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Effects of Dexmedetomidine Combined with Sufentanil on Postoperative Delirium in Young Patients After General Anesthesia

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Manuscript Preparation E
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Background: This study was designed to evaluate the effects of combined usage of dexmedetomidine (DEX) and sufentanil on young patients with postoperative delirium (POD) after general anesthesia.





Material/Methods: We randomized 100 young patients with POD into 4 groups: Group D, Group S, Group DS1, and Group DS2, with loading and maintenance doses of DEX and/or sufentanil administered according to the experimental protocol. Hemodynamic variables, standard visual analogue scale (VAS) scores, sedation agitation scale (SAS) scores, stress hormones, and inflammatory biomarkers were assessed at 5 time-points: baseline (T_1); 1 h (T_2), 2 h (T_3), 4 h (T_4), and 8 h (T_5) after completion of the loading dose.

Results: At T_3 - T_5 , hemodynamic indicators in group D were obviously higher than in the other groups ($P < 0.05$). At T_2 - T_5 , the VAS and SAS scores were noticeably lower than those at T_1 in each group ($P < 0.05$). The VAS and SAS scores were remarkably higher in group D than those in the other groups ($P < 0.05$). Compared with DS1, the incidence of respiratory distress decreased and the incidence of POD increased in group DS2. Compared to T_1 , plasma concentrations of epinephrine, norepinephrine, IL-6, and TNF- α all decreased at T_2 and T_5 ($P < 0.05$).

Conclusions: DEX and sufentanil decrease the incidence of POD, ameliorate the abnormalities of hemodynamic indicators, and decrease VAS scores, SAS scores, stress hormones, and inflammatory biomarkers, but increase the incidence of respiratory distress. DEX combined with sufentanil may play a synergistic reaction in causing respiratory distress, but remarkably decreases the incidence of POD.

MeSH Keywords: Delirium • Dexmedetomidine • Pain • Sufentanil • Young Adult

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 2512  2  5  30



Background

Postoperative delirium (POD) is a common neurological complication after general anesthesia, which can lead to patients being unable to tolerate a variety of body cavity drainage tubes and endotracheal tubes [1]. POD increased complications such as cardiovascular events, pneumonia, and urinary tract infection during hospitalization, prolonged hospital stay, and increased medical costs [2]. The long-term prognosis of POD is mainly cognitive impairment and increased mortality.

The mechanism of POD is not fully known. Relevant studies primarily focused on neurotransmitter abnormalities, inflammatory response, hypoxia-ischemia, and genetic factors of delirium [3]. Postoperative pain is an acute response to noxious stimuli, which causes changes in neuroendocrine function, such as anxiety, tension, and fear. Postoperative pain may be the major source of POD and a series of physiological disorders [4,5]. Currently, various analgesic drugs are clinically used. However, recent use of analgesic drugs often fails to adequately reduce postoperative pain and POD. Exploring new methods of using analgesic drugs is an issue that anesthesiologists need to pay attention to.

The current research on POD mainly focuses on the elderly and rarely on the young [6]. However, pain is an important and independent factor for POD in young patients, which has not been given enough attention [7]. Dexmedetomidine (DEX) is a novel α_2 receptor agonist that inhibits the transmission of pain signals through activation of the spinal α_2 receptor. Recent studies have proved that DEX is efficient for postoperative analgesia [8]. With excellent hemodynamic stability, sufentanil is also a potent opioid analgesic [9]. DEX and sufentanil are usually separately used in clinical practice [10]. Combined usage of DEX and sufentanil has rarely been investigated in recent research. This study was designed to evaluate the effects of combined usage of dexmedetomidine (DEX) and sufentanil on young patients with POD after general anesthesia.

