Effect of small-dose ketamine combined with dexmedetomidine on emergence stress response as well as postoperative pain and Th cell deviation in patients with cervical cancer surgery under general anesthesia

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ABSTRACT

**Objective:** To study the effect of small-dose ketamine combined with dexmedetomidine on emergence stress response as well as postoperative pain and Th cell deviation in patients with cervical cancer surgery under general anesthesia. **Methods:** A total of 136 patients who received radical operation for cervical cancer in our hospital between May 2013 and May 2016 were selected and randomly divided into control group, dexmedetomidine group (Dex), ketamine group (Ket group) and combined group, and serum was collected to determine the levels of stress hormones, pain mediators and Th cytokines. **Results:** During anesthesia recovery, serum NE, E, Cor, Ins and C-P levels of combined group, Dex group and Ket group were significantly lower than those of control group, and serum NE, E, Cor, Ins and C-P levels of combined group were significantly lower than those of Dex group and Ket group; after surgery, serum SP, PGE2, \( \beta \)-EP, NO, IL-4, IL-5 and IL-10 levels of combined group, Dex group and Ket group were significantly lower than those of control group while IL-2, TNF-\( \alpha \) and IFN-\( \gamma \) levels were significantly higher than those of control group, and serum SP, PGE2, \( \beta \)-EP, NO, IL-4, IL-5 and IL-10 levels of combined group were significantly lower than those of Dex group and Ket group while IL-2, TNF-\( \alpha \) and IFN-\( \gamma \) levels were significantly higher than those of Dex group and Ket group. **Conclusion:** Small-dose ketamine combined with dexmedetomidine can more effectively reduce emergence stress response and postoperative pain, and improve Th cell deviation than single drug intervention.

1. Introduction

Radical operation under general anesthesia is a clinical common method to treat cervical cancer, and fentanyl is required during operation to maintain anesthetic effect and inhibit the pain response. Remifentanil belongs to ultra short-acting \( \mu \) receptor agonist, has definite analgesic effect and is with rapid metabolism and no cumulative effect, and therefore, the recovery is quick after drug withdrawal. However, remifentanil metabolism is rapid after drug withdrawal, and blood drug concentration rapidly declines in a short period of time, which will lead to acute opioid tolerance and hyperalgesia, and cause emergence agitation during recovery period. Emergence agitation after general anesthesia can lead to accidental injury and hemodynamic fluctuations, and severe cases will also threaten life safety[1,2]. Dexmedetomidine and ketamine are the highly selective 2 adrenergic receptor agonist and nonselective N-methyl-D-aspartate receptor blocker respectively, their separate application can improve the hyperalgesia and agitation during general anesthesia recovery[3,4], but the combined effect of the two drugs has not yet been reported. In the following study, the effect of small-dose ketamine combined with dexmedetomidine on emergence stress response as well as postoperative pain and Th cell deviation in patients with cervical cancer surgery under general anesthesia was analyzed.
2. Subjects and methods

2.1 Research subjects

A total of 136 patients who received radical operation for cervical cancer in our hospital between May 2013 and May 2016 were selected as the research subjects, all the patients were diagnosed with cervical cancer by pathological examination, conformed to the radical surgical indications and were with ASA I or II grade, and after signing informed consent, they were divided into control group, Dex group, Ket group and combined group by random number table, 34 cases in each group. Control group of patients were 45-64 years old and with BMI (23.2±3.6) kg/m²; Dex group of patients were 43-66 years old and with BMI (23.8±3.3) kg/m²; Ket group of patients were 44-65 years old and with BMI (23.7±3.4) kg/m²; combined group of patients were 42-65 years old and with BMI (23.1±3.2) kg/m². Four groups of patients were not significantly different in general data.

2.2 Anesthesia methods

After four groups of patients entered the operating room, ECG monitoring was connected, venous channel was built and drug intervention was conducted before anesthesia induction, control group of patients received intravenous injection of 10 mL of saline, Dex group received intravenous injection of dexmedetomidine 0.5 μg/kg, Ket group received intravenous injection of ketamine 0.5 μg/kg + ketamine 0.5 mg/kg and cis atracurium 0.15 mg/kg, propofol 4-8 mg/(kg·h) and remifentanil 0.1-0.3 μg/(kg·h) during anesthesia maintenance and anesthesia recovery among four groups of patients was as follows: during anesthesia maintenance, serum NE, E, Cor, Ins and C-P levels were not significantly different among four groups ($P>0.05$), and serum NE, E, Cor, Ins and C-P levels of combined group were significantly lower than those of Dex group ($P<0.05$). During anesthesia recovery, serum NE, E, Cor, Ins and C-P levels of four groups of patients was significantly lower than those of control group ($P<0.05$), during anesthesia recovery, serum NE, E, Cor, Ins and C-P levels of combined group, Dex group and Ket group were significantly lower than those of control group ($P<0.05$) and serum NE, E, Cor, Ins and C-P levels of combined group were significantly lower than those of Dex group ($P<0.05$) and Ket group ($P<0.05$).

