Int J Clin Exp Med 2020;13(9):6747-6755
www.ijcem.com /ISSN:1940-5901/IJCEM0113379

*Original Article*

# Intrathecal dexmedetomidine for sedation and anesthesia during lower limb fracture surgery

Canjin Qiu, Xiaobin Wu, Weibin Ma, Yanqin Chen, Shiwei Yang, Shizhong Yang

*Department of Anesthesiology, China Coast Guard Hospital of The People's Armed Police Force, Jiaxing, Zhejiang Province, China*

Received April 27, 2020; Accepted June 2, 2020; Epub September 15, 2020; Published September 30, 2020

**Abstract:** Objective: To explore the analgesic and sedative effects of intrathecal dexmedetomidine (DEX) during lower limb fracture surgery. Methods: We prospectively studied 88 patients undergoing elective lower limb fracture surgery and divided them into the DEX group (n=44) and midazolam (MID) group (n=44) by a random number table. Either dexmedetomidine infusion (DEX group) at a dose of 1 μg/kg, or midazolam infusion (MID group) at a dose of 0.05 mg/kg was used for the patients who received successful intrathecal anesthesia to maintain the anesthetic effect. The levels of sedation and anesthesia and parameters of stress reactions, hemodynamic, respiratory and circulatory functions were compared perioperatively at different time points between the two groups, and the post-operative mental status, cognitive function and incidence of adverse reactions were compared between the two groups. Results: At T2 and T3, the mean arterial pressure, heart rate and arterial partial pressure of carbon dioxide showed significantly better results in the DEX group than in the MID group (all $P<0.05$). The pressure pain threshold was significantly higher ($P<0.001$), and the auditory evoked potential index, Ramsay Sedation Score ($P<0.05$ or $P<0.001$), and serum levels of norepinephrine, epinephrine and cortisol ($P<0.001$) were significantly lower in the DEX group than in the MID group. After the surgery, the Mini-Mental State Examination scores were significantly higher ($P<0.01$), and the total incidence of adverse reactions such as agitation and respiratory depression were significantly lower in the DEX group than in the MID group ($P<0.05$). Conclusion: Intrathecal DEX is ideal for procedural anesthesia and sedation during lower limb fracture surgery, which reduces intraoperative stress reactions significantly, maintains respiratory and circulatory stability, and exerts mild postoperative effects on mental and cognitive functions, with few adverse reactions such as respiratory depression.

**Keywords:** Dexmedetomidine, intrathecal anesthesia, lower limb fracture surgery, sedative effect

## Introduction

Lower limb fractures are common orthopedic injuries. As transportation and economy develop rapidly, lower limb fractures such as fractures of the tibia, fibula, femur and phalanges have increased in recent years due to various reasons, accounting for 25.0% of all limb fractures [1]. Intrathecal anesthesia is commonly used for lower limb fracture surgery, with the advantages of being a simple operation, rapid onset of action, and effective anesthetic blockage. However, it is reported that intrathecal anesthesia can cause complications like cognitive dysfunctions, and intraoperative procedures (e.g., traction) can result in stress reactions of different degrees of severity and induce changes in blood pressure (BP), respiration and other vital signs, which further lead to perioperative metabolic disorders, abnormal cardiac function, etc. Meanwhile, most patients endure severe postoperative pain, which seriously affects their rehabilitation and quality of life [2]. Generally, sedative and analgesic drugs are supplemented to ensure the safety of anesthesia, and reduce the physical and mental damage so as to minimize stress reactions and relevant complications caused by surgical anesthesia. Hence the use of such drugs is of great concern in clinical practice [3]. Dexmedetomidine (DEX) is a new type of α-2 adrenoreceptor agonist characterized by potent effect, high selectivity, short onset time and rapid recovery, which can effectively decrease sympathetic nerve activity. Owning to having potent sedative, analgesic and hypnotic properties, dexme-

**Table 1.** Comparison of general data ($\bar{x}$ ± sd, n)

| General data | | MID group (n=44) | DEX group (n=44) | P | t/$\chi^2$ |
|---|---|---|---|---|---|
| Gender (male/female) | | 24/20 | 23/21 | 0.831 | 0.045 |
| Age (year) | | 58.9±13.3 | 59.2±14.1 | 0.892 | 0.135 |
| ASA grading (Grade I/II) | | 25/19 | 24/20 | 0.830 | 0.045 |
| Cause of injury | High falling | 12 | 11 | 0.724 | 0.124 |
| | Traffic accident | 19 | 20 | | |
| | Direct violence | 8 | 9 | | |
| | Others | 5 | 4 | | |
| Operative method | Open reduction | 19 | 21 | 0.776 | 0.080 |
| | Closed reduction | 17 | 16 | | |
| | Replacement | 8 | 7 | | |

Note: DEX: dexmedetomidine; MID: midazolam; ASA: American Society of Anesthesiologists.

detomidine has become a commonly used adjuvant for surgical anesthesia [4]. To date, studies of intrathecal dexmedetomidine during lower limb fracture surgery have showed certain positive results, but there is still a lack of research on its sedative and analgesic effect, stress reactions and adverse reactions. Therefore, we investigated the analgesic and sedative effects of intrathecal dexmedetomidine during lower limb fracture surgery, hoping to provide a theoretical basis for clinical practice.

