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Original Article

Effects of Dexmedetomidine on the Incidence of Postoperative Delirium and Plasma S-100β Protein Levels Following Hip Surgery in the Elderly Population

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SUMMARY

Background: To evaluate the effects of dexmedetomidine on the incidence of postoperative delirium (POD) and plasma S-100β protein levels in elderly patients undergoing hip surgery.
Methods: A total of 110 elderly patients who underwent hip surgery were enrolled in this study and grouped using the random number table method. The study group (55 patients) received 0.5 μg/kg dexmedetomidine before anesthesia induction and the control group (55 patients) received an equal dose of 0.9% sodium chloride injection before anesthesia induction.
Results: Compared with the control group, the study group had lower fentanyl and propofol consumption, shorter time to waking up, shorter time to respiratory recovery, shorter extubation time, and lower incidence of POD ($p < 0.05$). Mean arterial pressure, oxygen saturation, and heart rate at T_1 and T_2 were lower than those at T_0 in the control group as well as lower than those in the study group at the same time point ($p < 0.05$). Both groups showed higher S-100β levels at T_1, T_2, and T_3 compared with those at T_0 ($p < 0.05$); however, the levels were lower in the study group than in the control group at the abovementioned time points ($p < 0.05$).
Conclusion: Dexmedetomidine could decrease the consumption of anesthetic drugs, shorten postoperative recovery time, stabilize hemodynamics, decrease adverse reactions caused by anesthesia, and decrease the incidence of POD, which may be achieved by improving cerebral metabolism, regulating serum S-100β levels.

1. Introduction

The hip joint is a ball-and-socket synovial joint formed by an articulation between the acetabulum and femoral head. It is primarily innervated by the sciatic, femoral, and obturator nerves. Hip surgery is an effective surgical procedure to correct deformities caused by fractures and helps restore joint function, minimizes pain levels, and maintains joint mobility.[1,2] However, owing to heavy bleeding and long operation time, coupled with decreased cardiovascular function and osteoporosis in elderly patients, hip surgery can easily result in hemodynamic fluctuations and induce stress and inflammatory responses, leading to decreased immune function, psychological stress, and endothelial dysfunction and increased risk of postoperative complications.[3,4] Postoperative delirium (POD) is a common complication following hip joint surgery in the elderly population. The incidence of POD after hip surgery in patients aged > 65 years ranges from 4% to 53%. Patients with POD are mainly manifested by inattention, altered consciousness, and emotional and cognitive dysfunction, which not only impairs patients' cognitive function but also increases the risk of complications, such as pulmonary infection and artificial joint loosening, as well as prolongs recovery time.[5] Therefore, it is particularly important to explore safe anesthetic modalities and anesthetic drugs to decrease the incidence of postoperative complications.

As an α2 adrenergic receptor-selective agonist, dexmedetomidine functions as a neuroprotectant, analgesic, sedative, anxiolytic, and sympathetic inhibitor and is widely used in anesthesia for neurosurgery.[6,7] It can protect patients by decreasing central adrenaline and norepinephrine levels, inhibiting sympathetic nerve activity, decreasing inflammation, regulating cerebral metabolism, decreasing stress responses, and decreasing cerebral oxygen uptake rate, which could protect nerve function and prevent complications.[8] S-100β protein is an acidic calcium ion-binding protein that can enhance memory and learning ability. Elevated serum S-100β protein levels can directly affect neurons or via microglial activation to induce neuronal apoptosis; therefore, it can be used as a marker to reflect early cerebral injury.[9] This study analyzed the effects of dexmedetomidine on the incidence of POD and plasma S-100β protein levels following hip surgery in the elderly population with the aim of guiding the rational application of clinical anesthesia.