3. Results

3.1 Serum stress hormone levels of four groups of patients

Analysis of serum stress hormones NE (ng/mL), E (ng/mL), Cor (pmol/mL), Ins (U/mL) and C-P (pmol/mL) levels during anesthesia maintenance and anesthesia recovery among four groups of patients was as follows: during anesthesia maintenance, serum NE, E, Cor, Ins and C-P levels were not significantly different among four groups of patients ($P>0.05$); during anesthesia recovery, serum NE, E, Cor, Ins and C-P levels of four groups of patients were significantly higher than those during anesthesia maintenance ($P<0.05$); during anesthesia recovery, serum NE, E, Cor, Ins and C-P levels of combined group, Dex group and Ket group were significantly lower than those of control group ($P<0.05$), and serum NE, E, Cor, Ins and C-P levels of combined group were significantly lower than those of Dex group ($P<0.05$) and Ket group ($P<0.05$).

2.3 Serum sample collection and detection methods

During anesthesia maintenance and anesthesia recovery, 5 mL of peripheral venous blood was collected from two groups of patients and centrifuged to separate serum, enzyme-linked immunosorbent assay kits were used to detect norepinephrine (NE), epinephrine (E) and cortisol (Cor) levels, and the electrochemical luminescence kits were used determine insulin (Ins) and C peptide (C-P) levels; immediately after operation and 1 day after operation, 5 mL of peripheral venous blood was collected from two groups of patients respectively and centrifuged to separate serum, and enzyme-linked immunosorbent assay kits were used to determine substance P (SP), prostaglandin E2 (PGE2), β-endorphin (β-EP), nitric oxide (NO), interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), IL-4, IL-5 and IL-10 levels.

2.4 Statistical methods

SPSS 20.0 software was used to input and statistically process data, measurement data analysis between two groups was by $t$ test and $P<0.05$ indicated statistical significance in differences.

Table 1. Comparison of serum stress hormone levels among four groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time points</th>
<th>NE</th>
<th>N</th>
<th>Cor</th>
<th>Ins</th>
<th>C-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>34</td>
<td>Anesthesia maintenance</td>
<td>59.4±7.7</td>
<td>47.5±6.1</td>
<td>87.7±10.3</td>
<td>12.5±1.6</td>
<td>0.89±0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anesthesia recovery</td>
<td>97.5±11.4</td>
<td>92.4±10.2</td>
<td>194.4±25.1</td>
<td>23.6±3.1</td>
<td>1.84±0.25*</td>
</tr>
<tr>
<td>Dex group</td>
<td>34</td>
<td>Anesthesia maintenance</td>
<td>60.2±8.3</td>
<td>48.1±6.8</td>
<td>89.1±9.8</td>
<td>12.9±1.4</td>
<td>0.91±0.12±</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anesthesia recovery</td>
<td>78.6±9.4*</td>
<td>74.2±9.4*</td>
<td>146.6±18.5*</td>
<td>19.3±2.6*</td>
<td>1.59±0.18±</td>
</tr>
<tr>
<td>Ket group</td>
<td>34</td>
<td>Anesthesia maintenance</td>
<td>59.7±7.9</td>
<td>48.5±6.9</td>
<td>88.4±10.1</td>
<td>12.4±1.8</td>
<td>0.88±0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anesthesia recovery</td>
<td>79.8±9.1*</td>
<td>75.1±7.7*</td>
<td>143.6±16.8*</td>
<td>18.9±2.0*</td>
<td>1.60±0.20*</td>
</tr>
<tr>
<td>Combined group</td>
<td>34</td>
<td>Anesthesia maintenance</td>
<td>59.1±7.9</td>
<td>47.9±6.7</td>
<td>89.4±10.7</td>
<td>12.7±1.9</td>
<td>0.90±0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anesthesia recovery</td>
<td>68.4±8.4**</td>
<td>60.3±8.4**</td>
<td>120.8±15.7**</td>
<td>15.1±1.8**</td>
<td>1.24±0.16**</td>
</tr>
</tbody>
</table>

*: compared with anesthesia maintenance, $P<0.05$; +: compared with control group at the same point in time, $P<0.05$; #: compared with Dex group at the same point in time, $P<0.05$; *: compared with Ket group at the same point in time, $P<0.05$. 

