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Original Article

Effect of dexmedetomidine vs midazolam vs propofol on cytokines production in esophagectomy patients under TIVA: a randomized, controlled clinical study

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Abstract: Objective: To compare the effects of total intravenous anesthesia (TIVA) with midazolam, propofol or dexmedetomidine on the cytokine production and pulmonary complications following esophagectomy. Methods: Forty-five patients of ASA I~II grade scheduled for esophagus surgery were randomly divided into three groups with 15 each: midazolam group (group Midaz), propofol group (group Pro) and dexmedetomidine group (group Dex). All patients received the same treatment perioperatively except for the sedative drugs. Venous blood samples were taken before anesthesia (T0), 2 h after skin incision (T1), and 24 h after surgery (T2) to determine serum tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-10 by ELISA. Arterial blood sample was extracted at the same time to analyze arterial body gas and calculate PaO_2/FiO_2 ratio. Results: There are no intergroup differences in demographics, operative, and postoperative pulmonary complications. The circulating TNF-α level in all groups was higher at T1 than those at T0, T2, with no significant intergroup differences. The circulating IL-6 and IL-10 showed similar trends, but at T2 the IL-6 value in Dex group was lower than the other two groups, while the IL-10 value was higher. The PaO_2/FiO_2 ratio in all groups decreased insignificantly at T1, T2 compared with that at T0, while the PaO_2/FiO_2 ratio in Dex group was higher than those in the other two groups. Conclusion: Dexmedetomidine based TIVA was associated with significantly lower pro-inflammatory cytokine IL-6 and higher anti-inflammatory cytokine IL-10 levels than propofol or midazolam based TIVA, indicating that dexmedetomidine might produce a protective effect on postoperative pulmonary function.

Keywords: TIVA, dexmedetomidine, midazolam, propofol, cytokine production

Introduction

Transthoracic esophagectomy, one of the standard treatments for esophageal cancer [1, 2], has been recognized as the most minimal invasive gastrointestinal surgery. Respiratory complications are the most frequent causes for morbidity and mortality following esophagectomy. Surgical stress induces the release of pro-inflammatory cytokines, and overproduction results a systemic inflammatory response syndrome, which may lead to acute lung injury (ALI) or even the more severe acute respiratory distress syndrome (ARDS). Cytokines play a critical role as signaling molecules that initiate, amplify, and perpetuate inflammatory responses on a local and systemic basis. Previous studies have revealed that elevated plasma cytokine levels correlate with postoperative morbidity and mortality rates [3, 4]. Tsujimoto and his colleagues propose that the elevation of pleural IL-6 levels immediately after surgery and on postoperative day 1 may predict the incidence of pneumonia following esophagectomy [5]. Moreover, Xavier et al. reported that plasma levels of IL-6, IL-10 and TNF-α after esophagectomy were much higher in patients who experienced pulmonary complications than those who did not, thus high plasmatic cytokine levels predicts the onset of these complications [6].

Many studies have demonstrated that sedative agents may potently suppress the surgical stress-induced inflammatory perturbation [7-9]. The modulatory effect of sedatives may be clinically important if they attenuate the early pro-

inflammatory or stimulate the anti-inflammatory responses associated with ALI and ARDS. However, the impact of administration of midazolam, propofol and dexmedetomidine during surgery procedure on cytokine production and postoperative complications remains unclear. Therefore, the present study was designed prospectively to investigate the differences among the three sedative drugs during transthoracic esophagectomy by measuring concomitant levels of IL-6, IL-10 and TNF-α production, and the prognosis.

Materials and methods

The study protocol was approved by the hospital ethics committee and written informed consent was obtained from each of the participants. Forty-five patients, 53-77 years of age, ASA physical status of I~II, scheduled for transthoracic esophagectomy under TIVA were averagely divided into three groups by a computer-generated randomization scheme: midazolam group (group Midaz), propofol group (group Pro) and dexmedetomidine group (group Dex). Patients with neurologic or psychiatric disorders, cardiac disease classified as NYHA classes II-IV, liver or renal dysfunction, hemostatic disorders, immunodeficiency syndromes, or perioperative use of immunosuppressive medication were excluded. Preoperative routine pulmonary function tests were performed and patients with severe pulmonary dysfunction were also excluded. Subjects were removed if they exhibited systemic or local active infections (elevated C-reactive protein (CRP) levels, leukocytosis or body temperature of >38°C).

