Effect of dexmedetomidine pretreatment on postoperative immune function and inflammatory stress response in patients with non-small cell lung cancer surgery

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Objective: To study the effect of dexmedetomidine pretreatment on postoperative immune function and inflammatory stress response in patients with non-small cell lung cancer surgery.

Methods: Patients with non-small cell lung cancer who underwent radical operation for lung cancer in Xi’an Aerospace General Hospital between August 2014 and September 2017 were selected and randomly divided into the Dex group who received dexmedetomidine pretreatment combined with general anesthesia and the control group who received routine general anesthesia. The same day after surgery and 3 d after surgery, the peripheral blood was collected respectively to determine the contents of immune cells and the serum was collected respectively to determine the contents of inflammatory stress response indexes.

Results: The same day after surgery and 3 d after surgery, CD3⁺CD4⁺T cell, CD3⁺CD8⁺T cell and CD16⁺CD56⁺NK cell contents in peripheral blood of Dex group were significantly higher than those of control group whereas CD11b⁺CD15⁺CD33⁺CD14⁻G-MDSC, CD11b⁺CD15⁺CD33⁺CD14⁺M-MDSC and CD4⁺CD25⁻CD127lowTreg contents in peripheral blood as well as TNF-α, SAA, CRP, IL-8, IL-10, Cor, Ins, NE, E and AT-II contents in serum were significantly lower than those of control group.

Conclusion: Dexmedetomidine pretreatment can improve the immune function and inhibit the inflammatory stress response in patients with non-small cell lung cancer surgery.

1. Introduction

Non-small cell lung cancer is the most common type of lung cancer in clinic, and its incidence has been increasing in recent years. Radical operation is a major means for clinical treatment of non-small cell lung cancer, and along with the further promotion of thoracoscopic surgery and its replacement of thoracotomy, both trauma and postoperative pain from surgical treatment significantly reduce in patients with lung cancer[1]. However, the pulling of local tissue by thoracoscopic operation will still cause different degrees of trauma and postoperative incision pain, and the trauma and pain will inhibit the body’s immune response and also activate the inflammatory stress response. The changes of perioperative immune function and inflammatory stress response can affect the body’s postoperative recovery. In recent years, different effects of different anesthesia programs on surgical trauma as well as perioperative immune function and inflammatory stress response have received more and more attention[2,3]. Dexmedetomidine is a highly selective 2 receptor agonist, which not only has sedative and analgesic effect, but also has antioxidant and anti-inflammatory activity[4,5]. The effects of dexmedetomidine pretreatment on postoperative immune function and inflammatory stress response in patients with non-small cell lung cancer surgery were specifically analyzed in the following studies.

2. Case information and research methods

2.1 General case information

Patients with non-small cell lung cancer who underwent radical operation for lung cancer in Xi’an Aerospace General Hospital...
between August 2014 and September 2017 were selected, all patients were diagnosed with non-small cell lung cancer by postoperative pathological examination, they were without the history of other operation and the patients combined with autoimmune diseases and infectious diseases were ruled out. A total of 102 patients were enrolled and divided into two groups by random number table, 51 cases in each group. Dex group included 29 males and 22 females who were 35-59 years old; control group included 27 males and 24 females who were 33-61 years. There was no statistically significant difference in general information between the two groups ($P$ > 0.05).

### 2.2 Anesthesia methods

Two groups of patients were given routine monitoring of vital signs after admitted to hospital, and Dex group of patients were given intravenous injection of dexmedetomidine load dose 1 μg/kg 10 min before anesthesia induction, and then continued to be given micropump injection of dexmedetomidine 0.6 μg/kg/h until the end of the operation; control group were given intravenous injection of same dosage of saline 10 min before anesthesia induction. The anesthesia induction method was as follows: intravenous injection of midazolam 0.04 mg/kg, cis-atracurium 0.2 mg/kg, fentanyl 4 μg/kg and propofol 0.5 mg/kg; after endotracheal intubation, they were given target controlled infusion of propofol for anesthesia maintenance, the target concentration of plasma propofol was 4 μg/mL, fentanyl 0.1-0.2 μg/kg and cis-atracurium 0.05-0.10 mg/kg were complementally injected when it was necessary, and the BIS value was maintained between 40-60.

