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Effect of dexmedetomidine on immune function of patients undergoing radical mastectomy: a double blind and placebo control study

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Abstract. – OBJECTIVE: To observe and evaluate the effect of dexmedetomidine on the perioperative immune function of patients undergoing a radical mastectomy.

PATIENTS AND METHODS: 124 patients undergoing radical mastectomy were divided into the observation group (treated with dexmedetomidine) and the control group (treated with saline) by randomized digital table and double blinded and randomized design. 10 min before anesthesia induction, the patients in the observation group were injected with dexmedetomidine 0.1 ug.kg-1.min-1. The injection of 0.9% sodium chloride solution was given to the control group at the same rate. In the experiment, the medications of anesthesia induction and anesthesia maintain were identical. Venous blood at five times: T0 (before anesthesia), T1 (6 h after surgery), T2 (24 h after surgery), T3 (48 h after surgery), T4 (72 h after surgery) were collected. ELISA (Enzyme Linked Immunosorbent Assay) was used to detect concentrations of IL-2, IFN-γ, IL-4, IL-6 and IL-10; FACS flow cytometry was used to determine the level of T-lymphocyte subsets (CD3+, CD4+, CD8+) and NK cells.

RESULTS: Compared with the control group, the cell levels of CD3+ and CD4+ in the observation group rose remarkably at T3 and T2 ($p<0.05$). The cell level of CD8+ fell at T2 with significant difference; NK cell level increased noticeably at T1 and T2, and CD4+/CD8+ rose dramatically at all postoperative time points. Obviously, the patients' immune function, to some extent, has been affected; in addition, the concentration of INF-γ in observation group increased prominently at T1, T2 and T3 ($p<0.05$), and the concentration of IL-2 at T2, IL-10 at T1 and T2, and IL-6 at T2 and T3 in the observation group all rose significantly ($p<0.05$), and less cytokine Th1 drifted to Th2.

CONCLUSIONS: The dexmedetomidine can effectively maintain the homeostasis of cell immune function of patients undergoing a radical mastectomy.

Key Words:
Dexmedetomidine, Breast cancer, Immunity.

Introduction

Surgical trauma may induce a variety of stress reactions, strong ones of which can inhibit the immune function and aggravate the inflammatory reaction, and eventually go against prognosis of patients. After radical mastectomy, many causes can lead to the low immune function of patients, and they will be easily susceptible to infection. Besides, the residuary tumor cells after surgeries are very likely to transfer[1]. The specific immune response of T-lymphocytes plays an important role in antitumor immunity. However, various factors such as anesthesia and operation are inhibition of specific immune responses mediated by T-lymphocytes, which leads to decreased immunity to tumors cells[2]. As such, it is significant for efficacy of radical mastectomy to lessen inhibition of immunity at perioperative period by using medicine. Dexmedetomidine, a new type of α adrenergic receptor agonist, works mainly by combining with the central nervous system and the peripheral nervous system of α adrenergic receptor[3]. Moreover, it has analgesic, sedative, anxiolytic and inhibitory effect of sympathetic nerve[4]. At the same time, it can improve the stability of the cardiovascular system during operation and has a sound inhibitory effect on the stress response in surgery patients[5]. Nevertheless, there are few types of research on the effect of dexmedetomidine on immune function of patients undergoing radical

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mastectomy. In this study, the dynamic changes of T-lymphocyte subsets and natural killer cells (NK) were analyzed to explore the effect of dexmedetomidine on the perioperative immune function in different periods of patients undergoing radical mastectomy, thus providing reference for further clinical medication.

Patients and Methods

General materials

124 patients who underwent radical mastectomy in our hospital (the Second Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China) from June 2012 to October 2015 were selected in this study.

Inclusion criteria: (1) Female patients with breast cancer at stage II by American Society of Anesthesiologists (ASA). (2) Female patients without receiving any tumor treatment before hospitalization such as chemotherapy and radiotherapy.

Exclusion criteria: (1) The patients with history of taking in any drug affecting immune system, ASA III above, the history of systemic immune system diseases or important viscera system disease. 124 patients met the criteria aged from 38 to 62 years old, weighted from 47 to 79 kg. A double blind and randomized design method was adopted to divide them into two groups, the control group (Group C) and the dexmedetomidine group (Group D) with 62 cases in each group. They can be compared because there's little difference between the two groups (p>0.05) in age, weight and ASA grade, as shown in Table I. This study was approved by ethical committee of The Second Affiliated Hospital of Zhengzhou University.

