Effect of preemptive analgesia with parecoxib sodium on inflammatory cytokine and stress in puerpera after cesarean section

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Objective: To explore the effect of preemptive analgesia (PA) with parecoxib sodium on the inflammatory cytokine and stress in puerpera after cesarean section. Methods: A total of 70 pregnant women who were admitted in our hospital from May, 2015 to May, 2016 for cesarean section were included in the study and randomized into the observation group and the control group with 35 cases in each group. A venous channel was established. The heart rate, blood pressure, and oxygen saturation were continuously monitored by the monitor. The patients in the observation group were intravenously injected with parecoxib sodium (40 mg) and normal saline (2 mL), while the patients in the control group were intravenously injected with normal saline (2 mL) 30 min before anesthesia induction. The venous blood when entering the operation room, after operation, 4 h, 8 h, and 12 h after operation was extracted. The plasma IL-6, TNF-α, P substance, E, and NE levels were detected. Results: IL-6 and TNF-α levels after operation in the two groups were elevated, reached the peak 4 h after operation, and were gradually reduced 8 h after operation. IL-6 and TNF-α levels at each timing point after operation in the observation group were significantly lower than those in the control group (P<0.05). P substance after operation in the two groups was elevated, reached the peak 4 h after operation, and was gradually reduced 8 h after operation. P substance level at each timing point after operation in the observation group was significantly lower than that in the control group (P<0.05). N and NE levels after operation in the two groups were elevated, reached the peak 4 h after operation, and were reduced to the levels when entering the operation time 12 h after operation. N and NE levels at each timing point after operation in the observation group were significantly lower than those in the control group (P<0.05). Conclusions: PA with parecoxib sodium in application of puerpera after cesarean section can effectively reduce the stress reaction, decrease the production of inflammatory cytokines, with a favorable analgesic effect, and further reduce the occurrence of postoperative complications.

1. Introduction

The postoperative pain is an acute nociceptive pain, resulting in a series of pathological and physiological changes, such as accelerated respiration and heart rate, elevated blood pressure, and arrhythmia, which can directly affect the postoperative recovery[1]. In recent years, the concept of paying high attention to the postoperative pain and positive analgesia has been an important renewal conception in the fields of surgery and anesthesiology. Preemptive analgesia (PA) is gradually and widely accepted. PA refers to that measures are taken before the occurrence of noxious stimulation and pain to prevent the introduction of receptive damage and the sensitization of central nervous system in order to reduce the stress and inflammatory reaction, alleviate or eliminate the pain caused by the stimulation[2]. The various postoperative cytokines and inflammatory mediators are involved in the repairing of incision, and meanwhile can release a
large amount of lysosome and poison to cause the local tissue injury. It is reported that the serum IL-6, TNF-α, and P substance play an important role in the tissue injury[3]. Parecoxib sodium is a new type non-steroidal drug, has efficacies of antipyresis, analgesia, and anti-inflammation, and is widely applied in the operative analgesia. Some researches demonstrate that parecoxib sodium in application of PA has a favorable clinical effect[4]. The study is aimed to explore the effect of PA with parecoxib sodium on the inflammatory cytokine and stress in puerpera after cesarean section.

2. Materials and methods

2.1. General materials

A total of 70 pregnant women who were admitted in our hospital from May, 2015 to May, 2016 for cesarean section were included in the study, ASA c cx-II grade, aged from 24 to 35 years old, with an average age of (27.5±3.6) years old; body weight from 59 to 69 kg, with an average weight of (61.2±5.8) weight; single birth with a full term, gestational week from 37 to 42 weeks, with an average of (38.5±1.5) weeks. All the puerperal were performed with the cesarean section successfully. Those who had cardiac insufficiency, serious fetal distress, PIH, high-risk pregnancy, endocrine diseases, coagulation disorder, abnormal liver and kidney function, and had contraindications or were allergic to related drugs were excluded from the study. The puerpera were randomized into the observation group and the control group with 35 cases in each group. The difference of the general materials between the two groups was not statistically significant (P>0.05).

2.2. Methods

A venous channel was established. The heart rate, blood pressure, and oxygen saturation were continuously monitored by the monitor. The patients in the observation group were intravenously injected with parecoxib sodium (produced by Pfizer Ltd, Approval No. J20080044, 40 mg) and normal saline (2 mL), while the patients in the control group were intravenously injected with normal saline (2 mL) 30 min before anesthesia induction. The epidural catheter was removed after operation. A routine intravenous analgesia after operation was performed, ie. sufentanil (100 μg) + dezocine (10 mg) + Aubers (4 mg) + normal saline (100 mL), background dose of 2 mL/h, PCA of 0.5 mL/time, and locking time of 15 min.

