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Effects of dexmedetomidine on patients undergoing radical gastrectomy

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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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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