Effect of flurbiprofen axetil intervention before induction on incision pain and inflammatory stress response after orthopedic surgery

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ABSTRACT

Objective: To study the effect of flurbiprofen axetil intervention before induction on incision pain and inflammatory stress response after orthopedic surgery. Methods: A total of 86 cases of elderly patients who underwent operative treatment of femoral neck fracture in Guangyuan Hospital of Traditional Chinese Medicine between March 2014 and December 2017 were selected as the research subjects. All patients were randomly divided into the experimental group who accepted flurbiprofen axetil intervention before induction + routine anesthesia induction and maintenance, and the control group who accepted routine anesthesia induction and maintenance, and each group included 43 cases. The pain levels of the two groups were assessed 24 h after surgery; the levels of pain mediators and inflammatory stress molecules in serum as well as the expression intensity of inflammatory stress molecules in peripheral blood were determined before surgery and 24 h after surgery. Results: 24 h after surgery, serum SP, NPY, PGE2, TNF-α, IL-1β, IL-18, ACTH, COR and NE levels as well as peripheral blood NF-κB, NLRP3, Caspase-1, GLUT4 and FOXP3 expression intensity of both groups were significantly higher than those before surgery, and NRS pain score, serum SP, NPY, PGE2, TNF-, IL-1β, IL-18, ACTH, COR and NE levels as well as peripheral blood NF-κB, NLRP3, Caspase-1, GLUT4 and FOXP3 expression intensity of experimental group 24 h after surgery were significantly lower than those of control group. Conclusions: Flurbiprofen axetil intervention before induction can improve and inhibit the incision pain and inflammatory stress response after orthopedic surgery.

1. Introduction

Local incision pain after orthopedic surgery is the most common postoperative complication and also an important factor affecting postoperative recovery of body function. Elderly patients have body hypofunction and reduced organ reserve function, they are prone to more significant inflammation and stress reaction when undergoing surgical trauma and anesthesia, and they also have weak tolerance to postoperative pain and easily have more obvious postoperative pain, which will aggravate the activation of inflammatory and stress reaction and increase the occurrence risk of severe complications such as postoperative cognitive dysfunction and deep venous thrombosis of lower extremity[1]. In clinical practice, according to the characteristics of postoperative pain in elderly patients, a more perfect analgesic method is needed to reduce the pain degree caused by orthopedic surgery trauma. Multi-mode analgesia is a concept of analgesia developed in recent years, and preemptive analgesia is an important part of this analgesia mode, which provides analgesics before surgery to block the generation of pain perception and thus reduce postoperative pain[2,3]. Flurbiprofen axetil is a nonselective cyclooxygenase inhibitor that can exert the anti-inflammatory and analgesic effect by inhibiting the synthesis of prostaglandins catalyzed by cyclooxygenase. In this study, the patients undergoing femoral neck fracture surgery were taken as the study subjects, and the effect of flurbiprofen axetil intervention before induction on incision pain and inflammatory stress response after orthopedic surgery was specifically analyzed in order to provide a new idea for pre-intervention of pain in subsequent similar patients.
2. Materials and methods

2.1. General information

The elderly patients who underwent femoral neck fracture surgery in Guangyuan Hospital of Traditional Chinese Medicine between March 2014 and December 2017 were collected as the research subjects. The results of imageological examination showed that they were consistent with the diagnosis of femoral neck fracture and the indications of open surgery, and the patients with traumatic fracture and those combined with chronic pain disease before surgery were excluded. A total of 86 patients were included in the study and divided into the experimental group and the control group by random number table method, and there were 43 cases in each group. In the experimental group, there were 24 males and 19 females who were 59-74 years old; in the control group, there were 26 males and 17 females who were 61-75 years old. There was no significant difference in gender composition or age distribution between the two groups (P>0.05).

2.2. Anesthesia and analgesia methods

Before anesthesia induction, experimental group were given intravenous drip of flurbiprofen axetil (manufactured by Beijing Tide Pharmaceutical Co., Ltd., 50 mg/pc, Batch No. 20161107) 50 mg + 0.9% sodium chloride injection 100 mL at the speed of 40-60 drops/min; control group were given intravenous drip of 0.9% sodium chloride injection 100 mL at the speed of 40-60 drops/min. After the above intervention was completed, patients in both groups were given intravenous injection of propofol 1-2 mg/kg for anesthesia induction and isoflurane inhalation for anesthesia maintenance.

2.3. Clinical indicator determination methods

24 h after the operation, numerical rating scale (NRS) for pain was used to evaluate the pain degree of the two groups, and the higher the score, the more intense the pain degree. Before and 24 h after surgery, two doses of cubital venous blood were collected respectively, one was directly centrifuged for the separation of serum and the contents of SP, NPY, PGE2, TNF-α respectively, the other was anticoagulated with EDTA to incubate the fluorescent antibodies of NF-κ B, NLRP3, Caspase-1, GLUT4 and FOXP3, and Attune NxT flow cytometer was used to determine their expression intensity.