2.3. Observation indicators

The venous blood when entering the operation room, after operation, 4 h, 8 h, and 12 h after operation was extracted to be centrifuged for the plasma. ELISA was used to detect IL-6 and TNF-α. The radioimmunoassay was used to detect P substance. HPLC-ECD was used to detect E and NE.

2.4. Statistical analysis

SPSS 18.0 software was used for the statistical analysis. The measurement data were expressed as mean±SD, and t test was used. Chi-square test was used for the enumeration data. P<0.05 was regarded as statistically significant difference.

3. Results

3.1. Comparison of inflammatory cytokines at each timing point

IL-6 and TNF-α levels after operation in the two groups were elevated, reached the peak 4 h after operation, and were gradually reduced 8 h after operation. IL-6 and TNF-α levels at each timing point after operation in the observation group were significantly lower than those in the control group (P<0.05) (Table 1).

3.2. Comparison of P substance level at each timing point

P substance after operation in the two groups was elevated, reached the peak 4 h after operation, and was gradually reduced 8 h after operation. P substance level at each timing point after operation in the observation group was significantly lower than that in the control group (P<0.05) (Table 2).

3.3. Comparison of the stress reaction at each timing point

N and NE levels after operation in the two groups were elevated, reached the peak 4 h after operation, and were reduced to the levels when entering the operation time 12 h after operation. N and NE levels at each timing point after operation in the observation group were significantly lower than those in the control group (P<0.05) (Table 3).

4. Discussion

The postoperative pain after cesarean section is a painful memory experienced by most puerpera, and will bring much pain to them. Due to being fear of pain and being unable to provide analgesia technique, the out-of-bed activity time for puerpera after operation...
is greatly extended, and their emotions are nervous, which can affect the normal lactation[5]. The postoperative pain can cause a strong stress reaction. The activated inflammatory cytokines can induce various pathological and physiological reactions. Initially, PGE2 release and COX-2 expression are induced to reduce the pain threshold. After tissue injury, the released inflammatory mediators can stimulate the peripheric receptors to feed back on the thalamus and cerebral cortex to produce a feeling of pain[6]. Parecoxib sodium, a selective COX-2 inhibitor, can reduce the synthesis and release of PGs to enhance the pain threshold in order to alleviate or remove the pain. After intravenous injection, parecoxib sodium can be rapidly hydrolyzed into valdecoxib, which can block the synthesis of PGs by AA to play an analgesia effect, and inhibit the activation and proliferation of monocytes or macrophages to reduce the production of inflammatory cytokines[7].

In a physiological state, the anti-inflammatory and pro-inflammatory cytokines are in a weak balance, and will be easily destroyed under the stimulation of trauma, resulting in the elevated pro-inflammatory cytokines, while a feedback cascade effect exists between the pro-inflammatory cytokines and noxious stimulation[8]. Some researches demonstrate that IL-6 and TNF-α can be expressed in the early stage of trauma or operation, and are the most sensitive markers of tissue injury, whose levels are proportional to the tissue injury degree[9]. IL-6, an important cytokine with multi-directional regulatory function, can regulate the systemic or local inflammatory reaction and immune response, induce stem cells and B cell to produce the immunoglobulin, and is acknowledged to be the strongest endogenous inflammatory mediator, whose elevated degree and duration are positively correlated with the trauma degree[10]. IL-6 is produced 2-4 h after trauma, and is served as the indicator to reflect the inflammatory reaction degree during the perioperative period in the clinic, whose elevated level can suggest that the peripheral and central nervous system sensitivity is increased[11]. TNF-α is a kind of monocyte factor, is an early important cytokine of systemic or local inflammatory reaction, and has triggering action and initiation effect during the process of inflammation. After the stimulations of pain or infection, a large amount of TNF-α is synthetized, whose level in the blood is rapidly elevated, and will be correspondingly reduced when the trauma is gradually healed[12]. The results in the study showed that IL-6 and TNF-α levels after operation in the two groups were elevated, reached the peak 4 h after operation, and were gradually reduced 8 h after operation; IL-6 and TNF-α levels at each timing point after operation in the observation group were significantly lower than those in the control group (P<0.05), indicating that parecoxib sodium can inhibit the release of inflammatory cytokines after cesarean section to alleviate the tissue injury. P substance is released by the primary sensory neuron end, and is a kind of neurotransmitter which can transfer the information of pain[13]. The damaged C and A fibers caused by the operative trauma can release P substance,

