Analgesic effect of different dosage of *Flurbiprofen axetil* in laparoscopic cholecystectomy in comparison with other analgesic drugs

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Abstract: Flurbiprofen axetil is a non-selective cyclooxygenase inhibitor. It can target the aggregation with lipid micro sphere as drug carrier, and exert analgesic effect in surgical incision and inflammatory site. In laparoscopic cholecystectomy comparative study on analgesic effect of parecoxib and flurbiprofen axetil is relatively less. Therefore, this paper is mainly based on the observation of patients after resting VAS score, adverse reaction time and movement, to evaluate the analgesic effect of different drug dose of flurbiprofen and parecoxib sodium, which provides reference for clinical medication. The results show that the intravenous injection of parecoxib could provide effective analgesic effect in laparoscopic cholecystectomy. Also, compared with flurbiprofen, parecoxib shows a more significant analgesic effect.

Keywords: Analgesic effect, Flurbiprofen axetil, Anti-inflammatory drugs, Laparoscopic cholecystectomy.

INTRODUCTION

Compared with open cholecystectomy, laparoscopic cholecystectomy (LC) has less trauma and quicker recovery (Fang *et al*. 2017). It has been widely carried out in clinics. Although its incision pain is less serious than laparotomy, but postoperative pain still exists, a considerable number of patients complained of both hypochondrium and shoulder pain, and sometimes pain are quite obvious, even more than the incision pain, known as the syndrome of pain after laparoscopic surgery (Li *et al*. 2015; Abu, 2017). Research shows that 73% to 80% of patients in the laparoscopic surgery still need to use analgesics to relieve pain, of which nearly 20% to opioids; and after laparoscopic surgery of shoulder pain caused by respiratory and pulmonary complications limit (Liu *et al*. 2017). Therefore, it is of important clinical significance to pay attention to relieve the pain after LC operation. Surgical trauma can stimulate the body stress response, causing tissue release various inflammatory mediators and cytokines (such as prostaglandins, interleukin, tumor necrosis factor), direct activation of nociceptors, increase their excitability, reduced pain threshold, the formation of peripheral sensitization. Peripheral sensitization further increases the excitability of neurons in the dorsal horn of the spinal cord, causing sensitization to the central nervous system. Peripheral and central sensitization is the major causes of pain persistence (Nayir *et al*. 2015).

Non-steroidal anti-inflammatory drugs (NSAIDs) through inhibition of cyclooxygenase (COX), blocking arachidonic acid (AA) into prostaglandins (prostaglandin, PG) play antipyretic, analgesic and anti-inflammatory effect (Ostojic *et al*. 2015). Its analgesic effect is widely used in the treatment of postoperative pain after. COX has two isoenzymes, COX-1 and COX-2. COX-1 is expressed mainly in normal tissues, and the catalytic generation of PGs plays an important role in protecting gastric mucosa, regulating renal function, maintaining vasodilatation and regulating platelet aggregation. COX-2 is mainly expressed in inflammatory cells and can be induced by a variety of factors (Paccez *et al*. 2014). The level of expression increases rapidly, which increases the synthesis of PGE in inflammatory sites and aggravates inflammatory reaction and tissue damage. Traditional NSAIDs inhibits COX-2 and inhibits COX-1, which leads to gastrointestinal ulcer, postoperative bleeding and other adverse reactions (Shi *et al*. 2015). Selective COX-2 inhibitors significantly reduce the most common gastrointestinal adverse effects of NSAIDs and have no effect on platelet aggregation without increasing the risk of perioperative bleeding. *Flurbiprofen axetil* is a non selective cyclooxygenase inhibitor. It can target the aggregation with lipid micro sphere as drug carrier, and exert analgesic effect in surgical incision and inflammatory site. In laparoscopic cholecystectomy, comparison of parecoxib and flurbiprofen axetil analgesia effect is relatively less reported (Sun *et al*. 2015). So that, we have conducted research on their comparative effects.