Intramuscular atropine 0.5 mg was pre-medicated 30 minutes before surgery. Every patient received noninvasive blood pressure monitoring, electrocardiography using lead II and pulse oximetry monitor on arriving in the operating room. A central venous catheter was placed for fluid administration, and a radial arterial cannula was placed for continuous arterial blood pressure monitoring and blood gas analysis. Bispectral index (BIS) electrodes were used to monitor the anesthesia depth. In the Midaz group, anesthesia induction was performed through the intravenous injection of midazolam (0.3 mg/kg), fentanyl (5 μg/kg) and vecuronium bromide (0.15 mg/kg), and maintained by intravenous infusion of midazolam (0.5-1.5 μg/kg/min) and fentanyl (0.05 μg/kg/min). In the Pro 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 Dex 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, with an end-tidal CO_2 of 30-40 mmHg during surgery procedure in the three groups. Operation would not start until the BIS value achieved at 50, keeping BIS value 50±5 intraoperatively by adjusting the dose of anesthetics agents. Intra-operative mean arterial pressure was maintained within 20% of baseline and hypotension or hypertension lasting >5 min was treated with bolus injection of phenylephrine (20 μg/mL) or nicardipine (500 μg/mL), respectively.

After the operation, all of the patients were transferred to the intensive care unit ICU or the post anesthesia care unit PACU overnight. Special group physicians were in charge of postoperative treatment. The parameters of the postoperative period include length of stay at the PACU/ICU, the duration of supported ventilation and the total length of stay in hospital were collected and analyzed.

Postoperative pulmonary complications were defined as dysfunction or identifiable diseases of the respiratory system that were clinically relevant and affected the clinical course and that occurred within the hospital stay. The diagnosis of postoperative pulmonary complications was based on the clinical manifestations, radiological examination and laboratory tests. Postoperative pulmonary complications included pneumonia, atelectasis, pleural effusions, pulmonary embolism, pulmonary edema, pneumothorax, ALI and ARDS. Additional, prolonged mechanical ventilation (more than 15 h postoperatively) and re-intubation were also defined as postoperative pulmonary complications excluding other indications (e.g. need for redo surgery).

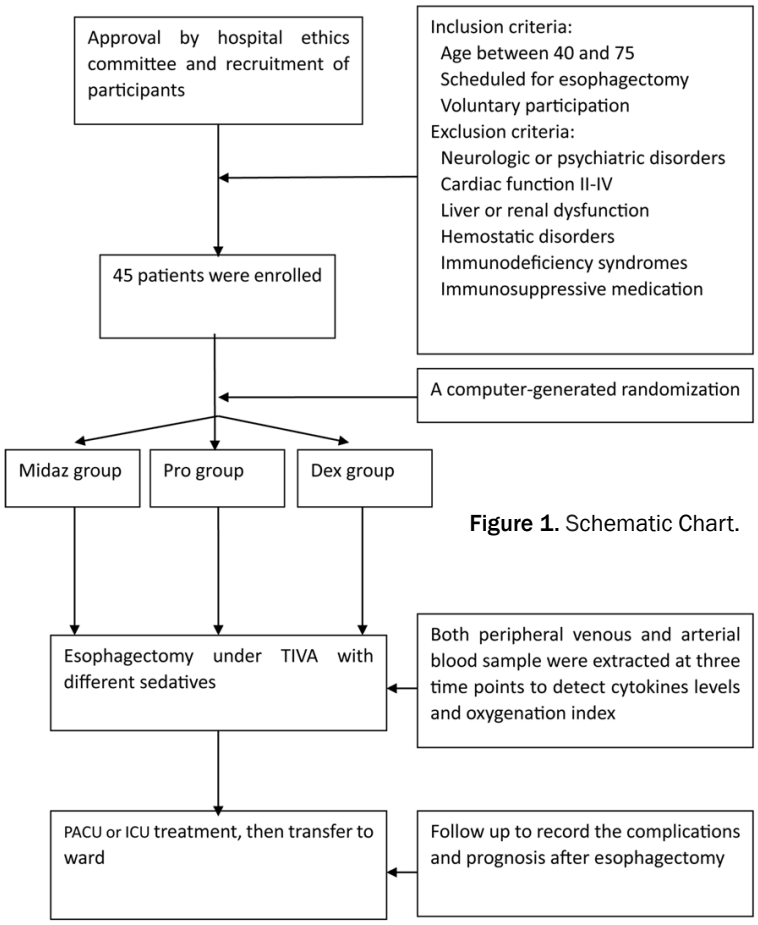

Figure 1. Schematic Chart.

