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Original Article

A comparion of the effects of dexmedetomedine and propofol on stress response in patients undergoing open esophagectomy under total intravenous anesthesia: a randomized controlled trail

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Abstract: Backgroud: The effect of dexmedetomidine on surgical stress has still not been documented when compared with propofol. Objective: Our aim was to compare the effects of dexmedetomedine and propofol on stress response in patients undergoing open esophagectomy under total intravenous anesthesia and study the feasibility of dexmedetomedine as the sole anesthetic agent in total intravenous anesthesia (TIVA). Methods: Thirty patients of ASA I~II, 60-75 years of age, scheduled for open esophagectomy under general anesthesia were randomly divided into two groups of 15 each. Group P received propofol 2 mg/kg bolus followed by infusion 100~200 μg/kg/min and Group D received dexmedetomidine 1 μg/kg bolus followed by infusion 0.04~0.08 μg/kg/min. Both groups were administered standard general anesthesia with routine monitoring. Bispectral index (BIS) were applied to monitor the depth of anesthesia with the target BIS value setting 50±5 intraoperatively by adjusting the dose of sedative drug. Blood samples were tested for plasma concentrations of epinephrine, norepinephrine, cortisol, ACTH, IL-6 at piror anesthesia, 2 h after surgery and 24 h postoperatively. Modified Brice questionnaire was used to define intraoperative awareness 24 h after operation. Results: Plasma NE, epinephrine, cortisol, ACTH levels in both groups increased significantly at T1, T2, while NE, epinephrine level were significantly higher in P group. Plasma IL-6 concentrationsin in both groups increased with time, while was higher in P group at two time points. Plasma glucose levels increased versus baseline at T1, and significantly higher in D group. Conclusions: Dexmedetomidine has similar effect on surgical stress response in patients undergoing open esophagectomy under general anaesthesia compared with propofol. Then, dexmedetomidine can be used as the sole anesthetic agent in total intravenous anesthesia.

Keywords: Propofol, dexmedetomidine, stress response, open esophagectomy.

Introduction

Stress response to surgery is characterized by activation of the hypothalamus-pituitary-adrenal (HPA) axis, which stimulates adrenocorticotrophic hormone (ACTH) release from the anterior pituitary gland, and subsequently, cortisol release from the adrenal cortex and sympathetic nervous system (SNS) activation, which augments norepinephrine (NE) release from presynaptic sympathetic fibers and NE and epinephrine release from the adrenal medulla [1]. Major surgery always evokes a high stress response and contributes to an increase in postoperative morbidity and mortality [2]. Then, blunting the stress response has been the goal of many anesthetist in an effort to improve clinical outcome after surgery [3]. Previous study has verified that propofol could attenuate surgical stress [4], continuous infusions of the intravenous anesthetic propofol are commonly used to induce and maintain in total intravenous anesthesia during decades [5]. Dexmedetomidine, a selective α-2a adrenergic receptor agonist, has been used for sedation in ICU and for short surgical procedures [6-8], and also as an adjunct resulting in reduced intraoperative requirements of anesthetics [9, 10]. Latest research has demonstrate the possibility of dexmedetomidine as the sole maintenance sedative agent [11]. However, the effect of dexmedetomidine on surgical stress has still not been documented when compared with propofol. Present study was designed to discovery

Table 1. Demographics and clinical characteristics

	Group P	Group D
Age (yr)	68.7±4.4	70.1±3.8
Gender (M/F)	11/4	10/5
Weight (kg)	61.6±5.8	59.3±6.2
Height (cm)	168.4±8.7	165±7.6
Fluid balance in surgery (ml)	1643±335	1607±297
Intraoperative fentanyl requirement (mg)	0.63±0.06	0.66±0.05
Nicardipine requirement (n)	7	5
Phenylephrine requirement (n)	5	4
Duration of Surgery (min)	152.8±34.3	155.5±40.9
Consciousness time (min)	18.5±5.6	23.7±5.8
Tracheal extubation time (min)	26.3±4.4	31.2±3.8
Postoperative VAS	5.2±1.8	4.1±1.4*
Length of stay in the PACU (min)	53.7±7.4	58.6±8.3
Rescue analgesics requirement (mg)	163.6±24.4	103.6±32.5*
Intraoperative awareness (n)	0	0

*Compared with P group, P < 0.05. Results are presented as the mean ± standard deviation.

the two sedative drugs as sole maintenance sedative agent in major surgery (open esophagectomy), then compare their effects on stress response.

