Effect of dexmedetomidine on Th1/Th2 cytokine and immune function in patients undergoing radical mastectomy

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ABSTRACT

Objective: To investigate the effect of dexmedetomidine on Th1/Th2 cytokines and immune function in patients with breast cancer after radical mastectomy. Methods: In our hospital from July 2016 to July 2017 undergoing radical mastectomy for breast cancer were studied in 79 patients, were randomly divided into observation group and control group. Two groups of patients with routine preoperative preparation, monitoring blood pressure, electrocardiogram, heart rate, pulse, oxygen saturation, establish vein channel, using propofol, remifentanil, vecuronium induced anesthesia, observation group before induction of anesthesia, dexmedetomidine 1 μg/kg, 10 min after infusion, followed by 0.5 μg/kg/h continuous infusion to the end of the operation, the control group with normal saline continuous infusion till the end of the operation. Two groups of patients before induction of anesthesia (T0), 6 h after operation (T1), 24 h after operation (T2), 72 h after operation (T3) from peripheral venous blood determination of interleukin-2 by ELISA method (IL-2), interleukin-4 (IL-4), interleukin-10 (IL-10) and interferon gamma (IFN-γ), calculated IFN-γ/IL-4 in T0, T1, T2, T3, T4 from peripheral blood. CD3+, CD4+, CD8+, NK cells were determined by flow cytometry and CD4+/CD8+ were calculated. Results: Two groups of IL-2 and IFN-γ in T1, T2, T3, T4 higher than the control group, IL-10 was lower than the control group, significant difference between the 2 groups. Conclusion: Dexmedetomidine can inhibit the stress response during the perioperative period of radical mastectomy, correct the balance disorder of Th1/Th2, improve the level of T lymphocyte subsets, and exert better immune protection function.

1. Introduction

Radical mastectomy is the main method for the treatment of breast cancer, and the surgical trauma and stress response can induce immunosuppression in varying degrees, and the extent of inhibition is related to the degree of trauma, anesthesia and other factors[1]. Research shows that[2] plays an important role in T lymphocyte specific immune response in anti-tumor immunity, immune function, and can lead to residual cancer cell growth, metastasis and postoperative infection, surgery and anesthesia can inhibit T lymphocyte mediated specific immune response, Th1/Th2 right can cause postoperative tumor cell growth, transfer and diffusion, so the use of drugs to reduce the perioperative immune function inhibition,
prevent the imbalance of Th1/Th2 cells has important significance in prognosis after radical surgery for breast cancer. Dexmedetomidine has analgesic, sedative, anxiolytic, anti sympathetic effects, research shows that dexmedetomidine can reduce peri operative stress and inflammation, can affect the imbalance of Th1/Th2 play a role in immune regulation[3]. Objective to study the effect of dexmedetomidine on Th1/Th2 cytokines and immune function in patients undergoing radical mastectomy for breast cancer.

2. Clinical information

2.1. General information

Methods 79 cases of radical mastectomy for breast cancer were selected from July 2016 to July 2017 in our hospital. They were randomly divided into observation group and control group. The observation group of 40 cases, aged 42 to 59 years old, the average (51.6±5.3) years; body mass of 48 to 63 kg, the average (58.7±6.9) kg; 27 cases of infiltrating ductal carcinoma, 6 cases of invasive lobular carcinoma, 4 cases of ductal carcinoma in situ, 3 cases of basal cell carcinoma; American Society of anesthesiologists (ASA) classification: 23 cases of grade I, grade II in 17 cases. The control group of 39 cases, aged 41 to 59 years old, the average (52.1±5.5) years; body mass of 50 to 64 kg, the average (58.7±7.4) kg; 25 cases of infiltrating ductal carcinoma, 6 cases of invasive lobular carcinoma, 5 cases of ductal carcinoma in situ, 3 cases of basal cell carcinoma; ASA grade: 22 cases of grade I, grade II in 17 cases. There was no significant difference between the 2 groups in terms of age (t=0.4115, P=0.6819), body mass (t=0.0000, P=1.0000), lesion type (χ²=0.1754, P=0.9815), and the ASA classification (Z=0.0915, P=0.9271) showed no statistical difference (P>0.05).

2.2. Inclusion criteria

Primary female breast cancer patients, ASA I-II; heart, liver and kidney function was normal; without chemotherapy, hormone and immunosuppressive therapy before operation; metabolic diseases, blood diseases, acute and chronic infection, endocrine diseases not associated with patients and their families; and signed the informed consent.

2.3. Method

Two groups of patients with routine preoperative preparation, a 30 min atropine (Anyang Jiuzhou pharmaceutical, Zhunzi H41023676) 0.5 mg, diazepam (Tonghua Maoxiang pharmaceutical, Zhunzi H2022685) 0.2 mg/kg intramuscular injection, ECG, heart rate, pulse, blood pressure, blood oxygen saturation monitoring, establish vein the channel, infusion of compound sodium chloride 6 mL/kg/h.

