Flurbiprofen axetil: Analgesic effect and adverse reaction

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Abstract: Flurbiprofen axetil is a targeted analgesic and non steroidal analgesic with lipid microspheres as drug carrier. It can selectively accumulate in surgical incision and reduce the allodynia a caused by surgical trauma. In this paper, the experimental subjects were divided into three groups to analyze the difference in the analgesic effect of different doses of flurbiprofen axetil for postoperative analgesia. The patients in group A, B and C were treated with flurbiprofen axetil injection 100, 150, 200mg, respectively. The results showed that MAP, HR, static and dynamic VAS scores and postoperative pain incidence in group B and group C were lower than those in group A, and B group had better analgesic effect and lower incidence of adverse reactions. In the future, we should continue to explore the correlation between the effect of flurbiprofen axetil for postoperative analgesia on coagulation function and the range of dose safety.

Keywords: Flurbiprofen axetil, laparoscopic cholecystectomy, drug reaction, VAS score.

INTRODUCTION

Flurbiprofen axetil is a new nonsteroidal anti infection analgesic. It has significant analgesic effect on various kinds of pain (Balmadrid *et al.,* 2015; Gao, 2015). Laparoscopic cholecystectomy (LC) is a common minimally invasive surgery currently (Liu *et al.,* 2016). As part of the postoperative pain in patients with manifestation of the diversity and complexity of (mainly visceral pain, abdominal pain and right shoulder pain), so for more analgesia after LC surgery, the preemptive analgesia or compound opioid analgesics combined with analgesic and more, Flurbiprofen axetil combined with non opioid analgesics less(Bhatt *et al.,* 2015). Therefore, this study compared the different doses of Flurbiprofen axetil combined with tramadol and ondansetron LC for postoperative patient-controlled intravenous analgesia (PCIA) effect (Dindo *et al.,* 2004). Preemptive pain refers to the analgesic method of preventing the impulsive impulse from peripheral injury to the center before injurious stimulation to the body (Emir *et al.,* 2014). Preemptive analgesia and reduction of harmful stimuli during operation can prevent nerve center sensitization, minimize and eliminate pain caused by injury, so as to reduce postoperative pain and reduce the dosage of analgesic.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase, reduce the production of peripheral and central prostaglandins, and weaken the central sensitization caused by harmful stimuli, resulting in analgesic effect (Gunaldi *et al.,* 2015). These properties make the non - Street - body anti - inflammatory drugs an ideal drug for the prior form of drug delivery (Hu, 2013; Rivosecchi *et al.,* 2014). It has been proved that the preemptive analgesic model of non - Street - body anti - inflammatory drugs has a certain analgesic effect in clinical practice (Salengros *et al.,* 2010; Koh *et al.,* 2013). Flurbiprofen is a nonselective, non-Phantom anti-inflammatory drug widely used in the clinic, which has anti- inflammatory and analgesic effects (Bergström *et al.,* 1967; Kertmen *et al.,* 2015). Flurbiprofen axetil injection is composed of lipid microspheres and its wrapped flurbiprofen axetil. Because of the presence of lipid microspheres, flurbiprofen axetil has the following characteristics, which can specifically aggregate at surgical wound sites, thereby enhancing the controlled release of effective drug components (Ai, 2015; Kim *et al.,* 2015), prolonging the time of drug action, accelerating the transmembrane absorption of drugs, and shortening the onset time.

MATERIALS AND METHODS

Research object

A total of 150 patients with LC in our hospital in 2016 were selected and divided into A, B and C groups according to the random number table method, each with 50 cases. The general data of the 3 groups were compared. The difference was not statistically significant (P>0.05), and was comparable in comparison with table 1. The project has been approved by the medical ethics committee of the hospital. The informed consent of the patients and their families was signed.

Inclusion and exclusion criteria

Inclusion criteria: (1) American Society of Anesthesiologists (ASA) grade I to II; (2) Age 18~65 years old. Exclusion criteria: (1) Non steroidal anti-inflammatory drugs (NSAIDs) or other analgesic drugs were received within 24 h before operation; (2) People allergic to NSAIDs or tramadol; (3) The use of NSAIDs

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in patients with complications such as gastrointestinal ulcer, coagulation dysfunction, heart failure and ischemic heart disease; (4) People who cannot understand the meaning of visual simulation (VAS).

