analysis was applied in this paper for the scientific data processing.

Comparing with the control group, the study group has lower VAS scores within 30 min, 1 h, and 4 h after analepsia, indicating good preventive effect on the remifentanil OIH. At each time point, the difference of Ramsay score between the two groups was not significant, ranging in 2~3, which showed that the satisfactory and similar calm effects could be obtained. There was no significant difference between the two groups in the dosages of propofol and remifentanil, which indicates that the effect of anesthesia and the influence on the OIH were not statistically significant. The tramadol dosages in study group were significantly more than those in the control group, indicating that more cases and enhanced intensity of analgesia were required in the control group, which certified the preventive effect of butorphanol on the OIH.

For the adverse reactions, within 4 h after analepsia, the incidence rates of nausea, vomiting, shivering, somnolence and dizziness in the study group were all lower than those in control group with significant difference, which mainly attribute to the larger amount of additional tramadol in the control group, indicating the less adverse reactions of butorphanol than tramadol. It could be noticed that the tramadol was applied in only 8 cases of study group, while somnolence in 11 cases and vertigo in 15 cases, suggested that these two adverse reactions occurred without tramadol. Hence, butorphanol may also lead to the somnolence and vertigo, which should be seriously handled during the treatment.

In summary, Butorphanol could safely and effectively prevent the postoperative remifentanil hyperalgesia.

Disclosure of conflict of interest

None.

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