2. Material and Methods

2.1. Clinical data

A total of 110 elderly patients who underwent hip surgery at

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our hospital from March 2019 to April 2020 were included in this study. They were grouped using the random number table method into the control and study groups (55 patients in each group). The inclusion criteria were age ≥ 60 years; requiring hip surgery due to hip fracture; absence of cardiopulmonary abnormalities; Class I and II by the American Society of Anesthesiologists (ASA); clear consciousness and ability to communicate and read; and voluntary provision of informed consent. The exclusion criteria were presence of coagulation disorders; combination of chronic and acute infections before surgery; recent treatment with immunosuppressants, sedatives, hormones, and antibiotics; allergic to anesthesia; history of heart disease; presence of atrioventricular conduction block and sinus bradycardia; severe visual and hearing impairments; cognitive dysfunction; concomitant immune system and endocrine system diseases; and contraindications to hip surgery. This study was approved by the ethics committee of General Hospital of Taiyuan Iron & Steel (Group) Co., Ltd. All patients or their families were informed of the study and signed the written informed consent prior to participating in the study.

2.2. Methods

After 6 h of fasting for water, venous access was established and vital signs, such as pulse and blood pressure, were monitored. An atropine sulfate injection was intramuscularly administered at a dose of 0.01 mg/kg before anesthesia induction. Before anesthesia induction, the study group was injected with 0.5 μg/kg dexmedetomidine (2 mL: 200 μg, C13H16N2, Shandong Hilkant Pharmaceutical Co.). The control group was injected with an equal dose of 0.9% sodium chloride injection via an infusion pump for 15 min. Anesthesia induction: tracheal intubation was performed after intravenous injection of 0.03 mg/kg midazolam, 1.5 mg/kg propofol, 0.1 mg/kg vecuronium bromide and 0.3 μg/kg sufentanil. Before skin incision, 0.3 μg/kg sufentanil was added. Anesthesia maintenance: inhalation of 0.5%-1% sevoflurane, 0.1-0.25 μg/ (kg·h) remifentanil, and 2-4 mg/ (kg·h) propofol. The skin was sutured and connected to an intravenous patient-controlled analgesia pump.

2.3. Outcome measurements

(1) Anesthesia-related indicators. The consumption of fentanyl and propofol, time to waking up, time to respiratory recovery, and extubation time were recorded in both groups.
(2) Hemodynamics. Mean arterial pressure (MAP), oxygen saturation (SaO_2), and heart rate (HR) were continuously measured using the Solar 8000M multifunctional monitor in both groups 5 min after admission (T_0), at the time of sectioning (T_1), immediately after surgery (T_2), and 6 h after surgery (T_3).
(3) Laboratory parameters. Five milliliters of peripheral blood was collected from the patients at the four mentioned time points and was centrifuged at 3000 rpm for 15 min. The supernatant was obtained and stored in a -20 °C refrigerator. Serum S-100β levels, brain-derived neurotrophic factor (BDNF), and tropomyosin receptor kinase B (TrkB) levels were measured via enzyme-linked immunosorbent assay. Blood samples from the radial artery and internal jugular venous bulb were collected at the four mentioned time points, and jugular venous oxygen saturation ($SjvO_2$), SaO_2, arteriovenous oxygen difference (Ca-jvO_2), internal jugular venous O_2 content (i$CjvO_2$), and cerebral extraction ratio for oxygen ($CERO_2$) were determined using a blood gas analyzer according to the FICK formula: Ca-jvO_2 = CaO_2 – $CjvO_2$; $CjvO_2$ = hemoglobin (Hb) × $SjvO_2$ × 1.34 + $PjvO_2$ × 0.0031; and $CERO_2$ = Ca-jvO_2/CaO_2 × 100%, where CaO_2 = Hb × SaO_2 × 1.34 + PaO_2 × 0.0031.
(4) POD and adverse reactions. The diagnostic criterion of POD was based on the Chinese Expert Consensus on the Prevention and Treatment of Postoperative Delirium in Elderly Patients,[10] and the adverse reactions were hypotension, tachycardia, and gastrointestinal reactions.