Induction of anesthesia: vecuronium (Zhejiang Xianju pharmaceutical, Zhunzi H19991172) 0.1 mg/kg and propofol (Xi’an Libang pharmaceutical, Zhunzi H20123318) 2 mg/kg and remifentanil (Yichang humanwell pharmaceutical, Zhunzi H20030197) 3 μg/kg, lost consciousness after tracheal intubation and mechanical ventilation. The respiratory frequency of 12-20/min, tidal volume 6-8 mL/kg, end tidal carbon dioxide (Pet CO₂) for 35-40 mmHg.

Anesthesia was maintained with remifentanil 0.2-0.4 μg/kg/min and propofol 4-8 mg/kg/h to maintain anesthesia, intermittent vecuronium, inhaled 1%-3% sevoflurane, maintain bispectral index (BIS) ranged from 45 to 55. Stop inhaling seven halothane before sewing and stop pumping remifentanil at the end of the operation.

The observation group was given dexmedetomidine before induction of anesthesia (Jiangsu nhwa pharmaceutical, Zhunzi H20110085) 1 μg/kg, 10 min after infusion, followed by 0.5 μg/kg/ h continuous infusion to the end of the operation, the control group with normal saline continuous infusion till the end of the operation.

2.4. Observation index

(1) Th1/Th2 cell factor: 2 groups of patients before induction of anesthesia (T₀), at the end of operation (T₁), 6 h after operation (T₂), 24 h after operation (T₃), 72 h after operation (T₄) from peripheral venous blood determination of interleukin (IL-2), interleukin-4 (IL-4), interleukin-10 (IL-10) and interferon gamma (IFN-γ), calculation of IFN-γ/IL-4 by the method of ELISA. (2) immune function: peripheral blood samples were taken from 2 groups of patients at T₀, T₂, T₃, and T₄ CD₃⁺, CD₄⁺, CD₈⁺, and NK cells were measured by flow cytometry, and CD₄⁺/CD₈⁺ was calculated.

2.5. Statistical processing

Data were analyzed by SPSS 19 software. Enumeration data were checked by χ², and rank data by Wilcoxon rank sum test. The data measured by Mean ± SD were used to express the difference between the two groups. The independent sample t test (Homogeneity) or the approximate t test (variance variance) were used, and the paired time t test was used to compare the time points in the group. With P<0.05 as the difference, there was statistical significance.
3. Result

3.1. Comparison of Th1/Th2 cytokines

There was no significant difference in IL-2, IL-4, IL-10, IFN-γ, T0, IFN-γ/IL-4 between the 2 groups (P>0.05). 2 groups of IL-2 and IFN-γ in T1, T2, T3 and T4 is higher than T0, IL-10 less than T0, and the observation group IFN-γ/IL-4 is higher than T0, the control group was lower than that of T0 when compared with T0 significant difference (P<0.05), 2 in group IL-4 had no significant change. The IL-2, IFN-γ, IFN-γ/IL-4 in the observation group was higher than those in the control group at T1, T2, T3 and T4 and IL-10 was lower than that of the control group. The difference between the 2 groups was significant (P<0.05). See Table 1.