MATERIALS AND METHODS

General data

This project has appeared from Chongqing Medical University ethics committee, we have selected 150 patients from January to May 2016 that those who have laparoscopic cholecystectomy in Yongchuan Hospital, Chongqing Medical University, aged 18 to 60 years, weighing 50~80kg, American Society of Aneshesiologists (ASA) physical status classification system ~I II, no prior cardiopulmonary disease, preoperative normal liver and

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kidney function. No, ulcers, blood coagulation dysfunction, chronic pain, drug allergy history, preoperative a week taking narcotic drugs or non steroidal anti-inflammatory drugs (NSAIDs), patient controlled town without the use of postoperative pain (PCA). All projects were approved by the ethics committee of the hospital, signed with informed consent.

Experimental grouping

The selected cases were randomly divided into five groups, 30 cases in each group. They were in before skin incision 15min intravenous saline 2ml (group C), parecoxib 40mg (group P1), 80mg (group P2), flurbiprofen 50mg (group F1), 100mg (group F2).

Anesthesia method

All the patients were treated with total intravenous anesthesia. All the patients were fasted 12 hours before the operation and 8 hours off the bottle. Open the vein after admission, routine monitoring ECG, non-invasive blood pressure and oxygen saturation (SP02). All patients were followed by intravenous injection of midazolam 0.03mg/kg, etomidate 0.4mg/kg, cisatracurium 0.15mg/kg, 1.5ug/kg induced by remifentanil (Sheng *et al*. 2015). After the patient consciousness, breathing, coughing and swallowing reflex were recovered, the endotracheal tube has removed(Tang *et al*. 2017). Routine intravenous injection of neostigmine, 2mg, atropine, and 1mg antagonized the residual effects of muscle relaxation. The patients were sent back to the ward after the restoration of the patient's directional force. PCA analgesia was not used in all patients. After the operation, the 1h (T1), 2h (T2), 6h (T3), 12h (T4), 24h (T5) record of rest and exercise (1h=1 hour, T1-T5 means number, cough, turn over or from supine position when sitting up) VAS pain score (i.e., visual analogue scale, 0 is "no pain", 10 is the "worst pain"). The use of pethidine in 24h was recorded: (dosage mode of administration, duration of administration). Adverse reactions such as nausea, vomiting, respiratory depression and drowsiness were recorded in 24h.

STATISTICAL ANALYSIS

SPSS17.0 was used for statistical treatment. The measurement data were expressed by X±s. The comparison between groups was made by one-way ANOVA and repeated measures analysis of variance. The LSD-t test was used to compare. The enumeration data were compared by χ^2 test and rank sum test. P<0.05, the difference was statistically significant.

RESULTS

General situation

There was no significant difference in gender, age, weight, operation time and anesthesia time between the five groups (P>0.05), as shown in table 1.

Postoperative VAS score

Repeated measures analysis of variance was used in these groups, F=2.183, P, =0.034, VAS scores in each treatment group were statistically significant. Among them, compared with the C group, P1, P2, F2 group VAS score was significantly lower (P, <0.05), P1, P2, F2 group 22, the difference was not statistically significant. Time factor comparison, F=2.735, P=0.024, between the time groups, the difference was statistically significant. There is no interaction between time effect and treatment effect. As shown in table 2

Repeated measures analysis of variance was used in these groups, F=12.253, P and =0.012 were compared, the difference was statistically significant. Among them, compared with group C, P1, P2, F1, F2 group, VAS score was significantly lower (P <0.05); group F2 and P1, P2, F1 group, VAS score was lower (P <0.05); no significant P1, P2, F1 22 group difference. Time factor was compared with F=13.142, P=0.017, and there was significant difference between the different time groups. There is no interaction between time effect and treatment effect. As shown in table 3

Adverse reactions

Compared with C group, P2 group of nausea and vomiting incidence and severity were significantly decreased (P <0.05); P1 F1 group, only the incidence and severity of vomiting was significantly lower (P<0.05); the difference between the F2 group and the incidence of nausea and vomiting and the severity of C group were not statistically significant (table 4). No drowsiness, respiratory depression and other adverse reactions occurred in each group.

