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Original Research Article

Effect of dexmedetomidine on convalescence quality after general anesthesia and postoperative delirium, and on cognitive function in elderly patients undergoing lower limb surgery

Wenbo Wei, Lele Guo*
Department of Anesthesiology, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China

For correspondence:* ***Email:* *haodaoketer@163.com*

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Abstract

Purpose: *To investigate the effect of different doses of dexmedetomidine on the quality of postoperative recovery, incidence of postoperative delirium, and cognitive function in elderly patients undergoing lower limb surgery.*
Methods: *A total of 112 patients who received treatment in the Department of Anesthesiology, Affiliated Hospital of Inner Mongolia Medical University, Hothot, China from January 2021 to January 2023 were divided into 3 groups, consisting of low-dose group (35 patients received 0.2 mg/kg), medium-dose group (39 patients received 0.4 mg/kg), and high-dose group (38 patients received 0.6 mg/kg). Parameters including, convalescence quality of general anesthesia, incidence of postoperative delirium, adverse reactions, Mini-mental State Examination (MMSE) scores, sedation effect (Ramsay), analgesia effect (visual analogue scale (VAS)), and stress indices, viz, norepinephrine (NE), epinephrine (E), and cortisol (COR) levels), were evaluated and compared.*
Results: *There was no significant difference in tracheal extubation time, recovery time of spontaneous breathing, calling eye-opening time, or full awakening time among the three groups ($p > 0.05$). However, MMSE score was significantly higher in low-dose group on days 1 and 3 after surgery ($p < 0.05$) and VAS scores were significantly higher in low-dose group at 12 and 24 h after recovery compared to other groups ($p < 0.05$). Ramsay score was significantly higher in high-dose group ($p < 0.05$). Levels of NE, E, and COR were significantly lower in medium-dose group compared to other groups ($p < 0.05$). Incidence of adverse reactions were significantly lower in low and medium-dose groups compared to high-dose group ($p < 0.05$).*
Conclusion: *Medium-dose dexmedetomidine demonstrates favorable sedative and analgesic effects with minimal impact on cognitive function and stress response in elderly patients undergoing lower limb surgery. Furthermore, it does not affect quality of postoperative recovery nor incidence of postoperative delirium. More large-scale, randomized controlled studies are needed to confirm these results.*

Keywords: *Elderly lower limb surgery, Dexmedetomidine, Convalescence quality, general anesthesia, Delirium, Cognitive function*

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INTRODUCTION

Lower extremity surgery is common in elderly group (63 – 73 years old), and it is often due to fracture, osteoarthritis or femoral head necrosis. Surgical treatment, which is a clinically recommended intervention program, helps to improve impaired lower limb function in such patients [1,2]. However, due to degeneration of central nervous function in these categories of individuals, cognitive function is likely to decline during anesthesia and surgery, and postoperative delirium can occur in severe cases, which weakens neurological function of the brain.

In anesthesia recovery period, especially due to various factors such as tracheal catheter and pain, physiological changes occur in adrenal cortex function of patients after surgery, resulting in abnormal sympathetic excitation and severe physiological stress response [3]. As a result, it becomes necessary to select appropriate narcotic analgesic drugs for such treatment.

Dexmedetomidine, an alpha-2 adrenergic receptor agonist, exerts anti-sympathetic and sedative effects and is widely used in perioperative period of surgery [4,5]. Dexmedetomidine is an alpha-2 adrenoceptor agonist that produces sedative, stress-reducing, and analgesic effects by reducing sympathetic nervous system activity. This dual effect contributes to patient comfort and cardiovascular stability during surgery. Dexmedetomidine circulates through blood and acts on central nerve fiber receptors to help constrict blood vessels and prolong effect of narcotic drugs. Studies have shown that dexmedetomidine has the advantages of causing arousal easily, and does not exert any inhibitory effect on respiration when administered clinically [6,7].

