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The effect of dexmedetomidine on expressions of inflammatory factors in patients with radical resection of gastric cancer

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Abstract. – OBJECTIVE: To investigate the effect of dexmedetomidine on the expressions of inflammatory factors, T-lymphocyte subgroups and nuclear factor kappa-B (NF-κB) in peripheral blood monocytes in the perioperative period of radical resection of gastric cancer.

PATIENTS AND METHODS: We selected 74 patients who were admitted to our hospital for radical resection of gastric cancer between January 2012 and October 2015. All patients were randomly divided into the dexmedetomidine group and the control group. Within 15 min before anesthesia induction, patients in the dexmedetomidine group received the intravenous injection of dexmedetomidine, while the same volume saline in the control group. During the operation, the initial dosage in the dexmedetomidine group was set as 1 μg/kg followed by 0.2 μg/kg·h intravenous injection to the end of operation. Three time points were selected: 15 min before anesthesia induction (T0), 1 h before the end of operation (T1) and 24 h after operation (T2). At these time points, we detected the levels of serum inflammatory factors using enzyme-linked immune sorbent assay (ELISA), immunoturbidimetry, and flow cytometer, respectively.

RESULTS: The levels of IL-1β, IL-6, TNF-α, NF-κB and CRP at T1 and T2 were significantly elevated compared with the levels at T0, and the amplitude of elevation in the control group was significantly larger than that in the dexmedetomidine group. The expression levels of T-lymphocyte subgroup in patients in both groups were decreased at T1 (compared with the levels at T0), and the decreasing extent of the ratio of CD4+ to CD8+ in the control group was significantly larger than that in the dexmedetomidine group. Meanwhile, we found that the percentages of CD3+ and CD4+ at T1 and T2 in the control group were significantly lower than those in the dexmedetomidine group.

CONCLUSIONS: Dexmedetomidine can effectively reduce the release of inflammatory factors in patients that received the radical resection of gastric cancer, and the anti-inflammation effect may be exerted through downregulating the expression of NF-κB. Besides, dexmedetomidine can also alleviate the reduction in subgroups of CD3+ and CD4+, thereby ameliorating the impaired immune functions.

Key Words:
Dexmedetomidine, Radical resection of gastric cancer, Inflammatory factors, T-lymphocyte subgroup, NF-κB.

Introduction

Radical resection of gastric cancer is the major treatment for gastric cancer, but several changes in physiology and biochemistry can be induced by the long duration, wide scope and severe injuries, which will further increase the content of inflammatory factors, such as IL-1 and IL-6, thereby leading to the injuries of organs. Due to the declined functions in tissues, organs and immune systems of patients with gastric cancer, plus the stress responses to general anesthesia, surgical trauma and postoperative acute pains,

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the metastasis of tumor cells can be accelerated, which can increase the mortality rate[1,2]. Hence, inhibiting the perioperative inflammatory responses is essential to improving the prognosis of patients. According to some studies[3,4], it has been reported that α2-adrenergic agonists, with the anti-inflammatory effect, can effectively protect the cellular immune function of patients in the perioperative period. In this study, we investigated the effects of dexmedetomidine, the high-selective α2-adrenergic agonist, on inflammatory factors, T-lymphocyte subgroups and NF-κB in peripheral blood monocytes of patients in the perioperative period of radical resection of gastric cancer.

Patients and Methods

Patients

We selected a total of 74 patients aged between 28 and 70 years old who were admitted to the First Affiliated Hospital of Shantou University Medicine College for radical resection of gastric cancer between January 2012 and October 2015. According to the principle of balance, these patients were divided randomly into two groups, i.e. the dexmedetomidine group (n = 37) and the control group (n = 37). All patients were within Class I to III according to the American Society of Anesthesiologists (ASA). Exclusive criteria were set as follows: (1) patients with severe infection, or diseases in respiratory system; (2) patients with severe arrhythmia or bradycardia; (3) patients with severe diseases in liver, kidney, endocrine or immune system; (4) patients who had administrated the α-adrenergic agonists or β-receptor antagonist; e) patients who had fever before operation; (5) patients who received the chemotherapy, radiotherapy or immunotherapy within one month before operation; (6) patients with the smoking or excessive drinking habit. This study was approved by the Ethics Committee of our hospital, and all patients signed the written informed consents.

