Effect of dezocine pretreatment on emergence agitation and related internal environment changes in children with general anesthesia surgery

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ABSTRACT

Objective: To study the effect of dezocine pretreatment on the emergence agitation and related internal environment changes in children with general anesthesia surgery. Methods: A total of 200 children who underwent general anesthesia surgery in the Central Hospital of Xiaogan between January 2015 and December 2017 were enrolled in the study and divided into two groups by random number table method, dezocine group received routine general anesthesia and intravenous injection of dezocine 30 min before the end of surgery, and control group received routine general anesthesia and intravenous injection of saline 30 min before the end of surgery. The CHEPOS score of emergence agitation was performed during anesthesia recovery; the levels of inflammatory stress mediators in serum as well as the expression of stress signal molecules and inflammatory signal molecules in peripheral blood were measured before anesthesia induction and during anesthesia recovery. Results: The CHEPOS score of emergence agitation of dezocine group was lower than that of control group; compared with those of same group before anesthesia induction, serum ACTH, Cor, INS, ICAM1 and TNF- α levels as well as peripheral blood CHOP, GRP78, JNK, c-jun, CD14 and SR expression intensity of both groups of patients were significantly higher whereas IRS-1, IRS-2 and PKB expression intensity were significantly lower during anesthesia recovery, and serum ACTH, Cor, INS, ICAM1 and TNF- α levels as well as peripheral blood CHOP, GRP78, JNK, c-jun, CD14 and SR expression intensity of dezocine group during anesthesia recovery were significantly lower than those of control group whereas IRS-1, IRS-2 and PKB expression intensity were significantly higher than those of control group. Conclusions: Dezocine pretreatment has improving effect on the emergence agitation and related internal environment changes in children with general anesthesia surgery.

1. Introduction

Emergence agitation is the most common complication during recovery from general anesthesia in pediatric surgery, the agitation itself is self-limiting, but without control or prevention, it will affect the stability of vital signs in awakening period, and there may be serious consequences such as incision cracks in some children. In addition, the occurrence of emergence agitation can also cause disturbance in the internal environment, and excessive activation of inflammation and stress response is a prominent feature of the internal environment disturbance[1,2]. Traditional narcotic analgesics, such as morphine and fentanyl have powerful sedative and analgesic effects, they can effectively prevent the happening of the emergence agitation, but they easily produce different degrees of respiration and circulation inhibition, and are not suitable to be used in awaking after pediatric surgery anesthesia. Dezocine is a new type of opioid receptor agonist - antagonist drug, which has stronger agonistic action on κ receptors, has weaker agonistic action on δ receptors, and has partial agonistic and antagonistic actions on μ receptors[3]. In the following studies, we specifically analyzed the effect of dezocine pretreatment on the emergence agitation and related internal environment changes in children with general anesthesia surgery.

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2. Materials and methods

2.1. General information of research subjects

Prospective, randomized and controlled study was designed, 200 children who underwent general anesthesia surgery in the Central Hospital of Xiaogan between January 2015 and December 2017 were selected and enrolled in the study, they were with preoperative ASA I - II grade, and those with general anesthesia contraindications and those allergic to dezocine were ruled out. The children enrolled were divided into the dezocine group and the control group by random number table method. There were a total of 100 cases in the dezocine group, they were 4-11 years old, there were 55 males and 45 females, 57 cases were at ASA I grade and 43 cases were at grade II; there were a total of 100 cases in the control group, they were 4-10 years, there were 58 males and 42 females, 59 cases were at ASA I grade and 41 cases were at grade II. There was no significant difference in the general data between the two groups (P>0.05).

2.2. Anesthesia methods

After the two groups of children entered the operating room, the same methods were used for anesthesia induction and anesthesia maintenance, and the anesthesia was induced by midazolam 0.1 mg/kg, fentanyl 2 μg/kg, propofol 1-2 mg/kg and atracurium 0.6 mg/kg; anesthesia was maintained by continuous inhalation of 1%-3% sevoflurane, BIS value was controlled at 40-60, and atracurium was added according to the muscle relaxation. About 30 min before the end of the operation, dezocine group were given intravenous injection of 0.1 mg/kg dezocine, and control group were given intravenous injection of saline.

2.3. CHEPOS scoring of emergence agitation

In anesthesia recovery period, CHEOPS grading rules were used to evaluate emergence agitation from the facial expressions, limbs activities, crying, language and body, each index might be scored by 0, 1 or 2 points, and the total score was calculated after the evaluation of each index score.

