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Effects of dexmedetomidine on patients undergoing radical gastrectomy

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ARTICLE INFO

Article history:
Received 1 September 2014
Received in revised form
1 September 2014
Accepted 3 October 2014
Available online 8 October 2014

Keywords:
Dexmedetomidine
Th1/Th2
Catecholamines
Cytokines
VAS

ABSTRACT

Background: Surgical stress may cause immunosuppression especially in patients who have surgery for primary tumor removed. This study aimed to explore the effects of dexmedetomidine on immune and inflammatory response in patients undergoing radical gastrectomy.

Methods: After the institutional review board approval and written informed consent, forty patients undergoing radical gastrectomy were equally randomized to receive dexmedetomidine infusion (Dex group; 0.5 $\mu g \cdot kg^{-1}$ initial dose followed by a maintenance dose of 0.4 $\mu g \cdot kg^{-1}\ h^{-1}$) or normal saline infusion (NS group). Helper T lymphocytes (T helper 1 [Th1] and T helper 2 [Th2]), tumor necrosis factor-α, and interleukin-6 were measured during and after surgeries. Plasma catecholamine levels were also measured during surgery. Postoperative pain was measured by a visual analog scale.

Results: The percentage of Th1 increased significantly at the end of surgery, 24 h after surgery ($P = 0.045$ and 0.048, respectively), and Th2 decreased notably at the end of surgery in the Dex group ($P = 0.030$). Plasma levels of tumor necrosis factor-α ($P = 0.045$ and 0.036, respectively) and interleukin-6 ($P = 0.049$ and 0.042, respectively) differed significantly at the end of surgery and 24 h after surgery. Plasma epinephrine and norepinephrine levels decreased significantly at the beginning of surgery in the Dex group ($P = 0.020$ and 0.015, respectively). At the end of surgery, plasma dopamine levels decreased significantly in the Dex group ($P = 0.048$), but increased in the NS group. The visual analog scale pain score was lower in the Dex group than in the NS group 24 h after surgery ($P = 0.046$).

Conclusions: Dexmedetomidine has been shown to reduce surgical stresses and maintain Th1/Th2 balance. It has been shown to reduce inflammatory responses and exerts immunoprotective effect.

1. Introduction

The incidence of gastric cancer is increasing in the recent years, and it is the most common cause of cancer-related deaths in China [1]. In cancer patients, surgical removal of the primary tumor is one of the most important steps in treating the disease. Surgical stress results from activation of the hypothalamic-pituitary-adrenal axis and influences patient immune system.

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http://dx.doi.org/10.1016/j.jss.2014.10.008

Immunosuppression is induced by innate regulatory T-cells and tumor cytokines that can either suppress or stimulate immune responses [2]. T helper lymphocytes can be differentiated into two major subsets of effector cells as follows: T helper 1 (Th1) and T helper 2 (Th2) cells [3]. Th1 cells activate macrophages to stimulate the release of cytokines and induce cell-mediated immunity. Alternatively, Th2 cells stimulate B cells to produce antibodies and consequently induce humoral immunity. Th1 cells are essential for cell-mediated (anti-tumor) immunity, and a shift in the Th1/Th2 balance toward Th1 is beneficial in this regard. However, the ratio of Th1/Th2 decreases after surgery, resulting in a suppressed cell-mediated immunity [4]. Inflammatory cytokines suppress host anti-tumor immunity and lead to tumor growth and metastasis [5]. Surgical stresses also induce releases of catecholamines, which also stimulate tumor growth [6].

Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist and has sedative, anesthetic, analgesic, and sympatholytic properties [7,8]. Although the primary clinical use of dexmedetomidine is mainly for its effects on the central nervous system such as short-term sedation and antianxiety [9], more studies have shown that it can produce organ protective effects against ischemic and hypoxic injuries including cardioprotection, neuroprotection, and renoprotection [10–15]. In animal studies, dexmedetomidine has demonstrated anti-inflammatory effects by reducing the "cytokine storm" to reduce mortality and inhibit inflammatory responses in endotoxemic rats [16–18].