Anesthesia Methods

Patients were required to fulfill all the preoperative examinations. During the operation, the vital signs of patients were monitored with the venous channel being open, and surgical duration and the bleeding amount were recorded. Within 15 min before anesthesia induction, intravenous injection of dexmedetomidine (Batch No.: 11061436; Jiangsu Hengrui Medicine Co., Ltd, Nanjing, China) was performed for patients in the dexmedetomidine group, while the normal saline in the same volume was given to patients in the control group. During the operation, the initial dosage of the dexmedetomidine group was set as 1 μg/kg in a velocity of 0.2 μg/kg·h. Anesthesia induction was performed by intravenous injection of 0.3 to 0.4 μg/kg sufentanil, 1.5 to 2.0 mg/kg propofol, and 0.6 mg/kg rocuronium bromide. Before operation, trachea cannula was performed, while mechanical ventilation was provided for patients to maintain the end-tidal partial pressure of CO_2 at 35 to 40 mmHg and blood oxygen saturation (SaO_2) above 98%. During the operation, the heart rate and arterial pressure of patients were kept at about 80% to 110% of the preoperative levels through inhalation of 2.0 to 3.0% sevoflurane, while the anesthesia state was sustained through combined intravenous injection of 4 to 6 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol and intermittent injection of sufentanil (Jiangsu Hengrui Medicine Co., Ltd, Nanjing, China) and rocuronium bromide (Jiangsu Hengrui Medicine Co., Ltd, Nanjing, China).

Observation Indexes and Experimental Methods

Observation indexes: three time points (T0, T1 and T2) were selected for extracting 5 mL sample of peripheral blood from the patient, and samples were prepared for centrifugation to obtain the supernatant which was later preserved at -80°C for detection. The levels of IL-1β, IL-6 and TNF-α were detected using Biotek microplate reader (BD, Franklin Lakes, NJ, USA); the level of CRP was detected by ARRY360-System Rate Nephelometry (Beckman, Brea, CA, USA); FACS-Calibur flow cytometer (BD, Franklin Lakes, NJ, USA) was used for detecting the level of NF-κB; $CD3^+$, $CD4^+$ and $CD8^+$ subgroups were measured through immunofluorescence staining using Multi-test labeled antibodies.

Statistical Analysis

Statistical Package for Social Science 18.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Measurement data were presented as mean ± standard deviation ($\bar{x} \pm s$). The *t*-test was performed for comparison between two groups, and analysis of variance for comparisons among groups. $p < 0.05$ suggested that the difference had statistical significance.

Table I. Comparison of general condition of patients between the two groups ($\bar{x} \pm s$, n = 37).

Group	Gender (male/female)	Age (years)	Weight (kg)	BMI
Dexmedetomidine group	23/14	36.3 ± 7.4	55.9 ± 10.1	22.0 ± 1.7
Control group	20/17	38.7 ± 7.6	56.4 ± 8.9	22.2 ± 2.2

Note: Compared with the control group, $p > 0.05$.

Table II. Comparison of surgical condition of patients between the two groups ($\bar{x} \pm s$, n = 37).

Group	Surgical duration (min)	Anesthetic duration (min)	Bleeding amount (mL)
Dexmedetomidine group	269.4 ± 18.3	290.1 ± 21.5	359.6 ± 48.5
Control group	268.0 ± 17.7	288.3 ± 21.9	366.2 ± 33.8

Note: Compared with the control group, $p > 0.05$.

Results

Comparison of General Condition and Surgical Condition of Patients Between the Two Groups

The general condition and surgical condition of patients between the two groups were balanced and comparable ($p > 0.05$; Tables I-II).

Comparison of the Levels of Inflammatory Factors of Patients Between the Two Groups

In this study, the results showed that the levels of IL-1β, IL-6, TNF-α, NF-κB and CRP of patients in the two groups were remarkably elevated at T1 and T2, and the amplitude in the control group was more significantly than that in the dexmedetomidine group ($p < 0.05$; Tables III-IV).

Comparison of NF-κB Expression in Peripheral Blood Monocytes of Patients Between the Two Groups

Compared with the level at T0 of the same group, the expression levels of NF-κB at T1 and T2 in peripheral blood monocytes of patients in both groups were significantly increased, but the amplitude of elevation in the dexmedetomidine group was lower than that in the control group ($p < 0.05$; Table V).

Table III. Comparison of levels of IL-1β, IL-6 and TNF-α between the two groups ($\bar{x} \pm s$, n = 37).