## Materials and methods

### *General data*

A total of 88 patients undergoing elective lower limb fracture surgery in the China Coast Guard Hospital of the People's Armed Police Forces from October 2017 to June 2019 were enrolled and divided into the DEX group and midazolam (MID) group using a random number table, with 44 cases in each group.

The included patients aged 18 to 80 years old, were diagnosed with grade I or II lower limb fractures defined by the American Society of Anesthesiologists (ASA) and accorded with the indications for surgery [5]. All patients volunteered to participate in this study and gave their written informed consent. Additionally, patients were excluded if they had mental and psychological diseases (e.g., cognitive dysfunction, and depression), important organ diseases and malignant tumors (e.g., diseases in liver, kidney, spleen and lung), or other types of fractures (e.g., upper limb fractures). Patients were also excluded because of systemic infection, immune system diseases, incomplete data or death.

As is shown in **Table 1**, there was no significant difference in gender, age, ASA grading, cause of fracture, surgical methods, etc. between the two groups (all P>0.05), suggesting the two groups were comparable. Ethics approval for the study was given by the Ethics Committee of China Coast Guard Hospital of the People's Armed Police Forces.

### *Surgical methods*

All patients routinely fasted for 12 h. After admission to the operating room, complete preoperative preparation was performed, including nasal catheter oxygen inhalation (3 L/min), establishment of upper limb venous access, and infusion of sodium lactate Ringer's solution (Shanghai Zcibio Technology Co., Ltd., China) (8-10 mL/kg). Besides, the multifunctional electronic monitor (Criticare Systems Inc., USA) was also used for closely monitoring electrocardiogram, heart rate (HR), BP, saturation and other indicators. The patients were placed in the lateral decubitus position, and received intrathecal anesthesia at the $L_{3-4}$ interspace using 1.0% lidocaine (Guangzhou Hongcheng Biological Technology Co., Ltd., China) and 0.375% ropivacaine (Wuhan Biocar Bio-pharmaceutical Co., Ltd). All patients were anesthetized below $T_7$ level. After successful intrathecal anesthesia, the patients in the DEX group were given DEX (Anhui Dexinjia Biopharm Co., Ltd., China) at a dose of 1 μg/kg over a period of 15 min through intravenous pump, followed by a continuous dose of 0.2-0.4 μg/(kg·h), and patients in the MID group were given midazolam (MID) at a dose of 0.05 mg/kg through intravenous pump (Jiangsu Jiuxu Pharmaceutical Co., Ltd., China). Before the surgery, the patient's vital signs were closely monitored. If systolic BP decreased to less than 90 mmHg, ephedrine (Brilliant Pharmaceutical Co., Ltd., Chengdu, China) was moderately administered to increase the BP. If the heart rate reduced to 50 beats/min, 0.5 mg atropine (Changchun Changhong Pharmaceutical Co., Ltd., China) was administered to accelerate the heart rate.

*Outcome measures*

The parameters of respiratory and circulatory function and stress reactions, as well as levels of sedation and anesthesia were measured at the following stages: before surgery (T0), 10 minutes after administration (T1), 60 minutes after administration (T2), and immediately after surgery (T3).

Respiratory and circulatory parameters: The mean arterial pressure (MAP), HR, arterial partial pressure of oxygen ($PaO_2$) and carbon dioxide ($PaCO_2$) were compared at different time points between the two groups.

Levels of sedation and anesthesia: The auditory evoked potential index (AAI), pressure pain threshold (PPT) and Ramsay Sedation Score (RSS) were compared at different time points between the two groups [6-8]. Among them, the AAI was measured by Depth of Anesthesia Monitor TD-3200A. The RSS was evaluated using a double-blind protocol by senior anesthesiologists who did not participate in the surgery. The sedation level that ranged from 1 to 6 points was classified as anxious and agitated or restless or both (1 point), cooperative, oriented and tranquil (2 points), respondes to commands only (3 points), brisk response to glabellar tap or loud auditory stimulus (4 points), sluggish response to glabellar tap or loud auditory stimulus (5 points), and no response (6 points). One point was given for a poor sedative effect, 2-3 points for the best sedative effect, and 4-6 points for excessive sedation. The PPT was assessed using an IITC electric von Frey anesthesiometer in the medial side of the brachioradialis muscle in the forearm and the measurements were performed 3 times each to obtain the mean value.

Stress reaction parameters: The serum levels of norepinephrine (NE), epinephrine (E) and cortisol (COR) were compared at different time points between the two groups. Fasting venous blood (3 mL) was collected from each patient, followed by centrifugation of sediment at 3,000 r/min for 10 min. Then the serum E and NE levels were determined by high performance liquid chromatography, and the serum COR levels were measured by radioimmunoassay using a kit purchased from Shanghai Hengyuan Biological Technology Co., Ltd.

Cognitive function parameters: The scores of Mini-Mental State Examination (MMSE) at 2 hours and 1 day postoperatively were compared before and after surgery between the two groups. The total score of MMSE was 30 points, with a score of ≥27 indicating normal cognitive function.