Surgical stress may cause immunosuppression and slow down patients' recovery after surgery. It is important to design and use anesthetic techniques that can reduce surgical stresses [19]. The aim of the present study was to explore the role of dexmedetomidine, an anesthesia adjuvant, on immunity and inflammatory response in patients undergoing gastric cancer surgery.

2. Methods

2.1. Study population

This is a single-centered, prospective, randomized, and controlled study. The protocol was reviewed and approved by the local Institutional Review Board of the First Affiliated Hospital of Soochow University. All subjects provided written informed consent before participating in this study. The study was registered in the Chinese Clinical Trial Registry (ChiCTR-TRC-14004168).

Patients who met the following criteria were included in this study: clinically diagnosed gastric cancer and required elective radical gastrectomy, age >18 and <70 y, body mass index ≤30 $kg \cdot m^{-2}$, and American Society of Anesthesiologists physical status I–II. Exclusion criteria included severe hypertension (systolic blood pressure [SBP] >210 mm Hg) or hypotension (SBP <90 mm Hg), severe bradycardia (heart rate [HR] <50 beats/min), any type of atrial-ventricular conduction block on the electrocardiography, heart failure, infection, immune system diseases, receiving immunotherapy, recent history of blood transfusion, history of other systematic diseases, and previous laparoscopic radical gastrectomy. Each study lasted 2 d (started from the day of surgery to 2 d after surgery). Blood pressure and HR were monitored and recorded during the study. If HR was <50 bpm, 0.5 mg atropine was administered. If SBP dropped to <90 mm Hg, 10 mg ephedrine intravenous bolus was administered.

Forty patients were enrolled in this study. For randomization, each patient received a sealed envelope containing a random number selected from 1–40 and was assigned to one of the two groups: dexmedetomidine group (Dex group) and normal saline group (NS group), patients were blinded for what they received in this single-blinded study. Patients in both groups underwent surgical resection of gastric cancer.

2.2. Anesthetic management

No premedication was administered. Pulse oximetry, electrocardiography, temperature, expiratory end tidal carbon dioxide, bispectral index (Aspect Medical Systems, Inc, Newton, MA), noninvasive blood pressure HR were monitored for all patients. In Dex group, patients received a loading dose of 0.5 $\mu g \cdot kg^{-1}$ dexmedetomidine over 10 min before induction and then a maintenance dose of 0.4 $\mu g \cdot kg^{-1}\ h^{-1}$ dexmedetomidine until 30 min before closing peritoneum. In the NS group, patients received the normal saline.

General anesthesia was induced with propofol (2.5 $mg \cdot kg^{-1}$) and fentanyl (4 $\mu g \cdot kg^{-1}$) intravenously. Muscle relaxation was achieved with 0.15 $mg \cdot kg^{-1}$ of cisatracurium intravenously to facilitate endotracheal intubation. Volume-controlled ventilation was used to achieve an end tidal carbon dioxide of 35–45 mm Hg by adjusting respiratory rate and tidal volume. Anesthesia was maintained with 1.0%–2.0 % of isoflurane, propofol (2.0 $\mu g \cdot mL^{-1}$target effect site concentration) administered by target-controlled infusion pump (Graseby 3500, GRASEBY MEDICAL Ltd., Watford, England), fentanyl (2 $\mu g \cdot kg^{-1}$), and cisatracurium (0.1 $mg \cdot kg^{-1}\ h^{-1}$). The bispectral index was maintained between 50 and 60, and noninvasive blood pressure and HR variations were kept within 20% of the preoperative baseline values during surgery by adjusting the dosages of anesthetics. All patients received ondansetron (8 mg) toward the end of surgery. Patient-controlled intravenous analgesia (20 $\mu g \cdot kg^{-1}$ of fentanyl diluted with NS to 100 mL) was used for postoperative analgesia. After surgery, all patients were transferred to post anesthesia care unit (PACU).