Table 1.
Comparison of Th1/Th2 cytokines in two groups at different times.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>n</th>
<th>IL-2 (pg/mL)</th>
<th>IL-4 (pg/mL)</th>
<th>IL-10 (pg/mL)</th>
<th>IFN-γ (pg/mL)</th>
<th>IFN-γ/IL-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Control group</td>
<td>39</td>
<td>59.8±8.23</td>
<td>76.5±8.18</td>
<td>90.7±9.29</td>
<td>90.5±11.41</td>
<td>1.2±0.24</td>
</tr>
<tr>
<td>T0</td>
<td>Observation group</td>
<td>40</td>
<td>57.8±7.65</td>
<td>75.6±8.24</td>
<td>91.6±9.31</td>
<td>90.5±11.31</td>
<td>1.25±0.23</td>
</tr>
<tr>
<td>T1</td>
<td>Control group</td>
<td>39</td>
<td>64.1±7.32</td>
<td>75.2±7.74</td>
<td>84.2±8.61</td>
<td>81.3±10.32</td>
<td>0.87±0.24</td>
</tr>
<tr>
<td>T1</td>
<td>Observation group</td>
<td>40</td>
<td>71.4±9.21</td>
<td>75.1±7.63</td>
<td>78.3±8.17</td>
<td>86.4±11.28</td>
<td>1.45±0.31</td>
</tr>
<tr>
<td>T2</td>
<td>Control group</td>
<td>39</td>
<td>68.5±8.39</td>
<td>75.8±9.52</td>
<td>81.6±10.64</td>
<td>79.9±10.64</td>
<td>0.90±0.27</td>
</tr>
<tr>
<td>T2</td>
<td>Observation group</td>
<td>40</td>
<td>76.3±8.64</td>
<td>76.7±9.72</td>
<td>73.3±9.16</td>
<td>85.9±12.42</td>
<td>1.50±0.26</td>
</tr>
<tr>
<td>T3</td>
<td>Control group</td>
<td>39</td>
<td>78.1±9.38</td>
<td>75.6±8.33</td>
<td>73.4±8.79</td>
<td>77.1±9.52</td>
<td>0.93±0.26</td>
</tr>
<tr>
<td>T3</td>
<td>Observation group</td>
<td>40</td>
<td>83.2±9.17</td>
<td>75.1±9.82</td>
<td>68.5±8.31</td>
<td>83.1±9.93</td>
<td>1.56±0.41</td>
</tr>
<tr>
<td>T4</td>
<td>Control group</td>
<td>39</td>
<td>82.3±9.67</td>
<td>75.9±9.67</td>
<td>70.8±9.67</td>
<td>73.5±9.59</td>
<td>1.11±0.29</td>
</tr>
<tr>
<td>T4</td>
<td>Observation group</td>
<td>40</td>
<td>89.6±9.55</td>
<td>74.9±8.71</td>
<td>61.5±7.26</td>
<td>81.4±10.58</td>
<td>1.54±0.37</td>
</tr>
</tbody>
</table>

Note: compared with the same group T0, P<0.05.

Table 2.
Comparison of immune function between two groups at different time.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>n</th>
<th>CD4+ (%)</th>
<th>CD8+ (%)</th>
<th>CD4+/CD8+ (%)</th>
<th>CD4+/CD8+/%</th>
<th>NK cell (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Control group</td>
<td>39</td>
<td>57.1±6.15</td>
<td>32.4±3.61</td>
<td>22.7±3.13</td>
<td>1.38±0.15</td>
<td>12.4±1.57</td>
</tr>
<tr>
<td>T0</td>
<td>Observation group</td>
<td>40</td>
<td>57.1±6.13</td>
<td>32.5±3.56</td>
<td>22.8±2.51</td>
<td>1.37±0.14</td>
<td>12.4±1.64</td>
</tr>
<tr>
<td>T1</td>
<td>Control group</td>
<td>39</td>
<td>46.8±6.08</td>
<td>22.2±2.74</td>
<td>21.6±2.69</td>
<td>1.06±0.15</td>
<td>9.28±1.36</td>
</tr>
<tr>
<td>T1</td>
<td>Observation group</td>
<td>40</td>
<td>49.5±6.13</td>
<td>25.0±3.13</td>
<td>21.9±2.65</td>
<td>1.15±0.13</td>
<td>10.3±1.42</td>
</tr>
<tr>
<td>T2</td>
<td>Control group</td>
<td>39</td>
<td>47.5±6.22</td>
<td>24.3±3.55</td>
<td>21.7±3.04</td>
<td>1.15±0.14</td>
<td>9.57±1.63</td>
</tr>
<tr>
<td>T2</td>
<td>Observation group</td>
<td>40</td>
<td>52.3±6.12</td>
<td>26.2±4.53</td>
<td>21.8±2.74</td>
<td>1.25±0.15</td>
<td>11.25±1.51</td>
</tr>
<tr>
<td>T3</td>
<td>Control group</td>
<td>39</td>
<td>55.9±5.74</td>
<td>30.6±4.21</td>
<td>22.7±2.71</td>
<td>1.31±0.18</td>
<td>11.7±1.72</td>
</tr>
<tr>
<td>T3</td>
<td>Observation group</td>
<td>40</td>
<td>56.2±5.67</td>
<td>30.7±4.63</td>
<td>22.4±2.65</td>
<td>1.33±0.23</td>
<td>11.3±1.47</td>
</tr>
</tbody>
</table>

Note: compared with the same group T0, P<0.05.
4. Discussion

Operation involving breast lymph node dissection, radical breast cancer, surgical incision, heavy trauma, stress response, surgical trauma, pain and stress have certain inhibitory effect on T lymphocyte and T lymphocyte mediated immunosuppression associated with postoperative infection, tumor cell proliferation[4]. In patients with malignant tumor surgical trauma, postoperative pain and anesthesia can cause stress reaction of patients, and the stress response can cause immune suppression, therefore the use of immunosuppressive drugs to reduce perioperative curative effect, surgery for breast cancer has important significance[5].

