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ORIGINAL PAPER

Effects of Flurbiprofen Axetil on Postoperative Analgesia and Cytokines in Peripheral Blood of Thoracotomy Patients

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Abstract The objective is to study the effects of flurbiprofen axetil (FA) with fentanyl together in postoperative controlled intravenous analgesia (PCIA) on pain intensity, cytokine levels in peripheral blood and adverse reactions of thoracotomy patients. Fifty thoracotomy patients were divided into a FA and a control group, each with 25 cases. Postoperative analgesia was administered in the two groups using PCIA. The pressing times of analgesia pump, the visual analog scale (VAS) scores during resting and coughing at 2, 6, 24, 48, 72 h after surgery and the incidence of adverse drug reactions were recorded. Levels of IL-1β, IL-6, IL-8, IL-2, and TNF-α in peripheral blood were determined before the administration of FA (T_0), and at 24 h (T_1), 48 h (T_2), 72 h (T_3) after surgery. The analgesia pump pressing times in the FA group was less than that of the control group. The VAS scores during resting and coughing at 2, 6, 24, 48, 72 h after surgery, were statistically less than those of control group. The incidence rate of nausea and vomiting was insignificantly different between the two groups. Administration of FA together with PCIA in thoracotomy patients can improve postoperative analgesia.

Keywords Flurbiprofen axetil · Thoracotomy patients · Postoperative analgesia · Cytokines

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Introduction

As the incisions and wounds of the thoracic surgery are always large, severe pain and inflammatory reaction occur after thoracic surgery. This is not conducive to the rehabilitation after surgery. Effective analgesia can reduce the stress and pain around the surgery. It can also effectively keep breathing and circulation, and is beneficial to cough and expectoration of patients to reduce the probability of pulmonary infection, obstructive atelectasis, and other postoperative complications. In recent years, a variety of methods to balance analgesia and standardized postoperative analgesia are used more often. Flurbiprofen axetil is a non-steroidal targeted analgesic, which inhibits the cyclooxygenase (COX) in the spinal cord and the peripherals to reduce prostaglandin synthesis. This study is designed to observe the effects of perioperative intravenous administration of FA with fentanyl together in PCIA on pain intensity. We also observed the cytokine levels in peripheral blood and adverse reactions of thoracotomy patients at the same time.

Materials and Methods

General Information

Fifty thoracotomy patients with ASA grade I–II, aging from 31 to 64 years, weighing 45–75 kg, were divided into two groups of 25 cases each. In the test group (FA group), the FA was intravenously injected at 1 mg/kg to patients 30 min prior to surgery and 6 h after skin incision. In the control group, 1 mg/kg of physiological saline was used in the same way at the same two time points of surgery. Postoperative PCIA analgesia was practiced using PCIA

formula: fentanyl 20 μg/kg diluted with physiological saline to 100 ml, with background infusion dose of 2 ml/h and single dose of 2 ml, and a locking time of 15 min. First, fentanyl was injected intravenously at loading dose of 50 μg, and followed by maintenance dose for continuous infusion.

Anesthesia

For anesthesia, 0.1 g sodium pentobarbital and 0.5 mg atropine were intramuscularly injected before surgery. A catheter was arranged in radial artery to monitor the arterial pressure, and another catheter was arranged in the right internal jugular vein for infusion and monitoring of the central venous pressure (CVP). Anesthesia was induced with midazolam, fentanyl, etomidate, vecuronium, and endotracheal intubation was practiced for mechanical ventilation. Blood pressure, P, ECG, CVP, SPO_2, T and other vital signs were monitored during the surgery. After surgery, ondansetron hydrochloride was intravenously injected to prevent nausea and vomiting.

Observation Indexes

The pressing times of analgesia pump and the VAS scores during resting and coughing at 2, 6, 24, 48, 72 h after surgery were recorded. The pain intensity was graded according to a VAS system, and described with figures of 0–10, with 0 meaning painless ranging to 10 for severe pain (Table 1).