2.3. Data collection

Venous blood samples were taken for Th1, Th2, tumor necrosis factor (TNF)-α, and interleukin (IL)-6 measurements before surgery (T_0), at the beginning of surgery (T_1), at the end of surgery (T_2), at 24 h after surgery (T_3) and at 48 h after surgery (T_4). The percentage of Th1 and Th2 cells were measured using flow cytometry (BD FACSCalibur System FAQs, BD Bioscienc, Franklin Lakes, NJ) [20,21]. Plasma TNF-α and IL-6 were measured using enzyme-linked immunosorbent assay [22]. Plasma epinephrine, norepinephrine, and dopamine were also measured using enzyme-linked immunosorbent assay [23] at T_0, T_1, and T_2. Postoperative analgesia was measured using visual analog scale (VAS) performed with a 10-cm horizontal scale of 0 (no pain) to 10 (worst pain

Table – Baseline characteristics.

Characteristics	Dex group ($n = 20$)	NS group ($n = 20$)	P value
Male/female (*n*)	17/3	14/6	0.451
ASA I/II (*n*)	6/14	8/12	0.741
Age (y)	56.7 ± 9.0	57.2 ± 8.3	0.860
Weight (kg)	63.9 ± 6.8	64.3 ± 8.9	0.874
BMI (kg/m^2)	23.1 ± 2.1	24.1 ± 2.6	0.186
Length of surgery (min)	136.7 ± 35.9	127.8 ± 27.6	0.382
Fluid infusion during surgery (mL)	1120.1 ± 294.8	1086.5 ± 278.2	0.713
Fentanyl during surgery (mg)	0.5 ± 0.1	0.6 ± 0.1	0.418
Fentanyl after surgery (mg)	1.3 ± 0.1	1.3 ± 0.2	0.368
Total propofol (mg)	705.6 ± 87.2	737.8 ± 67.2	0.204
Hospital length of stay (d)	13 (12–19)	15 (12–22)	0.640

ASA = American Society of Anesthesiologists; BMI = body mass index.
Categorical variables were presented as numbers; categorical variables were reported as means and standard deviations.

imaginable) at the time of leaving PACU, at 24 h after surgery, and at 48 h after surgery.

2.4. Statistical methods

Statistical analysis was performed using SPSS version 17.0 software (SPSS Inc, Chicago, IL). Based on the preliminary study before formal study, the values of alpha, beta, and standard deviations were determined, and the sample size for the present study was calculated. Continuous and categorical variables were reported as means and standard deviations. Independent sample *t*-tests were used to compare normally distributed samples, and Wilcoxon rank-sum test was used to compare abnormally distributed independent samples. Abnormal distributed data was presented as median. Categorical variables were presented as numbers and percentages, and they were analyzed by χ^2 test. In all cases, $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline and demographic characteristics

The demographic data were presented in Table. There were no significant differences in patient characteristics (gender, age, American Society of Anesthesiologists status, weight, and body mass index) between the two groups ($P > 0.05$). There were also no differences in the length of surgery, intraoperative fluid infusion, dosage of fentanyl and propofol, and postoperative length of hospital stay between the two groups (Table). All patients returned to the ward after surgery, and no one received blood transfusion during surgery or postoperatively.

3.2. Th1 and Th2 levels

The percentage of Th1 cells increased in the first 24 h postoperatively in Dex group. Compared with the NS group, the percentage increase of Th1 cells was significantly at T_2 and T_3 in the Dex group. The differences at T_2 and T_3 were 23.5 ± 12.8% *versus* 32.0 ± 12.9% ($P = 0.045$) and 27.1 ± 15.1% *versus* 37.8 ± 17.9% ($P = 0.048$) between Dex and NS groups, respectively (Fig. 1). The percentage of Th2 cells decreased during surgery in the Dex group and slightly increased after the surgery. In the NS group, the percentage of Th2 cells increased throughout the surgery up to 48 h postoperatively. The difference at T_2 was significant between the two groups (2.8 ± 1.2% *versus* 2.0 ± 1.0%, $P = 0.030$, Fig. 1). The ratio of Th1/Th2 increased at T_2 and T_3 time points in the Dex group. It also increased in the NS group, but the increases were notably less than that in the Dex group. The differences at T_2 and T_3 were 16.6 ± 9.2% *versus* 22.9 ± 10.3% ($P = 0.049$) and 14.8 ± 5.2% *versus* 18.5 ± 5.9% ($P = 0.040$) between the two groups, respectively (Fig. 1).

