Effect of hydromorphone hydrochloride combined with ropivacaine for orthopedic postoperative PCEA on serum pain mediators and stress response

Ran Chen, Yuan-Hui Liu, Yan Yan, De-Xing Luo

Department of Anesthesiology, Central People’s Hospital of Huizhou City, Guangdong Province, Huizhou City, Guangdong Province, 516001, China

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ABSTRACT

Objective: To study the effect of hydromorphone hydrochloride combined with ropivacaine for orthopedic postoperative patient-controlled epidural analgesia (PCEA) on serum pain mediators and stress response. Methods: A total of 84 patients who received fracture surgery under combined spinal epidural anesthesia and required postoperative analgesia in our hospital from May 2012 to December 2015 were randomly divided into two groups, the observation group received ropivacaine combined with hydromorphone hydrochloride for postoperative PCEA, and the control group accepted ropivacaine combined with morphine hydrochloride for postoperative PCEA. PCEA, serum pain mediator levels and the degree of stress response were compared between two groups. Results: The number of additional pressing on analgesia pump and the dosage of anesthetics of observation group within 24 h after operation were significantly lower than those of control group; 1 d, 3 d and 5 d after operation, serum 5-HT, NO and PGE₂ as well as Cor, GH and PRL levels of observation group were significantly lower than those of control group; 1 d, 3 d, 5 d and 7 d after operation, REE levels of observation group were significantly lower than those of control group. Conclusions: Hydromorphone hydrochloride combined with ropivacaine for orthopedic postoperative PCEA can enhance analgesic effect, reduce the dosage of anesthetics, suppress the generation of pain mediators and reduce stress response.

1. Introduction

Fractures can cause strong pain in fracture sites, and although surgery can achieve fracture reduction and internal fixation, local muscle stretching will further aggravate local pain and affect postoperative early activities of the limbs. Postoperative analgesia is an important part after fracture surgery, and can alleviate the pain and create favorable conditions for the early activities of the affected limbs[1,2]. Patient-controlled epidural analgesia (PCEA) is suitable for the postoperative analgesia of patients receiving fracture surgery under combined spinal epidural anesthesia, and it pumps analgesics into the epidural space through the epidural catheter to achieve analgesic effect[3,4]. Morphine hydrochloride combined with ropivacaine is commonly used solution for PCEA, but the onset time of morphine hydrochloride is relatively slow and about 30min, which will affect the analgesic effect and increase the dosage of analgesics. Hydromorphone hydrochloride is a semisynthetic derivative of morphine, its analgesia intensity is 8-10 times of that of morphine, its onset time is faster and only 10 min, and it is more suitable for PCEA. In the following study, the effect of hydromorphone hydrochloride combined with ropivacaine for orthopedic postoperative PCEA on serum pain mediators and stress response was analyzed.
2. Materials and methods

2.1. Research subjects

A total of 84 patients who received fracture surgery under combined spinal epidural anesthesia and required postoperative analgesia in our hospital from May 2012 to December 2015 were selected, were with ASA I-II grade, received elective fracture surgery under combined spinal epidural anesthesia after admission and received postoperative patient-controlled epidural analgesia; the patients who took opioid drugs, non-steroidal drugs or other analgesic drugs for a long term were ruled out. Random number table was used to divide the included patients into observation group and control group (n=42). Observation group received hydromorphone hydrochloride combined with ropivacaine for PCEA, including 24 male cases and 18 female cases who were (48.75±6.23) years old; control group received morphine hydrochloride combined with ropivacaine for PCEA, including 26 male cases and 16 female cases who were (49.12±6.63) years old. The two groups of patients showed no significant difference in general data (P>0.05).