Materials and methods

Study subjects

Approval for the study was obtained from our Hospital ethics committee and written informed consent was obtained from each of the participants. Thirty patients, 63-75 years of age, ASA physical status of I~II, scheduled for open esophagectomy under general anesthesia were averagely divided into two groups by a computer-generated randomization scheme: P group and D group. Patients with liver or renal dysfunction, hemostatic disorders and perioperative use of sedative drugs were excluded.

Anesthesia

The patients were brought to the operating room and peripheral intravenous and arterial cannulae were inserted and electrocardiogram electrodes and pulse oximetry sensor were applied. BIS was also used to monitor the depth of anesthesia. In the P group, anesthesia was induced by intravenous injection of propofol (2 mg/kg), fentanyl (5 μg/kg) and vecuronium bromide (0.15 mg/kg), then maintained by intravenous infusion of propofol (100~200 μg/kg/min) and fentanyl (0.05 μg/kg/min). In the D group, anesthesia was induced by intravenous injection of dexmedetomidine (1 μg/kg), fentanyl (5 μg/kg) and vecuronium bromide (0.15 mg/kg), and maintained by intravenous infusion of dexmedetomidine (0.04~0.08 μg/kg/min) and fentanyl (0.05 μg/kg/min). All patients underwent tracheal intubation and mechanical ventilation with 100% oxygen, VT 8-10 mL/kg, frequency 10-14/min, for the goal of achieving an end-tidal carbon dioxide level of 35-40 mmHg in the surgical procedure. Operation would not begin until the BIS value achieve 50, and BIS value setting 50±5 intraoperative by adjusting the dose of the sedative drug. Intra-operative mean arterial pressure was kept within 20% of baseline and hypotension or hypertension lasting > 5 min was treated with intermittent doses of phenylephrine (20 μg/mL) or nicardipine (500 μg/mL), respectively.

Post-operative management

After the operation, all patients were admitted to the Post Anesthesia Care Unit (PACU) and monitored there. The trachea was extubated once spontaneous ventilation of the patient was adequate and the patient was alert. Patient-controlled analgesia (PCA), consisted of 100 μg sufentanil in 100 mL normal saline, was administered by an AutoMed 3,200 pump at a background rate of 1 mL/h and a bolus dose of 1 mL with a lockout interval of 10 minutes. Before being discharged from the PACU, patients were required to meet the following three criteria: 1) conscious; 2) arterial oxygen tension (PaO_2) > 74 mmHg on an inspired oxygen concentration (FIO_2) < 40%; 3) stable hemodynamics without vasoactive drugs.

Study protocol

Mean arterial pressure, heart rate (HR), oxygen saturation, BIS were continuously monitored in the surgical procedure and PACU. Consciousness time, tracheal extubation time and post-