3.3. TNF-α and IL-6 levels

In both groups, the plasma levels of TNF-α and IL-6 increased from the beginning of surgery and lasted for 48 h postoperatively. However, the increase of TNF-α was smaller at T_2 and T_3 time points in the Dex group compared with the NS group. The differences at T_2 and T_3 were 19.8 ± 9.5 pg/mL *versus* 26.8 ± 11.7 pg/mL ($P = 0.045$) and 25.4 ± 13.2 pg/mL *versus* 34.9 ± 14.4 pg/mL ($P = 0.036$; Fig. 2) between the two groups, respectively. IL-6 also increased in the Dex group compared with the NS group at T_2 and T_3 time points. The differences at T_2 and T_3 were 102.7 ± 54.0 pg/mL *versus* 146.1 ± 78.4 pg/mL ($P = 0.049$) and 161.3 ± 87.5 pg/mL *versus* 218.4 ± 83.6 pg/mL ($P = 0.042$) between the two groups, respectively (Fig. 2).

3.4. Plasma catecholamines

Plasma epinephrine, norepinephrine, and dopamine levels were elevated before surgery in both groups (Fig. 3). The plasma level of epinephrine decreased during surgery in both groups. But in the Dex group, the value was lower than in the NS group at T_1. The difference was 84.4 ± 27.3 pg/mL *versus* 106.3 ± 29.8 pg/mL ($P = 0.020$, Fig. 3). The plasma level of norepinephrine also decreased significantly at T_1. The difference was 194.6 ± 86.0 pg/mL *versus* 267.6 ± 94.4 pg/mL ($P = 0.015$, Fig. 3), but it increased again after surgery. At T_1, the plasma level of dopamine increased in the Dex group and the

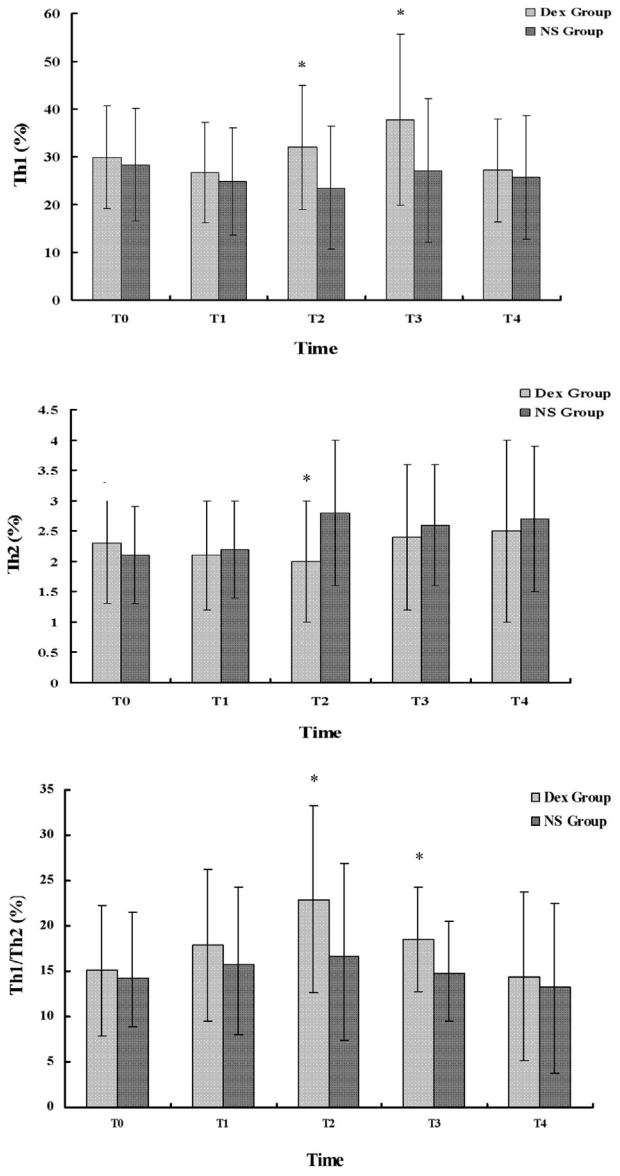

Fig. 1 – The percentages of Th1 and Th2 cells during surgery and after surgery in Dex and NS groups. Results are presented as mean ± standard deviation. $n = 20$ patients per group. T_0: before surgery, T_1: at the beginning of surgery, T_2: at the end of surgery, T_3: 24 h after surgery, and T_4: 48 h after surgery. $^*P < 0.05$ compared with NS group.