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Comparison of serum Th1/Th2/Treg cytokine levels among four groups of patients after operation.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time points</th>
<th>SP</th>
<th>PGE2</th>
<th>IFN-γ</th>
<th>IL-4</th>
<th>IL-5</th>
<th>IL-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>34</td>
<td>Immediately after operation</td>
<td>67.6±8.9</td>
<td>42.8±6.4</td>
<td>139.5±18.7</td>
<td>9.3±1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 after operation</td>
<td>89.4±10.2</td>
<td>63.5±9.2</td>
<td>176.2±20.3</td>
<td>14.2±1.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dex group</td>
<td>34</td>
<td>Immediately after operation</td>
<td>56.1±7.8</td>
<td>35.1±5.9</td>
<td>115.2±14.6</td>
<td>7.0±0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 after operation</td>
<td>71.3±9.4</td>
<td>53.7±8.3</td>
<td>145.5±18.8</td>
<td>11.3±1.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ket group</td>
<td>34</td>
<td>Immediately after operation</td>
<td>55.8±8.2</td>
<td>33.9±5.2</td>
<td>113.9±13.7</td>
<td>6.98±0.89</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 after operation</td>
<td>72.4±9.8</td>
<td>55.1±7.9</td>
<td>148.4±19.2</td>
<td>11.21±1.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined group</td>
<td>34</td>
<td>Immediately after operation</td>
<td>42.1±6.8</td>
<td>25.6±3.8</td>
<td>97.2±10.8</td>
<td>4.25±0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 after operation</td>
<td>57.8±8.9</td>
<td>39.7±6.2</td>
<td>124.2±16.7</td>
<td>8.93±1.18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: compared with control group at the same point in time, \( P<0.05 \); **: compared with Dex group at the same point in time, \( P<0.05 \); ***: compared with Ket group at the same point in time, \( P<0.05 \).

Comparison of serum pain mediator levels among four groups of patients after operation.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>IL-2</th>
<th>TNF-α</th>
<th>IFN-γ</th>
<th>IL-4</th>
<th>IL-5</th>
<th>IL-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>34</td>
<td>11.3±1.6</td>
<td>24.2±4.9</td>
<td>9.3±1.1</td>
<td>18.3±2.4</td>
<td>9.8±1.1</td>
<td>13.6±1.8</td>
</tr>
<tr>
<td>Dex group</td>
<td>34</td>
<td>17.8±2.4</td>
<td>35.0±4.2</td>
<td>16.4±2.1</td>
<td>12.5±1.8</td>
<td>7.6±0.8</td>
<td>10.3±1.4</td>
</tr>
<tr>
<td>Ket group</td>
<td>34</td>
<td>18.3±2.6</td>
<td>36.1±4.7</td>
<td>16.3±2.2</td>
<td>11.9±1.7</td>
<td>7.3±0.9</td>
<td>10.7±1.5</td>
</tr>
<tr>
<td>Combined group</td>
<td>34</td>
<td>28.5±4.2</td>
<td>58.3±7.8</td>
<td>25.5±3.2</td>
<td>7.8±0.9</td>
<td>5.2±0.8</td>
<td>7.2±0.9</td>
</tr>
</tbody>
</table>

*: compared with control group at the same point in time, \( P<0.05 \); **: compared with Dex group at the same point in time, \( P<0.05 \); ***: compared with Ket group at the same point in time, \( P<0.05 \).

3.2 Postoperative serum pain mediator levels

Immediately after operation and 1 d after operation, analysis of serum pain mediators SP (pg/mL), PGE2 (pg/mL), β -EP (pg/mL) and NO (μmol/L) among four groups of patients was as follows: serum SP, PGE2, β -EP and NO levels of combined group, Dex group and Ket group were significantly lower than those of control group (\( P<0.05 \)), and serum SP, PGE2, β -EP and NO levels of combined group were significantly lower than those of Dex group (\( P<0.05 \)) and Ket group (\( P<0.05 \)).

3.3 Postoperative serum Th1/Th2/Treg cytokine levels

1 d after operation, analysis of serum Th1/Th2/Treg cytokines IL-2, TNF-α, IFN-γ, IL-4, IL-5 and IL-10 levels among four groups of patients was as follows: serum IL-2, TNF-α and IFN-γ levels of combined group, Dex group and Ket group were significantly higher than those of control group while IL-4, IL-5 and IL-10 levels were significantly lower than those of control group (\( P<0.05 \)), and serum IL-2, TNF-α and IFN-γ levels of combined group were significantly higher than those of Dex group and Ket group while IL-4, IL-5 and IL-10 levels were significantly lower than those of Dex group (\( P<0.05 \)) and Ket group (\( P<0.05 \)).