Previous studies by Abdel-Rahman *et al* [8] found that 0.5 μg/kg dexmedetomidine reduces incidence of agitation during waking period in children with strabismus, and had a good effect on wakefulness, but its effects on cognitive function were neither studied nor discussed in the study. In addition, there are no studies on dosage of dexmedetomidine in perioperative period especially in elderly.

As a result, the purpose of this study was to investigate the effect of different doses of dexmedetomidine on convalescent quality, postoperative delirium, and cognitive function in elderly patients undergoing lower extremity surgery under general anesthesia.

METHODS

General information

A total of 112 patients with lower extremity orthopedic surgery who received treatment in the Department of Anesthesiology, Affiliated Hospital of Inner Mongolia Medical University, Hothot, China from January 2021 to January 2023 were selected. According to the dose of dexmedetomidine [8], patients were divided into low-dose group (35 patients received 0.2 mg/kg), medium-dose group (39 patients received 0.4 mg/kg), and high-dose group (38 patients received 0.6 mg/kg).

Low-dose group: male/female: 19 / 16 cases; Age range (mean age): 64 – 73 (68.35 ± 2.14) years; ASA Grade II /III: 26 / 9 cases. Medium-dose group: male/female: 22 / 17 cases; Age (mean age): 63 – 72 (67.36 ± 2.08) years old; ASA Grade II/III: 25 / 14 cases. High-dose group: male/female: 20 / 18 cases; Age (mean age): 63 – 73 (67.87 ± 2.32) years; ASA Grade II/III: 21 / 17 cases. This study conformed to basic guidelines of the Declaration of Helsinki and received ethical approval from Affiliated Hospital of Inner Mongolia Medical University (approval no. 20-ZA-12).

Inclusion criteria

Patients ≥ 60 years old, with fracture, internal fixation, and amputation as the types of lower extremity surgery and patients rated by the American Society of Anesthesiologists Rating (ASA): Class II and Class III.

Exclusion criteria

Patients with severe heart, liver and kidney function lesions, as well as patients with preoperative concomitant cognitive dysfunction, contraindications to general anesthesia, and concomitant hematological diseases were excluded.

Surgical procedures and treatments

All patients were placed in lateral decubitus position with chest flexion and knee bending and underwent combined lumbar and epidural anesthesia [9]. Epidural puncture was performed in L3 - L4 space with a lumbar puncture needle inserted into the subarachnoid space, and bupivacaine (8 – 12 mg) was injected slowly (Jiangsu Aosaikang Pharmaceutical Co. Ltd; 10 mL: 50 mg; National Medicine approval no. H20123147). An epidural catheter with a length of 3 cm was inserted into patient's head, and

anesthesia level was maintained at T7 – T10. After no obvious abnormality, anesthesia level was controlled at T10.

Low-dose, medium-dose, and high-dose groups were given 0.2 mg/kg, 0.4 mg/kg, and 0.6 mg/kg dexmedetomidine (Jiangsu Enhua Pharmaceutical Co. Ltd; 2 mL: 200 µg; National medicine approval no. H20110086) for 30 mins, respectively. After operation, 0.125 % of levobupivacaine (Yichang Renfu Pharmaceutical Co. Ltd; 10 mL: 50 mg; National drug approval no. H20193348) was administered, and epidural analgesia was performed at rate of 2 mL/h. Automatic infusion volume was 1 mL, time was 15 min, and the pumping drug was stopped 30 min before end of surgery.

Evaluation of parameters/indices

Convalescent quality of general anesthesia

Time of tracheal catheter removal, recovery time of spontaneous breathing, calling time of eye-opening, and full wakefulness were observed and compared during immediate postoperative period. These times were measured in hours or minutes after surgery to assess differences in recovery patterns and emergence from anesthesia.

Postoperative delirium occurrence

Delirium rating scale [9] was used to evaluate delirium, and delirium could be judged as total score ≥ 18 points or items with the most severe symptoms ≥ 15 points.

Cognitive function

Mini-mental State Examination (MMSE) was done 1 day before surgery, 1 day after surgery, and 3 days after surgery to evaluate patients' cognitive function level [10]. The score includes 11 items such as time, place, and orientation. The score ranges from 0 to 30 points. A higher score indicates better cognitive function.