Methods of Anesthesia and Sedative

Cases were divided into two groups (n=62), Group D and Group C (0.9% sodium chloride solution) by randomized digital table. After entry into the operation room, HR (heart rate), SpO_2 (Oxygen Saturation), MAP (mean arterial pressure) and BIS (Bispectral Index) were monitored. The descending radical artery puncture underwent local anesthesia to monitor the invasive arterial blood pressure and the internal jugular venipuncture to monitor the central venous preciously. Within 10 min, the patients lying down, underlying values (T0) of monitored indexes were recorded. Anesthesia induction: the patients in Group D were injected with dexmedetomidine at 0.1 $\mu g.kg^{-1}.min^{-1}$; the patients in Group C were injected with 0.9% sodium chloride solution at the same rate. After 10 min, both groups received intravenous injections of 0.6 μg/kg sufentanil, 1.0-1.5 mg/kg propofol, 0.6-1.0 mg/kg rocuronium and intubation for mechanical ventilation were performed. Maintenance of anesthesia: patients took injection of propofol at 3-8 $mg.kg^{-1}\cdot h^{-1}$, sufentanil at 0.1-0.3 $\mu g\cdot kg^{-1}\cdot h^{-1}$, Cisatracurium Besylate at 0.1-0.3 $mg\cdot kg^{-1}\cdot h^{-1}$; BIS value was maintained at 40-60 during operation.

Detection Indexes

4 ml right internal jugular venous blood at T0 (before anesthesia induction), T1 (6 h after surgery), T2 (24 h after surgery), T3 (48 h after surgery) and T4 (72 h after surgery) were collected respectively and blended in anticoagulant tubes. Then, after an ambient-temperature centrifugation at 3000 r/min for 5 min by low-speed centrifuge, plasma was taken and reserved in refrigerator at -40°C for backup. ELISA (Enzyme Linked Immunosorbent Assay) was used to detect concentrations of IL-2, IFN-γ, IL-4, IL-6 and IL-10, and all kits were purchased from Shanghai Excell Biological Products Corporation (Shanghai, China); FACS flow cytometry was used to determine the level of T-lymphocyte subsets ($CD3^+$, $CD4^+$ and $CD8^+$) and NK cell level. At meanwhile, adverse reactions including nausea, vomit, dizziness, drowsiness, flushing, itch, urinary retention, constipation, respiratory depression, abnormal bleeding, etc. were recorded.

Statistical Analysis

SPSS 16.0 software (SPSS Inc., Chicago, IL, USA) was adopted to perform the analysis. The measurement data were expressed as mean ±

Table I. General information of patients in the two groups ($\bar{x}\pm s$).

Group	Cases	Age (year)	Weight (kg)	ASA grade	Operation time (min)
Group D	62	50.32±12.24	59.85±10.63	II	112.35±16.87
Group C	62	49.62±11.41	60.74±12.60	II	115.83±18.27

Table II. Comparison between the two groups in the level of T-lymphocyte subsets and NK cells at different times.

Index (%)	Group	T0	T1	T2	T3	T4
CD3+	Group D	60.9±9.6	64.3±6.1	53.6±5.1	68.1±5.1*	61.4±7.3
	Group C	61.3±7.5	59.0±7.0	54.8±4.0	54.7±8.5	62.6±8.5
CD4+	Group D	41.0±1.16	41.4±1.7	43.6±1.1*	42.6±1.8	43.6±1.7
	Group C	42.1±1.34	41.2±2.06	41.3±1.8	41.9±1.4	42.1±1.5
CD8+	Group D	18.4±1.4	15.1±2.3*	14.2±1.3*	16.2±1.7	15.7±3.5
	Group C	18.0±1.8	17.6±1.9	17.1±1.8	18.0±1.3	16.7±3.8
CD4+/CD8+	Group D	2.4±0.3	2.7±0.5*	3.1±0.3	2.7±0.3*	2.8±0.7*
	Group C	2.2±0.2	2.3±0.3	2.4±0.3	2.3±0.2	2.6±0.4
NK	Group D	12.4±1.6	10.2±1.5*	10.9±1.6*	11.4±0.9	10.9±1.5
	Group C	12.6±1.2	9.1±1.4	9.6±1.7	10.9±1.6	10.3±1.2

Note: *refers to p <0.05 when compared with Group C at same time point.