Incidence of adverse reactions: The total incidence of agitation, respiratory depression and other adverse reactions was compared after the surgery between the two groups.

*Statistical analysis*

Data analyses were performed with SPSS 24.0 software. The measurement data with the normal distribution were expressed as mean ± standard deviation ($\overline{x}$ ± sd), and t-test was used for the comparison between the two groups. Chi-square test ($\chi^2$ test) was adopted for the comparison of enumeration data expressed as the case/percentage (n/%). P<0.05 was considered statistically significant.

## Results

*Comparison of respiratory and circulatory functions at different time points*

At T0 and T1, no significant difference was indicated in the MAP, HR, $PaO_2$ and $PaCO_2$ between the two groups (all P>0.05). At T2 and T3, MAP and HR levels were significantly lower (both P<0.001), and the $PaCO_2$ was significantly higher in the DEX group than in the MID group (P<0.05 or P<0.01). There was no significant difference in the $PaO_2$ between the two groups (P>0.05). Besides, MAP and HR levels in both groups were significantly lower, and the $PaO_2$ in both groups and the $PaCO_2$ in the DEX group were markedly higher at T1, T2 and T3 than at T0 (all P<0.05). See **Table 2** and **Figure 1**.

*Comparison of levels of sedation and anesthesia at different time points*

At T0 and T1, no significant difference was indicated in AAI, PPT and RSS between the two groups (all P>0.05). At T2 and T3, AAI and RSS

**Table 2.** Comparison of respiratory and circulatory functions at different time points ($\bar{x}$ ± sd)

| Items | Group | T0 | T1 | T2 | T3 |
|---|---|---|---|---|---|
| MAP (mmHg) | DEX group (n=44) | 98.63±10.39 | 86.92±8.87$^{*}$ | 73.07±8.52$^{*,\#\#\#}$ | 75.29±9.41$^{*,\#\#\#}$ |
| | MID group (n=44) | 99.45±9.82 | 90.61±9.43$^{*}$ | 87.36±8.96$^{*}$ | 91.04±10.39$^{*}$ |
| HR (beats/min) | DEX group (n=44) | 83.90±10.22 | 74.82±8.74$^{*}$ | 66.75±8.42$^{*,\#\#\#}$ | 69.15±8.98$^{*,\#\#\#}$ |
| | MID group (n=44) | 84.16±9.83 | 80.47±9.22$^{*}$ | 75.91±10.35$^{*}$ | 77.83±8.25$^{*}$ |
| $PaO_2$ (mmHg) | DEX group (n=44) | 98.73±13.29 | 192.53±20.40$^{*}$ | 213.27±24.43$^{*}$ | 230.74±20.86$^{*}$ |
| | MID group (n=44) | 98.31±14.06 | 188.39±18.68$^{*}$ | 205.58±22.91$^{*}$ | 211.82±21.45$^{*}$ |
| $PaCO_2$ (mmHg) | DEX group (n=44) | 35.87±4.25 | 41.21±4.40$^{*}$ | 40.18±5.07$^{*,\#}$ | 39.34±4.73$^{*,\#\#}$ |
| | MID group (n=44) | 36.05±4.17 | 39.52±4.95 | 37.25±4.51 | 36.85±4.04 |
| MAP (P, t) | | 0.705, 0.381 | 0.144, 1.476 | <0.001, 6.115 | <0.001, 7.043 |
| HR (P, t) | | 0.835, 0.209 | 0.113, 1.601 | <0.001, 4.849 | <0.001, 4.619 |
| $PaO_2$ (P, t) | | 0.807, 0.245 | 0.432, 0.790 | 0.291, 1.063 | 0.204, 1.281 |
| $PaCO_2$ (P, t) | | 0.849, 0.191 | 0.204, 1.281 | 0.032, 2.180 | 0.003, 3.052 |

Note: Compared with MID group, $^{\#}P<0.05$, $^{\#\#}P<0.01$, and $^{\#\#\#}P<0.001$; compared with T0 in the same group, $^{*}P<0.05$. DEX: dexmedetomidine; MID: midazolam; MAP: mean arterial pressure; HR: heart rate; $PaO_2$: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide.