2.2. Research methods

2.2.1. Postoperative PCEA methods

Mixture of 60 μg/mL ropivacaine mesylate and 10 μg/mL hydromorphone hydrochloride was configured, analgesia pump and epidural catheter were connected, background infusion speed was 4 mL/h, each additional dose was 4 mL and locking time was 10 min. PCEA scheme for control group was morphine hydrochloride combined with ropivacaine, specifically as follows: the mixture of 60 μg/mL ropivacaine mesylate and 50 μg/mL morphine hydrochloride was configured, analgesia pump and epidural catheter were connected, background infusion speed was 4 mL/h, each additional dose was 4 mL and locking time was 10 min. The number of additional pressing on analgesia pump and the dosage of anesthetics were observed within 24 h after surgery.

2.2.2. Serum sample collection methods

Before operation as well as 1 d, 3 d and 5 d after operation, about 6 mL of peripheral venous blood was collected respectively at 7:00-7:30 in the morning, let stand at room temperature for 30 min and then immediately centrifuged in the centrifugal machine for 10 min at a speed of 3 000 r/min, and serum was separated, then moved into the new 1.5 mL EP tubes, numbered and then placed in -80 ℃ ultra-low temperature refrigerator for preservation.

2.2.3. Serum index detection methods

Serum samples were taken out and placed at room temperature for thawing, then enzyme-linked immunosorbent assay kit and matched microplate reader were used to determine serum 5-hydroxytryptamine (5-HT), nitric oxide (NO) and prostaglandin E₂ (PGE₂) levels, and RIA kits were used to determine cortisol (Cor), growth hormone (GH) and prolactin (PRL) levels. All the experimental steps were conducted according to the kit instruction.

2.2.4. Resting energy expenditure (REE) assessment methods

Before operation as well as 1 d, 3 d, 5 d and 7 d after operation, CCM/D nutrition metabolism monitoring system was used to determine resting energy expenditure (REE) of two groups of patients.

2.3. Statistical methods

SPSS20.0 software was used to input and analyze data, measurement data was analyzed by t test and P<0.05 indicated statistical significant differences.

3. Results

3.1. PCEA usage of two groups

The number of additional pressing on analgesia pump of observation group within 24 h after operation was (16.82±2.65) times, and the dosage of hydromorphone hydrochloride was (1.52±0.42) mg; the number of additional pressing on analgesia pump of control group within 24 h after operation was (25.11±3.96) times, and the dosage of morphine hydrochloride was (5.89±0.95) mg. t test showed that the number of additional pressing on analgesia pump and the dosage of anesthetics of observation group within 24 h after operation were significantly lower than those of control group.

3.2. Perioperative pain mediator changes

Before operation, differences in serum pain mediators 5-HT, NO and PGE₂ levels of two groups were not statistically significant (P>0.05); 1 d, 3 d and 5 d after operation, serum 5-HT, NO and PGE₂ levels of both groups were significantly lower than those before operation, serum 5-HT, NO and PGE₂ levels of observation group were significantly lower than those of control group (P<0.05) (Table 1).

Table 1

Comparison of perioperative serum pain mediators of two groups.

<table>
<thead>
<tr>
<th></th>
<th>Groups</th>
<th>Time</th>
<th>5-HT (μmol/L)</th>
<th>NO (μmol/L)</th>
<th>PGE₂ (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observation</td>
<td>Before operation</td>
<td>0.83±0.11</td>
<td>26.92±3.52</td>
<td>38.94±5.12</td>
</tr>
<tr>
<td></td>
<td>group (n=42)</td>
<td>1 d after operation</td>
<td>0.34±0.06</td>
<td>15.62±1.96</td>
<td>20.32±3.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after operation</td>
<td>0.21±0.03</td>
<td>11.42±1.47</td>
<td>15.64±1.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 d after operation</td>
<td>0.14±0.02</td>
<td>8.72±1.02</td>
<td>12.12±1.86</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>Before operation</td>
<td>0.88±0.12</td>
<td>27.25±5.91</td>
<td>39.52±7.24</td>
</tr>
<tr>
<td></td>
<td>(n=42)</td>
<td>1 d after operation</td>
<td>0.65±0.08</td>
<td>22.12±3.06</td>
<td>31.33±5.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after operation</td>
<td>0.42±0.07</td>
<td>17.78±2.62</td>
<td>23.85±4.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 d after operation</td>
<td>0.30±0.05</td>
<td>13.02±1.95</td>
<td>18.89±3.28</td>
</tr>
</tbody>
</table>
3.2. Perioperative energy metabolism