Material and Methods

Ethics statement and patients

The present study was approved by the Ethics Committee of Renmin Hospital of Wuhan University, and was registered with the Chinese Clinical Trial Registry (ChiCTR) (registration number ChiCTR-OOC-16007782). After obtaining the informed consent, patients of either sex with American Society Anesthesiologists (ASA) physical status I-II, aged 20–40 years, and scheduled for general anesthesia were enrolled in this study. After surgery, the endotracheal tube was pulled out when the patients' spontaneous breath was resumed and the patients were then

sent back to the department of critical care medicine (CCM) for more than 24 h. Exclusion criteria were: known adverse reactions to DEX and sufentanil; delirium before surgery; history of certain central nervous system diseases or mental disorders; alcohol addiction or drug abuse; were unable to communicate properly; and serious adverse reactions during the operation, such as cardiac arrest or cardiopulmonary resuscitation.

Clinical anesthesia process

Patients were sent to the operating room without any premedication, then the left limb peripheral veins were opened, compound sodium lactate solution 8–10 ml/kg/h was infused and routine monitors were established, including 5-lead electrocardiography (ECG), oxygen saturation (SpO_2), and noninvasive blood pressure (NBP). Patients were monitored and managed by an anesthetist who was blind to the group assignments. All patients underwent surgical operations under general anesthesia. Immediately after intubation, a ventilator (Primus, Dräger, Germany) was connected. Respiratory parameters were set as follows: tidal volume (VT) 10 mL/kg, respiratory rate (RR) 12 times/min, fraction of inspiration (O_2) FiO_2 80%, and the partial pressure of end-tidal carbon dioxide (PETCO₂) was maintained at 35–45 mmHg. Anesthesia was maintained with sevoflurane 1% volume inhalation and propofol and remifentanyl target-controlled infusion (TCI) to control the variation of mean arterial blood pressures (MAP) and heart rate (HR) within 20% of the baseline and to maintain the bispectral index (BIS) values within 40–60. Propofol, remifentanyl, and sevoflurane were stopped at the end of the surgery. Before the patients resumed spontaneous breathing and responded to simple commands, gentle manual ventilatory assistance was provided. The endotracheal tubes were then removed and patients were transferred to CCM. The criteria for removal of the endotracheal tube were: 1) recovery of consciousness and muscle tension; 2) steady spontaneous breathing, PETCO₂ <45 mmHg, VT >7 mL/kg; 3) SpO_2 >97% after stopping oxygen supply for 5 min; 4) the frequency of spontaneous breathing <24 times/min; and 5) restoration of cough and swallowing reflex.

Groups

One hundred young patients with POD in CCM were recruited from May 2016 to April 2017 (Figure 1). Patients were randomly assigned to 4 groups by random number table method, which was prepared by a blinded statistician (n=25 each): in Group D, DEX was pumped at loading dose (1 mg/kg) for 10 min and then pumped for maintenance (0.4 mg/kg/h); in Group S, sufentanil was intravenously injected at loading dose (0.2 mg/kg) and was pumped for maintenance dose (0.04 mg/kg/h); in Group DS1, sufentanil was intravenously injected at the loading dose (0.2 mg/kg), then DEX (0.4 mg/kg/h) combined with sufentanil (0.04 mg/kg/h) were pumped for maintenance; in Group