2.4. Statistical analysis

Using Statistical Package for the Social Sciences (SPSS) 23.0, the measurement data conforming to normal distribution were expressed as $\bar{x} \pm s$. Between-group comparisons were performed using the independent samples *t*-test and within-group comparisons were performed using the paired samples *t*-test. Count data were expressed as % and were compared using the χ^2 test. A *p*-value of < 0.05 indicated that the difference is significant.

3. Results

3.1. General information

There were no significant differences ($p > 0.05$) in sex, age, body mass index, operation time, intraoperative bleeding volume, ASA grade, and lesion site between the two groups (Table 1).

3.2. Anesthesia-related indicators

Compared with the control group, the study group had lower consumption of fentanyl and propofol, shorter time to waking up and respiratory recovery, and shorter extubation time ($p < 0.05$), indicating that dexmedetomidine could decrease the consumption of anesthetics and shorten recovery time (Figure 1).

3.3. Hemodynamic parameters

The differences in MAP, SaO_2, and HR at T_0 were not significant between the two groups ($p > 0.05$). In addition, MAP, SaO_2, and HR did not differ at the different time points in the study group ($p > 0.05$). On the other hand, MAP, SaO_2, and HR at T_1 and T_2 were lower than those at T_0 in the control group as well as lower than those in the study group ($p < 0.05$), indicating that dexmedetomidine could maintain intraoperative hemodynamic stability in elderly patients (Figure 2).

3.4. Indicators related to cerebral metabolism

The differences in $SjvO_2$, Ca-jvO_2, $CjvO_2$, and $CERO_2$ at T_0 were not significant between the two groups ($p > 0.05$). However, $SjvO_2$

Table 1
Comparison of patient characteristics of the two groups.

Group	No. of patients	M/F	Age (years)	Body mass index (kg/m^2)	Operation time (min)	Intraoperative bleeding (mL)	ASA classification	Site of the lesion
							Class II/III	Left hip/right hip
Control group	55	28/27	69.15 ± 3.76	20.16 ± 2.54	126.57 ± 15.19	403.84 ± 38.16	31/24	29/26
Study group	55	30/25	68.28 ± 3.95	21.13 ± 2.06	124.65 ± 17.26	407.16 ± 39.64	29/26	27/28

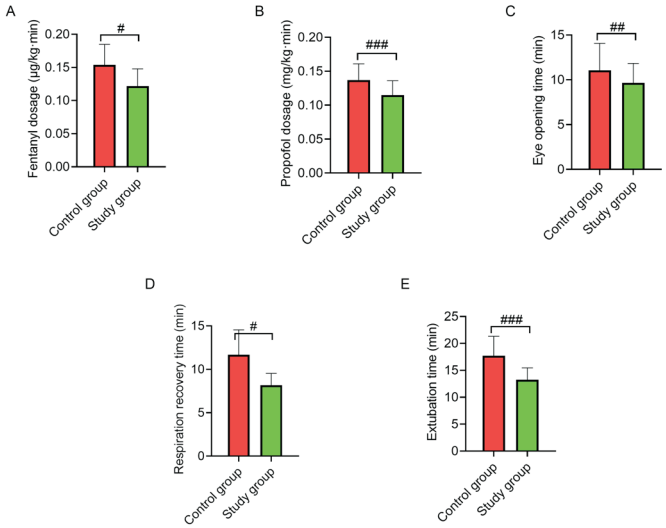

Figure 1. Comparison of anesthesia-related indicators between the two groups. Note: (A) fentanyl consumption, (B) propofol consumption, (C) time to waking up, (D) respiratory recovery time, and (E) extubation time. Compared with the control group, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$.

was higher at T_1, T_2, and T_3 than at T0, whereas Ca-jvO_2 and CERO_2 were lower at T_1, T_2, and T_3 than at T_0 in the study group ($p < 0.05$) and were better than those in the control group ($p < 0.05$). In the two groups, CjvO_2 was lower at T_1, T_2, and T_3 than at T_0 ($p < 0.05$), indicating that dexmedetomidine could improve cerebral metabolism-related parameters (Figure 3).