Sedative and analgesic effects

Ramsay sedation score [11] and Visual Analogue Scale (VAS) [12] were used to evaluate sedation and analgesia effects at 4, 12 and 24 h after recovery, respectively. Ramsay score ranged from 1 (restlessness) to 6 (deep sleep), and higher score, indicates better sedative effect. Visual analogue scale (VAS) score ranged from 1 to 10, and a higher score indicates poor analgesic effect.

Stress levels

Serum levels of Norepinephrine (NE), epinephrine (E), and cortisol (COR) were obtained by collecting blood samples from patients. Blood samples were taken 24 h before surgery as a baseline measurement, and 24 h after surgery to assess any changes in hormone levels. Serum levels of Norepinephrine (NE), epinephrine (E) and cortisol (COR) were determined by radioimmunoassay in strict accordance with instrument and kit instructions [6].

Adverse reactions

Incidence of adverse anesthetic reactions, including nausea, vomiting, respiratory depression and arrhythmia, were observed and recorded in three groups.

Statistical analysis

Statistical Packages for Social Sciences (SPSS) software (version 26.0) was used for data analysis. Measurement data satisfying normal distribution and homogeneous variance (tracheal catheter removal time, spontaneous breathing time, calling eye-opening time, full wakefulness time, MMSE score, VAS score, Ramsay score, NE, E and COR level) were presented as mean ± standard deviation (SD). One-way analysis of variance was used to compare differences among low-dose, medium-dose and high-dose groups. Repeated measure analysis of variance was used to compare intra-group differences at different time points in same group. The rate of count data was expressed in percentages.

RESULTS

Convalescent quality of general anesthesia

There was no significant difference in baseline data of three groups of elderly patients undergoing lower limb operation ($p > 0.05$). There was no statistical significance in removal time of tracheal catheter, recovery time of spontaneous breathing, calling time of eye-opening, and full waking time among three groups ($p > 0.05$; Table 1).

Postoperative delirium occurrence

There were 0 cases (0.00 %), 1 case (2.56 %) and 3 cases (7.89 %) in low-dose, medium-dose and high-dose groups respectively, with no statistical significance ($p = 0.176$).

Table 1: Comparison of convalescent quality of general anesthesia (mean ± SD)

Group	N	Time of tracheal catheter removal (min)	Time of spontaneous breathing (min)	Time of calling eyes open (min)	Time of full wakefulness (min)
Low-dose	35	9.82±2.23	3.12±0.96	9.34±2.67	162.35±50.80
Medium-dose	39	10.77±3.09	3.45±1.05	10.12±3.14	170.14±53.44
High-dose	38	11.56±3.97	3.70±1.16	10.95±3.29	179.62±55.37
F-value		2.698	2.724	2.534	0.963
P-value		0.072	0.070	0.084	0.385

Cognitive function

As Figure 1 shows, there was no significant difference in MMSE scores 24 h before surgery in three groups ($p > 0.05$). However, from day 1 to day 7 days after surgery, MMSE scores of three groups showed a trend of an initial decrease and then an increase, at 1 and 3 days after surgery respectively. Mini-mental State Examination (MMSE) scores of low-dose groups were significantly higher than medium and high-dose groups ($p < 0.05$). Also, MMSE scores of medium-dose group were significantly higher than high-dose group ($p < 0.05$).