Three milliliters of blood was sampled before surgery (T_0) and 24 h (T_1), 48 h (T_2), 72 h (T_3) after surgery, and centrifuged at 2,000 × *g* for 5 min, and preserved at −70 °C. The contents of IL-1, IL-6, IL-2, IL-8, TNF-α in plasma were determined via radioimmunoassay.

The number of cases, occurrences, symptoms, and adverse reactions were observed and recorded.

Table 1 VAS scores of the number of pressing times of analgesia pump in patients of two groups ($\bar{x} \pm S$, $n = 25$)

	FA group	Control group
VAS during resting (h)		
2	2.38 ± 0.65*	3.0 ± 0.82
6	2.08 ± 0.64*	2.85 ± 0.80
24	1.08 ± 0.95*	1.69 ± 0.48
48	0.15 ± 0.37*	0.62 ± 0.65
72	0.15 ± 0.28	0.23 ± 0.44
VAS during coughing (h)		
2	3.86 ± 0.64*	5.00 ± 0.75
6	4.20 ± 0.77*	5.33 ± 0.72
24	3.00 ± 0.65*	3.66 ± 0.62
48	2.26 ± 0.45*	3.06 ± 0.59
72	2.33 ± 0.48	2.60 ± 0.51
Pressing times of analgesia pump	1.00 ± 0.92*	3.90 ± 1.22

* $p < 0.05$

Statistical Analysis

Data obtained were analyzed using SPSS 13.0 and the results were expressed as a mean ± standard deviation (±s). The results of inter-group comparison were verified using independent *t* test, and those of the intra-group comparison checked using paired *t* test. The count data were tested using Chi-square (χ^2) test.

Results

Analgesia Pump Pressing Times and VAS Scores

The pressing times of the analgesia pump in the FA group were less than those in the control group. And the VAS scores during resting and coughing at 2, 6, 24, 48 h after surgery were statistically less than those of the control group (during resting at all time points: $p < 0.05$; during coughing at all time points: $p < 0.01$) (Table 2).

Levels of Cytokines in Peripheral Blood

There was a statistical difference in IL-1β levels in patients between two groups before surgery and at all postoperative time points. IL-6 and TNF-α levels (both at $p < 0.01$) in peripheral blood of the FA group were both significantly lower than those of the control group at either 24 or 48 h after surgery. The IL-8 level in peripheral blood of the FA group at 24 h after surgery was significantly lower than that of the control group ($p < 0.01$). The level of IL-2 in peripheral blood of the FA group was less statistically inhibited than that of the control group at 24 and 48 h after surgery ($p < 0.01$ at both time points).

There was no statistical difference between two groups in the incidence rate of nausea and vomiting (both at $p > 0.05$), as shown in Table 3.

Discussion

This study showed the following results: The pressing times of analgesia pump at 48 h after surgery in the FA group were less than those of the control group. The VAS scores during resting and coughing were less than the control group (during resting: $p < 0.05$; during coughing: $p < 0.01$). The IL-6 and TNF-α levels (both at $p < 0.01$) in peripheral blood in the control group were both higher than

Table 2 Levels of IL-1β, IL-6, IL-8, and IL-2 in peripheral blood of two groups (ng/kg, $\bar{x} \pm S$, $n = 25$)