4. Discussion

Emergence agitation is a common complication during general anesthesia recovery, it is the important reason that affects the quality of anesthesia, and improper handling will endanger patients' life safety. Remifentanil is a new opioid, it has the advantage of exact analgesic effect when used for anesthesia induction and anesthesia maintenance, the drug is metabolized by non-specific esterase in the body, is with short half-life and will not accumulate in the body, and patients can quickly regain consciousness after drug withdrawal[5]. However, the analgesic action of remifentanil will disappear quickly after its withdrawal, and the acute opioid tolerance and hyperalgesia will be easily induced after drug withdrawal, and thus increase the risk of emergence agitation. In clinical practice, preventing or reducing the emergence agitation has been the hot topic in the perioperative study. Dexmedetomidine and ketamine are the effective drugs to prevent emergence agitation, the former is highly selective 2 adrenergic receptor agonist[6], and the latter is a non-selective N-methyl-D-aspartate receptor blocker[7]. Studies have shown that single application of dexmedetomidine or ketamine before anesthesia induction can both reduce the extent of emergence agitation, and the effect of the two drugs is equivalent on reducing emergence agitation[8,9]. However, there is no report about the effect of combined application of the two drugs on emergence agitation.

On the one hand, dexmedetomidine excites the 2 receptor in synaptic structure to cause presynaptic or postsynaptic membrane hyperpolarization and thereby inhibit the excitability of neurons; on the other hand, it can also act on locus coeruleus and medulla-spinal cord adrenergic neurons to inhibit the stress reaction caused by external noxious stimulation[10,11]. Ketamine can be combined with NMDA receptors to reduce the increased nerve excitability caused by external noxious stimulation[12]. Dexmedetomidine and ketamine application before anesthesia induction can reduce the excitability of neurons and suppress the stress reaction caused by external trauma through different mechanisms, and it is expected that the combined application can obtain synergetic effect. In order to define the degree
of general anesthesia emergence agitation in patients with cervical cancer, the emergence stress reaction was analyzed in the study. The activation of stress response can cause the abnormal secretion of a variety of endocrine hormones, including promoting the adrenal medulla to secrete epinephrine and norepinephrine, promoting the adrenal cortex to release cortisol, and also promoting the secretion of insulin and C peptide as compensation\[13,14\]. In the study, analysis of the contents of the stress hormones showed that serum NE, E, Cor, Ins and C-P levels of four groups of patients during anesthesia recovery were significantly higher than those during anesthesia maintenance, both dexmedetomidine and ketamine can effectively restrain the secretion of stress hormones during anesthesia recovery, and the combined application of the two drugs has better inhibitory effect on stress hormone secretion than monotherapy. This means that both dexmedetomidine and ketamine can effectively restrain the stress reaction during anesthesia recovery, the two groups have synergetic effect and the combined application has better inhibitory effect on stress response than monotherapy.

Both dexmedetomidine and ketamine can reduce the excitability of neurons, and the dexmedetomidine and ketamine application before general anesthesia surgery can reduce the facilitating effect of surgical trauma on neurons, thus increase the pain threshold and relieve postoperative pain. Pain reaction caused by surgical trauma is associated with the secretion of SP, PGE2, β-EP, NO and multiple other pain mediators. SP is a transmitter with nerve conduction function, and can mediate the pain signal conduction from peripheral tissue to the central nerve tissue; β-EP and PGE2 mainly regulate pain perception in peripheral tissue, and can increase the peripheral tissue sensitivity to pain signals; NO is a kind of gas signal molecule with signal transduction effect, and can promote the generation of pain perception in peripheral tissue and central nerve\[15,16\]. In order to define the degree of postoperative pain, the serum pain mediator contents were analyzed in the study, and the results showed that serum SP, PGE2, β-EP and NO levels of combined group, Dex group and Ket group were significantly lower than those of control group, and serum IL-2, TNF-α and IFN-γ levels of combined group, Dex group and Ket group were significantly higher than those of control group while IL-4, IL-5 and IL-10 levels were significantly lower than those of control group, and serum IL-2, TNF-α and IFN-γ levels of combined group were significantly higher than those of Dex group and Ket group while IL-4, IL-5 and IL-10 levels were significantly lower than those of Dex group and Ket group. This means that both dexmedetomidine and ketamine can effectively restrain the Th cell deviation caused by surgical trauma and pain, and improve postoperative anti-tumor immune response, the two groups have synergetic effect and the combined application has better improving effect on Th cell deviation caused by postoperative pain than monotherapy.

To sum up, it shows that both small-dose ketamine and dexmedetomidine can reduce emergence agitation and pain, and improve Th cell deviation after general anesthesia surgery for cervical cancer, and the above effects of small-dose ketamine combined with dexmedetomidine are better than those of monotherapy.

References


of KETODEX on the incidence and severity of emergence agitation in children undergoing adenotonsillectomy using sevoflurane based-