### Table 1
Comparison of inflammatory cytokines at each timing point (n=35, pg/mL, mean±SD).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Indicators</th>
<th>Entering the operation room</th>
<th>Immediately after operation</th>
<th>After operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 h</td>
<td>8 h</td>
</tr>
<tr>
<td>Observation group</td>
<td>IL-6</td>
<td>14.17±2.36</td>
<td>84.71±23.52</td>
<td>93.72±22.36</td>
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<td>TNF-α</td>
<td>12.17±1.36</td>
<td>23.65±3.14</td>
<td>26.67±3.53</td>
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<tr>
<td>Control group</td>
<td>IL-6</td>
<td>14.23±2.61</td>
<td>148.87±68.42</td>
<td>189.56±41.12</td>
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<tr>
<td></td>
<td>TNF-α</td>
<td>12.21±1.24</td>
<td>38.84±4.55</td>
<td>60.18±2.52</td>
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</tbody>
</table>

*P<0.05, when compared with the control group.

### Table 2
Comparison of P substance level at each timing point (n=35, pg/mL, mean±SD).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Entering the operation room</th>
<th>Immediately after operation</th>
<th>After operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 h</td>
<td>8 h</td>
</tr>
<tr>
<td>Observation group</td>
<td>90.75±9.35</td>
<td>98.65±9.72</td>
<td>127.69±13.32</td>
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<tr>
<td>Control group</td>
<td>90.68±8.64</td>
<td>137.55±7.68</td>
<td>148.72±6.33</td>
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</table>

*P<0.05, when compared with the control group.

### Table 3
Comparison of the stress reaction at each timing point (n=35, pmol/mL, mean±SD).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Indicators</th>
<th>Entering the operation room</th>
<th>Immediately after operation</th>
<th>After operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 h</td>
<td>8 h</td>
</tr>
<tr>
<td>Observation group</td>
<td>N</td>
<td>237.6±123.4</td>
<td>532.6±128.9</td>
<td>418.7±126.7</td>
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<tr>
<td></td>
<td>NE</td>
<td>1 298.8±526.4</td>
<td>1 792.3±438.1</td>
<td>1 437.2±385.4</td>
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<tr>
<td>Control group</td>
<td>N</td>
<td>235.4±130.2</td>
<td>915.6±187.3</td>
<td>782.3±115.6</td>
</tr>
<tr>
<td></td>
<td>NE</td>
<td>1 297.9±589.3</td>
<td>2 316.4±441.5</td>
<td>1 886.5±438.1</td>
</tr>
</tbody>
</table>

*P<0.05, when compared with the control group.
whose content change in the spinal cord can affect the transmitting of nociceptive signal. P substance can also activate the adjacent nociceptor to promote its further release, which can activate more nociceptors[14]. Some researches demonstrate that P substance can strengthen AA metabolism, promote the release of IL-6 and TNF-α, facilitate the synthesis and secretion of interferon, and indirectly regulate the recognition and antigen presentation of macrophage and T cell; therefore, it is argued that a mutual interaction may exist among P substance, IL-6, and TNF-α [15]. The results in the study showed that P substance after operation in the two groups was elevated, reached the peak 4 h after operation, and was gradually reduced 8 h after operation; N and NE level at each timing point after operation in the observation group was significantly lower than that in the control group (P<0.05), indicating that PA with parecoxib sodium in application of cesarean section has a significant effect of preventing and reducing the postoperative pain.

The inflammation and damaged nerves will cause peripheral or central sensitization to induce chronic pain and oxidative stress reaction which can affect the cellular structure and function, which has a great effect on the neurotransmitters, especially for the pain ion channel, and also can affect the activities of glial cells and protein kinases[16]. N and NE are commonly served as the operative stress reaction indicators. Several minutes after trauma, the plasma CA level is immediately increased. The plasma CA level is an important indicator to reflect the noxious stimulation stress reaction, including N and NE. The postoperative pain can stimulate the body to cause reflectively accelerated heart rate and elevated blood pressure, resulting in the elevated plasma E and NE levels, whose elevated level is positively correlated with the stress reaction intensity[17]. The results in the study showed that N and NE levels after operation in the two groups were elevated, reached the peak 4 h after operation, and were reduced to the levels when entering the operation time 12 h after operation; N and NE levels at each timing point after operation in the observation group were significantly lower than those in the control group (P<0.05), indicating that PA with parecoxib sodium in application of cesarean section can block the operative nociception and effectively alleviate the postoperative stress reaction.

In conclusion, PA with parecoxib sodium in application of puerpera after cesarean section can effectively reduce the stress reaction, decrease the production of inflammatory cytokines, with a favorable analgesic effect, and further reduce the occurrence of postoperative complications.

References