Peripheral venous blood were collected before the administration of anesthetics (T0), 2 h after skin incision (T1), and 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. The cytokine (TNF-α, IL-6, IL-10) concentrations were measured by using the commercially available ELISA kits (Jiancheng Bioengineering Research Institute, Nanjing, China) according to the manufacturer's protocol. Arterial blood sample was extracted at the same three time points to analyze blood gas by using a GEM Premier 3000 (Instrumentation Laboratory, Lexington, MA), then calculate PaO_2/FiO_2 ratio (**Figure 1**).

Statistical analysis

Data were analyzed using the SPSS 12.0 package (SPSS Inc., Chicago, IL, USA). Results were expressed as the mean ± standard deviation or median (range) for continuous variables and as percentage for categorical variables. Chi-square and Mann-Whitney U tests were performed for categorical and continuous variable analyses. Differences between groups in different period were assessed using one way ANOVA. A two tailed $P<0.05$ was considered statistical significantly.

Results

Demographic and clinic data

The demographic and operative data are presenting in **Table 1**. There was no differences in age, gender, body mass index, smoking, preoperative co-morbidities, localization of the main tumor, stage of disease, preoperative pulmonary function, operation time, blood loss, fentanyl consumption, fluid administration, and blood transfusion (Supplementary Data).

Likewise, we observed no significant difference among the three groups in relation to postoperative pulmonary complications, mortality, length of stay at the PACU/ICU, the duration of supported ventilation and total length of stay in hospital (**Table 2**).

Serum cytokine level

The circulating TNF-α at T1 was significantly increased compared with at T0 ($p<0.05$), and decreased thereafter at T2. However, we observed no significant differences at the three time-points (**Figure 2A**).

The circulating IL-6 was significantly ascending with the time. The IL-6 value at T2 in all groups was significantly higher than that at T1, while T1 higher than T0 ($p<0.05$). There were no significant intergroup differences at T0, T1, but the IL-6 value in D group was lower than that in the other two groups at T2 ($p<0.05$) (**Figure 2B**).

The circulating IL-10 showed similar trends as IL-6. The IL-10 value at T2 in all groups was significantly higher than that at T1, while T1 higher

Table 1. Demographic and operative data of patients

Characteristics	Group Midaz	Group Pro	Group Dex	χ^2/F	*P*
N	15	15	15		
Gender (male/female)	12 (80%)/3 (20%)	11 (73.3%)/4 (26.7%)	12 (80%)/3 (20%)	0.25	0.87
Age (years)	63±5.2	65±6.3	66±5.9	1.03	0.36
Body mass index (kg/m^2)	24.1±1.0	24.2±1.2	24.3±0.9	0.13	0.87
Smoking (+/-)	8 (53.3%)/7 (46.7%)	9 (60%)/6 (40%)	10 (66.7%)/5 (33.3%)	0.55	0.75
Hypertension	4 (26.7%)	4 (26.7%)	5 (33.3%)	0.51	0.77
Diabetes mellitus	2 (13.3%)	1 (6.7%)	1 (6.7%)	1.67	0.44
Hyperlipidaemia	3 (20%)	2 (13.3%)	4 (26.7%)	0.83	0.65
Tumor stage					
I	2 (13.3%)	1 (6.7%)	2 (13.3%)	3.05	0.80
II	8 (53.3%)	9 (60%)	7 (46.7%)		
III	5 (33.3%)	4 (26.7%)	6 (40%)		
IV	0	1 (6.7%)	0		
Vital capacity (mL)	367.4±45.3	355.1±48.8	386.3±42.4	1.70	0.18
Forced expiratory volume in 1 sec (mL)	253.2±32.7	248.7±35.5	274.2±41.1	2.07	0.13
Squamous cell carcinoma	6 (40%)	4 (26.7%)	7 (46.7%)	2.22	0.32
Adenocarcinoma	9 (60%)	11 (73.3%)	8 (53.3%)		
Localization of the main tumor					
Mid esophagus (22-32 cm)	3 (20%)	2 (13.3%)	4 (26.7%)	0.08	0.65
Lower esophagus (33-39 cm)	9 (60%)	9 (60%)	8 (53.3%)		
Cardia ventriculi	3 (20%)	4 (26.7%)	3 (20%)	0.25	0.87
Operation time (min)	173±25	162±28	166±28	0.63	0.53
Blood loss (mL)	549±145	591±182	586±166	0.28	0.74
Fentanyl consumption (mg)	0.63±0.08	0.63±0.09	0.64±0.05	0.08	0.91
Fluid administration (mL)	1,387±187	1,417±226	1,437±193	0.23	0.79
Blood transfusion (mL)	253±252	250±203	270±210	0.03	0.96

