Effect of sufentanil analgesia for hip replacement on pain mediator, stress hormone and inflammatory cytokine secretion
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ABSTRACT

Objective: To study the effect of sufentanil analgesia for hip replacement on pain mediator, stress hormone and inflammatory cytokine secretion. Methods: Patients who underwent hip replacement in People’s Hospital of Dongxihu District Wuhan between August 2015 and October 2017 were selected as the research subjects and randomly divided into the sufentanil group who accepted postoperative sufentanil analgesia and the fentanyl group who accepted postoperative fentanyl analgesia. The expression levels of pain mediators and inflammatory cytokines in peripheral blood as well as the levels of pain mediators, stress hormones and inflammatory cytokines in serum were measured 1 day and 3 days after surgery. Results: Serum PGE2, SP, β-EP, GH, COR, ACTH, INS, AT-II, TNF-α and ICAM-1 levels as well as peripheral blood MKP1, p38MAPK, Caspase-1, IL-1β and IL-18 expression intensity of sufentanil group 1 day and 3 days after surgery were significantly lower than those of fentanyl group. Conclusion: Sufentanil analgesia for hip replacement can be more effective than fentanyl to reduce the secretion of pain mediators, stress hormones and inflammatory cytokines.

1. Introduction

Hip replacement is a common surgical approach for clinical treatment of hip fractures, and the early postoperative rehabilitation of affected-side limb can help to promote the recovery of limb function. However, significant incision pain after hip replacement will affect the activity of the affected-side limb, which is not conducive to the early rehabilitation exercise. In clinical practice, effective postoperative analgesia is needed to create favorable conditions for limb activity after hip surgery[1,2]. Fentanyl and sufentanil are clinical common opioid analgesics that can excite μ receptors to exert analgesic effect. Sufentanil is a new type of opioid, and its chemical essence is the derivative after fentanyl N-4 substitution. The lipotropism of sufentanil is twice as much as that of fentanyl, and it is easier to pass through the membrane and blood-brain barrier and act on nerve tissue, so it can exert a more powerful analgesic effect[3]. In the following studies, we specifically analyzed the effects of sufentanil and fentanyl analgesia for hip replacement on pain mediator, stress hormone and inflammatory cytokine secretion.

2. General case information

2.1 Case inclusion and general information

Patients who underwent hip replacement in People’s Hospital of Dongxihu District Wuhan between August 2015 and October 2017 were chosen as the research subjects, all the patients underwent hip replacement under combined spinal-epidural anesthesia due to hip fractures, and the patients combined with peripheral neuropathy or chronic pain and the patients allergic to opioids were excluded. A total of 86 patients were enrolled and divided into two groups by random number table method, each with 43 cases. There were 23 males and 20 females in the sufentanil group, who were 48-69
years old; there were 24 males and 19 females in the fentanyl group, who were 46-66 years old. There was no significant difference in the general data between the two groups ($P>0.05$).

### 2.2 Postoperative analgesia methods

Both groups received anesthesia induction and maintenance performed by the same group of anesthetists and received hip replacement operated by the same group of surgeons, and the postoperative analgesia methods were as follows: the intraspinal medication was stopped 30 min before the surgery was finished, PCA pump was connected after deltoid skin puncture; the configuration scheme of PCA pump for sufentanil group was sufentanil 100 μg + lidocaine 200 mg + dexamethasone 10 mg + saline 100 mL while the configuration scheme of PCA pump for fentanyl group was sufentanil 1 mg + lidocaine 200 mg + dexamethasone 10 mg + saline 100 mL, with the pumping rate of 2 mL/h, 1.5 mL of single additional dose, and 20 min of locking time.

### 2.3 Laboratory detection methods

One day and three days after surgery, 5-6 mL of morning venous blood was collected and divided into two parts, one part was 4-5 mL and centrifuged to separate serum, and Elisa kit instruction was referred to determine the contents of PGE2, SP, β-EP, GH, COR, ACTH, INS, AT-II, TNF-α and ICAM-1; the other part was 1-2 mL and anti-coagulated with EDTA to incubate MKP1, p38MAPK, Caspase-1, IL-1 and IL-18 fluorescence antibody, and then the MKP1, p38MAPK, Caspase-1, IL-1 and IL-18 expressions were measured on flow cytometer.

### 2.4 Statistical analysis

Software SPSS 20.0 was used for t test analysis of the difference in measurement data between groups and $P<0.05$ meant statistical significance in differences.

### 3. Results

#### 3.1 Pain mediators in peripheral blood and serum

One day and three days after surgery, analysis of pain mediators PGE2 (μg/L), SP (ng/L), β-EP (μg/L), MKP1 and p38MAPK in peripheral blood and serum between the two groups of patients was as follows: serum PGE2, SP and β-EP levels as well as peripheral blood MKP1 and p38MAPK expression intensity of sufentanil group 1 day and 3 days after surgery were significantly lower than those of fentanyl group, and the differences in serum PGE2, SP and β-EP as well as peripheral blood MKP1 and p38MAPK were statistically significant between the two groups of patients 1 day and 3 days after surgery ($P<0.05$).