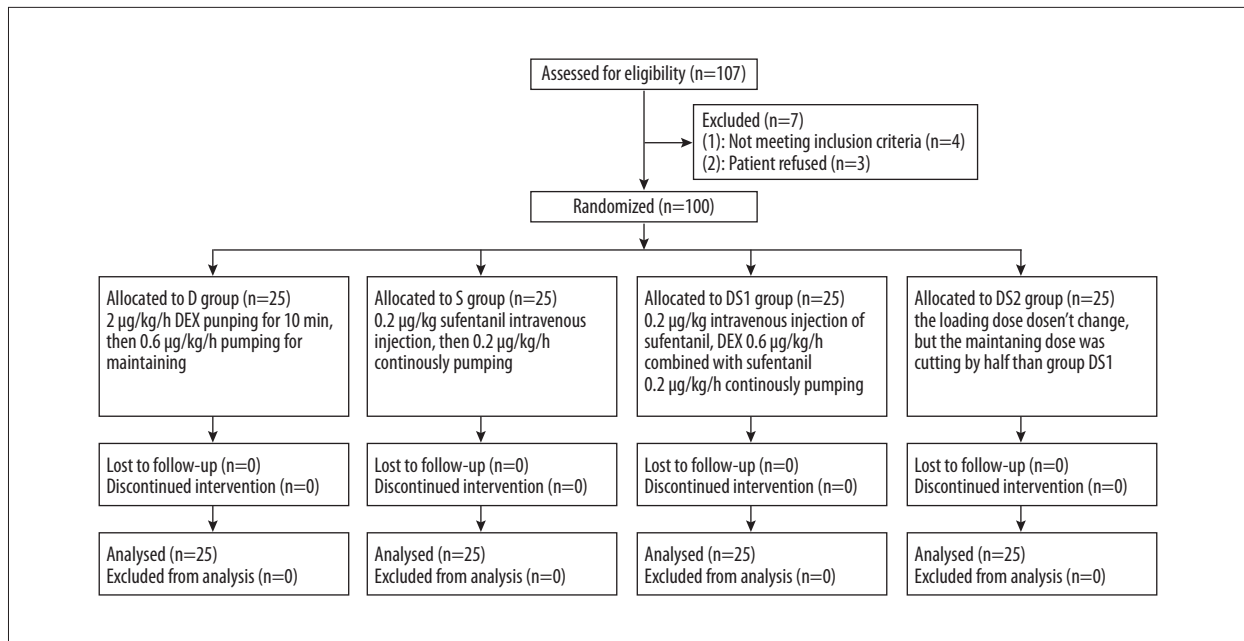


Figure 1. Flow diagram of patient recruitment.

DS2, sufentanil was intravenously injected at the loading dose (0.2 mg/kg), then DEX (0.2 mg/kg/h) combined with sufentanil (0.02 mg/kg/h) was pumped for maintenance. All pharmacological agents used in the study were prepared and administered by anesthesiologists blinded to the details of the study.

Observed parameters

Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), standard visual analogue scale (VAS) scores, sedation agitation scale (SAS) scores, stress hormones, and inflammatory markers were assessed at 5 time-points: baseline (T_0), 1 h (T_1), 2 h (T_2), 4 h (T_4), and 8 h (T_8) after completion of the loading dose. The standard VAS was used to evaluate postoperative pain: score 0, no pain or discomfort; score <3, slight pain; score 4–6, moderate pain that affects sleep but is tolerable; score 7–10, severe pain that is intolerable. The SAS was used to evaluate the depth of sedation: score 1, unable to rouse; score 2, very sedated; score 3, sedated; score 4, calm and cooperative; score 5, agitated; score 6, very agitated; score 7, dangerous agitation.

The frequency of respiratory distress and the incidence of POD were assessed. POD was diagnosed by the confusion assessment method for the intensive care unit (CAM-ICU), which includes assessments of 4 patient characteristics: 1) acute onset or repeated fluctuations of symptoms; 2) insufficient attention; 3) disorganized thinking; and 4) abnormal consciousness levels. Patient were diagnosed with POD when the symptoms were 1 + 2 + 3 or 1 + 2 + 4.

Venous blood was collected at T_1 , T_2 , and T_5 . The blood was centrifuged at 4000 rpm at 4°C for 10 min, and the plasma was prepared for the determination of epinephrine, norepinephrine, interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). All the assessed parameters were measured by enzyme-linked immunosorbent assay (Boster Biotechnology Co., Ltd).

Hemodynamic variables, VAS score, SAS score, and the incidence of POD were the primary outcome measures, and the levels of stress hormones and inflammatory markers were the secondary outcome indicators.

Statistical analysis

Statistical analyses were performed using SPSS v 17.0 for Windows (SPSS, Inc., Chicago, IL, USA) and were reviewed by a blinded statistician. Quantitative variables are expressed as mean \pm standard deviation, categorical variables are presented as percentages. Normally distributed data were compared using the independent-samples t test. The t test and ANOVA were performed for unpaired quantitative variables and the χ^2 test was used to analyze categorical variables. All reported P values are 2-sided, and P values less than 0.05 were considered significant.