2.4. Laboratory index detection

Before anesthesia induction and during recovery period, 5-6 mL of cubital venous blood was collected and divided into two parts. One part of cubital venous blood was centrifuged to separate serum, and the instructions of Elisa kit were followed to detect the contents of ACTH, Cor, INS, ICAM1 and TNF-α. The other part of cubital venous blood was anti-coagulated with EDTA to incubate the fluorescence antibodies of CHOP, GRP78, IRS-1, IRS-2, PKB, JNK, c-jun, CD14 and SR, and the expression intensity of the corresponding molecules was determined on the flow cytometer.

2.5. Statistical methods

Software SPSS20.0 was used to input data, the differences in the measurement data between groups were analyzed by t test and P<0.05 indicated statistical significance in the differences.

3. Results

3.1. CHEPOS score of emergence agitation

The CHEPOS score of emergence agitation of dezocine group was (2.31±0.35) points and the CHEPOS score of emergence agitation of control group was (4.29±0.55) points. The t test analysis of the differences in the CHEPOS scores of emergence agitation between the two groups of children showed that the CHEPOS score of emergence agitation of dezocine group was significantly lower than that of control group (P<0.05).

3.2. Serum inflammatory and stress mediator levels

Serum ACTH, Cor, INS, ICAM1 and TNF-α levels were not significantly different between the two groups of children before anesthesia induction (P>0.05) whereas serum ACTH, Cor, INS, ICAM1 and TNF-α levels were significantly different during recovery period (P<0.05), and serum ACTH, Cor, INS, ICAM1 and TNF-α levels of dezocine group were lower than those of control group; compared with inflammatory and stress mediators of same group before anesthesia induction, serum ACTH, Cor, INS, ICAM1 and TNF-α levels of both groups of patients were significantly lower than before anesthesia induction. The comparison of serum inflammatory and stress mediators before anesthesia induction and during recovery period is shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>ACTH (pmol/L)</th>
<th>Cor (ng/mL)</th>
<th>INS (U/mL)</th>
<th>ICAM1 (ng/mL)</th>
<th>TNF-α (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dezocine group</td>
<td>100</td>
<td>Before induction</td>
<td>9.12±1.25</td>
<td>190.2±20.3</td>
<td>5.48±0.75</td>
<td>318.5±46.2</td>
<td>30.85±4.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During recovery</td>
<td>13.21±1.56*</td>
<td>214.8±28.4*</td>
<td>7.22±0.93*</td>
<td>427.9±52.9*</td>
<td>45.12±6.46*</td>
</tr>
<tr>
<td>Control group</td>
<td>100</td>
<td>Before induction</td>
<td>9.05±1.08</td>
<td>188.9±19.4</td>
<td>5.51±0.71</td>
<td>320.1±39.4</td>
<td>31.22±3.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During recovery</td>
<td>17.58±2.21*</td>
<td>232.5±31.5*</td>
<td>9.93±1.1*</td>
<td>558.6±64.9*</td>
<td>59.53±6.95*</td>
</tr>
</tbody>
</table>

*: comparison between before induction and during recovery within group, P<0.05; #: comparison between groups during recovery, P<0.05.
Table 2
Comparison of peripheral blood stress signal molecules before anesthesia induction and during recovery period (x±sd).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>CHOP</th>
<th>GRP78</th>
<th>IRS-1</th>
<th>IRS-2</th>
<th>PKB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dezocine</td>
<td>100</td>
<td>Before induction</td>
<td>1.02±0.15</td>
<td>0.99±0.11</td>
<td>1.04±0.17</td>
<td>1.05±0.15</td>
<td>0.96±0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During recovery</td>
<td>1.41±0.18</td>
<td>1.55±0.22</td>
<td>0.72±0.06</td>
<td>0.61±0.08</td>
<td>0.68±0.08</td>
</tr>
<tr>
<td>Control group</td>
<td>100</td>
<td>Before induction</td>
<td>1.00±0.13</td>
<td>1.02±0.14</td>
<td>1.01±0.15</td>
<td>1.03±0.16</td>
<td>0.98±0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During recovery</td>
<td>1.98±0.25</td>
<td>2.21±0.30</td>
<td>0.47±0.08</td>
<td>0.35±0.04</td>
<td>0.37±0.04</td>
</tr>
</tbody>
</table>

*: comparison between before induction and during recovery within group, P<0.05; #: comparison between groups during recovery, P<0.05.