Before operation, REE levels of two groups showed no statistically significant difference ($P>0.05$); REE level of observation group showed increasing trend within 3 d after operation and decreased gradually after 3 d, and REE level of control group showed increasing trend within 5 d after operation and decreased gradually after 5 d; at various points in time after operation, REE levels of observation group were significantly lower than those of control group ($P<0.05$) (Table 2).

3.4. Perioperative stress hormone changes

Before operation, differences in serum stress hormones Cor, GH and PRL levels of two groups were not statistically significant ($P>0.05$); 1 d, 3 d and 5 d after operation, serum Cor, GH and PRL levels of both groups were significantly lower than those before operation, serum Cor, GH and PRL levels of observation group were significantly lower than those of control group ($P<0.05$) (Table 3).

4. Discussion

Patient-controlled intravenous analgesia or PCEA is mostly needed after fracture surgery. Combined spinal epidural anesthesia is mostly selected in fracture surgery, so the operation of pumping analgesics into the epidural space by epidural catheters is simpler, and meanwhile, its effect on nerve block is better than that of intravenous analgesia[5,6]. The compatibility of opioids and local anesthetics is the common solution for PCEA, the two drugs can realize the synergistic analgesic effect and the use of local anesthetics can reduce the dosage of opioids and reduce the risk of adverse reactions. Morphine is the commonly used opioid for PCEA, it can obtain more precise spinal analgesic effect, but the onset is relatively slow and about 30 min, but the locking time of patient-controlled analgesia pump is only 15 min, and when morphine is pumped into the epidural but is not functioning yet, patients press the pump again because of poor analgesic effect, causing the hyper-concentration of intraspinal morphine and increasing the occurrence risk of complications such as respiratory depression; if patients do not press the pump again, the analgesic effect will be affected to a certain extent[7,8].

Hydromorphone hydrochloride is a semisynthetic derivative of morphine and also belongs to the opioids, its analgesic mechanism is the same as that of morphine and the analgesic intensity is 8-10 times of that of morphine, the onset time is 10-15min and shorter than that of morphine, and it can interwork with the locking time of analgesia pump to avoid the increased intraspinal dosage and occurrence risk of adverse reactions that are caused because the drugs do not reach the onset time and patients add the dosage[9,10]. In the study, hydromorphone hydrochloride and morphine hydrochloride for PCEA after fracture surgery were analyzed, PCEA usage of the two drugs was compared at first, and the results showed that the number of additional pressing on analgesia pump and the dosage of anesthetics of observation group within 24 h after operation were significantly lower than those of control group. It confirms that hydromorphone hydrochloride for PCEA can reduce the number of additional dosage and the dosage of drugs, and the postoperative pain degree is smaller in patients with hydromorphone hydrochloride for postoperative PCEA.

In order to further clear the analgesic effect of hydromorphone hydrochloride and morphine hydrochloride for postoperative PCEA from molecular levels, the pain mediator levels and the degree of stress response of two groups were analyzed in the study. 5-HT can act on peripheral nociceptor and transmit signal into the center, which produces pain perception through the analysis of cerebral cortex[11]; PGE$_2$ is the product synthesized after cyclooxygenase

### Table 2
Comparison of perioperative REE levels of two groups [kcal/(kg•d)].

<table>
<thead>
<tr>
<th>Groups</th>
<th>Case No.</th>
<th>Before operation</th>
<th>1 d after operation</th>
<th>3 d after operation</th>
<th>5 d after operation</th>
<th>7 d after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>42</td>
<td>18.76±2.62</td>
<td>22.52±3.59</td>
<td>25.22±3.86</td>
<td>23.42±3.12</td>
<td>20.14±2.95</td>
</tr>
<tr>
<td>Control group</td>
<td>42</td>
<td>18.33±2.54</td>
<td>24.95±4.12</td>
<td>28.21±3.95</td>
<td>29.69±4.09</td>
<td>25.52±3.59</td>
</tr>
</tbody>
</table>