Results

No significant differences were observed for the basic characteristics of all patients at baseline ($P > 0.05$) (Table 1). No significant differences were found among SBP, DBP, and HR

Table 1. Patient characteristics (n =25, $\bar{x} \pm SD$).

Characteristic	D group	S group	DS1 group	DS2 group	P value
Age (years)	30.8±5.4	31.9±5.0	30.2±4.4	30.9±4.6	0.632
Sex (M/F)	15/10	16/9	12/13	11/14	0.434
Weight (kg)	68.2±8.6	64.2±8.0	65.3±8.2	67.1±7.5	0.289
Height (cm)	165.9±6.3	164.1±5.5	165.6±6.5	165.2±6.0	0.742

Values are given as mean \pm SD, or number of patients (%).

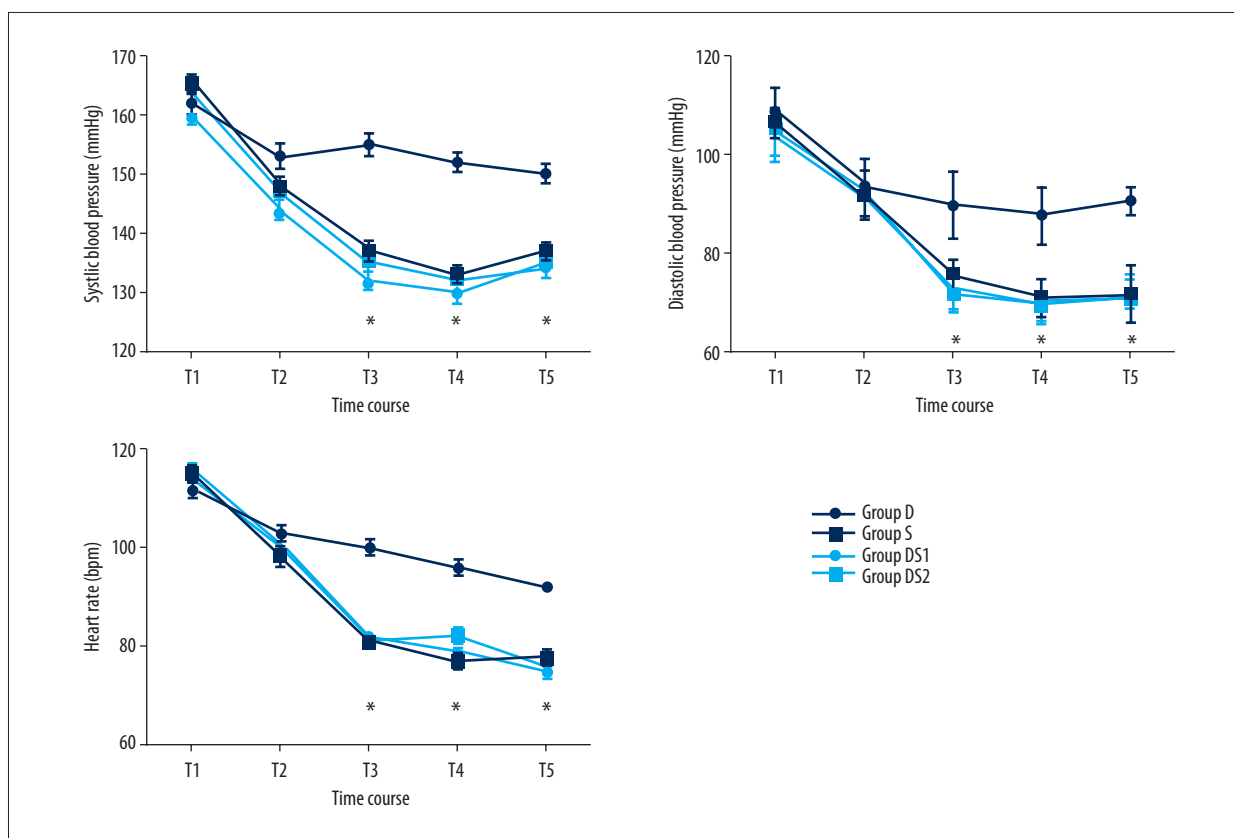


Figure 2. Hemodynamic indicators of patients receiving dexmedetomidine and/or sufentanil at 5 time-points: baseline (T₁), 1 h (T₂), 2 h (T₃), 4 h (T₄), and 8 h (T₅) after the completion of loading dose. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) in group D were higher compared to the other 3 groups from T₃ to T₅ (P<0.05). Values are given as mean \pm SEM. * P<0.05 compared with group D.