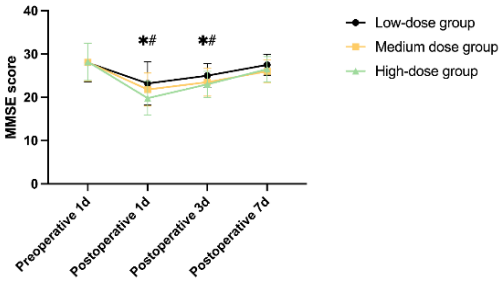

Figure 1: Comparison of cognitive function among the three groups. Compared with low-dose group, *$p < 0.05$; compared with medium-dose group, #$p < 0.05$. 1 d (One day), 3 d (three days), 7 d (seven days)

Sedative and analgesic effects

Visual analogue scale (VAS) and Ramsay scores were not significantly different ($p > 0.05$) at the 4th h after recovery among three groups (Figure 2 A and B). However, from the 12th to 48th h after recovery, VAS scores of three groups showed a trend of first increasing and then decreasing (Figure 2 A). At 12th and 24th h after recovery, VAS score of low-dose group was significantly higher than medium-dose and high-dose groups, while medium-dose group was significantly higher than high-dose group ($p < 0.05$; Figure 2 C).

From 12th to 48th h after awakening, Ramsay score of three groups showed a downward trend, but low-dose group was significantly lower than medium-dose and high-dose groups, while medium-dose group was significantly lower than high-dose group ($p < 0.05$; Figure 2 D).

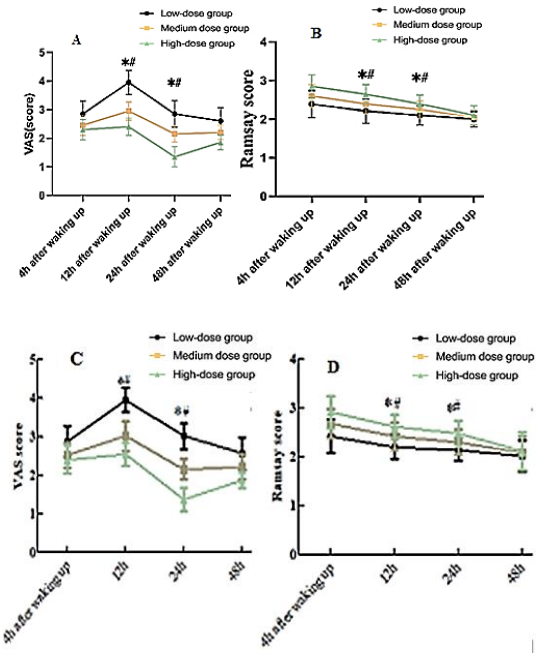

Figure 2: Comparison of sedative and analgesic effects among three groups. Compared with low-dose group, *$p < 0.05$; compared with medium-dose group, #$p < 0.05$

Stress levels

There was no significant difference in levels of NE, E and COR 24 h before surgery ($p > 0.05$). However, levels of NE, E and COR in three groups were significantly higher 24 h after surgery compared to 24 h before surgery ($p < 0.05$). Also, levels of NE, E and COR in medium-dose group were significantly lower than in low and high-dose groups ($p < 0.05$; Table 2).

Adverse reactions

Total incidence of adverse reactions in low-dose and medium-dose groups was significantly lower than that high-dose group ($p < 0.05$). There was no significant difference in incidence of adverse reactions between low-dose and medium-dose groups ($p > 0.05$; Table 3).

Table 2: Comparison of stress levels

Group	N	NE (ng/mL)		E (ng/mL)		COR (ng/mL)	
		24 h before surgery	***24 h after surgery***	***24 h before surgery***	***24 h after surgery***	***24 h before surgery***	***24 h after surgery***
Low-dose	35	0.25±0.05	0.89±0.04*	0.12±0.07	0.89±0.10*	90.21±10.14	168.34±19.33*
Medium-dose	39	0.28±0.09	0.60±0.08*#	0.15±0.05	0.50±0.06*#	91.56±11.55	121.30±18.65*#
High-dose	38	0.26±0.06	0.85±0.06*&	0.14±0.06	0.86±0.07*&	91.98±10.87	165.10±17.32*&
F-value		1.808	236.695	2.353	296.416	0.260	77.255
P-value		0.169	<0.001	0.100	<0.001	0.771	<0.001

Compared with 24 h before surgery, *$p < 0.05$; compared with low-dose group, #$p < 0.05$; and compared with medium-dose group, &$p < 0.05$. Values are presented as mean ± S.D