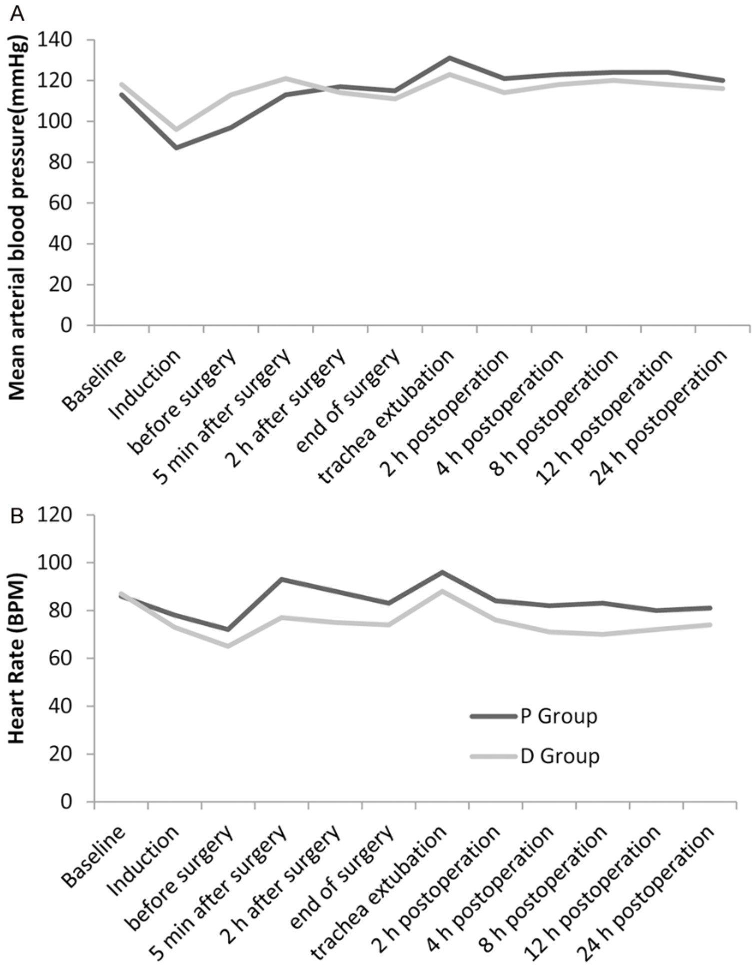

Figure 1. Mean arterial blood pressure (mmHg) and heart rate (beats/min) in the D and P groups 24 h perioperative.

operative VAS score were recorded by the same anesthesiologist in PACU. All patients were assessed for recall of intraoperative events using Modified Brice questionnaire 24 h after operation. Moreover, rescue analgesics within 24 h after operation were recorded.

Biochemical analysis

Venous blood samples were collected for determining concentrations of epinephrine, NE, cortisol, ACTH, glucose, IL-6. Blood cell counts at three time points, before the administration of anesthetics (T0), at 2 h after surgery (T1), and at 24 h after surgery (T2), then centrifuged at 1,000 g for 15 minutes and the serum samples were stored at -80°C until analysis. All procedures were performed according to the instructions provided with the kits from Jiancheng Bioengineering Research Institute.

Statistical analysis

Categorical variables were expressed as percentages and continuous variables as mean±standard deviation. Differences between categorical variables were assessed using t test. The χ^2 test was used to analyze differences between categorical variables. Data were analyzed using SPSS for windows version 14.0 (SPSS Inc, Chicago, IL, USA). A *P* value < 0.05 was considered significant.

Results

Patient characteristics

The clinical characteristics of the patients are summarized in **Table 1**. The groups were similar for age, gender, weight, height, operation time, blood loss, use of vasoactive agents, dose of intraoperative fentanyl, intraoperative fluid, consciousness time, tracheal extubation time and intraoperative awareness. However, requirement of rescue anesthetics and postoperative VAS in group P were significantly higher than group D respectively ($P < 0.05$). No patient reported intraoperative recall.

Hemodynamics

There were no intergroup statistically significant differences in MAP. The mean values of HR within 24 h perioperative in D group were significantly lower compared with the P group, but did not need intervention (**Figure 1**).