for all patients at baseline (P>0.05). Each group had a reductive tendency in SBP, DBP, and HR from their respective baseline to T₅. Of note, the hemodynamic indicators in group D were obviously higher than in the other 3 groups from T₃ to T₅ (P<0.05), while hemodynamic indicators showed no noticeable differences among group S, group DS1, and DS2 from T₃ to T₅ (P>0.05) (Figure 2).

At T₂-T₅, the VAS scores in group D fluctuated around score 6 and were higher than in the other 3 groups (P<0.05). At T₂-T₅, patients in group D had moderate postoperative pain, which

was lower than that at T₁ (P<0.05). The trends in VAS scores were similar among group S, group DS1, and DS2, and patients in these 3 groups felt mild postoperative pain, which was lower than that at T₁ (P<0.05). At T₃-T₅, the scores in group DS1 were the lowest among the 3 groups. The SAS score trends were consistent with the VAS scores (Figure 3).

Both DEX and sufentanil significantly increased the incidence of respiratory distress. For the 4 groups, the incidence of POD increased remarkably from T₁ to T₂ (P<0.05), and it subsequently exhibited a slight upward tendency from T₂ to T₅. The incidence

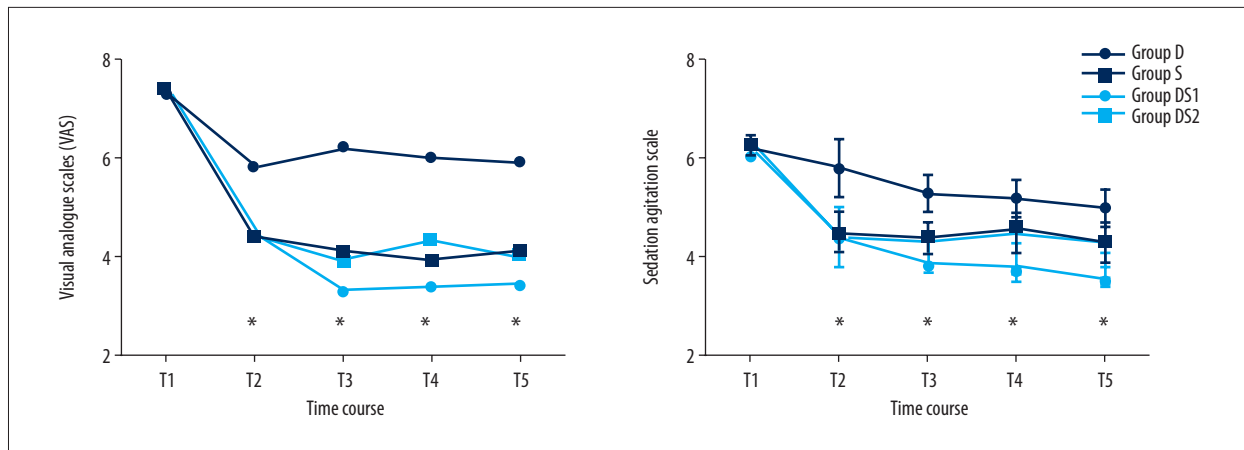


Figure 3. The postoperative standard visual analogue scale (VAS) scores and sedation agitation scale (SAS) scores of patients receiving dexmedetomidine and/or sufentanil at 5 time-points: baseline (T₁), 1 h (T₂), 2 h (T₃), 4 h (T₄), and 8 h (T₅) after the completion of loading dose. The VAS scores and SAS scores from T₂ to T₅ were significantly higher in group D than in the other 3 groups (P<0.05). Values are given as mean ±SEM. * P<0.05 compared with group D.

