Int J Clin Exp Med 2020;13(9):6703-6709
www.ijcem.com /ISSN:1940-5901/IJCEM0109926

Original Article

Mechanism of action of dexmedetomidine on hemodynamics, analgesic and sedative effects and postoperative delirium in elderly patients undergoing hip fracture surgery

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Received February 26, 2020; Accepted June 1, 2020; Epub September 15, 2020; Published September 30, 2020

Abstract: Objective: The research in this paper was to explore the mechanism of action of dexmedetomidine on hemodynamics, analgesic and sedative effects, and postoperative delirium in elderly patients undergoing hip fracture surgery. Methods: A total of 120 elderly patients with hip fracture were retrospectively analyzed for clinical data and divided into two groups based on anesthetics: Patients in group A (n=62) were given 0.5 μg/kg dexmedetomidine as loading dose followed by 10 min later anesthesia induction before maintenance dose of 0.4 $\mu g.kg^{-1}.h^{-1}$. Patients in group B (n=58) were given the same amount of normal saline. The bispectral index (BIS), diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR), Price-Henry pain score, Ramsay sedation score, postoperative delirium and intraoperative use of anesthetic drugs were compared between the two groups at different time points. Results: At T4 and T5, DBP in group A were lower than those in group B; the overall fluctuation of DBP in group A was smaller than that in group B. The same was true for SBP, and HR. Scores on the Price-Henry pain scale in group A were notably lower than those in group B as specified 10 min, 1 h, and 6 h after operation ($P<0.05$). Little difference was found in Post-operative Ramsay scores for sedation ($P>0.05$). The incidence of postoperative delirium in group A was 6.45% (4/62), which was lower than that of 41.37% (24/58) in group B, showing significant difference ($P<0.05$). Conclusion: Dexmedetomidine is conducive to lowering the incidence of post-operative delirium in elderly patients undergoing hip fracture surgery, which keeps perioperative haemodynamics and therefore ideal analgesic and sedative effects.

Keywords: Dexmedetomidine, elderly, hip fracture surgery, postoperative delirium, mechanism of action

Introduction

Postoperative delirium is clinically classified as acute encephalopathy syndrome. Most occurs 3-5 days after the related surgery. The course of the disease is fluctuating and mainly manifested as cognitive decline and attention disorders, especially in elderly patients [1, 2]. In general, the onset of postoperative delirium is followed by a series of cascading events that increase postoperative complications, patient disability and mortality [3].

In recent years dexmedetomidine serves as α2 adrenoreceptor agonist. Concentrated in the medulla oblongata and pons α2 adrenoreceptor plays an important role in sympathetic signaling [4, 5]. Stimulation to presynaptic α2 adrenoreceptor regulates the release of adrenaline by negative feedback. Stimulation to postsynaptic α2 adrenoreceptor promotes the hyperpolarization of nerve cell membranes [6]. For the past few years, the aging of population in China leads to more geriatric hip fracture [7], which is in general treated with surgeries that unfortunately causes postoperative delirium often [8]. Postoperative delirium increases the incidence of venous thrombosis, pulmonary infections, and bedsores, followed by complications such as falls, internal fixation breaking or loosening and even depression of the patient. Hence, scientific sedation is necessary for the treatment and nursing of elderly patients undergoing surgeries [9, 10].

In order to prevent post-operative delirium in elderly patients undergoing hip fracture surgery and maintain perianesthesia hemodynamics, dexmedetomidine was used in this study to test the effect on such disease as compared with the use of normal saline.

Material and methods

Material

A total of 120 elderly patients with hip fracture admitted to our hospital during January 2018-January 2020 were retrospectively analyzed for clinical data and divided into two groups based on anesthetics: Patients in group A (n=62) were given 0.5 μg/kg dexmedetomidine as loading dose followed by 10 min later anesthesia induction before maintenance dose of 0.4 $\mu g.kg^{-1}.h^{-1}$. 29 patients in group B (n=58) were given the same amount of normal saline. (1) Inclusion criteria: patient with age ≥ 65 years; >24 on preoperative MMSE scale; did not use any drugs affecting delirium before the surgery; was classified as ASA I-II; was free of severe cardiovascular and cerebrovascular or respiratory diseases. The research in this paper was approved by the Ethics Committee of Yichun People's Hospital. All patients have signed the informed consent. (2) Exclusion criteria: patient who was allergic to drugs; or has existing mental and cognitive dysfunction; or has a history of recovery from abnormal anesthesia; or has been using long-term sedative medication; or has severe hepatic and renal dysfunction.