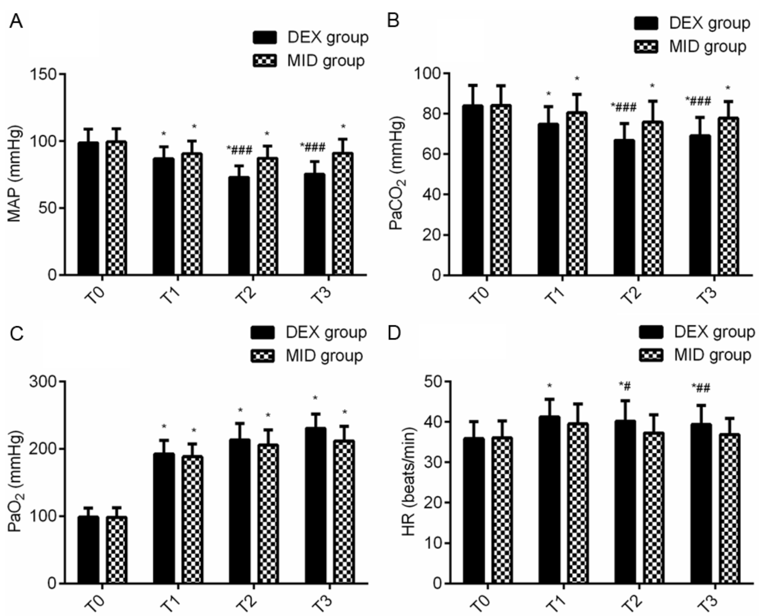



**Figure 1.** Comparison of respiratory and circulatory parameters at different time points. A: MAP at different time points; B: $PaCO_2$ at different time points; C: $PaO_2$ at different time points; D: HR at different time points; Compared with MID group, $^{\#}P<0.05$, $^{\#\#}P<0.01$ and $^{\#\#\#}P<0.001$; compared with T0 in the same group, $^{*}P<0.05$. DEX: dexmedetomidine; MID: midazolam; MAP: mean arterial pressure; HR: heart rate; $PaO_2$: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide.

were significantly lower (P<0.05 or P<0.001), and PPT was markedly higher in the DEX group than in the MID group (P<0.001). Furthermore, AAI in both groups was significantly lower, PPT in both groups was markedly higher, and RSS in the MID group was much higher at T1, T2 and T3 than at T0 (all P<0.05). RSS in DEX group was significantly higher at T2 and T3 than at T0 (P<0.05). See **Table 3** and **Figure 2**.

*Comparison of stress reactions at different time points*

At T0 and T1, no significant difference was indicated in serum levels of NE, E and COR between the two groups (P>0.05). At T2 and T3, the serum levels of NE, E and COR in the DEX group were significantly lower than those in the MID group (P<0.001). In addition, the serum levels of NE, E and COR in the MID group were significantly higher at T1, T2 and T3 than at T0; the serum levels of NE, E and COR in the DEX group were significantly higher, and the serum COR level in the MID group was markedly higher at T2 and T3 than at T0 (all P<0.05). See **Table 4** and **Figure 3**.

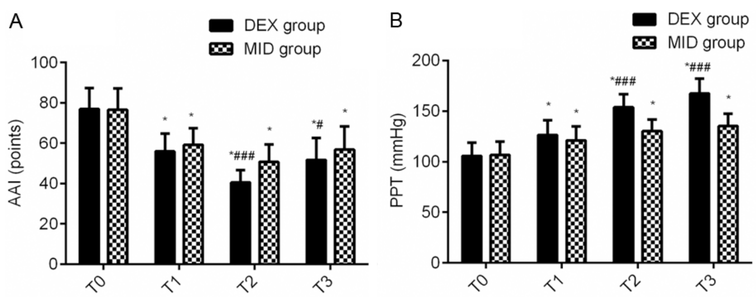
*Comparison of cognitive function before and after surgery*

At 1 day preoperatively, no significant difference was indicated in the MMSE scores between the two groups (P>0.05). At 2 hours and 1 day postoperatively, the MMSE scores in the DEX group were much higher than those in the MID group (all P<0.01). Moreover, the MMSE

**Table 3.** Comparison of levels of sedation and anesthesia at different time points ($\bar{x}$ ± sd)

| Items | Group | T0 | T1 | T2 | T3 |
|---|---|---|---|---|---|
| AAI (points) | DEX group (n=44) | 76.93±10.46 | 56.03±8.74$^{*}$ | 40.53±6.09$^{*,\#\#\#}$ | 51.70±10.83$^{*,\#}$ |
| | MID group (n=44) | 76.50±10.73 | 59.18±8.29$^{*}$ | 50.81±8.56$^{*}$ | 56.94±11.35$^{*}$ |
| PPT (mmHg) | DEX group (n=44) | 105.82±12.89 | 126.44±14.56$^{*}$ | 153.68±12.90$^{*,\#\#\#}$ | 167.43±14.48$^{*,\#\#\#}$ |
| | MID group (n=44) | 106.77±13.04 | 121.06±13.72$^{*}$ | 130.43±11.36$^{*}$ | 135.32±12.06$^{*}$ |
| RSS (points) | DEX group (n=44) | 1.90±0.41 | 2.11±0.36 | 2.47±0.51$^{*,\#\#\#}$ | 2.25±0.46$^{*,\#\#\#}$ |
| | MID group (n=44) | 1.88±0.39 | 2.45±0.40$^{*}$ | 3.62±0.66$^{*}$ | 3.28±0.62$^{*}$ |
| AAI (P, t) | | 0.849, 0.190 | 0.133, 1.518 | <0.001, 6.633 | 0.021, 2.345 |
| PPT (P, t) | | 0.634, 0.478 | 0.086, 1.735 | <0.001, 12.628 | <0.001, 11.998 |
| RSS (P, t) | | 0.815, 0.234 | 0.105, 1.641 | <0.001, 9.146 | <0.001, 8.198 |

Note: Compared with MID group, $^{\#}P<0.05$, $^{\#\#\#}P<0.001$; compared with T0 in the same group, $^{*}P<0.05$. DEX: dexmedetomidine; MID: midazolam; AAI: auditory evoked potential index; PPT: pressure pain threshold; RSS: Ramsay Sedation Score.