Table 2. Postoperative data of patients

Characteristics	Group Midaz	Group Pro	Group Dex	χ^2/F	P
Pneumonia	5 (33.3%)	6 (40%)	5 (33.3%)	0.19	0.91
Atelectasis	2 (13.3%)	2 (13.3%)	1 (6.7%)	0.45	0.79
Pleural effusions	2 (13.3%)	4 (26.7%)	3 (20%)	0.83	0.65
Pulmonary embolism	0	0	0	NA	NA
Pulmonary oedema	4 (26.7%)	3 (20%)	3 (20%)	0.25	0.87
Pneumothorax	1 (6.7%)	0	0	2.04	0.35
Acute lung injury (ali)	3 (20%)	2 (13.3%)	1 (6.7%)	1.15	0.56
Acute respiratory distress syndrome (ards)	0	1 (6.7%)	0	2.04	0.35
Prolonged mechanical ventilation	3 (20%)	3 (20%)	2 (13.3%)	0.30	0.85
Reintubation	1 (6.7%)	1 (6.7%)	0	1.04	0.59
Mortality	0	1 (6.7%)	0	2.04	0.35
Length of stay at the pacu/icu (d)	2.9±2.3	3.8±3.4	2.6±2.5	0.75	0.47
Duration of supported ventilation (h)	35.8±68.4	48.4±84.3	35.9±65.3	0.14	0.86
Total length of stay in hospital (d)	21.3±3.4	21.9±5.1	20.5±3.7	0.43	0.65

than T0 ($p<0.05$). We also observed no significant intergroup differences at T0, T1, but the IL-10 value in D group was higher than that in the other two groups at T2 (**Figure 2C**).

Oxygenation index

The PaO_2/FiO_2 ratio decreased insignificantly at T1, T2. However, we found that the PaO_2/FiO_2

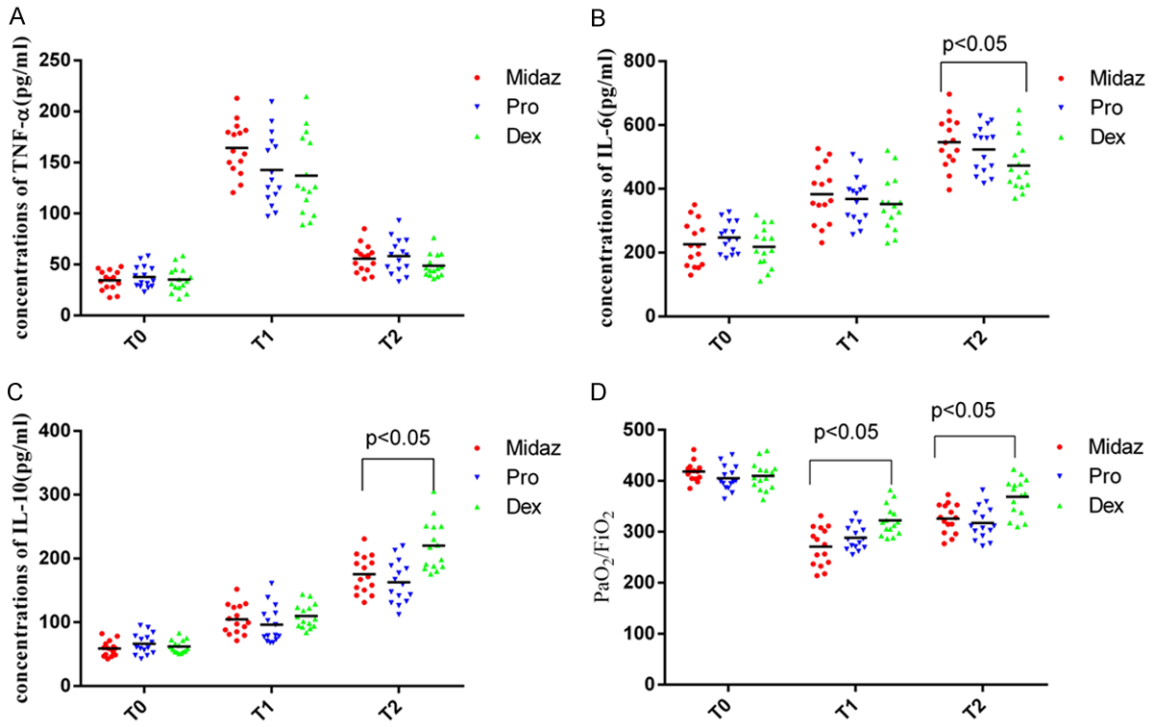

Figure 2. Comparison of TNF-α, IL-6, IL-10 and PaO_2/FiO_2 in different time point during esophagectomy. A. The circulating TNF-α levels of 3 groups at T0, T1 and T2. B. The circulating IL-6 levels of 3 groups at T0, T1 and T2. C. The circulating IL-10 levels of 3 groups at T0, T1 and T2. D. The PaO_2/FiO_2 ratio of 3 groups at T0, T1 and T2.

ratio in D group was higher than that in the other two groups at T1, T2 (**Figure 2D**).