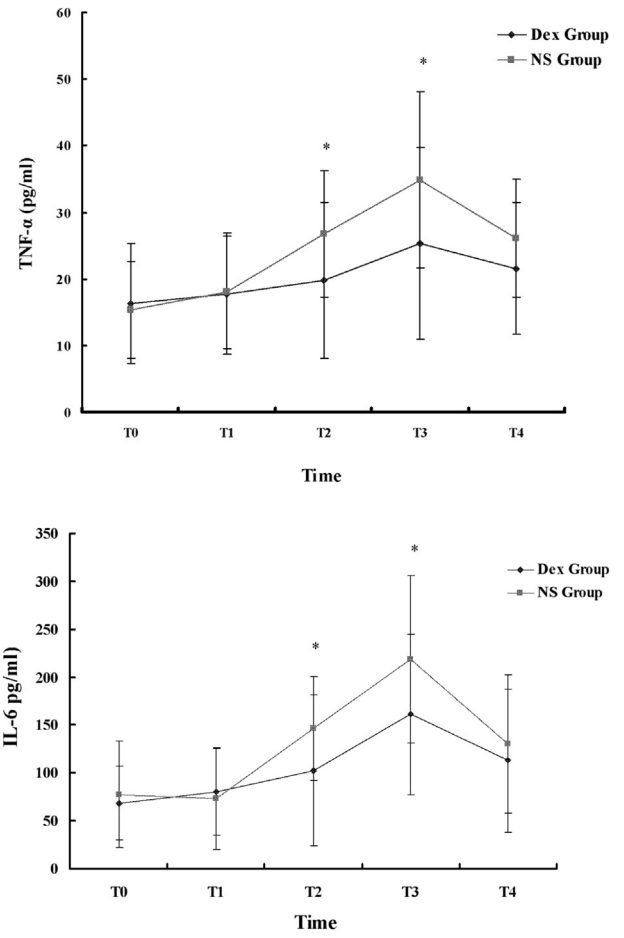

Fig. 2 – The plasma levels of IL-6 and TNF-α (picogram/milliliter) during and after surgery in Dex and NS groups. Results are presented as mean ± standard deviation. $n = 20$ patients per group. T_0: before surgery, T_1: at the beginning of surgery, T_2: at the end of surgery, T_3: 24 h after surgery, and T_4: 48 h after surgery. $^*P < 0.05$ compared with NS group.

NS group; but at T_2, it decreased significantly in the Dex group, whereas increased in the NS group (61.1 ± 25.7 pg/mL *versus* 79.9 ± 32.0 pg/mL, $P = 0.048$, Fig. 3).

3.5. *VAS pain score*

There was no difference in the VAS pain scores between the two groups at the time of leaving PACU and at 48 h after surgery. However, VAS pain score in the Dex group was lower than in the NS group (3.9 ± 1.4 *versus* 4.7 ± 1.2, $P = 0.046$, Fig. 4) at 24 h after surgery. No patient received any other supplemental analgesia medication after surgery in either group.

3.6. *Hemodynamic parameters*

SBP, diastolic blood pressure, and HR data were measured in both groups. Compared with the NS group, SBP was lower in Dex group at T_2 (112.7 ± 10.5 *versus* 122.3 ± 10.3, $P = 0.012$). Eleven patients had bradycardia (HR <60 bpm) in the Dex group, whereas seven patients had bradycardia in the NS group ($P = 0.34$). There were seven patients who had hypotension (SBP <90 mm Hg) in the Dex group, whereas three patients had hypotension in the NS group ($P = 0.27$). However, there were no severe bradycardia and hypotension that occurred during surgery in either group.