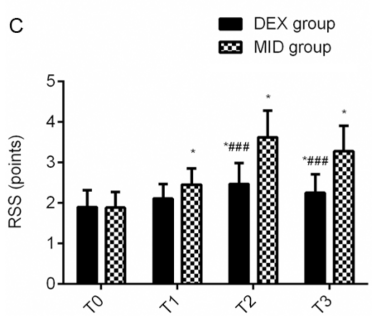




**Figure 2.** Comparison of levels of sedation and anesthesia at different time points. A: AAI at different time points; B: PPT at different time points; C: RSS at different time points. Compared with MID group, $^{\#}P<0.05$, $^{\#\#\#}P<0.001$; compared with T0 in the same group, $^{*}P<0.05$. DEX: dexmedetomidine; MID: midazolam; AAI: auditory evoked potential index; PPT: pressure pain threshold; RSS: Ramsay Sedation Score.

scores in the the MID group were significantly lower at 2 hours and 1 day postoperatively than at 1 day preoperatively (P<0.05). The MMSE scores in the DEX group were significantly lower at 2 hours postoperatively than at 1 day preoperatively (P<0.05). See **Table 5.**

*Comparison of incidence of adverse reactions postoperatively*

The incidence of adverse reactions (e.g., respiratory depression, agitation, nausea and vomiting, shivering, and dizziness) in the DEX group was significantly lower than that in the MID group (P<0.05). See **Table 6**.

## Discussion

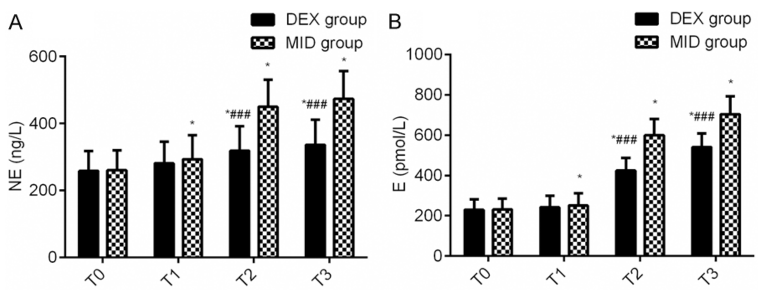
Intrathecal anesthesia is commonly used for patients undergoing lower limb and lower abdominal surgery, with the advantages of being a potent analgesic and having muscle relaxant effects as well as low cost. Intrathecal anesthesia is different from general anesthesia. During the whole process of intrathecal anesthesia, patients are conscious with complete memory of surgery when undergoing surgical procedures (e.g., invasive procedures, use of tourniquet, and immobilization). Since these procedures can cause stress reactions of different degrees of severity, and even induce respiratory depression, cognitive impairment and other serious complications, the use of sedative drugs is often required in surgery. Stress reactions mainly refer to the non-specific adaptive responses of the sympathetic nervous system and the hypothalamus-pituitary-adrenocortical axis to noxious stimulations such as surgery or trauma. Under normal circumstances, the changes are adaptive but can lead to direct health damage, reduce the quality of prognosis and increase the risk of complications when stress is excessive [9]. Hence, improving sedative effect during intrathecal anesthesia and reducing stress reaction is the basis for rapid recovery.

Adjuvant drugs for anesthesia and sedation are essential to reduce stress reactions. For instance, MID, a new benzodiazepine receptor agonist, can inhibit regulatory proteins to enhance the γ-aminobutyric acid (GABA) effect, inducing a sedative-hypnotic state, muscle-

**Table 4.** Comparison of stress reactions at different time points ($\overline{x}$ ± sd)

| Items | Group | T0 | T1 | T2 | T3 |
|---|---|---|---|---|---|
| NE (ng/L) | DEX group (n=44) | 258.91±58.26 | 280.83±65.02 | 318.76±72.93$^{*,\#\#\#}$ | 336.15±74.40$^{*,\#\#\#}$ |
| | MID group (n=44) | 260.15±59.03 | 293.40±71.58$^{*}$ | 449.58±80.62$^{*}$ | 473.78±83.07$^{*}$ |
| E (pmol/L) | DEX group (n=44) | 229.45±52.96 | 242.35±56.20 | 423.91±62.07$^{*,\#\#\#}$ | 540.73±67.95$^{*,\#\#\#}$ |
| | MID group (n=44) | 231.09±53.42 | 251.66±61.33$^{*}$ | 598.64±81.36$^{*}$ | 703.60±88.34$^{*}$ |
| COR (nmol/L) | DEX group (n=44) | 407.73±56.37 | 424.09±65.68 | 603.83±77.49$^{*,\#\#\#}$ | 721.46±92.52$^{*,\#\#\#}$ |
| | MID group (n=44) | 408.63±55.94 | 441.73±70.45 | 785.37±82.75$^{*}$ | 853.85±103.23$^{*}$ |
| NE (P, t) | | 0.878, 0.154 | 0.389, 0.866 | <0.001, 11.061 | <0.001, 8.131 |
| E (P, t) | | 0.810, 0.241 | 0.324, 0.993 | <0.001, 13.424 | <0.001, 9.675 |
| COR (P, t) | | 0.926, 0.094 | 0.114, 1.595 | <0.001, 10.775 | <0.001, 7.835 |

Note: Compared with MID group, $^{\#\#\#}P<0.05$; compared with T0 in the same group, $^{*}P<0.05$. DEX: dexmedetomidine; MID: midazolam; NE: norepinephrine; E: epinephrine; COR: cortisol.