Dexmedetomidine is a highly selective alpha adrenergic receptor 2 (alpha 2-AR) agonist binding selectively with alpha 2-AR, alpha 2-AR in the brain and spinal cord, exert analgesic and sedative and anti anxiety effects, no obvious inhibitory effect[6] on respiration. Dexmedetomidine also has anti-inflammatory and neuroprotective effects, and can inhibit the stress response induced by noxious stimulation, protect the heart and brain, regulate immunity and improve the postoperative cognitive function[7].

Th cells were divided into different functions of Th1 and Th2 cells, Th1 mainly secreted IFN-γ, IL-2, mediates the cellular immune response and activation of T lymphocytes and macrophages, reduce postoperative infection, the main mechanism for the anti-tumor immunity of the body; IL-4, IL-5, Th2 secreted IL-10, mediate humoral immunity, mediated by B cell secretory immunoglobulin[8]. Under normal conditions, Th1 and Th2 cells in a relatively balanced state, while the tumor patients showed Th1 to Th2 drift, Th1/Th2 balance, cell immunity mediated by Th1 inhibition, with dominant Th2 cells as the main performance, leading to immune surveillance system for tumor cell recognition regulation ability is reduced, at present, the ratio of cytokine Th1/Th2 drift secretion of common Th1, Th2 cells to measure, Th1/Th2 right, suggesting that patients are immunosuppressed[9,10]. This study shows that[11], anesthesia stress, sympathetic nerve to produce norepinephrine (NE), and activation of T lymphocytes and NK cells, resulting in the drift of Th1/Th2 right, but dexmedetomidine can activate CNS alpha 2-AR, inhibit the secretion of NE, corrected Th1/Th2 right, cell-mediated immune reaction, improve immune function. Some scholars study the effect of dexmedetomidine radical reaction and cell immune stress in patients of breast cancer, that dexmedetomidine can inhibit the release of NE, reduce the perioperative stress response, reduce the autonomic nervous system and the hypothalamic pituitary adrenal axis activation, reduce travel inhibitory signals of IFN-γ and IL-2 cells thus, effectively alleviate the immune suppression[12]. This study shows that 2 groups of IL-2 and IFN-γ T4, T5, T6, T7, T8, IL-10 less than T9, and the observation group IFN-γ /IL-4 is higher than T9, the control group was lower than that of T9, when compared with T9, significant difference (P<0.05), 2 in group IL-4 had no obvious changes were observed; group IL-2,ILFN-γ, IFN-γ /IL-4 in T1, T3, T5, T4 higher than the control group, IL-10 was lower than the control group, significant difference between the 2 groups (P<0.05). It is suggested that dexmedetomidine can correct right deviation of Th1/Th2, balance Th1/Th2 disturbance and improve cellular immune function in patients undergoing radical mastectomy. T lymphocytes and NK cells reflect the immune status of cells, and play a dominant role in the defense mechanism of tumor. T lymphocyte subsets can evaluate the cellular immune status[13]. CD4+ reflects the overall level of immune cells, are all mature T cell surface antigen expression marks, assist in the identification of antigen presenting cell histocompatibility complex antigens; CD2+ assisted other cells involved in the immune response; CD4+ as immunosuppressive cells play a negative role in the regulation of immune response; CD4+/CD8+ reflects the immune balance, reduce the that immune dysfunction, disease severity or prognosis; NK cells as the main body of innate immune cells, tumor immunity is an important regulatory immune cells can directly kill circulating tumor cells, the activity of the occurrence and development of disease prognosis and to determine the significance[14,15]. Research shows that[16], during the surgery, trauma, anesthesia drug application and stress all patients with perioperative immune state influence, dexmedetomidine can inhibit inflammation and stress response during operation period, play cell immune function. This study shows that CD4+, CD4+/CD8+, NK 2 cells in T1 group was lower than that of T0, T4, and CD4+ had no obvious change, compared with T0 significant difference (P<0.05); the observation group CD4+, CD4+/CD8+, NK2 cells in T2 group was lower than than the control group, significant difference between the 2 groups (P<0.05). That dexmedetomidine can improve breast cancer patients with radical resection of T lymphocyte subsets level, has a protective effect on perioperative immune cells, which may be due to dexmedetomidine sedation, analgesia, can inhibit sympathetic function, reduce inflammation and stress response among patients with breast cancer after mastectomy, immune protective effect.

To sum up, dexmedetomidine can inhibit the perioperative stress response in patients undergoing radical mastectomy, correct the imbalance of Th1/Th2 balance, improve the level of T lymphocyte subsets, and play better immune protection function.

Reference


[8] Qiu Chang Chen Qianjun, Dai Yan. Before the army, the new Chinese medicine, the study of effect on Th1/Th2 cell drift adjuvant chemotherapy in patients with breast cancer. *Fuzheng Yiqi* 2014; 46(8): 139-142.