Table 3
Comparison of peripheral blood inflammatory signal molecules before anesthesia induction and during recovery period (x±sd).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>JNK</th>
<th>c-jun</th>
<th>CD14</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dezocine</td>
<td>100</td>
<td>Before induction</td>
<td>1.04±0.17</td>
<td>0.99±0.12</td>
<td>1.01±0.15</td>
<td>0.97±0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During recovery</td>
<td>1.50±0.21</td>
<td>1.33±0.18</td>
<td>1.70±0.24</td>
<td>1.66±0.20</td>
</tr>
<tr>
<td>Control group</td>
<td>100</td>
<td>Before induction</td>
<td>1.02±0.15</td>
<td>1.01±0.13</td>
<td>0.97±0.13</td>
<td>1.00±0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During recovery</td>
<td>2.13±0.34</td>
<td>1.87±0.22</td>
<td>2.56±0.34</td>
<td>2.37±0.35</td>
</tr>
</tbody>
</table>

*: comparison between before induction and during recovery within group, P<0.05; #: comparison between groups during recovery, P<0.05.

3.3. Peripheral blood stress signal molecule expression

Peripheral blood CHOP, GRP78, IRS-1, IRS-2 and PKB expression intensity were not significantly different between the two groups of children before anesthesia induction (P>0.05) whereas peripheral blood CHOP, GRP78, IRS-1, IRS-2 and PKB expression intensity were significantly different during recovery period (P<0.05), and peripheral blood CHOP and GRP78 expression intensity of dezocine group were lower than those of control group whereas IRS-1, IRS-2 and PKB expression intensity were higher than those of control group; compared with stress signal molecules of same group before anesthesia induction, peripheral blood CHOP and GRP78 expression intensity of both groups of patients were significantly higher whereas IRS-1, IRS-2 and PKB expression intensity were significantly lower during recovery period (P<0.05) (Table 2).

3.4. Peripheral blood inflammatory signal molecule expression

Peripheral blood JNK, c-jun, CD14 and SR expression intensity were not significantly different between the two groups of children before anesthesia induction (P>0.05) whereas peripheral blood JNK, c-jun, CD14 and SR expression intensity were significantly different during recovery period (P<0.05), and peripheral blood JNK, c-jun, CD14 and SR expression intensity of dezocine group were lower than those of control group; compared with inflammatory signal molecules of same group before anesthesia induction, peripheral blood JNK, c-jun, CD14 and SR expression intensity of both groups of patients were significantly higher during recovery period (P<0.05).

4. Discussion

Inhalational anesthetics are mainly adopted for the anesthesia maintenance in pediatric surgery, they have good controllability to anesthesia and cause less effect on the respiration and circulation, but the risk of emergence agitation greatly increases after inhalational anesthetics are used. The main manifestations of emergence agitation include excitement, struggle, unconscious action and other consequences, and cause both physical and mental damage to the children. The harm caused by emergence agitation raises higher requirement for pediatric anesthesia, and it is necessary to carry out the necessary drug intervention before the recovery period to reduce the degree of emergence agitation[4,5]. Traditional opioid drugs such as fentanyl can directly excite μ receptor and exert analgesic and sedative effects, it has preventive value for emergence agitation, but it has inhibiting effect on respiration and circulation, and does not apply to the pediatric population. Dezocine is a new opioid receptor agonist-antagonist drug, which can on the one hand, strongly excite the κ receptor and exert strong analgesic effect and weak sedative effect, and on the other hand, has both agonistic and antagonistic effects on the μ receptor, and has weaker respiratory inhibition and addiction[6,7]. Analysis of the differences in emergence agitation score between the two groups showed that the CHEPOS score of emergence agitation of dezocine group was significantly lower than that of control group. This shows that dezocine pretreatment 30 minutes before the end of the operation can reduce the level of emergence agitation after the operation.