Cytokines	Groups	T_0	T_1	T_2	T_3
IL-1β	FA group	0.14 ± 0.04	0.17 ± 0.04	0.16 ± 0.06	0.15 ± 0.04
	Control group	0.13 ± 0.05	0.16 ± 0.05	0.16 ± 0.05	0.14 ± 0.06
IL-6	FA group	0.21 ± 0.07	0.34 ± 0.06*,#	0.27 ± 0.06*,#	0.24 ± 0.07
	Control group	0.24 ± 0.06	0.57 ± 0.04#	0.45 ± 0.05#	0.25 ± 0.05
IL-8	FA group	0.41 ± 0.09	0.55 ± 0.08*,#	0.49 ± 0.12	0.42 ± 0.14
	Control group	0.48 ± 0.12	0.64 ± 0.09#	0.53 ± 0.12	0.39 ± 0.12
IL-2	FA group	4.59 ± 1.02	2.69 ± 0.99*,#	3.98 ± 0.82*,#	5.57 ± 1.31
	Control group	4.98 ± 1.45	2.01 ± 0.54#	3.12 ± 1.05#	5.40 ± 1.24
TNF-α	FA group	9.49 ± 0.83	11.29 ± 0.86*,#	10.53 ± 1.08*,#	8.89 ± 1.50
	Control group	9.96 ± 1.74	12.77 ± 2.02#	11.87 ± 0.93#	9.17 ± 1.51

Means statistical difference at $p < 0.05$ compared with the preoperative value, and *means the statistical difference at $p < 0.05$ compared with the control group

Table 3 Incidence rate of adverse reactions

Groups	Nausea	Vomiting	Respiratory inhibition
Control group	7 (28 %)	5 (20 %)	0
FA group	5 (20 %)	3 (12 %)	0

those of the FA group at either 24 or 48 h after surgery. The IL-8 level in peripheral blood in the control group at 24 h after surgery was higher than that of the FA group ($p < 0.01$). The release of IL-2 into peripheral blood of the FA group was less statistically inhibited than that of the control group at 24 and 48 h after surgery ($p < 0.01$ at both time points). The IL-1β level in peripheral blood at all time points prior to and after surgery was insignificantly different between the two groups (all at $p > 0.05$). The results showed that the IL-6, TNF-α, and IL-8 levels in peripheral blood in the FA group were lower compared to the control group for the same time points. The concurrent VAS scores of the FA group were lower than the control group, indicating that the release of inflammatory cytokines may be associated with subjective pain perception. Perioperative intravenous injection of FA can relieve the postoperative release of IL-6, IL-8, and TNF-α, reduce inflammation and relieve postoperative pain.

Surgery-related tissue damage can cause a series of related reactions including nociceptive and inflammatory responses. Damages in tissues and peripheral nerve caused local inflammatory response coupling with the increased secretion of inflammatory cytokines, including IL-1β and IL-6. These cytokines may induce sensitization of the peripheral and central nervous system, resulting in hyperalgesia.

Within a few minutes of injury, immune factors which include pro-inflammatory cytokines were produced by the glial cells in the central nervous system. The pro-inflammatory cytokine IL-6 acted on the IL-6 receptor of the neurons to result in nociceptive senses or regulate pain sense by activation of glial cells which secreted substance P, glutamic acid, and nitric oxide synthase. These substances affect pain transmission in the central nervous system. Studies suggest that the release of IL-6 is relevant to the neuropathic pain after peripheral nerve injury [1]. The release of IL-6 was increased in the rat model of ischium pain [2], and intrathecal injection of IL-6 induced nerve injury, thes tactile allodynia and thermal hyperalgesia in normal rats. IL-8 is the first discovered endogenous regulatory substance which was associated with the hyperalgesia. TNF-α is an important inflammatory factor in pain models, which regulates the activation of nuclear factor-KB (NF-KB) and stress-activated protein kinases (SAPKs) in apoptotic pathways with two surface receptors: $TNFR_1$, $TNFR_2$. When complete Freund's adjuvant is injected into the rat pons, the TNF-α and IL-1β are increased, leading to mechanical pain and thermal hyperalgesia. However, the injection of anti-TNF-α antiserum before the injection of the Freund's adjuvant can postpone inflammatory hyperalgesia and reduce IL-1β [3]. Damage in the tissue and peripheral nerve can result in local inflammatory reactions, including the increased release of IL-6, IL-8, TNF-α, and other pro-inflammatory cytokines, and the concurrent thermal hyperalgesia and mechanical allodynia. The results showed that perioperative intravenous injection of FA together with postoperative PCIA can reduce the release of IL-6, IL-8, and TNF-α, reduce nociceptive stimuli and hyperalgesia, thus relieving the postoperative pain.