2.4. Statistical methods

The data obtained in this paper were all recorded into the software SPSS19.0. The NRS pain score, the contents of pain mediators as well as the expression levels of inflammation and stress molecules were all measurement data. The comparison within or between groups was performed by t test, and the difference was statistically significant if P<0.05.

3. Results

3.1. Postoperative pain degree and perioperative pain mediator change

24 h after surgery, NRS pain score of experimental group was (2.48±0.35), NRS pain score of control group was (3.88±0.51) and t test showed that NRS pain score of experimental group 24 h after surgery was lower than that of control group. Analysis of perioperative serum pain mediators SP (ng/L), NPY (ng/L), PGE2 (μg/L) and TNF-α (ng/L) between the two groups of patients was as follows: before surgery, serum SP, NPY, PGE2 and TNF-α levels were not significantly different between the two groups of patients (P>0.05); 24 h after surgery, serum SP, NPY, PGE2 and TNF-α levels of both groups were significantly higher than those before surgery (P<0.05), and serum SP, NPY, PGE2 and TNF-α levels of experimental group 24 h after surgery were significantly lower than those of control group (P<0.05), as shown in Table 1.

3.2. Perioperative inflammation molecule change

Analysis of perioperative inflammation molecules IL-1β (μg/L), IL-18 (ng/L), NF-κ B, NLRP3 and Caspase-1 in serum and peripheral blood between the two groups of patients was as follows: before surgery, serum IL-1β and IL-18 levels as well as peripheral blood NF-κ B, NLRP3 and Caspase-1 expression intensity were not significantly different between the two groups of patients (P>0.05); 24 h after surgery, serum IL-1β and IL-18 levels as well as peripheral blood NF-κ B, NLRP3 and Caspase-1 expression

Table 1

Perioperative pain mediator change (Mean±SD).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>SP</th>
<th>NPY</th>
<th>PGE2</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>43</td>
<td>Before surgery</td>
<td>93.5±11.2</td>
<td>147.2±19.3</td>
<td>1.03±0.14</td>
<td>4.23±0.66</td>
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<td>After surgery</td>
<td>128.4±16.2</td>
<td>216.3±24.4</td>
<td>1.42±0.18</td>
<td>8.15±1.03</td>
</tr>
<tr>
<td>Control</td>
<td>43</td>
<td>Before surgery</td>
<td>94.2±10.8</td>
<td>146.7±18.4</td>
<td>1.01±0.12</td>
<td>4.19±0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After surgery</td>
<td>171.5±20.4</td>
<td>264.1±26.2</td>
<td>2.14±0.32</td>
<td>11.31±1.83</td>
</tr>
</tbody>
</table>

*Comparison between experimental group and control group after surgery, P<0.05; †Comparison between before and after surgery within group, P<0.05.
intensity of both groups were significantly higher than those before surgery ($P<0.05$), and serum IL-1β and IL-18 levels as well as peripheral blood NF-κB, NLRP3 and Caspase-1 expression intensity of experimental group 24 h after surgery were significantly lower than those of control group ($P<0.05$), as shown in Table 2.

### 3.3. Perioperative stress molecule change

Analysis of perioperative stress molecules ACTH (pmol/L), COR (ng/mL), NE(ng/mL), GLUT4 and FOXP3 in serum and peripheral blood between the two groups of patients was as follows: before surgery, serum ACTH, COR and NE levels as well as peripheral blood GLUT4 and FOXP3 expression intensity were not significantly different between the two groups of patients ($P>0.05$); 24 h after surgery, serum ACTH, COR and NE levels as well as peripheral blood GLUT4 and FOXP3 expression intensity of both groups were significantly higher than those before surgery ($P<0.05$), and serum ACTH, COR and NE levels as well as peripheral blood GLUT4 and FOXP3 expression intensity of experimental group 24 h after surgery were significantly lower than those of control group ($P<0.05$), as shown in Table 3.