DISCUSSION

Laparoscopic surgery is a minimally invasive surgery, but many patients complained of postoperative bilateral hypochondria and shoulder pain, and sometimes pain is quite obvious, even more than the incision pain, known as the "syndrome of pain after laparoscopic surgery". Studies show that 73% to 80% of patients still need analgesics to relieve pain after laparoscopic surgery (Sheng *et al*. 2015; Tang *et al*. 2017). In this study, 50% of patients in group C required pethidine analgesia postoperatively, which further demonstrated the need for postoperative analgesia with laparoscopy.

Parecoxib sodium is a highly selective COX-2 inhibitor, which exerts dual analgesic effect by inhibiting the expression of peripheral and central COX-2(Tural *et al*. 2015). At the periphery, it reduces prostaglandin production and exerts anti-inflammatory and analgesic effects; in the center, it inhibits pain hypersensitivity and improves pain threshold.

Table 1: General comparison of groups of patients

Group	Sex (male/female)	Age(year)	Weight (kg)	Operative time (min)	Time of anesthesia (min)
Group C	14/16	42.17±6.43	67.50±8.13	61.15±13.25	95.14±26.26
Group F1	15/15	41.02±6.14	63.12±7.52	64.28±11.13	98.26±21.48
Group F2	17/13	43.59±5.72	64.73±8.55	58.72±12.08	101.49±20.52
Group P1	12/18	46.15±6.21	62.19±8.02	62.55±13.06	97.52±22.17
Group P2	14/16	42.36±6.16	63.46±7.84	65.42±11.24	103.21±21.34

Table 2: Resting VAS score

Intervention group	Time grouping						time effect	
	T1	T12	T3	T4	T5	mean value	F	P
Group C	2.15±1.43	2.63±1.29	2.54±1.16	2.61±1.29	2.82±1.31	2.15±1.24		
Group F1	1.36±1.17	1.62±1.34	1.48±1.21	1.35±1.17	1.24±1.56	1.42±1.37		
Group F2	0.42±1.33	0.59±1.02	0.64±1.13	0.82±1.05	0.85±1.13	0.94±1.29	2.735	0.024
Group P1	1.08±1.52	1.27±1.92	1.27±1.83	1.31±1.65	1.23±1.34	1.36±1.42		
Group P2	0.73±1.26	0.96±1.16	0.96±1.02	0.91±1.18	1.01±1.21	0.93±1.26		
Treatment effect	F=2.183 P =0.034						1.061	0.379

Table 3: VAS score during exercise

Intervention group	Time grouping						time effect	
	T1	T12	T3	T4	T5	mean value	F	P
Group C	3.15±1.32	3.57±1.31	3.24±1.36	3.41±1.31	3.72±1.51	3.15±1.17		
Group F1	1.52±1.17	1.64±1.15	1.48±1.09	1.35±1.12	1.24±1.32	1.42±1.24		
Group F2	1.02±1.33	1.29±1.11	0.64±1.24	0.82±1.11	0.85±1.25	0.94±1.17	13.142	0.017
Group P1	2.14±1.52	2.25±1.65	1.27±1.47	1.31±1.43	1.23±1.26	1.36±1.26		
Group P2	1.69±1.26	1.46±1.24	0.96±1.15	0.91±1.21	1.01±1.13	0.93±1.13		
Treatment effect	F=12.253 P =0.012						1.154	0.425