3.5. S-100β and BDNF/TrkB signaling pathway

The differences in S-100β, BDNF and TrkB levels at T_0 were not significant between the two groups ($p > 0.05$). S-100β levels were higher at T_1, T_2, and T_3 than at T_0 in the two groups ($p < 0.05$), but S-100β levels were lower in the study group than in the control group at the time points above. Furthermore, in the study group, BDNF and TrkB levels were higher at T_1, T_2, and T_3 than at T_0, and were higher than those in the control group ($p < 0.05$), indicating that dexmedetomidine could regulate serum S-100β levels and exert cerebral protection by upregulation of the expression of the BDNF/TrkB signaling pathway (Figure 4).

3.6. POD and adverse reactions

The incidence of POD was lower in the study group than in the control group within 24 h after surgery ($p < 0.05$). On the other hand, the incidence of adverse reactions was not significantly different between the two groups ($p > 0.05$). These results suggest that dexmedetomidine can prevent POD in elderly patients without increasing the incidence of adverse reactions (Table 2).

4. Discussion

During hip surgery, pressure in the bone marrow cavity can re-

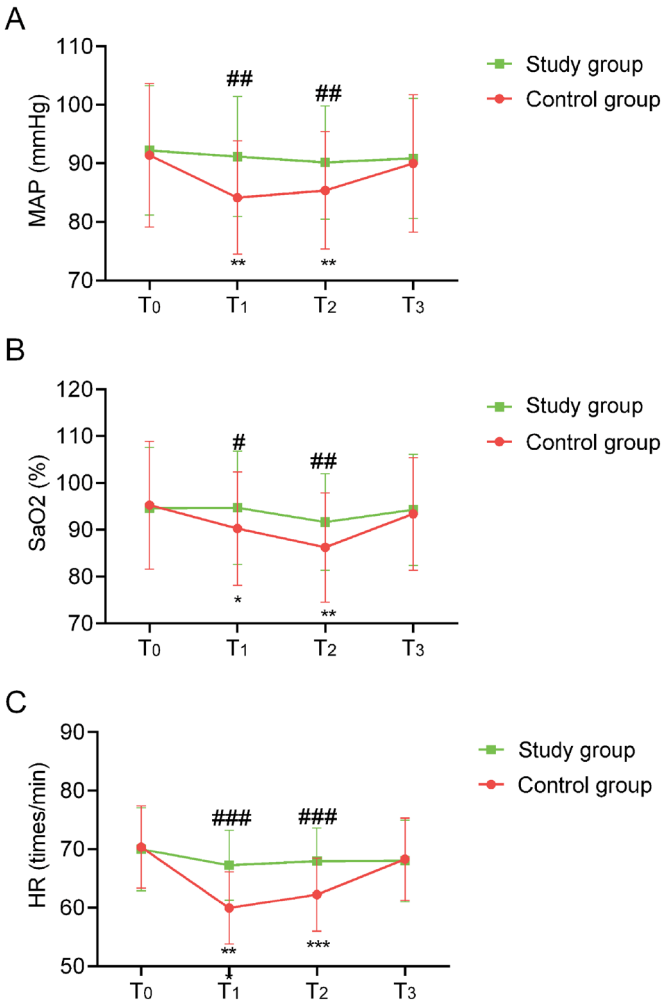

Figure 2. Comparison of hemodynamic parameters between the two groups. Note: (A) MAP, (B) SaO_2, and (C) HR. Compared with the control group at the same time point, $^{\#}p < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}p < 0.001$; compared with T_0 in the same group, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