Table III. Comparison between the two groups in concentration of INF-γ, IL-2, IL-4, IL-10 and IL-6 at different times.

Index (pg/mL)	Group	T0	T1	T2	T3	T4
INF-γ	Group D	21.4±2.6	46.6±3.4*	61.7±4.7*	42.3±4.1*	36.4±3.7
	Group C	23.3±2.1	29.6±2.7	34.1±3.4	26.1±2.7	22.1±2.0
IL-2	Group D	72.8±8.4	73.7±10.1	78.3±9.3*	78.1±7.7	77.1±7.3
	Group C	74.1±7.6	68.4±10.7	64.7±9.4	68.4±8.7	71.8±6.9
IL-4	Group D	62.4±9.3	73.1±7.6	79.4±9.1	73.1±5.9	73.2±6.7
	Group C	63.2±8.7	77.3±8.1	80.6±8.1	74.3±5.6	72.7±5.9
IL-10	Group D	32.6±5.9	261.4±54.8*	304.1±81.6*	280.3±69.8	293.7±53.3
	Group C	41.0±6.2	184.6±41.6	225.7±67.4	234.9±67.9	240.1±70.7
IL-6	Group D	49.6±6.9	51.5±9.1	416.7±71.3*	665.4±126.6*	227.9±53.4
	Group C	53.8±7.4	69.9±8.9	272.1±60.2	481.2±106.5	181.8±50.9

Note: *refers to p <0.05 when compared with Group C at same times.

standard deviation ($\bar{x}\pm$ s); the interior-group comparison was tested by group t-test; the inter-group comparison was analyzed by variance analysis with repeated measurement design and LSD (L) method was adopted for post-hoc test; count data were inspected by X^2-test. $p < 0.05$ indicates statistical significance.

Results

Comparison between the Two Groups in level of T-lymphocyte Subsets and NK Cells at Different Times

As shown in Table II, compared with Group C, $CD3^+$ and $CD4^+$ levels at T2 and T3, NK at T1 and T2 rose distinctly in Group D (p<0.05), but $CD8^+$ level showed a downward trend at T2 with statistical significance (p<0.05). $CD4^+/CD8^+$ levels rose significantly at all time points, which could relieve and maintain the immune function well. Results indicated that the dexmedetomidine, to some extent, positively influenced the cellular immune function of patients.

Comparison Between the Two Groups in Concentration of INF-γ, IL-2, IL-4, IL-10 and IL-6 at Different Times

Concentration changes of INF-γ, IL-2, IL-4, IL-10 and IL-6 in the two groups at different times were shown in Table III. Compared with Group C, concentration of INF-γ in Group D rose prominently at T1, T2 and T3 (p<0.05), and so did that of IL-2 at T2, IL-10 at T1 and T2, IL-6 at T2 and T3 (p<0.05). At T0 and T4, the concentration of INF-γ, IL-2, IL-4, IL-10 and IL-6 of the two groups had no significant changes (p<0.05), indicating that dexmedetomidine inhibits cytokine Th1 from drifting to Th2 in breast cancer.

Adverse Drug Reactions

No respiratory depression and abnormal bleeding cases were observed in Group C and Group D. There were 3 cases nausea, 6 cases vomiting and a 14.5% occurrence of adverse reactions in Group C, while there were 4 cases nausea, 4 cases vomiting, and a 12.9% occurrence of adverse reactions in Group D. However, there was no significant difference between the two groups.

Those patients were given palonosetron 0.25 mg by intravenous injection, and the symptoms were improved.