4. Discussion

The removal of the primary tumor is the most important step in cancer treatment. Surgical stress induces dysfunction in the immune system and potentially affects postoperative infections [24–27]. It is well documented that dexmedetomidine

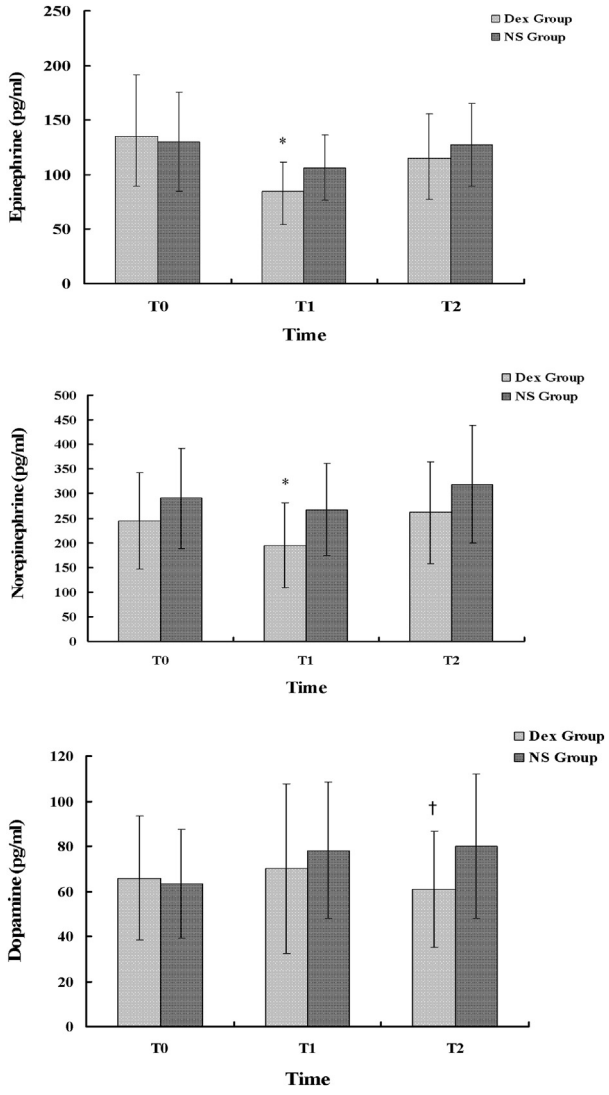

Fig. 3 – The plasma levels of epinephrine, norepinephrine, and dopamine (picogram/milliliter) during surgery in Dex and NS groups. Results are presented as mean ± standard deviation. $n = 20$ patients per group. T_0: before surgery, T_1: at the beginning of surgery, and T_2: at the end of surgery. *The significances of epinephrine and norepinephrine are both at T1.† The significance of dopamine is at T2.

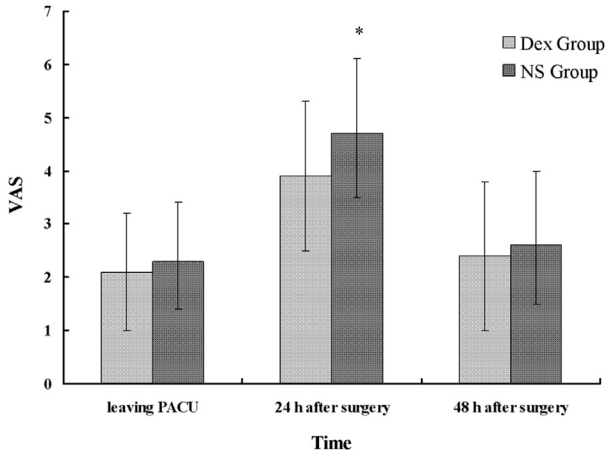

Fig. 4 – The change of VAS after surgery in Dex and NS groups. Results are presented as mean ± standard deviation. $n = 20$ patients per group. *$P < 0.05$ compared with NS group.

inhibits the neuroendocrine and inflammatory responses in both experimental and clinical settings [28–32]. However, little is known on its effect on tumor immunity and inflammatory response.