Table 2. The adverse effects and incidence of delirium in 4 groups (n=25).

		T1 (0h)	T2 (1h)	T3 (2h)	T4 (4h)	T5 (8h)
Group D	Respiratory distress	0	1	2	2	2
	The incidence of delirium	100%	56%	40%	36%	36%
Group S	Respiratory forgotten	0	6*	7*	8*	8*
	The incidence of delirium	100%	24%*	24%*	16%*	16%*
Group DS1	Respiratory forgotten	0	9*#	13*#	15*#	16*#
	The incidence of delirium	100%	20%*	8%*#	8%*#	8%*#
Group DS2	Respiratory distress	0	6*	8*	9*	9*
	The incidence of delirium	100%	24%*	16%*	16%*	16%*

At the same point in time, compared with group D, * P<0.05; compared with group S, # P<0.05.

of respiratory distress was the highest in group DS1 and the lowest in group D at T₂-T₅. Both DEX and Sufentanil significantly decreased the incidence of POD. For the 4 groups, the incidence of POD decreased remarkably from T₁ to T₂ (P<0.05), and it subsequently exhibited a slight downward tendency from T₂ to T₅. The incidence of POD was the highest in group D and the lowest in group DS1 at T₂-T₅ (Table 2).

Plasma epinephrine and norepinephrine showed no significant differences among the 4 groups at T₁. Compared with T₁, plasma epinephrine and norepinephrine both decreased at T₂ and T₅ in each group. Plasma epinephrine and norepinephrine were significantly lower in group S, group DS1, and DS2 at T₂ and T₅ compared to group D (P<0.05). Plasma epinephrine and norepinephrine in group DS1 at T₂ and T₅ were lower than those in group DS2 and group S (P<0.05) (Figure 4).

Plasma IL-6 and TNF-α showed no significant differences among the 4 groups at T₁. Compared with T₁, plasma IL-6 and TNF-α both decreased at T₂ and T₅ in each group. Plasma IL-6 and TNF-α were significantly lower in group S, group DS1, and group DS2 at T₂ and T₅ compared to group D (P<0.05). Plasma IL-6 and TNF-α in group DS1 at T₂ and T₅ were lower than in group DS2 and group S (P<0.05) (Figure 5).

Discussion

POD, as a reversible cognitive dysfunction syndrome, is a common complication in patients after general anesthesia, usually occurring 1-3 days after surgery. It is characterized by dysfunction in consciousness, attention, and cognition [11]. Excessive and prolonged POD may cause severe adverse reaction and influence the postoperative outcomes [12,13]. The exact pathophysiological mechanisms of POD in adults following general