### 4. Discussion

Postoperative pain is the most common complication after orthopedic surgery. It not only affects limb movements and increases the risk of postoperative deep venous thrombosis, but also amplifies inflammatory stress response on the basis of surgical trauma and increases the risk of postoperative cognitive dysfunction. Multimodal analgesia is an effective way to relieve pain after orthopedic surgery, in which preemptive analgesia can achieve analgesic effect by blocking or reducing the influx of noxious stimuli. Flurbiprofen axetil is a common drug for preemptive analgesia and can block the process of prostaglandin synthesis catalyzed by cyclooxygenase, and its administration before anesthesia induction can inhibit the influx of noxious stimuli such as anesthetic stress and surgical trauma so as to relieve postoperative pain[5]. In the above study, in order to clarify the postoperative analgesic value of flurbiprofen axetil intervention before induction for orthopedic surgery, we analyzed the postoperative pain score, and the results showed that the NRS pain score of the experimental group was lower than that of the control group 24 h after surgery. This suggests that flurbiprofen axetil intervention before induction of orthopedic surgery can alleviate postoperative pain. The noxious stimuli caused by surgical trauma can promote the generation of pain perception by increasing the secretion of various pain mediators. SP and NPY are polypeptide neurotransmitters, which can mediate the transmission of pain signals from the periphery to the central nervous system; PGE2 and TNF-α are inflammatory mediators that can increase peripheral tissue sensitivity to pain and enhance pain signals[8]. In this paper, analysis of the change of the perioperative pain mediators above showed that the contents of SP, NPY, PGE2 and TNF-α in serum of both groups of patients were on the rise after surgery, but the rising degree of the above index contents in serum of experimental group was lower after surgery, which indicates that operation trauma can increase the secretion of pain mediators and cause postoperative pain, and that flurbiprofen axetil intervention before induction can alleviate the increasing trend of pain mediator secretion and relieve postoperative pain.

Surgical trauma can directly lead to over-activation of inflammatory response and the secretion of various inflammatory factors increases, which can amplify pain perception; however, the persistent postoperative incision pain will aggravate and amplify the inflammatory response, which will lead to the mutual promotion and continuously amplification of postoperative pain and inflammatory response[9,10]. The IL-1β and IL-18 in the interleukin family are cytokines with potent pro-inflammatory activity, and they are massively expressed and secreted into the blood circulation during the activation of postoperative inflammation. NF-κB is a transcription factor that activates IL-1β and IL-18 gene expression. Under physiological conditions, it binds to the specific inhibitor IκB and is inactivated. External stimuli such as surgical trauma will activate multiple signal transduction pathways in the body and make NF-κB dissociate with IκB, and the free NF-κB enters the cell nucleus and starts the expression of IL-1β and IL-18 gene[11,12]. The encoding products of IL-1β and IL-18 gene are the inactive precursors of IL-1β and IL-18 cytokines, which split into mature

<table>
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<th>Table 2</th>
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<tr>
<td>Perioperative inflammation molecule change ( irresistible).</td>
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<td>Groups</td>
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<tr>
<td>Experimental group</td>
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<td>Control group</td>
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*: Comparison between experimental group and control group after surgery, $P<0.05$; #: Comparison between before and after surgery within group, $P<0.05$.

<table>
<thead>
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and pro-inflammatory IL-1β and IL-18 under the mediation of NLRP3 inflammasome. Caspase-1 is a key molecule involved in IL-1β and IL-18 precursor split in NLRP3 inflammasome. NLRP3 recruits and activates Caspase-1 through downstream ASC, and the activated Caspase-1 directly splits cytokine precursors and promotes the secretion of mature cytokines.[13] In this paper, we analyzed the perioperative change of above inflammation molecules and found that serum IL-1β and IL-18 contents as well as peripheral blood NF-κ B, NLRP3 and Caspase-1 expression intensity of both groups of patients were on the rise after surgery, while the rising degree of above molecule expression intensity in serum and peripheral blood of experimental group was lower after surgery, it suggests that surgical trauma and postoperative persistent pain can promote inflammation activation and that flurbiprofen axetil intervention before induction can reduce the activation rate of the inflammatory response, and this is one of the immanent causes of lower pain score before induction can reduce the activation rate of the inflammatory response, and this is one of the immanent causes of lower pain score.

Surgical trauma and postoperative pain activate the inflammatory response and directly lead to the stress response activation.[14] In this process, the ACTH released by the hypothalamus acts on the adrenal cortex and increases the secretion of COR, which can enhance the body’s ability to withstand traumatic stress to a certain extent and is a protective response of the body; after the activation of sympathetic nerve, the adrenal medulla secretes a large amount of NE and acts on myocardial and peripheral blood vessels, resulting in hemodynamic changes.[15,16]. In addition to cause the changes in adrenal endocrine functions, the stress response also affects the glucose metabolism and immune response process through the biological effects of COR. On the one hand, COR can promote gluconeogenesis, and the increased expression of GLUT4 after activation of IRS1/2 is a compensatory change in the process of gluconeogenesis; on the other hand, COR can suppress immune response, and the increased expression of FOXP3, a negative immunoregulatory molecule, is an important way to suppress immune response.[17] In this paper, we analyzed the perioperative changes of above stress molecules of the two groups and found that serum ACTH, COR and NE contents as well as peripheral blood GLUT4 and FOXP3 expression intensity of both groups of patients were on the rise after surgery, while the changes in above indexes of experimental group were smaller after surgery, indicating that surgical trauma and postoperative persistent pain can promote stress reaction activation, and that flurbiprofen axetil intervention before induction can reduce the activation rate of the stress response.

The results of the above studies show that the flurbiprofen axetil intervention before induction of orthopedic surgery can reduce postoperative incision pain and reduce the secretion of pain mediators, and it can also inhibit the activation of inflammatory stress response.

References