### 2.3 Detection indexes and methods

#### 2.3.1 Peripheral blood indexes

The same day after surgery and 3 d after surgery, analysis of peripheral blood was collected, anti-coagulated with EDTA to incubate the fluorescent antibody of CD3, CD4, CD8, CD11b, CD14, CD15, CD16, CD25, CD33, CD56 and CD127, then joined incubate the fluorescent antibody of CD3, CD4, CD8, CD11b, whereas CD11b

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>CD3$^{+}$CD4$^{+}$T cell</th>
<th>CD3$^{+}$CD8$^{+}$T cell</th>
<th>CD4$^{+}$CD25$^{+}$Treg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dex group</td>
<td>51</td>
<td>Same day after surgery</td>
<td>41.83±5.95</td>
<td>27.51±3.85</td>
<td>14.22±1.89</td>
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<tr>
<td></td>
<td></td>
<td>3 d after surgery</td>
<td>44.65±6.24</td>
<td>30.21±4.57</td>
<td>16.94±2.31</td>
</tr>
<tr>
<td>Control group</td>
<td>51</td>
<td>Same day after surgery</td>
<td>33.29±5.37</td>
<td>21.25±3.28</td>
<td>10.38±1.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after surgery</td>
<td>37.13±6.49</td>
<td>24.08±4.19</td>
<td>12.04±1.78</td>
</tr>
</tbody>
</table>

*: compared with control group, $P$ < 0.05.

#### 2.3.2 Serum indexes

The same day after surgery and 3 d after surgery, 5-8 mL of peripheral blood was collected and centrifuged to separate serum, and enzyme-linked immunosorbent assay kit was used to determine the serum contents of TNF-α, SAA, CRP, IL-8, IL-10, Cor, Ins, NE, E and AT-II.

#### 2.4 Statistical methods

SPSS 21.0 software was used to input data, the differences in measurement data between two groups were analyzed by t test and $P$ < 0.05 meant statistical significance in differences in test results.

### 3. Results

#### 3.1 Peripheral blood immune cell contents

The same day after surgery and 3 d after surgery, analysis of peripheral blood immune cells CD3$^{+}$CD4$^{+}$T cell, CD3$^{+}$CD8$^{+}$T cell, CD16$^{+}$CD56$^{+}$NK cell, CD11b$^{+}$CD15$^{+}$CD33$^{+}$CD14$^{-}$G-MDSC, CD11b$^{+}$CD15$^{+}$CD33$^{+}$CD14$^{+}$M-MDSC and CD4$^{+}$CD25$^{+}$CD127lowTreg contents between two groups of patients was as follows: CD3$^{+}$CD4$^{+}$T cell, CD3$^{+}$CD8$^{+}$T cell and CD16$^{+}$CD56$^{+}$NK cell contents in peripheral blood of Dex group were significantly higher than those of control group whereas CD11b$^{+}$CD15$^{+}$CD33$^{+}$CD14$^{-}$G-MDSC, CD11b$^{+}$CD15$^{+}$CD33$^{+}$CD14$^{+}$M-MDSC and CD4$^{+}$CD25$^{+}$CD127lowTreg contents were significantly lower than those of control group.

#### 3.2 Serum inflammatory stress index contents

The same day after surgery and 3 d after surgery, analysis of serum contents of inflammatory response indexes TNF-α (ng/mL), SAA (mg/L), CRP (mg/L), IL-8 (pg/mL) and IL-10 (pg/mL) as well as...
stress response indexes Cor (nmol/L), Ins (U/mL), NE (ng/mL), E (ng/mL) and AT-II (pg/mL) between two groups of patients was as follows: TNF-α, SAA, CRP, IL-8, IL-10, Cor, Ins, NE, E and AT-II contents in serum of Dex group were significantly lower than those of control group.