#### 3.2 Stress hormone levels in serum

One day and three days after surgery, analysis of stress hormones GH (ng/L), COR (μg/L), ACTH (ng/L), INS (U/mL) and AT-II (ng/L) in serum between the two groups of patients was as follows: serum GH, COR, ACTH, INS and AT-II levels of sufentanil group 1 day and 3 days after surgery were significantly lower than those of fentanyl group, and the differences in serum GH, COR, ACTH, INS and AT-II were statistically significant between the two groups of patients 1 day and 3 days after surgery ($P<0.05$).

#### 3.3 Inflammatory cytokines in serum and peripheral blood

One day and three days after surgery, analysis of inflammatory cytokines TNF-α (μg/L), ICAM-1 (μg/L), Caspase-1, IL-1β and IL-18 in peripheral blood and serum between the two groups of patients was as follows: serum TNF-α and ICAM-1 levels as well as peripheral blood Caspase-1, IL-1β and IL-18 expression intensity of sufentanil group 1 day and 3 days after surgery were significantly

### Table 1.

Comparison of pain mediators in peripheral blood and serum between the two groups of patients after surgery.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>PGE2</th>
<th>SP</th>
<th>β-EP</th>
<th>MKP1</th>
<th>p38MAPK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil</td>
<td>43</td>
<td>1 d after surgery</td>
<td>1.52±0.17</td>
<td>121.3±16.2</td>
<td>22.8±2.9</td>
<td>0.77±0.11</td>
<td>0.79±0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after surgery</td>
<td>1.21±0.15</td>
<td>106.1±13.5</td>
<td>18.9±2.3</td>
<td>0.42±0.07</td>
<td>0.38±0.06</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>43</td>
<td>1 d after surgery</td>
<td>2.48±0.34</td>
<td>158.4±17.8</td>
<td>29.5±4.2</td>
<td>1.01±0.15</td>
<td>1.02±0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after surgery</td>
<td>2.12±0.26</td>
<td>139.4±17.1</td>
<td>24.1±3.6</td>
<td>0.78±0.09</td>
<td>0.72±0.09</td>
</tr>
</tbody>
</table>

*: comparison between sufentanil group and fentanyl group, $P<0.05$.

### Table 2.

Comparison of stress hormones in serum between the two groups of patients after surgery.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>GH</th>
<th>COR</th>
<th>ACTH</th>
<th>INS</th>
<th>AT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil</td>
<td>43</td>
<td>1 d after surgery</td>
<td>2.96±0.36</td>
<td>201.3±26.8</td>
<td>27.6±4.2</td>
<td>8.3±1.1</td>
<td>9.3±1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after surgery</td>
<td>2.11±0.34</td>
<td>189.4±22.5</td>
<td>22.1±3.4</td>
<td>7.0±0.8</td>
<td>7.2±0.9</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>43</td>
<td>1 d after surgery</td>
<td>4.95±0.62</td>
<td>236.4±29.4</td>
<td>34.8±4.9</td>
<td>13.2±1.7</td>
<td>14.8±1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after surgery</td>
<td>3.56±0.42</td>
<td>213.2±26.8</td>
<td>29.3±3.6</td>
<td>11.8±1.5</td>
<td>12.1±1.5</td>
</tr>
</tbody>
</table>

*: comparison between sufentanil group and fentanyl group, $P<0.05$. 

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facilitate the generation of pain perception of a variety of other pain mediators, reduce the pain threshold and capillary permeability in peripheral tissue, help the local infiltration generated from the catalysis of COX2, and it can increase the PGE2 is the product during arachidonic acid metabolism, it is that regulates endocrine homeostasis, the endocrine function of hormones. The pituitary gland is an important endocrine gland region and induce the production of pain perception reaction activation are involved in the generation and amplification inflammatory response; the inflammatory cytokines that are inflammatory mediators in the process of inflammatory response, the former has stronger liposolubility and better analgesic effect[4]. Postoperative incision pain is mediated by a variety of pain mediators, and PGE2, SP and β-EP are common pain mediators. PGE2 is the product during arachidonic acid metabolism, it is generated from the catalysis of COX2, and it can increase the capillary permeability in peripheral tissue, help the local infiltration of a variety of other pain mediators, reduce the pain threshold and facilitate the generation of pain perception[5]; SP and β -SP are neuropeptides that mediate pain signal transduction, and they can transmit pain signals generated by local tissue trauma to the central region and induce the production of pain perception[6,7]. When pain mediators mediate the pain signal transmission, a variety of signal molecules in peripheral nerve and central nerve are abnormally activated and participate in the signal transmission, the p38MAPK in MAPks signaling molecule family plays an important role in the conduction of pain signals, and PGE2, SP, β -EP and other pain mediators can promote MKP-1 activation, and then activate p38MAPK and promote pain conduction through the activation of MKP-1 on p38MAPK[8,9]. Analysis of the changes in above pain mediator secretion after hip replacement showed that serum PGE2, SP and β -EP levels as well as peripheral blood MKP1 and p38MAPK expression intensity of sufentanil group after surgery were significantly lower than those of fentanyl group. This shows that sufentanil can be more effective than fentanyl to reduce pain mediator secretion and relieve postoperative pain.