The occurrence of emergence agitation can not only cause the mental states in while the consciousness and behavior are separated, but can also cause homeostasis change, and its important feature is the excessive activation of inflammatory and stress response.
The excessive activation of stress response is manifested as the changes in the secretion of a variety of endocrine hormones, the Cor secreted by the adrenal cortex is the most important endocrine hormone involved in stress response, its secretion is regulated by pituitary hormone ACTH, and its mass secretion can produce glycemic effect and stimulate the compensatory release of INS[8,9]. Excessive activation of the inflammatory response is manifested as the changes in the secretion of various cytokines, ICAM1 and TNF-α are two important cytokines involved in inflammation, the former promotes intercellular adhesion and can mediate the adhesion and infiltration of a variety of inflammatory cells to the inflammatory site, and the latter has pro-inflammatory activity and can mediate the activation of a variety of inflammatory cells and promote the cascade amplification of inflammation[10,11]. Analysis of the changes in inflammatory stress mediators before anesthesia induction and during anesthesia recovery showed that serum ACTH, Cor, INS, ICAM1 and TNF-α levels of both groups of patients were significantly higher during recovery period, and serum ACTH, Cor, INS, ICAM1 and TNF-α levels of dezocine group during recovery period were lower than those of control group. This means that the inflammatory and stress reaction are activated to different degrees during anesthesia recovery, and dezocine pretreatment can significantly weaken the activation of inflammatory and stress reaction during anesthesia recovery.

Activation of stress response during operation and anesthesia involves the activation of multiple signaling pathways in the cells[12]. Endoplasmic reticulum stress is an important form of stress reaction activation, it is characterized by endoplasmic reticulum physiological dysfunction and the accumulation of misfolded or unfolded proteins in the endoplasmic reticulum, and moderate endoplasmic reticulum stress in the process of trauma helps to enhance the body’s tolerance to trauma; CHOP is a specific transcription factor of endoplasmic reticulum stress, which increases the chaperone protein GRP78 to mediate multiple pathophysiological changes during endoplasmic reticulum stress[13,14]. In addition to endoplasmic reticulum stress, the persistent stress response can also induce different levels of insulin resistance and inhibit the transduction of insulin signals; IRS1 and IRS2 are the important receptors mediating the biological effects of insulin, and they may be combined with insulin to increase the expression of GLUT4 through the activation of downstream signaling molecule PKB, and achieve the biological effect of insulin to promote glucose uptake and utilization[15,16]. To further clarify the effects of dezocine pretreatment on stress reaction activation during anesthesia recovery, the changes of stress signaling molecule expression in peripheral blood were analyzed in the study, and the results showed that peripheral blood CHOP and GRP78 expression intensity of both groups of patients were significantly higher whereas IRS-1, IRS-2 and PKB expression intensity were significantly lower during recovery period, and peripheral blood CHOP and GRP78 expression intensity of dezocine group during recovery period were lower than those of control group whereas IRS-1, IRS-2 and PKB expression intensity were higher than those of control group. This means that multiple stress pathways have changed to different degrees during anesthesia recovery period, and dezocine pretreatment can significantly reduce the change of stress pathway during anesthesia recovery period so as to weaken the degree of stress reaction.

The activation of inflammatory response and the large secretion of inflammatory cytokines during operation and anesthesia are also associated with the abnormal activation of multiple signaling pathways in the cells. The JNK signaling pathway is a member of the MAPK signaling pathway family. After the extracellular inflammatory activation signals cause the phosphorylation activation of JNK, p-JNK can activate the transcription factor c-Jun in the cell nucleus; the activated c-Jun has extremely strong transcriptional regulation activity, and can be combined with the promoter regions of multiple inflammatory genes and initiate their expression to enhance the inflammation[17]. CD14 and SR are the important receptors in cell membrane that identify inflammatory signal and transmit them to the cells, both of which are widely distributed in the surface of mononuclear macrophages, and can mediate the cascade activation of mononuclear macrophages in the process of inflammation[18].

In order to further clarify the effect of dezocine pretreatment on the inflammatory response activation during anesthesia recovery, the changes of inflammatory signaling molecule expression in peripheral blood were analyzed in the study, and the results show that peripheral blood JNK, c-jun, CD14 and SR expression intensity of both groups of patients were significantly higher during recovery period, and peripheral blood JNK, c-jun, CD14 and SR expression intensity of dezocine group during recovery period were lower than those of control group. This means that multiple inflammatory pathways have been activated to different degrees during anesthesia recovery period, and dezocine pretreatment can significantly antagonize the activation of inflammatory pathways during anesthesia recovery period so as to relieve the degree of inflammation.

Dezocine pretreatment 30 min before the end of surgery can reduce the degree of emergence agitation of pediatric general anesthesia surgery, and also has improving effect on inflammatory reaction activation, stress reaction activation and other internal environment changes.

References