Observation indexes	Group	T0	T1	T2
IL-1β (pg/mL)	Dexmedetomidine group	5.98 ± 0.39	16.73 ± 0.89*,#	23.53 ± 1.09*,#
	Control group	5.97 ± 0.41	33.81 ± 1.88*	38.36 ± 1.39*
IL-6 (pg/mL)	Dexmedetomidine group	65.09 ± 2.53	74.38 ± 3.01*,#	83.71 ± 3.13*,#
	Control group	65.11 ± 1.97	80.13 ± 2.81*	87.21 ± 2.64*
TNF-α (pg/mL)	Dexmedetomidine group	14.97 ± 3.16	28.61 ± 4.12*,#	32.64 ± 3.78*,#
	Control group	15.81 ± 2.91	31.85 ± 3.42*	39.11 ± 2.69*

Note: *$p < 0.05$ (compared with the level at T0); #$p < 0.05$ (compared with the level in the control group).

Table IV. Comparison of CRP level between the two groups ($\bar{x} \pm s$, n = 37).

Observation indexes	Group	T0	T1	T2
ICRP (mg/L)	Dexmedetomidine group	8.99 ± 3.48	14.79 ± 2.98*,#	20.62 ± 3.56*,#
	Control group	9.32 ± 3.73	19.38 ± 3.39*	31.27 ± 4.24*

Note: *$p < 0.05$ (compared with the level at T0); #$p < 0.05$ (compared with the level in the control group).

Table V. Comparison of expression of NF-κB in peripheral blood monocytes of patients between the two groups ($\bar{x} \pm s$, %, n = 37).

Observation indexes	Group	T0	T1	T2
NF-κB (U/L)	Dexmedetomidine group	20.41 ± 11.48	32.66 ± 15.27*,#	27.13 ± 13.42*,#
	Control group	23.17 ± 12.36	40.45 ± 16.71*	30.36 ± 14.16*

Note: *$p < 0.05$ (compared with the level at T0); #$p < 0.05$ (compared with the level in the control group).

Comparison of T-Lymphocyte Subgroups of Patients Between the Two Groups

In this study, we showed that the expression levels of T-lymphocyte subgroups of patients in the two group at T1 were lower than that at T0 ($p < 0.05$); in comparison of the ratios of $CD4^+$ to $CD8^+$ between the two groups, a more significant decrease was observed in the control group ($p < 0.05$). Meanwhile, we found that the percentages of $CD3^+$ and $CD4^+$ at T1 and T2 in the control group were significantly lower than those in the dexmedetomidine group ($p < 0.05$; Table VI).

Discussion

Dexmedetomidine, as a new type of α2-adrenergic agonists, has widely been applied as the adjuvant drug for regional and general anesthesia and as the sedative and analgesic for surgeries[5]. IL-1β, a pro-inflammatory factor with a potent inhibitory effect on secretion of gastric acid, is closely associated with the susceptibility of gastric cancer; as a kind of acute-phase regulatory factor of inflammatory response[6-8], IL-6 is not only one of the most important and sensitive markers for stress responses in the body, but also associated with the pathological development and progress of gastric cancer[9]. TNF-α is a kind of mediator generated in the host response to body injuries that can influence the body metabolism and hemodynamic status, and surgical trauma can induce the synthesis and release of TNF-α by the activated T cells in the body, which can further aggravate the general inflammatory responses[10]. CRP is generally served as an acute-phase response indicator that can be significantly increased in the serum of patients with acute trauma, infection, inflammation or tumors. Thus, monitoring the changes in levels of IL-1β, IL-6, TNF-α and CRP is conducive to evaluation of the prognosis after radical resection of gastric cancer. In a study on pulmonary injury model of mouse, researchers found that high-dosage dexmedetomidine could reduce the concentrations of chemotactic factors in the lung (e.g. the macrophage inflammatory protein-2) and inflammatory factors (e.g. TNF-α and IL-1β). After dexmedetomidine was given to the shock animal model of endotoxemia, scholars detected the significant decreases in the levels of cytokines in the serum of mice, including TNF-α and IL-6, and found that the survival rate of model animals was significantly elevated. In this study, we found that in the two groups, the levels of IL-1β, IL-6, TNF-α and CRP at T1 and T2 were significantly elevated compared with the levels at T0, and the amplitude of elevation in the control group was significantly larger than that in the dexmedetomidine group, indicating that dexmedetomidine can suppress the augmentation of inflammatory factors in the perioperative period of patients. In a study[11], it

Table VI. Variations in T cell subgroups at different time points in the two groups ($\bar{x} \pm s$, %, n = 37).