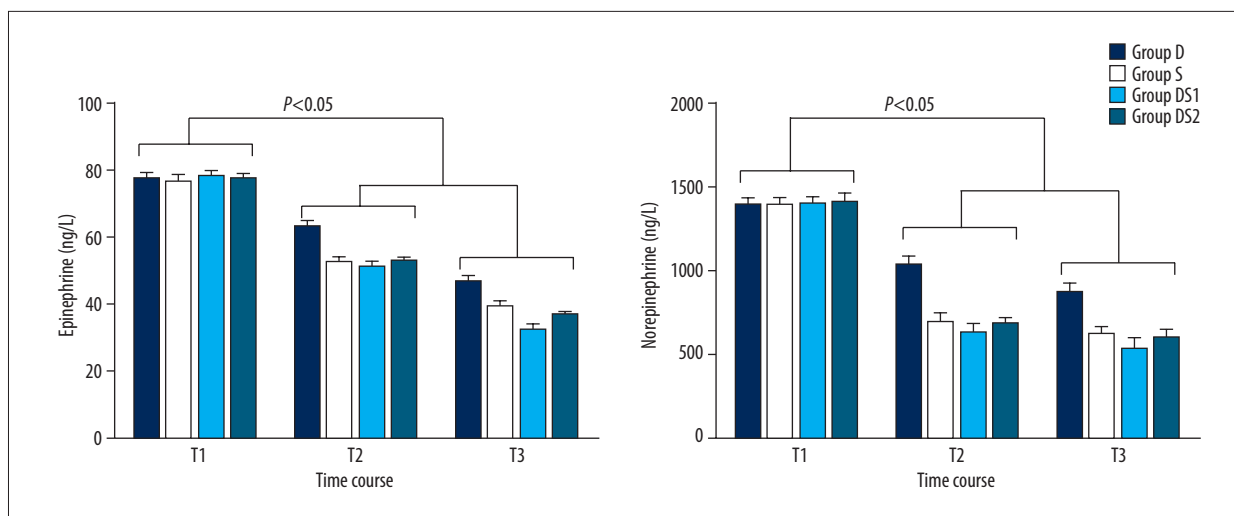


Figure 4. Plasma epinephrine and norepinephrine of patients receiving dexmedetomidine and/or sufentanil at 3 time-points: baseline (T_1), 1 h (T_2), 8 h (T_3) after the completion of loading dose. Compared with T_1 , plasma epinephrine and norepinephrine both decreased at T_2 and T_3 in each group. Plasma epinephrine and norepinephrine were significantly lower in group S, group DS1, and DS2 at T_2 and T_3 compared to group D ($P < 0.05$). Values are given as mean \pm SEM.

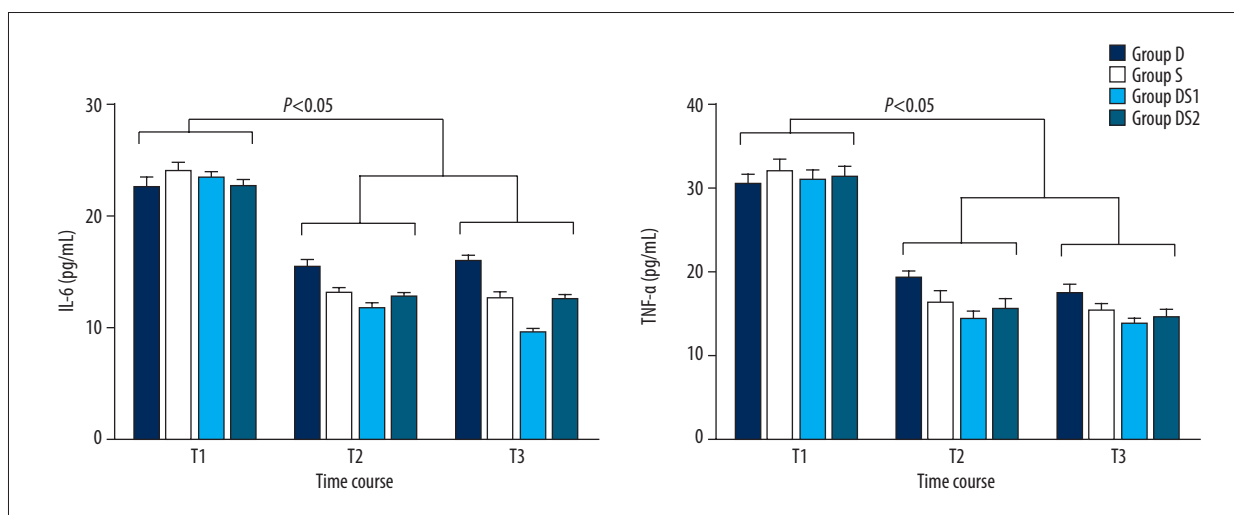


Figure 5. Plasma interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) of patients receiving dexmedetomidine and/or sufentanil at 3 time-points: baseline (T_1), 1 h (T_2), and 8 h (T_3) after the completion of loading dose. Compared with T_1 , plasma IL-6 and TNF- α both decreased at T_2 and T_3 in each group. Plasma IL-6 and TNF- α were significantly lower in group S, group DS1 and DS2 at T_2 and T_3 compared to group D ($P < 0.05$). Values are given as mean \pm SEM.

anesthesia are not fully known. Relevant studies demonstrated that neurotransmitter abnormalities, inflammatory response, hypoxia-ischemia, and genetic factors play critical roles in the development of delirium [14–16]. Recently, there had been a growing interest in POD in elderly patients, but the present study focuses more on young patients with POD.