Discussion

Breast cancer, a common malignant tumor in the glandular epithelium of the mammary gland, has a severe effect on the feminine physical and mental health, even endangers life. At present, the main treatment method for breast cancer is surgical resection. However, radical mastectomy has a wide range of damage, large incision, severe trauma, severe postoperative pain and other stress factors. Some anesthetic drugs can also directly act on the immune system or activate the sympathetic adrenal medulla system, thus they can reduce the number or activity of T cells and NK cells, which causes immune suppression, and even accelerate the transfer of residual tumor cells[6,7]. Dexmedetomidine, with a full function of sedation, anti-anxiety and anti-sympathia[8], can lessen acute psychological stress reaction by blocking positive feedback of Hypothalamic-Pituitary-target gland axis. Its protective effect on immune stress is mainly manifested from the following aspects: (1) it reduces acute psychological stress reaction by sedation, thereby indirectly playing the role of immune protection. Studies[9] show that effect of acute psychological stress on immune function is expressed as the increase of $CD8^+$ and NK cells as well as proliferation decline of $CD4^+$ and T-lymphocytes, which then lead to infectious diseases. (2) by lessening immune inhibition, which can be reached by dexmedetomidine itself through inflammation reduction[10], it plays a role of postoperative immune protection. All mature peripheral T-lymphocytes, labeled by $CD3^+$, represent the general level of immunity[11] and reduction of $CD4^+/CD8^+$ indicates low immune function. NK cells, a significant member in nonspecific cell-mediated antitumor immunoregulation[7], fall to show the inhibition of immune function. In Group D of this study, postoperative level of $CD3^+$, $CD4^+$ and NK cell rose significantly at all times (p<0.05). $CD8^+$ level dropped distinctly at T1 and T2 (p<0.05); postoperative level of $CD4^+/CD8^+$ rose obviously. These results are aligned with previous reports that dexmedetomidine has a protective effect on T-lymphocyte subsets and NK cells of patients with radical resection and reduces perioperative cell immune function and is beneficial to patients' recovery and prognosis. Because of less study on the effect of dexmedetomidine on immune function currently, it needs further studies whether dexmedetomidine can reduce the psychological stress reaction of patients by sedation or improve postoperative immune function through immune suppression. T-lymphocyte can, to some extent, reflect cellular immune state. $CD4^+$ positive cells can be differentiated into two cell subsets with different function, Th1 type and Th2 type. Th1/Th2 is relatively balanced under normal condition unless the tumor occurs. When there is a tumor, Th2 cells are dominant, but the cellular immune reaction mediated by Th1 is inhibited, which arouse the immune inhibition, significant weakening of anti-tumor function, and immune escape of tumor cell finally leading to tumor recrudesce[12,13]. Currently, IFN-γ and IL-4 are main indicators for the measurement of Th1/Th2[14,15]. Th1 mainly secretes IL-2 and IFN-γ, activates T-lymphocytes and macrophages, mediates the cellular immune response, and reduces the postoperative infection. When the cellular immune function is inhibited, the lymphocyte transformation and IL-2 inducible level will be declined distinctly[16]. Th2 mainly secretes IL-4, IL-6 and IL-10, induces B-lymphocytes to secrete immunoglobulin and mediates humoral immunity[17,18]. IL-6 is the "gold index" reflecting surgical stress, which plays anti-inflammatory and pro-inflammatory role[19] by activating Hypothalamic-Pituitary-Adrenocortical Axis system in the process of stress reaction and immune response, etc. Studies[20] show that after one-hour external stimulation on organism, IL-6 level in circulation rises significantly and reaches a peak at the 3rd h. According to relevant researches[21], IL-10 can induce inflammation as well as activate anti-inflammation, which maintains relative stability of immune function. IFN-γ can inhibit Th2-mediated humoral immunity so as to balance Th1/Th2. Surgical anesthesia stress may lead to Th1 drifting to Th2 resulting in immune inhibition of organism. Through randomized double-blind study, Zhao et al[22] found that dexmedetomidine can reduce perioperative immune suppression in patients with rectal cancer, which was beneficial to improve the immune function. Morse et al[23] found that dexmedetomidine was favorable to postoperative stabilization and activation of immune function by studying the effects of dexmedetomidine on expression of MAGE-3/MAGE-4 in patients with small cell carcinoma. This study showed that in Group D, the level of IL-2 and IFN-γ secreted by Th1 increased, but the level of IL-4 secreted by Th2 changed little by contrast with Group C, which indicated that dexmedetomidine can inhibit Th1 drifting to Th2 and that dexmedetomidine would be significant for maintaining and improving the immune function of organism.

Conclusions

The intravenous dexmedetomidine may significantly reduce the inhibition of cellular immune function of perioperative patients undergoing radical mastectomy, and is very significant in maintaining and improving the immune function of the body, and in rehabilitation and prognosis of surgical patients. Thus, it is suitable for clinical application.

Conflict of interest

The authors declare no conflicts of interest.

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