Methods

No use of drugs for the two groups of patients before surgery. In the operating room, intravenous access was rapidly available so as to closely monitor Bispectral index (BIS), diastolic blood pressures (DBP), systolic blood pressure (SBP), and heart rate (HR). Following local anesthesia, a catheter was placed in the left radial artery for invasive blood pressure monitoring. Patients in group A were given 0.5 μg/kg loading dose from 2 mg of dexmedetomidine hydrochloride injection (Manufacturer: Heng Rui Pharmaceutical Co., Ltd. Approval number: SFDA H20090248 Specification: 2 ml: 200 ug) in 50 ml normal saline, followed by 10 min later anesthesia induction before maintenance dose of 0.4 $\mu g.kg^{-1}.h^{-1}$. Patients in group B were given the same amount of normal saline. The anesthesia induction in both groups: 0.08 mg/kg vecuronium bromide (Approval No.: SFDA H20-133079 Manufacturer: Yichang Humanwell Pharmaceutical Co., Ltd. Specification: 4 mg), 1.5 mg/kg propofol injection (Approval No.: SFDA H20010368 Manufacturer: Xi'an Libang Pharmaceutical Co., Ltd. Specification: 10 ml: 100 mg), 0.4 μg/kg sufentanil citrate injection (Approval No.: SFDA H20054171 Manufacturer: Yichang Humanwell Pharmaceutical Co., Ltd. Specification: 1 ml: 50 μg), 0.02 mg/kg midazolam injection (Approval No.: SFDA H10-980025 Manufacturer: Jiangsu Nhwa Pharmaceutical Co., Ltd. Specification: 2 ml: 10 mg × 5). The induction continued for 5-10 min during which 5 ml/kg hydroxyethyl starch sodium chloride injection (Approval No.: SFDA H20-103246 Manufacturer: Fresenius Kabi (Beijing) Specification: 500 ml: 30 g) was used for dilatation. In the absence of special circumstances, 1-2 $ml.kg^{-1}.h^{-1}$ sodium lactate Ringer's solution (Approval No.: SFDA H20057107 Manufacturer: Cisen Pharmaceutical Co., Ltd. Specification: 500 ml/bottle) was applied. If the blood pressure was <30% of the basal value, 0.1 mg/kg ephedrine hydrochloride injection (Approval No.: SFDA H20133025 Manufacturer: Shandong Luoxin Pharmaceutical Co., Ltd. Specification: 2 ml: 15 mg) was sued. If the heart rate was <50 beats/min, 0.2-0.5 mg atropine sulfate injection (Approval No.: SFDA H31021172 Manufacturer: Shanghai Harvest Pharmaceutical Co., Ltd. Specification: 1 ml: 0.5 mg) was used. If the blood pressure was >30% of the basic value, 0.5 $\mu g.kg^{-1}.h^{-1}$ nitroglycerin injection (Approval No.: SFDA H20073990 Manufacturer: Beijing Yanjing Pharmaceutical Co., Ltd. Specification: 1 ml) was pump injected in addition to regulation of dose of nitroglycerin based on the patient's blood pressure. The standard disposable laryngeal mask airway connected to the ventilator offered volume-controlled breathing. Appropriate tidal volume and breathing frequency kept the PetC0 at 30-40 mmHg. By propofol BIS was maintained as 40-60. At the same time, the patients were intravenously injected with 0.1-0.3 μg/kg sufentanil (Approval No.: SFDA H20054171 Manufacturer: Yichang Humanwell Pharmaceutical Co., Ltd. Specification: 5 ml: 250 μg × 5) intermittently to hold the intraoperative heart rate at 55-80 beats/min and the blood pressure within the range

Table 1. General data of patients in both groups [n (%)]/($\bar{x}$ ± sd)

Item		Group A (n=62)	Group B (n=58)	t/X^2	*P*
Sex (case)	M	36 (58.06)	32 (55.17)	0.051	0.821
	F	26 (41.94)	26 (44.83)		
Age (year)		72.15±0.28	72.06±0.22	1.378	0.174
BMI (kg/m^2)		22.15±0.85	22.19±0.82	0.185	0.854
MMSE (score)		28.56±1.28	28.69±1.15	0.413	0.681

of ±30% of the basic value. Before suturing and incision operations, patients were intravenously injected with 50 mg Flurbiprofen Axetil injection (Approval No.: SFDA H20041508 Manufacturer: Beijing Tide Pharmaceutical Co., Ltd. Specification: 5 ml: 50 mg × 5/box). Half an hour before the end of the operation, dexmedetomidine pumping was stopped and when the patient woke up, the laryngeal mask was removed.

Outcome measures

(1) BIS, DBP, SBP, and HR were measured respectively at T1 (entering the surgery room), T2 (after the injection of normal saline or the loading dose of dexmedetomidine), T3 (after laryngeal mask wearing), T4 (10 min since the start of the surgery), T5 (upon the laryngeal mask was removed), and T6 (when leaving the surgery room).

(2) Price-Henry pain scale [11]: which was applied at 10 min, 1 h, 6 h, 24 h, and 48 h respectively after surgery. 0, no pain when coughing; 1, cough with pain; 2, no pain at rest but feel pain when in deep breath; 3, mild pain at resting state; and 4, acute pain at resting state.

(3) Ramsay score for sedation [12]: which was applied at 10 min, 1 h, 6 h, 24 h, and 48 h respectively after surgery with a total score of 1-6. 1, dysphoria; 2, cooperative; 3, responsive to instructions with unclear pronounce; 4, arousable sleeping; 5, slow in reacting to calling; 6, in anesthesia or deep sleep and nonresponsive to calling.