Group/Time point	CD3+	CD4+	CD8+	CD4+/CD8+2
Dexmedetomidine group				
T0	52.3 ± 3.8	33.4 ± 3.2	25.8 ± 2.3	1.29 ± 0.13
T1	43.1 ± 3.6*,#	28.1 ± 3.1*,#	26.0 ± 2.1	1.01 ± 0.14*,#
T2	51.6 ± 4.0#	33.1 ± 3.4#	26.3 ± 2.2	1.26 ± 0.14
Control group				
T0	53.2 ± 4.4	34.1 ± 3.3	26.3 ± 2.4	1.30 ± 0.14
T1	37.5 ± 3.5*	24.3 ± 3.4*	26.5 ± 2.5	0.79 ± 0.13*
T2	44.9 ± 4.2*	29.8 ± 4.5*	25.9 ± 2.6	1.12 ± 0.13*

Note: *$p < 0.05$ (compared with the level at T0); #$p < 0.05$ (compared with the level in the control group).

was reported that the NF-κB activated by lipopolysaccharide (LPS) can initiate the expression of TNF-α, which, together with the LPS, can commonly activate the monocyte/macrophages and neutrophils to release the inflammatory mediators; thus, the increased release of inflammatory factors is associated with the increase the activity of NF-κB. In this work, the results showed that compared with the level of NF-κB at T0, levels at T1 and T2 were elevated, and a significant elevation was observed at T2, but the amplitude of elevation in the control group was significantly larger than that in the dexmedetomidine group ($p < 0.05$). Patients with gastric cancer usually suffer from the poor metabolic function, surgical trauma and stress responses caused by administration of anesthetic drugs, which can affect the acute release of inflammatory factors in the body[12]. Inevitably, variations in neurological and endocrine systems affect the immune functions. Some hormones and inflammatory factors released during the stress responses can suppress the activity of immune cells through a variety of pathways[13]. According to several studies[14,15], it was revealed that after operations for patients who received the dexmedetomidine, the levels of IL-1, IL-6 and TNF-α were decreased, suggesting that dexmedetomidine could effectively inhibit the inflammatory responses, thereby ameliorating the cellular immune functions of patients to a certain degree. In this study, we confirmed that dexmedetomidine can alleviate the adverse effect produced by stress responses without any influences on the basic condition of patients in radical resection of gastric cancer. T-lymphocyte subgroup (including $CD3^+$, $CD4^+$ and $CD8^+$) has the vital anti-tumor immune activity, in which the decreased $CD4^+/CD8^+$ ratio suggested the declined immune functions and warned the physicians about the poor prognosis[16,17]. Yang et al[18] found that dexmedetomidine can effectively improve the immune condition of patients in the perioperative period, but the subjects in this study were not patients who would receive radical resection of gastric cancer. In this research, we found that the expression levels of T-lymphocyte subgroup in patients in both group were decreased at T1 (compared with the levels at T0, $p < 0.05$), and the decreasing extent of the ratio of $CD4^+$ to $CD8^+$ in the control group was significantly larger than that in the dexmedetomidine group ($p < 0.05$). Meanwhile, we observed that the percentages of $CD3^+$ and $CD4^+$ at T1 and T2 in the control group were significantly lower than those in the dexmedetomidine group ($p < 0.05$). The findings indicated that the suppression on cellular immune functions caused by stress responses to surgery can be improved to a certain extent after the administration of dexmedetomidine, which might be caused by the following action mechanisms: on one hand, the reduced sympathetic nerve activity inhibit the stress responses to surgical trauma; on the other hand, preemptive analgesic effect could alleviate, or eliminate the stress responses to surgery, thereby relieving the suppression on immune functions[19,20]. However, specific mechanisms remain to be verified by future in-depth investigations.

Conclusions

Dexmedetomidine can effectively reduce the release of inflammatory factors of patients in radical resection of gastric cancer, including CRP, IL-1β, TNF-α and IL-6, and it may exert its anti-inflammatory effect through downregulating the expression of anti-inflammation pathways by affecting the activity of NF-κB. Also, dexmedetomidine can mitigate the decrease in the levels of $CD3^+$ and $CD4^+$ subgroups to ameliorate the impaired immune functions.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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