Currently, antipsychotics, sedative-hypnotics of benzodiazepines, and antidepressants have been used to treat POD [17,18]. Haloperidol, which was once recommended as the first choice for treating POD by the American Psychiatric Association, now

has been replaced by benzophenones because of its serious cardiovascular adverse effects. However, several studies also showed that benzodiazepines are associated with prolonged or even worsening symptoms of delirium. As a highly selective α_2 adrenergic receptor agonist, DEX has pharmacological properties of sedative hypnosis, analgesia, inhibition of sympathetic activity, and potential neuroprotective effects [19–21]. DEX plays important roles in analgesia and anxiety alleviation [8]. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit showed that dexmedetomidine can prevent adult delirium [22].

Opioid drugs such as sufentanil are strongly recommended as the first choice for treating serious non-neuralgia conditions [22]. The present study was designed to evaluate the effects of the combined usage of DEX and sufentanil on young patients with POD after general anesthesia.

Hemodynamic indicators fluctuate in response to pain and stress, such as increases in blood pressure and heart rate. Hemodynamic stability may be useful for clinical treatment and the need for vasopressors or anticholinergic support may be significantly reduced [23]. Our results indicate that HR and blood pressure were improved in the 4 study groups from T₂ to T₅, which agrees with previous research [24]. The phenomenon may result from decreased sympathetic activity [25]. This issue was further elucidated by our results showing that plasma epinephrine and norepinephrine were significantly decreased in the 4 groups from T₂ to T₅.

Recent studies show that postoperative pain is an important and independent factor in delirium [26,27]. Pain can lead to delirium and trigger the inflammation response, and the released inflammatory factors in turn increase the pain further, which can become a vicious cycle. Our study shows that, except for ameliorating the abnormalities of hemodynamic indicators, both DEX and sufentanil decrease VAS scores, SAS scores, and the incidence of POD, but increase the incidence of respiratory distress. DEX combined with sufentanil may play a synergistic reaction in respiratory distress, but remarkably decreases the incidence of POD.

The amelioration of stress and inflammatory response is useful in attenuating postoperative pain and delirium and improving postoperative outcomes [14,15]. Proinflammatory cytokines such as IL-6 and TNF- α play essential roles in pain sensitization [28]. Systemic or regional analgesic regimens which limit the release proinflammatory cytokines can prevent both peripheral and central sensitization, attenuating the postoperative amplification of pain sensation [29]. Significantly increased IL-6 and TNF- α serum levels were detected in our patients after delirium in the 4 study groups. Plasma IL-6 and TNF- α in group DS1 at T2 and T5 were lower than those in group DS2 and

group S, which is consistent with our finding that postoperative VAS scores and SAS scores were the lowest in group DS1.

It needs to be mentioned that some patients still suffer from malaise or delirium after the usage of DEX and sufentanil, and most of the patients also had urinary catheter pain. When they were given diclofenac sodium suppositories, some of them felt better.

Some limitations exist in our study. First, it was a single-center study and the sample size was limited by the consideration of the safety and shortage the patients. Second, although CAM-ICU has been shown to be a reliable and valid measure of POD [30], we noticed that, despite use of 4 objective criteria, the individual score for each item was still subjective to some degree. Third, individual differences are inevitable and pain tolerance varies from person to person, while the dosage of DEX and/or sufentanil are commonly used in the same way. In addition, this was only an exploratory study, and multiple-center, large-sample, randomized, controlled trials of high quality are required.

Conclusions

Both DEX and sufentanil decrease the incidence of POD, ameliorate the abnormalities of hemodynamic indicators, decrease VAS scores, SAS scores, stress hormones, and inflammatory biomarkers, but increase the incidence of respiratory distress. DEX combined with sufentanil may play a synergistic role in causing respiratory distress, but remarkably decreases the incidence of POD.

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Conflicts of interests

None.

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