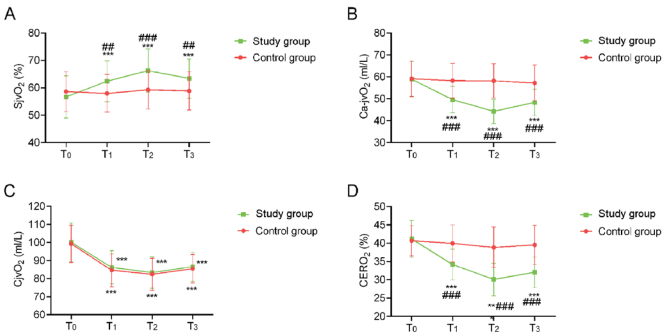

Figure 3. Comparison of cerebral metabolism-related indexes between the two groups. Note: (A) SjvO_2, (B) Ca-jvO_2, (C) CjvO_2, and (D) CERO_2. Compared with the control group at the same time point, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$; compared with T_0 within the same group, $^{***}p < 0.001$.

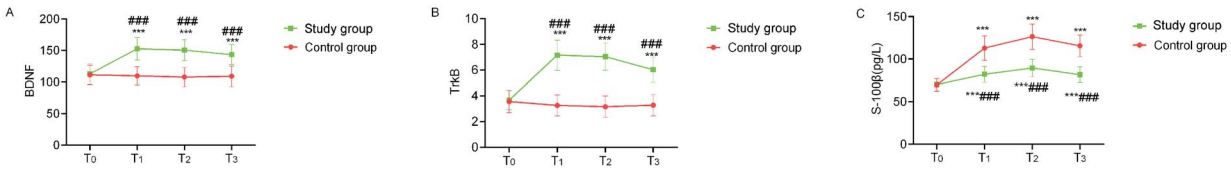

Figure 4. Comparison of the S-100β levels and BDNF/TrkB signaling pathways. Note: (A) BDNF, (B) TrkB levels and (C) S-100β. Compared with the control group at the same time point, $^{\#\#\#}p < 0.001$; compared with T_0 within the same group, $^{***}p < 0.001$.

Table 2
Comparison of POD and adverse reactions in the two groups at 24 h after surgery, n (%).

Groups	No. of patients	POD	Adverse reactions			
			Hypotension	Tachycardia	Gastrointestinal reactions	Incidence
Control group	55	8 (14.55)	1 (1.82)	1 (1.82)	1 (1.82)	3 (5.45)
Study group	55	2 (3.64)$^{\#}$	1 (1.82)	1 (1.82)	3 (5.45)	5 (9.09)

Note: Compared with the control group, $^{\#}$ $p < 0.05$.

sult in the entry of fat particles into the bloodstream, affect cerebral tissue perfusion, and induce cerebral fat embolism and POD.[11,12] POD is caused by many factors, including neurotransmitter abnormalities, anesthetic drugs, central cholinergic system weakness, and degenerative changes in the brain, which affect the postoperative rehabilitation process and quality of life; therefore, research on the mechanism of POD is a clinical hotspot.[13,14] In this study, dexmedetomidine was used in hip surgery to observe its effect on the prevention of POD.