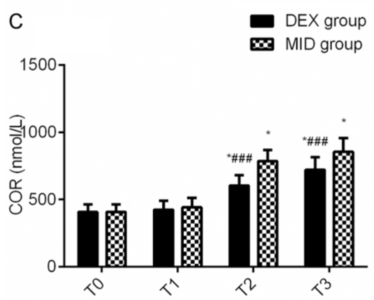




**Figure 3.** Comparison of stress reactions at different time points. A: NE at different time points; B: E at different time points; C: COR at different time points. Compared with MID group, $^{\#\#\#}P<0.001$; compared with T0 in the same group, $^{*}P<0.05$. DEX: dexmedetomidine; MID: midazolam; NE: norepinephrine; E: epinephrine; COR: cortisol.

**Table 5.** Comparison of cognitive funtion before and after surgery ($\overline{x}$ ± sd, points)

| Group | 1 day preoperatively | 2 hours postoperatively | 1 day postoperatively |
|---|---|---|---|
| DEX group (n=44) | 29.41±5.33 | 26.49±3.54$^{*}$ | 28.75±4.68 |
| MID group (n=44) | 29.86±5.15 | 23.84±3.36$^{*}$ | 25.90±3.87$^{*}$ |
| T | 0.401 | 3.367 | 3.115 |
| P | 0.693 | 0.002 | 0.003 |

Note: Compared with cognitive function at 1 day preoperatively, $^{*}P<0.05$. DEX: dexmedetomidine; MID: midazolam.

relaxant, anxiolytic and anterograde amnesia effects; which can provide satisfactory sedation while helping patients maintain consciousness, eliminating the pain caused by anesthesia and surgical procedures, and reducing psychological and physical stress to a certain extent. Nevertheless, it has been identified that MID can cause adverse reactions (e.g., nervous system disorders, mental disorders, and disorientation) and hemodynamic and respiratory instability, reduce patient compliance, and thus affect the outcomes of surgery and rehabilitation [10]. DEX as a highly potent, selective α2-adrenergic receptor agonist is an new adjuvant for intrathecal anesthesia, which has a short *in-vivo* half-life with sedative, anxiolytic and stress relaxation properties [11]. A pharmacological study demonstrated that DEX rapidly entered the medulla oblongata and pons, efficiently binds to α2 adrenergic receptors, and inhibites NE release to achieve sedative effects after intravenous administration. Meanwhile, it was revealed that DEX activated postsynaptic α2-adrenergic receptors in the posterior horn of the spinal cord, inhibited the excitatory synaptic transmission of pain signals and the presynaptic release of neurotransmitters (e.g., substance P), blocked peripheral conduction in Aδ- and C-fibers, and thus produced a potent analgesic effect [12]. Additionally, DEX can bind to presynaptic α2-adrenergic receptors, stimulate parasympathetic nerves and inhibit sympath-

**Table 6.** Comparison of incidence of adverse reactions (n, %)

| Group | Respiratory depression | Agitation | Nausea and vomiting | Shivering | Dizziness | Total incidence (%) |
|---|---|---|---|---|---|---|
| DEX group (n=44) | 0 (0.00) | 1 (2.27) | 2 (4.55) | 0 (0.00) | 0 (0.00) | 6.82 |
| MID group (n=44) | 2 (4.55) | 1 (2.27) | 4 (9.08) | 3 (6.82) | 2 (4.55) | 27.27 |
| $\chi^2$ | | | | | | 5.446 |
| P | | | | | | 0.013 |

Note: DEX: dexmedetomidine; MID: midazolam.

etic nerves, thereby reducing peripheral BP and HR as well as enhancing sedative and analgesic effects [13]. As a result, DEX is considered to be an ideal adjuvant for intrathecal anesthesia, yet clinical results for evidence-based medicine is still lacking.