4. Discussion

Dexmedetomidine is a drug that has been used for general anesthesia in recent years, which can highly selectively excite α2 adrenergic receptor to inhibit the stress response and reduce the generation of inflammatory mediators and oxygen free radicals, and can relieve the inflammatory and stress response caused by external trauma. Surgical trauma can affect immune response and inhibit the differentiation and maturation of multiple immune cells. T cells is the important cell group mediating immunity in the body, CD3 is the common marker on mature T cell surface in the body, and it can differentiate into CD3+CD8+T cell and CD3+CD4+T cell in the maturation of positive and negative selection. CD3+CD4+T cells can secrete IL-2 and IFN-γ and kill tumor cells, and CD3+CD8+T cells can accept the signals presented by MHC-I molecules and differentiate into cytotoxic T cells to directly kill tumor cells. The analysis of the changes in above positive immune cell contents in the peripheral blood after surgery in the study showed that CD3+CD4+T cell1, CD3+CD8+T cell and CD16+CD56+NK cell contents in peripheral blood of Dex group were significantly higher than those of control group the same day and 3 d after surgery. This indicates that the dexmedetomidine pretreatment before radical operation for lung cancer can alleviate the immune suppression caused by surgical trauma and improve the immune response mediated by T cells.

The immune response mediated by T cells is regulated by a variety of inhibitory immune cells, and the currently known negative immune regulation cells include MDSC and Treg. MDSC can be divided into the M-MDSC and G-MDSC, which were from the monocytes and granulocytes respectively, can restrain the activation of T cells, the differentiation of DC cells and the cytotoxic effect of NK cells, and can also promote the differentiation and maturation of inhibitory T cell Treg.10-12 The negative immunomodulation effect of Treg cells is on the one hand, achieved by direct intercellular contact, and on the other hand, realized by secreting TGF-β, IL-4, IL-5 and other inhibiting cytokines.13,14 In order to further clarify the effects of dexmedetomidine on immune function after radical operation for lung cancer, the contents of the above negative immune cells in peripheral blood were analyzed after surgery, and the study results showed that CD11b+CD15+CD33+CD14+M-MDSC, CD11b+CD15+CD33+CD14+M-MDSC and CD4+CD25+CD127lowTreg contents in peripheral blood of Dex group were significantly lower than those of control group the same day and 3 d after surgery. This indicates that the dexmedetomidine pretreatment before radical operation for lung cancer can suppress the hyperactivation of negative immune cells after surgery to reduce the immune suppression and improve the immune response.

The operation trauma can cause the postoperative inflammatory stress response to be significantly activated. The secretion of multiple cytokines and acute phase proteins changes significantly in the activation of inflammatory response. TNF-α is the cytokine that first changes in the process of inflammatory response, and it can not only mediate the tissue injury caused by inflammation, but can also promote the secretion of SAA, CRP and other acute phase proteins as well as IL-8, IL-10 and other pro-inflammatory cytokines. In the activation process of stress response, the function of multiple endocrine systems changes and the secretion of corresponding hormones increases significantly; Cor as well as NE and E are the hormones that are secreted by the adrenal cortex and medulla respectively, cortical hormone secretion is associated with the increase of pituitary ACTH secretion, and it enhances the body’s capacity to tolerate trauma, has glycemic effect and increases the compensatory secretion of Ins; the secretion of medullary
hormones is associated with sympathetic nervous excitement, and it could result in hemodynamic changes, compensatory RAS system activation and increased AT-II generation. The changes in postoperative serum inflammatory stress index contents were analyzed in the study to reflect the degree of surgical trauma, and the results showed that serum TNF-α, SAA, CRP, IL-8, IL-10, Cor, Ins, NE, E and AT-II contents of Dex group were significantly lower than those of control group. This indicates that the dexmedetomidine pretreatment before radical operation for lung cancer can reduce the surgical trauma and inhibit the activation of postoperative inflammatory and stress response.

Dexmedetomidine pretreatment improves the postoperative immune function, promotes the differentiation and maturation of positive immune cells and inhibits the differentiation and maturation of negative immune cells in patients with non-small cell lung cancer, and it can also reduce the secretion of inflammatory mediators and stress hormones and inhibit the activation of inflammatory stress response.

References