In the present study, the incidence of POD was lower in the study group than in the control group at 24 h after surgery and the incidence of adverse reactions was not significantly different from that in the control group. This indicates that dexmedetomidine can effectively prevent the incidence of POD in the elderly population. The reason may be that dexmedetomidine can highly selectively agitate the central nervous system and peripheral $\alpha 2$ adrenergic receptors, attenuate sympathetic nerve activity, minimize the increase in blood pressure under stress, decrease HR, decrease the synthesis and release of cortisol, effectively maintain cerebral perfusion pressure, and stabilize hemodynamics, thereby preventing POD.[15] Moreover, it can inhibit inflammation of the cerebral tissue caused by ischemia and hypoxia and decrease catecholamine levels, thereby improving cognitive function.[16] Li et al.[17] found that the incidence of adverse reactions in the dexmedetomidine group was significantly lower than that in the sodium chloride group; this inconsistency with the results of the present study may lie in the small sample size of the present study. S-100β protein is mainly found in astrocytes and Schwann cells and is synthesized and secreted by glial cells. When the central nervous system and blood-brain barrier are damaged, serum S-100β protein level increases, which can be used to assess neurological damage.[18] In the present study, S-100β levels at T_1, T_2, and T_3 were lower in the study group than in the control group, indicating that dexmedetomidine prevented neuronal apoptosis by modulating serum S-100β levels. This may be because dexmedetomidine can inhibit the expression of inflammatory factors and minimize the inhibitory effect of inflammatory responses on hippocampal neurons, thereby reducing secondary cerebral injury caused by high levels of inflammatory factors. Dexmedetomidine can also decrease serum complement levels and attenuate cerebral injury caused by the lack of complement, thereby reducing the degree of cerebral injury and exerting a cerebral protective effect.[19,20] Cerebral oxygen demand can be used as an indicator of the degree of cerebral injury and cerebral metabolic status; therefore, it is crucial to closely monitor the changes in cerebral metabolism-related indicators. $SjvO_2$ indicates cerebral oxygen saturation in both hemispheres and ranges from 55% to 75%. $SjvO_2$ of < 55% suggests that the brain is in a state of hypoperfusion or focal ischemia caused by insufficient oxygen supply.[21] In the present study, $SjvO_2$ at T_1, T_2, and T_3 was > 55%, indicating that the patients in the study group had adequate oxygen supply. Ca-jvO_2 and $CERO_2$ can be used as indicators to reflect the status of oxygen consumption. A decrease in these levels indicates that oxygen consumption is weakened and the level of oxygen metabolism is decreased. On the other hand, high levels suggest that cerebral blood flow is relatively sufficient to meet cerebral oxygen demand, thereby exerting a protective effect.[22] Ca-jvO_2 and $CERO_2$ at T_1, T_2, and T_3 were lower than those at T_0 in the study group and were higher than those in the control group, indicating that dexmedetomidine can decrease cerebral metabolism following surgery, decrease oxygen consumption, relatively increase oxygen supply, promote oxygen uptake by neurons, and enhance the tolerance of tissues and cerebral cells, thereby preventing hypoperfusion. Zhou et al.[23] showed that dexmedetomidine could decrease the rate of cerebral oxygen uptake during the rewarming period, alleviate ischemic injury, and prevent the imbalance between cerebral oxygen supply and demand during the rewarming period; these results are basically consistent with those of the present study. BDNF can be induced to increase the levels of antioxidant enzymes against oxidative stress, scavenge oxygen free radicals, and protect the nerves. TrkB also plays a protective role in neurodegenerative diseases caused by oxidative stress. The combination of BDNF and TrkB can activate various signaling pathways, including phospholipase C-γ, phosphatidylinositol-3 kinase, and mitogen-activated protein kinase, which can maintain Ca^{2+} balance in the neurons, inhibit excitotoxicity, and regulate neuronal excitability and the expression of many apoptotic proteins, including caspase-3. In turn, it decreases neuronal apoptosis during cerebral injury and alleviates neurological damage.[24,25] In the present study, BDNF and TrkB levels at T_1, T_2, and T_3 were higher than those at T_0 in the study group as well as higher than those in the control group. Therefore, we speculated that dexmedetomidine plays a protective role by upregulating the expression of the BDNF/TrkB signaling pathway.

In summary, dexmedetomidine could decrease the consumption of anesthetics, shorten recovery time, stabilize hemodynamics, decrease the incidence of adverse reactions, and decrease the incidence of POD, which may be related to improvements in cerebral metabolism, serum S-100β levels, and increase in the expression of the BDNF/TrkB signaling pathway. However, the present study still has some shortcomings, such as small sample size and few time points; therefore, further discussion is still warranted.

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Declarationof interest statement

The authors confirm that there are no conflicts of interest.

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