Furthermore, Rajan et al. found that DEX was more effective in inhibiting BP and HR variability, maintaining intraoperative hemodynamic stability, and reducing postoperative pain [14]. It was confirmed that DEX could effectively inhibit sympathetic nerve activity and stress-induced increases in BP, HR and other parameters by activation of postsynaptic α2-adrenergic receptors, which was especially suitable for patients with poor physical function. At the same time, DEX can inhibit NE release and the excitatory synaptic transmission of pain signals by activation of presynaptic α2-adrenergic receptors. Moreover, the research also pointed out that DEX can maintain stable respiratory function, and help patients be extubated in a short time after withdrawal. Hence DEX had little effect on the pH and $PaO_2$, tidal volume, respiratory rate, etc., and only caused adverse reactions (e.g., mild sleep apnea and hypoxemia) with large doses [15]. In this study, we found that MAP and HR were significantly lower, and $PaCO_2$ was higher in the DEX group than in the MID group at T2 and T3. This may be due to the relatively slow respiratory movement caused by deeper anesthesia in the DEX group, improper body position and ventilator setting. Besides, $PaO_2$ in both groups was significantly higher at T1, T2 and T3 than at T0, which may result from oxygen inhalation, ventilator use and other operations that promoted respiration, but there was no significant difference between the two groups. The results suggest that DEX can provide satisfactory sedation, and reduce the respiratory and circulatory dynamic fluctuations caused by surgery, which was basically consistent with the current study [16].

One of the most important goals of anesthesia is to alleviate surgical stress. As indicators of stress, catecholamines and COR highly reflect the stress intensity and time in the body, with high specificity and sensitivity [17]. In this study, we identified that the serum levels of NE, E and COR at T2 and T3 were much lower in the DEX group than in the MID group, further consolidating that DEX can effectively reduce surgical stress reactions. Besides, AAI and RSS are reliable parameters for assessing the depth of anesthesia and sedation [18]. AAI can continuously and accurately reflect the excitability of cortical and subcortical structures, and evaluate the response to noxious stimulation as PPT by a simple numerical method. As to RSS, the target range of optimal sedation was defined as the scores of 2 to 3 [19]. In this study, we demonstrated that the AAI and RSS were significantly lower, and the PPT was markedly higher in the DEX group than in the MID group at T2 and T3, suggesting once again the ideal sedative effects of DEX. Moreover, abnormal cerebral oxygen metabolism was confirmed to be closely related to cognitive dysfunction. Normally, cerebral blood flow autoregulation can be achieved via vasodilatation, while anesthesia may lead to insufficient cerebral blood supply and possible damage to the brain parenchyma to induce cognitive impairment during surgery [20].

In addition, Memaria et al. reported that DEX can protect hippocampal neurons, down-regulate brain metabolism and thus reduce ischemic brain injury in the mouse model of cerebral ischemia [21]. The results reveal that DEX may be possible to protect postoperative cognitive function, but there is no sufficient clinical evidence. In our study, we identified that the postoperative MMSE scores in the DEX group were significantly higher than those in the MID group, suggesting that DEX can better protect the neurological and cognitive function. This may be due to its improvement in cerebral oxygen metabolism caused by inhibition of sympathetic nerve activity, vasodilation and BP decrease, and reduction of perfusion pressure and blood flow. Furthermore, the incidence of adverse reactions (e.g., agitation and respiratory depression) in the DEX group was lower than that in the MID group, indicating once again that DEX has a slight effect on the respiratory and circulatory system, while individual cases of adverse reactions may result from sympathetic activation after withdrawal [22]. With the small sample size in this wide-range study, we are aware that more detailed and in-depth studies with a larger sample size are needed to get a more precise conclusion in the future.

In summary, intrathecal DEX is an ideal anesthetic adjuvant with obvious analgesic and sedative effects during lower limb fracture surgery. It can markedly reduce intraoperative stress reactions, maintain respiratory and circulatory function, and exert mild effects on mental and cognitive function, with few adverse reactions such as respiratory depression.

### Acknowledgements

This work was supported by the Clinical Scientific Research Fund Project of Zhejiang Medical Association (2016ZYC-A77).

### Disclosure of conflict of interest

None.

**Address correspondence to:** Shizhong Yang, Department of Anesthesiology, China Coast Guard Hospital of The People's Armed Police Force, No.16 Nanhu Road, Jiaxing 314000, Zhejiang Province, China. Tel: +86-13516838606; E-mail: yangshizhonguy65@163.com

### References

[1] Dingemans SA, Birnie MFN, Backes M, de Jong VM, Luitse JS, Goslings JS and Schepers T. Prophylactic negative pressure wound therapy after lower extremity fracture surgery: a pilot study. Int Orthop 2018; 42: 747-753.

[2] Shi R and Tie HT. Dexmedetomidine as a promising prevention strategy for cardiac surgery-associated acute kidney injury: a meta-analysis. Crit Care 2017; 21: 198.

[3] Chang YF, Chao A, Shih PY, Hsu YC, Lee CT, Tien YW, Yeh YC and Chen LW. Comparison of dexmedetomidine versus propofol on hemodynamics in surgical critically ill patients. J Surg Res 2018; 228: 194-200.

[4] Song Y, Kim DH, Kwon TD, Han DW, Baik SH, Jung HH and Kim JY. Effect of intraoperative dexmedetomidine on renal function after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a randomized, placebo-controlled trial. Int J Hyperthermia 2019; 36: 1-8.

[5] Zhou H, Zhou D, Lu J, Wu C and Zhu Z. Effects of pre-cardiopulmonary bypass administration of dexmedetomidine on cardiac injuries and the inflammatory response in valve replacement surgery with a sevoflurane postconditioning protocol: a pilot study. J Cardiovasc Pharmacol 2019; 74: 91-97.