Plasma detection

Baseline concentrations of NE, epinephrine, ACTH, cortisol, glucose, IL-6 in two groups were comparable (**Figure 2**). Plasma NE, epinephrine, cortisol, ACTH levels in both groups increased significantly at T1, T2, while NE, epinephrine level were significantly higher in P group ($P < 0.05$), but no significant intergroup

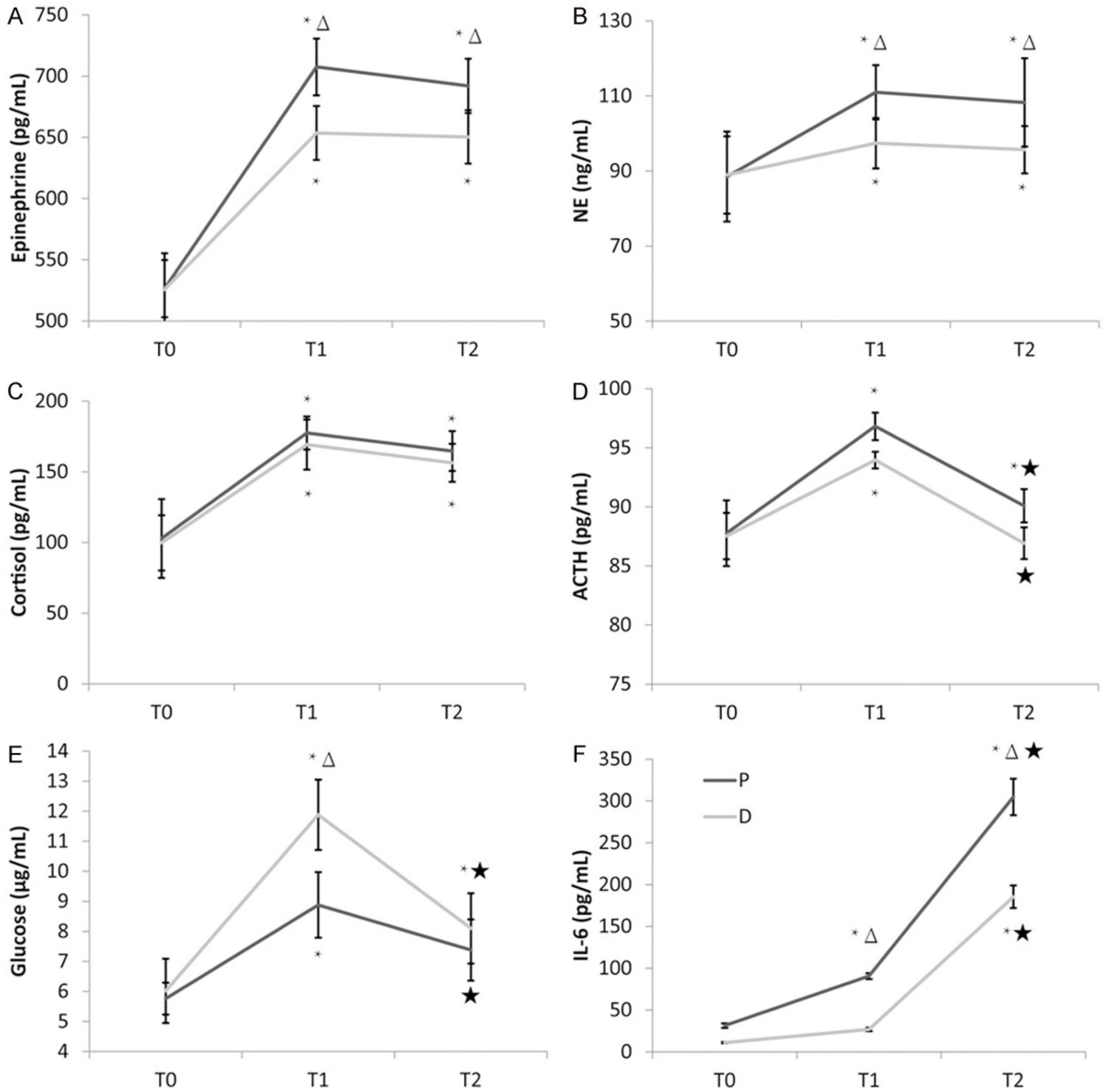

Figure 2. Changes in neuroendocrine hormone and glucose levels during the perioperative period. A. Changes in plasma norepinephrine levels. B. Changes in plasma epinephrine levels. C. Changes in plasma cortisol levels. D. Changes in plasma ACTH levels. E. Changes in plasma glucose levels. F. Changes in plasma IL-6 levels. T0: before induction of anesthesia; T1: at 2 h after surgery; T2: at 24 h after surgery. △P < 0.05 between two groups. *P < 0.05 compared with T0 within group. ★P < 0.05 compared with T1 within group.