### Table 3
Comparison of perioperative serum stress hormones of two groups (ng/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>Cor</th>
<th>GH</th>
<th>PRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before operation</td>
<td>425.39±62.52</td>
<td>9.39±1.05</td>
<td>93.42±11.35</td>
</tr>
<tr>
<td>(n=42)</td>
<td>1 d after operation</td>
<td>353.44±57.81</td>
<td>6.69±0.83</td>
<td>56.23±7.83</td>
</tr>
<tr>
<td></td>
<td>3 d after operation</td>
<td>284.51±40.38</td>
<td>4.15±0.56</td>
<td>40.22±5.62</td>
</tr>
<tr>
<td></td>
<td>5 d after operation</td>
<td>221.35±32.54</td>
<td>2.89±0.33</td>
<td>23.62±3.64</td>
</tr>
<tr>
<td>Control group</td>
<td>Before operation</td>
<td>440.12±65.68</td>
<td>9.69±1.15</td>
<td>95.14±10.59</td>
</tr>
<tr>
<td>(n=42)</td>
<td>1 d after operation</td>
<td>395.12±48.92</td>
<td>8.14±0.94</td>
<td>78.94±9.24</td>
</tr>
<tr>
<td></td>
<td>3 d after operation</td>
<td>331.45±46.74</td>
<td>6.75±0.84</td>
<td>60.29±6.79</td>
</tr>
<tr>
<td></td>
<td>5 d after operation</td>
<td>294.52±30.49</td>
<td>4.42±0.55</td>
<td>42.23±5.82</td>
</tr>
</tbody>
</table>
2 catalyzes arachidonic acid, and it can increase the sensitivity of nociceptor and reduce the pain threshold, thus increasing the postoperative pain[12]. NO is a new gaseous signal molecule discovered in recent years, which can regulate the generation of pain at central and peripheral levels, and is a mediator with algogenic effect[13]. In the study, analysis of perioperative pain mediator levels of two groups proved that serum 5-HT, NO and PGE2 levels of both groups after operation were significantly lower than those before operation, and serum 5-HT, NO and PGE2 levels of observation group were significantly lower than those of control group. This means that hydromorphone hydrochloride for PCEA after fracture surgery can inhibit the synthesis and release of pain mediators, thus alleviating the pain degree.

The trauma that is caused by both fracture itself and surgical operation will cause the body's stress response, and postoperative continuous pain will further amplify stress response. Stress state of the body can raise the metabolism levels and increase energy expenditure[14]. In the study, comparison of perioperative REE between two groups showed that REE of both groups increased at first and then decreased, the REE of observation group were lower than those of control group, early postoperative REE decrease might be related to the stress state caused by surgical trauma and pain, and hydromorphone hydrochloride had better analgesic effect than morphine hydrochloride and could improve postoperative hypermetabolism state and reduce the stress response. Cor is a common index to reflect stress level, Cor is the hormone synthesized and secreted by adrenal cortex after the hypothalamus and pituitary function are enhanced, and in the process, the synthesis of GH and PRL will also increase[15,16]. In the study, analysis of the stress hormones in serum of two groups confirmed that serum Cor, GH and PRL levels of observation group after operation were significantly lower than those of control group. This means that hydromorphone hydrochloride for PCEA after fracture surgery can inhibit the synthesis and release of stress hormones and reduce the stress response.

To sum up, hydromorphone hydrochloride combined with ropivacaine for orthopedic postoperative PCEA can enhance analgesic effect, reduce the dosage of anesthetics, suppress the generation of pain mediators and reduce stress response.

References