Discussion

Pro-inflammatory cytokine and anti-inflammatory cytokine, maintaining a certain balance in healthy population, and the major surgery, in particular esophagectomy, induced traumatic inflammation could aggravate their imbalance and disorder. The body attempts to reestablish homeostasis. However, cytokine is overproduction, resulting in an exaggerated systemic response (clinically known as SIRS) and can subsequently develop into multiple organ dysfunction syndromes (MODS). In our study, we analyzed the serum cytokines levels of circulating TNF-α, IL-6, and IL-10 at different time points in patients who underwent transthoracic esophagectomy with different sedative drugs, and assessed the impact on postoperative pulmonary complications.

TNF-α and IL-6, function as pro-inflammatory molecules, were involved in the early phase of inflammatory response. There was strong evidence that TNF-α and IL6 were useful circulating markers of the severity of the inflammatory response and the prognosis of patients at the onset of lung injury [10, 11]. Various literatures concerning effects of intravenous anesthetics on TNF-α and IL6 production had been published. *In vitro*, midazolam and propofol both increased TNF-α and IL-6 production from human monocytes [12], while dexmedetomidine suppressed TNF-α and IL-6 production in human whole blood [13]. In ICU sedation, propofol caused a significant increase in cytokine IL-6 and TNF-α serum concentrations in critically ill patients, whereas midazolam caused their significant decrease [9, 14]. In another pilot study on the effects of propofol and dexmedetomidine on inflammatory responses, dexmedetomidine infusion decreased TNF-α, IL-1, and IL-6 levels and IAP more than propofol infusion [9]. Furthermore, several studies reported that dexmedetomidine had similar effect on IL-6 production compared with propofol during ICU 8 h postoperative sedation [15, 16]. In our study, we found that TNF-α and IL-6 levels increased due to surgery stimulation, and insignificant differ among three groups except for lower IL-6 concentration in Dex group at post-

operative 24 h. Our results differ from previous studies, for our study was designed in perioperation not during postoperative sedation. Surgical injury induces a systemic endocrine-metabolic response, leading to activation of monocytes and endothelial cells, characterized with the release of TNF-α and IL-6. Dexmedetomidine had been reported superior stress-inhabiting ability to propofol [17], then probably explains the lower TNF-α and IL-6 levels at postoperative 24 h.

IL-10 is an anti-inflammatory cytokine that has immune-regulating function in cellular immunity, which can inhibit monocytes from secreting pro-inflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-8, and reduce major histocompatibility complex II (MHCII) on antigen-presenting cells. Evidence suggested that the anti-inflammatory response with the production of IL-10 is an important factor for reducing the complications of major abdominal surgery [18]. *In vitro*, propofol appeared to inhibit IL-10 production while midazolam do not alter IL-10 concentration in LPS-stimulated PBMCs [19]. A meta-analysis demonstrated that dexmedetomidine treatment increases significantly IL-10 levels a day after surgery [20]. Similarly, the present study results revealed that dexmedetomidine increase the level of IL-10 more significantly than propofol and midazolam at postoperative 24 h, indicating dexmedetomidine had a superior anti-inflammatory effect.

However, in our study, we did not find significant differences in postoperative pulmonary complications, length of hospital stay and mortality among three groups. We speculated that it might be attributed to our insufficient sample size. On the other hand, PaO_2/FiO_2 ratio was significant higher in Dex group than in Midaz and Pro group. PaO_2/FiO_2 ratio, easy to calculate, was widely used as an indicator of oxygenation status. An intraoperative PaO_2/FiO_2 ratio <300, which reflect mild hypoxemia, is correlated with increased incidences of postoperative pulmonary complications [21, 22]. Our results suggest that dexmedetomidine might produce protective effect on pulmonary function.

In conclusion, our study showed that dexmedetomidine based TIVA was associated with significantly lower pro-inflammatory cytokine IL-6 and higher anti-inflammatory cytokine IL-10 levels than propofol or midazolam based TIVA, indicating that dexmedetomidine might produce protective effects on pulmonary function despite comparable postoperative respiratory complications, length of hospital stay of all three groups. More prospective researches with larger sample size were needed to confirm our conclusion.

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Disclosure of conflict of interest

None.

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