Table 3: Comparison of adverse reactions

Group	N	Nausea	Vomiting	Respiratory depression	Arrhythmia	Total incidence of adverse reactions
Low-dose	35	1 (2.86)	0	0	0	1 (2.86)*
Medium-dose	39	1 (2.56)	0	0	1 (2.56)	2 (5.13)*
High-dose	38	1 (2.63)	2 (5.26)	3 (7.89)	2 (5.26)	8 (21.05)
χ^2						8.299
P-value						0.016

Compared with high dose group, *$p < 0.05$. Values are presented as N (%)

DISCUSSION

Convalescence period of general anesthesia refers to the period when administration of anesthetic drugs is stopped when the patient wakes up. During this period, several factors such as decreased anesthetic effect, increased wound pain and catheter irritation, and various clinical complications such as delayed recovery, nausea, vomiting, and delirium are likely to occur, which affect both health and postoperative recovery of patients [13,14]. Once handled improperly, patients may have a strong stress response, leading to changes in circulatory and respiratory systems, and in severe cases, is life-threatening. It is therefore of great importance to select an appropriate anesthesia analgesic program that will reduce stress response and improve anesthesia recovery period. As a common adrenergic receptor agonist in clinical anesthesia, dexmedetomidine has a central anti-sympathetic effect, which produces sedative effect similar to natural sleep and also possesses analgesic, diuretic and anti-anxiety effects [15,16].

Dexmedetomidine is an adrenergic agonist widely used in clinical anesthesia. Unlike conventional agonists, it has a dual effect, as it antagonizes sympathetic nervous system and reduces sympathetic activity while providing powerful sedative and hypnotic effects. This makes it widely applicable before and after surgery, helping to maintain patient's physiological stability and thus reducing risk of postoperative complications. Dexmedetomidine is highly valuable in clinical practice. Previous studies have shown that dexmedetomidine activates A2a adenosine receptors, thereby inhibiting the release of adrenaline [17]. At same time, activation of α2B receptor leads to vasoconstriction. Continuous pumping of drugs increases activity of vagus nerve, participates in human circulation, and acts as nerve fiber receptors, thus achieving good analgesic, calming and organ protective effects, but no obvious inhibitory effect on respiratory system center.

This study revealed that there was no significant difference in quality of recovery during anesthesia (tracheal catheter removal time, spontaneous breathing time, calling eye-opening time, and full wakefulness time) among treatment groups. Perioperative stimulation transmission to central system causes hemodynamic fluctuations in patients, affects postoperative respiratory recovery, prolongs tracheal catheter extubation time, increases risk of postoperative complications, and leads to adverse clinical outcomes [18]. Therefore, it is important to select appropriate doses of anesthetic drugs that will promote postoperative recovery and shorten extubation time to ensure a good prognosis. Results of this study showed that there was no significant difference among groups of patients in convalescent period of general anesthesia, indicating that different doses of dexmedetomidine had similar effects and that dose differences would not affect tracheal

catheter extubation and spontaneous respiratory recovery.

Delirium is a common neurological reaction in surgery, which is often related to a patient's age, position, anesthesia and other factors, such as postoperative infections, drug use, metabolic disorders, cardiovascular problems, neurological disorders, drug withdrawal, and sensory deprivation. Elderly patients have a high incidence of postoperative delirium due to hypoplasia of their central nervous system [19]. Results of this study showed that there was no significant difference in the number of postoperative delirium cases in low-dose, medium-dose and high-dose groups when compared. Previous studies have shown that the application of dexmedetomidine during general anesthesia in elderly patients can significantly reduce incidence of postoperative delirium [20] which is not consistent with the findings of this study. This may be attributed to small sample size selection, thus hopefully the sample size will be expanded in the future for further research.