[6] Bidelman GM, Pousson M, Dugas C and Fehrenbach A. Test-retest reliability of dual-recorded brainstem versus cortical auditory-evoked potentials to speech. J Am Acad Audiol 2018; 29: 164-174.

[7] Ruscheweyh R, Wersching H, Kugel H, Sundermann B and Teuber A. Gray matter correlates of pressure pain thresholds and self-rated pain sensitivity: a voxel-based morphometry study. Pain 2018; 159: 1359-1365.

[8] Franken LG, de Winter BCM, Masman AD, van Dijk M, Baar FPM, Tibboel D, Koch BCP, van Gelder T and Mathot RAA. Population pharmacodynamic modelling of midazolam induced sedation in terminally ill adult patients. Br J Clin Pharmacol 2018; 84: 320-330.

[9] Hofmann K, Rauh A, Harlizius J, Weiß C, Scholz T, Schulze-Horsel T, Escribano D, Ritzmann M and Zöls S. Pain and distress responses of suckling piglets to injection and castration under local anaesthesia with procaine and lidocaine - Part 1: cortisol, chromogranin A, wound healing, weights, losses. Tierarztl Prax Ausg G Grosstiere Nutztiere 2019; 47: 87-96.

[10] Hu S, Li Y, Wang S, Xu S, Ju X and Ma L. Effects of intravenous infusion of lidocaine and dexmedetomidine on inhibiting cough during the tracheal extubation period after thyroid surgery. BMC Anesthesiol 2019; 19: 66.

[11] Wei LX, Deng XM, Sui JH and Wang L. Induction of anesthesia with dexmedetomidine and sevoflurane for a pediatric difficult airway. Chin Med J (Engl) 2017; 130: 1997-1998.

[12] Yang GZ, Xue FS and Liu YY. Use of a meta-analysis to assess the preventive effect of dexmedetomidine on cardiac surgery-associated acute kidney injury. Crit Care 2018; 22: 85.

[13] Hernando B, Martinez-Simon A, Cacho-Asenjo E, Troconiz IF, Honorato-Cia C, Panadero A, Naval LL and Nunez-Cordoba JM. Recovery time after oral and maxillofacial ambulatory surgery with dexmedetomidine: an observational study. Clin Oral Investig 2019; 23: 391-397.

[14] Rajan S, Arora V, Tosh P, Mohan P and Kumar L. Effectiveness of transtracheal lidocaine as an adjunct to general anesthesia in providing patient immobility during total parotidectomy: a comparison with dexmedetomidine infusion. J Anaesthesiol Clin Pharmacol 2017; 33: 193-196.

[15] Mohamed SA, Sayed DM, El Sherif FA and Abd El-Rahman AM. Effect of local wound infiltration with ketamine versus dexmedetomidine on postoperative pain and stress after abdominal hysterectomy, a randomized trial. Eur J Pain 2018; 22: 951-960.

[16] Abdel-Ghaffar HS, Mohamed SA, Fares KM and Osman MA. Safety and efficacy of dexmedetomidine in treating post spinal anesthesia shivering: a randomized clinically controlled dose-finding trial. Pain Physician 2016; 19: 243-253.

[17] Shelton KT, Qu J, Bilotta F, Brown EN, Cudemus G, D'Alessandro DA, Deng H, DiBiasio A, Gitlin JA, Hahm EY, Hobbs LE, Houle TT, Ibala R, Loggia ML, Pavone KJ, Shaefi S, Tolis G, Westover MB and Akeju O. Minimizing ICU neurological dysfunction with dexmedetomidine-induced sleep (MINDDS): protocol for a randomised, double-blind, parallel-arm, placebo-controlled trial. BMJ Open 2018; 8: e020316.

[18] Shetty RM, Bellini A, Wijayatilake DS, Hamilton MA, Jain R, Karanth S and Namachivayam A. BIS monitoring versus clinical assessment for sedation in mechanically ventilated adults in the intensive care unit and its impact on clinical outcomes and resource utilization. Cochrane Database Syst Rev 2018; 2: CD011240.

[19] Alhammad AM, Baghdady NA, Mullin RA and Greenwood BC. Evaluation of the impact of a prescribing guideline on the use of intraoperative dexmedetomidine at a tertiary academic medical center. Saudi Pharm J 2017; 25: 144-147.

[20] De Tournay-Jette E, Dupuis G, Bherer L, Deschamps A, Cartier R and Denault A. The relationship between cerebral oxygen saturation changes and postoperative cognitive dysfunction in elderly patients after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2011; 25: 95-104.

[21] Memari E, Hosseinian MA, Mirkheshti A, Arhami-Dolatabadi A, Mirabotalebi M, Khandaghy M, Daneshbod Y, Alizadeh L and Shirian S. Comparison of histopathological effects of perineural administration of bupivacaine and bupivacaine-dexmedetomidine in rat sciatic nerve. Exp Toxicol Pathol 2016; 68: 559-564.

[22] Zhang B, Wang G, Liu X, Wang TL and Chi P. The opioid-sparing effect of perioperative dexmedetomidine combined with oxycodone infusion during open hepatectomy: a randomized controlled trial. Front Pharmacol 2017; 8: 940.