Therapeutic method

3 groups of patients after upper limb vein infusion channel establishment, Compound Sodium Chloride Injection, continuous monitoring of blood pressure (BP), heart rate (HR), electrocardiogram (ECG), oxygen saturation (SpO2) and respiratory rate (RR), after endotracheal intubation of general anesthesia, double lung auscultation breath sounds symmetrical, fixed the endotracheal tube, with mechanical ventilation. Propofol was maintained at 2~3 mg/ (kg·h) and remifentanil 0.1 to 0.2ug/ (kg·min), and IVGTT maintained no more than 20% of HR and BP level. LC after the start of surgery for patients with intraperitoneal injection of CO_2 gas 12~15 mm Hg, adjust the patient position was head down tilt high 20 degrees to 30 degrees, postoperative immediately after PCIA.A, B, C group were treated with flurbiprofen axetil 100, 150, 200 mg injection, composite Tramadol hydrochloride injection 0.6g and ondansetron hydrochloride injection 4 mg, sodium chloride injection added 0.9% diluted to 100 ml, 2 ml/h, ivgtt, The lock time is 20 min.

Observation index

Observe 3 groups of patients after operation and postoperative 4, 12, 24 h after the mean arterial pressure (MAP), HR, VAS score, and recorded in 24 h after operation incision, neck, hypochondriac pain rate and respiratory depression, nausea and vomiting, urinary retention, drowsiness, dizziness and other adverse reactions. The evaluation criterion of VAS, 0 was painless, 10 points for the severe pain, less than 3 into effective analgesia.

STATISTICAL ANALYSIS

SPSS 17 software was used to analyze the data. The measurement data were expressed in X±s and t test was used. The count data were expressed in % and X^2 test was used. The difference of $P<0.05$ was statistically significant.

RESULTS

Comparison of the hemodynamic levels at each time point in the 3 groups

After the operation, there was no significant difference in the level of MAP and HR between the 3 groups ($P > 0.05$). At 4 h, 12 h and 24 h after operation, the levels of MAP and HR in B and C groups were significantly lower than those in the A group at the same time ($P<0.05$), but there was no significant difference in the above indexes between the B group and the C group ($P>0.05$). The hemodynamic levels of the 3 groups at each time point were compared to table 2.

Comparison of VAS score at each time point

At the end of the operation, there was no significant difference in the static and dynamic VAS scores between the 3 groups ($P>0.05$). At 4, 8, 24, and 36 h after operation, the static and dynamic VAS scores of the 3 groups increased significantly, and the A group was higher than that of B and C group. The difference was statistically significant ($P<0.05$), while there was no significant difference between the B group and C group in the above indicators. The VAS scores at each time point in the 3 groups were compared to table 3.

Comparison of the incidence of pain in various parts after operation

After operation, patients in group A incision, neck, hypochondriac pain incidence was significantly higher than that of B group and C group, the difference was statistically significant ($P<0.05$); while the B and C groups in different parts of the incidence of pain between the two groups, the difference was not statistically significant ($P>0.05$). The incidence of pain in each part of the 3 groups was compared to table 4.

Adverse reaction

There was no obvious adverse reaction in the 3 groups. Nausea and vomiting patients with ondansetron 4 mg or 10 mg dexamethasone Murphy's dropper infusion relief; patients with urinary retention by listening to the acoustic flow conditioned reflex micturition or encourage ambulation and promote urination; low flow oxygen inhalation and relieve sleepiness and dizziness patients. After operation, the incidence of adverse reactions in group A and B was significantly lower than that in group C, the difference was statistically significant ($P<0.05$), while the incidence of adverse reactions in group A and B was not statistically significant ($P>0.05$). The incidence of adverse reactions in the 3 groups was compared to table 5.

DISCUSSION

Flurbiprofen axetil is a lipid microspheres as drug carrier targeted analgesic and non steroidal analgesics, because its structure has the characteristics of targeting, controlled release, transport (Mellotte *et al.,* 2015). The drug can be selectively gathered in the incision, tumor and vascular injury, inhibition of cyclooxygenase by spinal cord and peripheral prostaglandin (COX) decreased the synthesis, reduce surgical trauma induced hyperalgesia state(Okada *et al.*,2011). It has no obvious effect on respiratory function after PCIA, and can prolong the time of analgesia, inhibit the stress reaction and reduce the inflammatory reaction (Pu, 2015; Qi *et al.,* 2015). It has no bacteria and fungi growth within 48 h at room temperature, and it is safe and effective (Ono *et al.,* 2009).

Table 1: General data comparison

Group	Gender		Age	Height, cm	Body mass index, kg/m2
	Male	Female			
A group	26	24	42.3±8.7	160.5±10.2	21.4±1.8
B group	27	23	42.8±7.9	158.6±11.5	22.0±2.0
C group	24	26	42.9±9.1	158.2±11.3	21.5±1.5

Table 2: Comparison of hemodynamic levels

Index	Group	Post operation	4 h	12 h	24 h
MAP, mm Hg	A group	129.2±13.5	126.1±15.2	123.5±12.6	118.3±11.0
	B group	127.6±12.6	121.3±11.8	119.6±8.2	115.3±5.6
	C group	122.5±13.8	120.1±8.9	115.4±6.4	107.2±5.2
HR, times/min	A group	92.4±11.5	89.7±10.3	85.2±9.6	84.3±8.4
	B group	91.6±10.3	75.6±8.4	73.6±7.9	70.5±8.6
	C group	89.2±11.2	76.3±10.3	65.3±8.4	64.2±7.9