The FA is a new non-steroidal anti-inflammatory drug. Its mechanism of anti-inflammatory, analgesic and antipyretic effects lies in the inhibition of COX activity and metabolism of arachidonic acid, and therefore the targeted action to local inflammation or tumor lesion and prostate biosynthesis. The study of Aoki et al. showed that preoperative application of FA reduced the postoperative pain of surgery in the ear and neck [4]. Yamashita et al. confirmed that the preoperative administration of FA at 1 mg/kg was better for analgesia compared with the postoperative administration [5]. Domestic researches showed that the FA administered postoperatively can target and gather in the surgical incision and tumor site, increase the pain

threshold, thus showing the effects of preemptive analgesia [6]. In this study, FA was injected 30 min before the incision and 6 h after the incision. It reduced postoperative pain intensity and eased the release of pro-inflammatory cytokines. It was difficult to judge whether the relief of the pain caused the postoperative release of the cytokines or postoperative release of the pro-inflammatory cytokines relieved the postoperative pain.

Perioperative intravenous injection of FA can reduce the postoperative inhibition of IL-2 release. IL-2 is an immune regulatory factor secreted by T helper cell (Th), can enhance the immune function and play a significant role in the dual-directional regulation of immune and central nervous system. It cannot induce killer T cells (Tc), activate the proliferative response of B cells, but can enhance the activity of T lymphocytes and NK cells to produce lymphokine-activated killer cells and the secretion of interferon. The IL-2 release in peripheral blood in FA group was less inhibited than that of control group. The study by Beilin [7] confirmed that PA + PCEA reduced Th_1 cells. Jiang et al. [8] found that IL-2 is similar to neurotransmitter opioid in the structure, so can be combined with the opioid receptors in peripheral and central nerve system to realize the analgesic effect; therefore, the inhibition of IL-2 release may relieve the postoperative pain.

This study showed that there were no differences in IL-1β levels in peripheral blood between the two groups of patients at all pre- and postoperative time points (all at $p > 0.05$). The IL-1β is secreted by monocytes and macrophages. The injection of IL-1β into the abdominal cavity, ventricles, and pons can improve the synthesis and release of substance P by nerve and glial cells; meanwhile, elevated levels of IL-1β in the central nervous system can increase the synthesis of COX-2 and PGE2. PGE2 can increase the sensitivity to pain. Wolf et al. [9] verified that IL-1β in a rat model with incisional pain increased in the local wound, and IL-1β played an important role in the mechanisms of nociceptive hyperalgesia. The reason there were no differences in IL-1β level in peripheral blood between the two groups of patients at all pre- and postoperative time points is that the IL-1β level changes less in the peripheral blood in perioperative phase than that in exudate around surgical incision. According to Lu et al. [10], the reason for no significant changes of postoperative contents of the IL-1β in peripheral blood was that it did not release into the blood, and their researches showed that the content of IL-1β in peripheral blood remained low even in severe inflammation. Ching et al. [11] found no significant changes of perioperative contents of IL-1β in peripheral blood in their studies of the effects of auto-controlled epidural analgesia on the cytokine response in colorectal surgery. The results are consistent with the findings of Lu et al. Because of constraints, we did not detect perioperative cytokines secreted around wound.

Conclusion

In conclusion, this study confirmed that perioperative intravenous injection of FA together with PCIA reduced the postoperative pain intensity and cytokine release of IL-6, TNF-α, IL-8, and other pro-inflammatory cytokines, indicating a correlation between the subjective pain and the immune response. Pro-inflammatory cytokines are important mediators causing diseases including fever and protein synthesis and release in acute phase, reducing food and water intake and hyperalgesia. This study suggested that reduction of the postoperative secretion of pro-inflammatory cytokines could relieve postoperative pain intensity, reduce postoperative complications, and help surgery patients' prognosis.

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