The surgical trauma itself and postoperative incision pain are strong stressors for the body, and will cause internal environment to change and increase the synthesis and secretion of a variety of endocrine hormones. The pituitary gland is an important endocrine gland that regulates endocrine homeostasis, the endocrine function of pituitary gland is significantly abnormal and the secretion of various pituitary hormones changes in the stress process[10]. GH is a kind of endocrine hormone that is secreted by the pituitary gland, and regulates bone growth as well as glucolipid and energy metabolism, and the mass secretion of GH during stress process can enhance the metabolic rate of the body[11]; ACTH is the hormone that is secreted by adrenohypophysis and can regulate the endocrine function of adrenal cortex, and the mass secretion of ACTH in the stress process can further increase the COR secreted by adrenal cortex, and then stabilize lysosomal membrane and enhance the ability of the body to tolerate stress through the action of COR[12]. Both GH and COR have certain regulatory effect on blood glucose, which can elevate the blood glucose and increase the compensatory secretion of endogenous INS[13]. In addition, the stress process will also cause the activation of the RAS system, the increase of AT-II secretion and the changes in the systemic hemodynamic characteristics[14]. Analysis of the changes in above stress hormone secretion after hip replacement showed that serum GH, COR, ACTH, INS and AT-II levels of sufentanil group after surgery were significantly lower than those of fentanyl group. This indicates that sufentanil can be more effective than fentanyl to reduce the secretion of stress hormones and relieve the postoperative stress level.

Surgical trauma can activate not only the stress response, but also the inflammatory response; the inflammatory cytokines that are massively secreted in the process of postoperative inflammatory reaction activation are involved in the generation and amplification of pain perception[15]. TNF-α and ICAM-1 are the cytokines that play an important role in the process of inflammation, the former is a kind of pro-inflammatory factor that activates a variety of inflammatory cells and can increase the cascade release of other inflammatory mediators in the process of inflammatory response, and the latter is a kind of intercellular adhesion molecule that can promote the adhesion and infiltration of inflammatory cells to the inflammatory lesions, which in turn is conducive to the amplification of inflammatory response[16,17]. NLRP3 inflammasome is the newly discovered inflammatory regulatory molecule in recent years, which activates Caspase-1 through the activation of upstream molecule NLRP3, then splits IL-1 β and IL-18 precursor and generates a lot of IL-1 β and IL-18. Analysis of the changes in above stress hormone secretion after hip replacement showed that serum TNF-α and ICAM-1 levels as well as peripheral blood Caspase-1, IL-1 β

### Table 3.
Comparison of inflammatory cytokines in peripheral blood and serum between the two groups of patients after surgery.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time After Surgery</th>
<th>TNF-α</th>
<th>ICAM-1</th>
<th>IL-1 β</th>
<th>IL-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil</td>
<td>43</td>
<td>1 d after surgery</td>
<td>7.6±0.9</td>
<td>253.3±33.6</td>
<td>0.72±0.09</td>
<td>0.76±0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after surgery</td>
<td>6.3±0.8</td>
<td>227.1±31.4</td>
<td>0.52±0.08</td>
<td>0.51±0.06</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>43</td>
<td>1 d after surgery</td>
<td>11.5±1.4</td>
<td>326.8±42.4</td>
<td>1.03±0.14</td>
<td>1.02±0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after surgery</td>
<td>9.2±1.2</td>
<td>289.3±34.9</td>
<td>0.84±0.11</td>
<td>0.79±0.08</td>
</tr>
</tbody>
</table>

*: comparison between sufentanil group and fentanyl group, P<0.05.
and IL-18 expression intensity of sufentanil group after surgery were significantly lower than those of fentanyl group. It means that sufentanil is more effective than fentanyl to reduce the secretion of inflammatory cytokines and relieve the degree of postoperative inflammatory response.

Based on the analysis and discussion of above results, this research can be summarized as follows: compared with postoperative fentanyl analgesia, sufentanil analgesia for hip replacement can more effectively decrease the secretion of pain mediators, stress hormones and inflammatory cytokines.

References