Table 3: VAS score comparison

Group	Static VAS score				Dynamic VAS score			
	After operation	Postoperative 4 h	Postoperative 12h	Postoperative 24 h	After operation	Postoperative 4 h	Postoperative 12h	Postoperative 24 h
A group	1.1 ±0.2	2.6±1.5	3.7±1.4	3.8±1.2	1.4±0.3	2.5±0.8	3.2±1.1	3.6±1.3
B group	1.1±0.2	1.5±0.4	2.3±1.1	2.5±1.4	1.3±0.2	2.1±0.9	2.8±1.5	3.0±1.4
C group	1.0±0.3	1.4±0.3	1.9±0.8	2.2±1.2	1.2±0.2	2.3±1.1	2.8±1.2	3.2±1.3

Table 4: Comparison of the incidence of pain in various parts

Group	Incisional section	Neck and shoulder	Hypochondrium
A group	9(18%)	11(22%)	7(14%)
B group	5(10%)	7(22%)	3(6%)
C group	4(8%)	4(8%)	2(4%)

Table 5: Comparison of the incidence of adverse reactions

Group	Nausea and vomiting	Urinary retention	Dizzy	Other
A group	5(10%)	2(4%)	2(4%)	7(22%)
B group	1(2%)	3(6%)	1(2%)	6(12%)
C group	5(10%)	4(8%)	2(4%)	12(24%)

Tramadol inhibits neuronal synapse's reuptake of norepinephrine through the action of weak mu receptor and non opioid action, increases the concentration of 5-hydroxytryptamine outside the neuron and affects the pain transmission (Shi, 2010). The analgesic effect of this drug has been reported for a long time (Tsiaras *et al.*, 2016). It is also reported that the effect of tramadol on postoperative PCIA effect is related to the CYP2D6 polymorphism of the cytochrome P_{450} enzyme (CYP) allele. Tramadol was used for postoperative PCIA to produce a significant morphine effect, but this effect was not related to morphine adverse reactions (Mukai *et al.*, 2012). The results of this study showed that tramadol dose did not increase the adverse effects of morphine in the 3 groups. No respiratory depression occurred. It is consistent with Martinez V reports, indicating that the dose is safe.

This study shows that, after each time B, C group MAP, HR, static and dynamic VAS score and postoperative pain were lower than group A, but the B and C groups in the above indicators between the two groups, the difference was not statistically significant; incidence of adverse reactions of C group was higher than that of A in B group, while no significant difference between group A and B. May be related to the following reasons: (1) under anesthesia self regulating ability, at the same time by force of CO_2 pneumoperitoneum extrusion, pleural pressure and central venous pressure increased, the distraction caused by CO_2 hypoxemia pull diaphragmatic muscle fibers and residual phrenic nerve stimulation at the end of the thin branch is mainly caused by neck and shoulder pain, therefore, the size of CO_2 pneumoperitoneum pressure and residual CO_2 volume caused by the different degree of neck and shoulder pain

(Yoshio *et al.,* 2013); (2) CO_2 pneumoperitoneum intra abdominal pressure, diaphragmatic elevation, thoracic volume reduced, tidal volume reduction, in order to avoid hypoxemia, the use of traditional mechanical ventilation increase in tidal volume and respiratory frequency(Zhu *et al.*,2015), the airway pressure is further increased; (3) Different doses of flurbiprofen axetil.

CONCLUSION

In this study, there are still shortcomings in the determination of static and dynamic VAS scores. Although there is no significant difference in the general data of the 3 groups, but because of the patient's occupation, education level, economic status, compliance, mental capacity, pain and pain sensitivity and understanding of individual differences and different surgical operation of abdominal residual amount of CO_2 affects VAS score. All patients had no adverse reactions and abnormal bleeding after gastrointestinal analgesia. Similar to previous studies, we should continue to explore the correlation between flurbiprofen axetil for postoperative analgesia and the safety range of blood coagulation. For dizziness, except by special position operation reasons, the synergistic effect may be related to individual patients to flurbiprofen axetil, tramadol adverse reaction sensitivity and/or the two side effects of drugs; and two drugs used to be synergistic effect of side effects of dizziness and correlation of surgical position and the incidence of postoperative intravenous analgesia drug research.

In summary, the flurbiprofen axetil 150 mg compound tramadol 600 mg and ondansetron 4 mg to improve the hemodynamics of the patients after laparoscopic cholecystectomy and patient-controlled intravenous analgesia is better and the low incidence of adverse reactions.

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