difference was evident at cortisol, ACTH levels. Plasma IL-6 concentrations in both groups increased with time, while was higher in P group at two time points (P < 0.05). Both groups plasma glucose levels increased versus baseline at T1, and significantly higher in D group (P < 0.05).

Discussion

The definition of TIVA is a combination of sedative agent, analgesic drugs and muscle relaxants, excluding simultaneous administration of any inhaled drugs [12]. Dexmedetomidine exhibits sedative as well as analgesic and anxiolytic effects [13], thus could be the sole maintain agent in TIVA theoretically. Previous study has shown dexmedetomidine attenuates various stress responses and maintains the haemodynamic stability during surgery procedure [14, 15]. In these studies, dexmedetomidine was used only as adjuvant, and thus cannot exclude the intervention of other anesthetics in the operations. Present study aimed to evaluate the efficacy and safety of dexmedetomidine on the aspect of surgical stress compared with propofol in open esophagectomy. In our research model, perioperative treatment was similar except the use of sedative drugs. Intraoperative BIS value had been set to ensure patients in similar depth of anesthesia without intraoperative awareness, so the effects of the two sedatives on surgical stress response can be revealed effectively.

When used in combination with analgesic drugs, propofol is suitable for the provision of total intravenous anaesthesia in last decades [16]. Previous studies found that TIVA with propofol inhibited the ACTH-cortisol axis and reduced NE, epinephrine[17].

Surgical stimulation may activate the sympathetic nervous system, increase the blood level of catecholamines. The pharmacokinetic data indicate that dexmedetomidine infusion during the immediate postoperative decrease the release of catecholamine [18]. Our study showed that dexmedetomidine is superior to propofol in the inhibition of the sympathetic nervous system. It can be explained that alpha-2-receptor activation depresses ganglionic transmission through both postsynaptic inhibition of muscarinic stimulation and reduction of presynaptic neurotransmitter release [19].

Meanwhile, dexmedetomidine has similar inhibitory effect with propofol on ACTH-cortisol axis in our comparative study, and we also found that dexmedetomidine infusion does not inhibit adrenal steroidogenesis when used for perioperative sedation, which is consistent with the Venn's result [20].

Blood glucose concentrations increased after major surgeries due to cortisol and dexmedetomidine facilitating hepatic glycogenolysis and gluconeogenesis and insulin resistance. Many studies show that dexmedetomidine infusion during general anesthesia decreased blood glucose [21, 22], however, we found that blood glucose level in D group is significantly higher than P group. As blood concentrations of NE, epinephrine, ACTH, cortisol in D group was lower than in P group at T1, we speculated insulin resistance maybe is the main reason of phenomenon. Further research is needed to clarify the mechanism.

Serum interleukin-6 was the best marker for acute surgical stress, which could not be induced by anesthetic interventions alone [23]. Present study found less IL-6 level in D group, indicating dexmedetomidine inhibiting inflammatory reaction better than propofol, which is probably association with dexmedetomidine suppressing TLR4/MyD88/NF-κB pathway [24].

In conclusion, dexmedetomidine has similar effect to propofol on surgical stress response, even superior inhibitory effect on sympathetic nervous system. Considering its hemodynamic stability and no intraoperative awareness, dexmedetomidine can be used as the sole anesthetic agent in total intravenous anesthesia. However, large sample size is required to draw further conclusions and to consolidate the usage of dexmedetomidine in TIVA.

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Disclosure of conflict of interest

None.

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