Table 4: Postoperative nausea and vomiting occurred in each group

Group	nausea				vomit			
	cases	light	moderate	severe	cases	light	moderate	severe
Group C	21 (70%)	6	11	4	18 (60%)	8	7	3
Group F1	18 (60%)	7	5	6	12 (40%)	5	6	1
Group F2	20 (66%)	10	8	2	15 (50%)	10	5	0
Group P1	16 (53%)	9	6	1	9 (30%)	6	1	1
Group P2	6 (20%)	3	3	0	6 (20%)	4	2	0

Studies have shown that parecoxib 40mg preoperative intravenous injection for gynecological laparoscopic surgery can reduce the score of VAS, reduce the postoperative pethidine requirement of ceftazidime (Udagawa *et al*. 2012; Takahashi, 2017). But the study shows that intravenous injection of 40mg parecoxib is invalid analgesia, while 80mg parecoxib can enhance the analgesic effect. The different is in this study is that we have selected before skin incision 15min intravenous injection of parecoxib sodium. This is mainly to ensure the effectiveness of anesthesia, as reduce harmful afferent stimulation caused by peripheral and central sensitization and protective effect on pain perception system. The results showed that after 24h, rest and exercise VAS scores decreased significantly in P1 and P2 group, postoperative use of parecoxib cases nifedipine significantly reduced, indicating the preoperative application of parecoxib 40mg or 80mg can effectively relieve the pain after LC. VAS score and pethidine use no significant difference in P1, P2 group, it cannot confirm that the analgesic effect of 80mg parecoxib is better. *Flurbiprofen axetil* injection is a traditional nonsteroidal anti-inflammatory and analgesic drug (NSAIDs) commonly used in clinic, and its microspheres can target the aggregation and relieve pain at the incision and inflammatory sites (Vekov *et al*., 2015). Due to comparison, this study on the analgesic effect of parecoxib and flurbiprofen showed that F1 group only exercise reduced VAS score, F2 group resting and exercise VAS scores were reduced, and the motion VAS score than the other four groups were decreased. That parecoxib (40mg) analgesic effect is good than flurbiprofen (50mg), but Parecoxib (80mg) analgesic effect on motion pain is not good than flurbiprofen

(100mg).

Postoperative, nausea and vomiting (PONV) is often positively related to the dose of opioid postoperative analgesia. In this study, the use of pethidine was less in the F2 group than in the C group, but the incidence of PONV was similar to that of the group, possibly because flurbiprofen inhibited both COX-1 and COX-2, thereby increasing the gastrointestinal adverse effects. Inhibition of parecoxib sodium on COX-1 is not obvious, does not affect the function of gastric mucosa. In this study, P1, P2, F2 three groups of postoperative pethidine were no significant difference, but compared with the F2 group, P2 group, PONV incidence and severity decreased significantly, that of parecoxib 80mg than the adverse reaction of flurbiprofen 100mg less, more conducive to postoperative recovery, further explained, Rui celecoxib has NSAIDs better than traditional gastrointestinal safety; compared with P1 group, P2 group reduced the incidence of nausea, improve satisfaction. So, considering from the two aspects of the safety and efficacy of parecoxib 80mg is the best choice.

CONCLUSION

Flurbiprofen axetil is a non-selective cyclooxygenase inhibitor. It can target the aggregation with lipid micro sphere as drug carrier and exert analgesic effect in surgical incision and inflammatory site. In laparoscopic cholecystectomy, comparison of parecoxib and *Flurbiprofen axetil* analgesia effect is relatively less. Therefore, this paper mainly through the observation of patients after resting and exercise VAS score, the incidence of adverse reactions and patient satisfaction index, evaluate the efficacy of parecoxib sodium 40mg, 80mg preoperative intravenous analgesia effect of LC, and compared with flurbiprofen 50mg, 100mg, to provide reference for clinical medication. The results showed that before the intravenous injection of parecoxib 40mg or 80mg can provide effective analgesia in laparoscopic cholecystectomy and postoperative pethidine use reduction, reduce the incidence of PONV, and improve the patient satisfaction; the parecoxib 80mg is more comfortable and safer.

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