This study showed that MMSE score initially decreased followed by an increase from 1 to 7 days after surgery, and at 1 and 3 days after surgery, MMSE score of low-dose group was higher compared to medium and high-dose groups, while that of medium-dose was higher than those of high-dose group. Mini-mental State Examination (MMSE) score is a tool commonly used in clinical evaluation of patient's cognitive function. In this study, administration of low-dose dexmedetomidine reduced cognitive function impairment in elderly patients. This indicated that lower dose of dexmedetomidine lessens its side effects on neurocognitive function of patients. This is an important advantage because elderly patients with concomitant diseases and physical function degradation, are prone to postoperative cognitive dysfunction. However, it is noteworthy that a low dose of dexmedetomidine has relatively less stimulation on nerve tissue, which may be the reason for better recovery of MMSE scores in low-dose group.

Patients under general anesthesia often have severe pain after surgery, which alters stability of body's internal environment and affects postoperative rehabilitation process. In this study, from 12^{th} to 48^{th} h after recovery, VAS scores initially increased and then started to decrease at 12^{th} and 24^{th} h after recovery across groups. The visual analogue scale (VAS) of low-dose group was higher than other groups, also VAS score of medium-dose group was higher than high-dose group. From 12^{th} to 48^{th} h after awakening, Ramsay's score showed a downward trend, but scores of low-dose group were lower than medium and high-dose groups. Also, scores of medium-dose group were lower than high-dose group. On absorption into systemic circulation, dexmedetomidine participates in circulation and stimulates α2 receptors in central nervous system, thus reducing release of pain neurotransmitters. At same time, it partially blocks conduction function of pain nerves and acts on α2 receptors in brain locus coeruleus, reducing release of norepinephrine in the body and hence achieving effective analgesia and sedation during surgery [21]. Results of this study showed that increasing doses of dexmedetomidine produced better analgesic and sedative. This might be due to longer metabolism time following an increase in dose; hence sedation and analgesia are maintained for a longer time.

In this study, levels of NE, E and COR were significantly higher 24 h after surgery than 24 h before surgery but were lower in medium-dose group. Cortisol (COR), epinephrine (E), and norepinephrine (NE) are all important physiological indicators to evaluate stress response levels. Surgery and pain, as external stressors lead to physiological responses that improve sympathetic nerve excitability, thus resulting in abnormal changes in levels of COR, E and NE [22]. Results of this study revealed that medium-dose dexmedetomidine had greatest effect in improving postoperative stress response in elderly patients and thus possesses an obvious anti-stress response effect. The reason may be that dexmedetomidine has an inhibitory effect on secretion of norepinephrine and regulates activity of neurons to a certain extent, thus reducing stress levels.

Also, this study showed that total incidence of adverse reactions in low-dose and medium-dose groups was lower in high-dose group, and there was no significant difference across groups. Low-dose and medium-dose groups have better safety compared to high-dose group. This is because, low-dose dexmedetomidine has relatively little effect on human physiology and hemodynamics, and minimal effect on respiratory muscle and nerve functions.

Limitations of this study

This study has several limitations. The sample size was relatively small, which may limit generalizability of results. This study adopted a retrospective design and cannot determine cause and effect, but can only observe correlation. Additionally, patients may have differences in clinical characteristics and medical history, and

these factors may affect these findings. This study mainly focused on short-term effects and further research is needed to verify long-term effects. Finally, although many potential confounding factors were controlled other factors not considered may still have an impact.

CONCLUSION

Different doses of dexmedetomidine have good effect on quality of general anesthesia in the convalescent period of elderly patients undergoing lower extremity surgery and do not increase the incidence of postoperative delirium. Low-dose dexmedetomidine has relatively little effect on cognitive function of patients, while high-dose shows better sedative and analgesic effect, although it is prone to postoperative adverse reactions. Medium-dose dexmedetomidine, apart from possessing good sedative and analgesic effect, exhibits relatively little negative effect on cognitive function and stress response in elderly patients, with no noticeable adverse reactions. It also possesses good efficacy and safety. More large-scale, randomized controlled studies are needed to validate these findings.

DECLARATIONS

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Ethical approval

This study received ethical approval from Affiliated Hospital of Inner Mongolia Medical University (approval no. 20-ZA-12).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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