Cancer patients usually present with immunosuppression [33,34]. Host immunosuppression influences anti-tumor immune responses. As a tumor develops, it creates a microenvironment that supports tumor growth and metastasis [35]. Surgery aggravates the immunosuppression [36], which is mainly marked by T cell immunity suppression [2,37]. The Th1/Th2 ratio decreases after surgery, resulting in a suppressed cell-mediated immunity [4]. The Th2 polarization has been reported in gastric cancer [38]. As the gastric cancer progresses, the blood Th2 cells increases [39]. Dexmedetomidine was reported to play an immune-modulatory role in shifting the Th1/Th2 cytokine balance toward Th1 in patients with underwent surgery [40]. In this study, the percentages of Th1 and Th2 were high before surgery, and the ratio of Th1/Th2 was lower after surgery. Dexmedetomidine attenuated Th2-polarizing state and maintained the balance of Th1/Th2 relative stabilization. Therefore, dexmedetomidine can keep the immune-balance in this patient population.

Inflammation has been hypothesized to play a significant role in the etiology of gastric cancer [5]. Study shown circulating levels of inflammation-related cytokines such as IL-4, IL-6, IL-8, IL-10, and TNF-α were increased in patients with gastric cancer [41]. Some clinical investigations have suggested the potential significance of IL-6 as a prognostic factor in patients with gastric cancer [42,43]. Studies have also found that dexmedetomidine has a significant anti-inflammatory effect against endotoxin-induced inflammation [17,28,44]. Studies suggested the anti-inflammatory effect of dexmedetomidine could be resulted by reducing the serum levels of inflammatory cytokines [44–51]. In the present study, inflammation-related cytokines increased during surgery because of surgical stress and the underline disease itself. Dexmedetomidine suppressed the rapid increasing of cytokines TNF-α and IL-6. To the best of our knowledge, this is the first clinical study to demonstrate the effects of dexmedetomidine in patients undergoing radical gastrectomy.

Surgical stress causes the increasing release of catecholamines. Adrenergic catecholamines are known to influence immune responses and inflammation [52]. It has been reported that dexmedetomidine can decrease plasma catecholamines [29,53,54]. Catecholamines enhance tumor growth [6,55] and are found to be involved in the processes of immunosuppression and inflammation [25]. This study showed that dexmedetomidine reduced the release of epinephrine, norepinephrine, and dopamine. These findings are consistent with the previously published results [53].

Furthermore, our study demonstrated that dexmedetomidine improved postoperative analgesia and maintained hemodynamic stability, which was consistent with other reports

[56,57]. Dexmedetomidine has complex vasodilative and vasoconstrictive effects especially to its activation of presynaptic and postsynaptic α_2-receptors. The most common adverse event after dexmedetomidine administration is bradycardia and an initial short-term increase in blood pressure followed by a longer period of low blood pressure. Therefore, cautions in patients at risk are warranted [58,59].

There were some limitations in this study. This was a single-center study with a small sample size. Patients were observed only for 48 h after surgery. We only measured selective parameters, and this does not exclude other proinflammatory parameters that may also involve in the process. This study did not explore the mechanism of dexmedetomidine in impacting the immune system and inflammatory response in gastric cancer. Nuclear factor-κB is critical in the anti-inflammatory process [60]. Studies showed that α_2 stimulation or the direct activation of nuclear factor-κB was essential to the anti-inflammatory mechanism of dexmedetomidine [5,61].

5. Conclusions

Dexmedetomidine reduces surgical stress, promotes T helper cells to differentiate into Th1 cells, and maintains the Th1/Th2 balance. It also demonstrated its anti-inflammatory effect in gastric cancer surgery patients. Hence, dexmedetomidine may be used as an adjuvant in regulating anti-inflammatory and immune responses in gastric cancer surgery patient population.

Acknowledgment

The authors thank Dechun Li, Haitao Zhang, Hong Zhao, Liang Wang, Hao Hu, Xiaoqiang, Dong in the General Surgery Department of the First Affiliated Hospital of Soochow University for assisting in the study.

This study was supported by grant from the National Natural Science Foundation of China (No. 81471835), by Jiangsu Province's Key Provincial Talents Program of China (F.J.), by Jiangsu Province's six major peak talents program of China (F.J.), and by Suzhou science and Technology Bureau's program No.SYSD2013074 (F.J.) of China.

Disclosure

The authors had no conflicts of interest to declare in relation to this article.

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