(4) Postoperative delirium [13, 14]: strictly following the evaluation criterion: (1) acute onset with and fluctuating condition; (2) inattention or absent-minded; (3) messy mind and disordered; (4) significant changes in consciousness. In addition to (1) and (2), (3) or (4) indicated delirium.

Statistics

SPSS 22.0 was used for statistical analysis. Measurement data were expressed as mean ± standard deviation where those following the normal distribution were subject to *t* test; otherwise Mann-Whitney U was applied. Enumeration data was expressed in [n (%)]. Comparison between groups was performed by X^2 test. P<0.05 indicated statistical significance.

Results

Comparison of general data in both groups

No significant difference was found between the two groups in gender, age, BMI, MMSE score and other general information (P>0.05) (**Table 1**).

Comparison of BIS in both groups

BIS in group A recorded at T1, T2, T3, T4, T5, and T6 were 96.52±2.16, 90.75±3.25, 56.96±6.12, 50.42±5.19, 88.96±8.15, and 96.52±2.63, respectively. These were no differences from those in group B: 96.59±2.12, 90.82±3.22, 55.86±7.15, 49.99±6.15, 90.12±8.25, and 95.96±2.99 separately (P<0.05). For both groups, BIS at T3 and T4 was reduced and significantly different from that at T1 (P<0.05) (**Figure 1**).

Dexmedetomidine reduces the fluctuation of DBP

DBP at T1, T2, and T3 in group A were 68.45±6.12 mmHg, 65.25±9.15 mmHg, and 63.95±8.56 mmHg respectively. DBP at T1, T2, and T3 in group B were 68.12±6.09 mmHg, 65.29±9.06 mmHg, and 63.98±8.53 mmHg respectively. By contrast, DBP at T4 and T5 in group A: 64.15±8.15 mmHg, 68.02±8.88 mmHg, were notably different from those in group B: 85.69±9.15 mmHg, 83.69±9.36 mmHg (P<0.05). At T6, DBP in group A was 77.45±8.18 mmHg, which was not different from that in group B (78.02±8.06 mmHg) (P>0.05). Overall, the fluctuation of DBP in group A was smaller than that in group B with significant differences (P<0.05) (**Figure 2**).

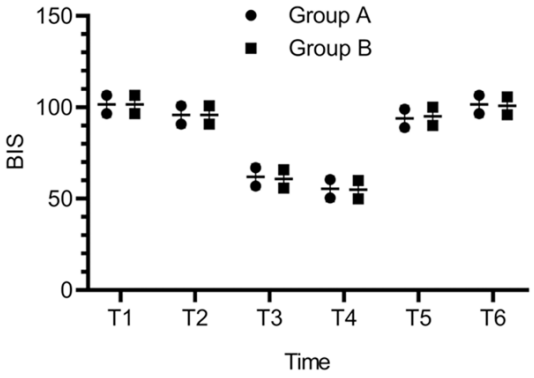

Figure 1. BIS of patients in both groups. BIS at T1, T2, T3, T4, T5, and T6 showed little differences between the two groups, *P*>0.05.

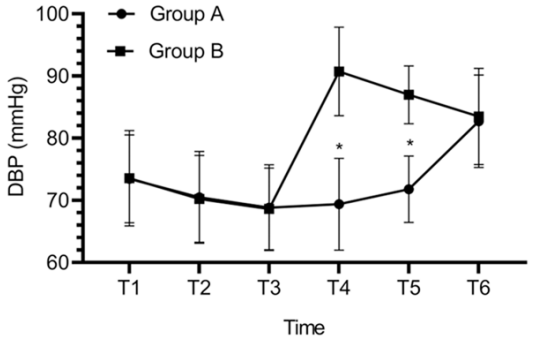

Figure 2. DBP of patients in both groups. DBP at T1, T2, and T3 showed little differences between the two groups, *P*>0.05; The same was true for DBP reported at T6. DBP at T4 and T5 in group A were smaller than those in group B, *P*<0.05. * indicates *P*<0.05 as compared with group B.

Dexmedetomidine reduces the fluctuation of SBP

SBP at T1, T2, and T3 in group A were 136.58±10.25 mmHg, 134.69±10.22 mmHg, and 112.58±8.63 mmHg respectively. SBP at T1, T2, and T3 in group B were 134.56±10.28 mmHg, 135.02±10.26 mmHg, and 128.69±8.76 mmHg respectively. By contrast, SBP at T4 and T5 in group A: 120.12±8.02 mmHg and 130.12±8.88 mmHg, were notably lower than those in group B: 149.96±9.69 mmHg and 150.12±9.98 mmHg (P<0.05). At T6, SBP in group A was 134.52±9.16 mmHg, which was not different from that in group B (134.59±9.11 mmHg) (P>0.05). Overall, the fluctuation of SBP in group A was smaller than that in group B with significant differences (P<0.05) (**Figure 3**).

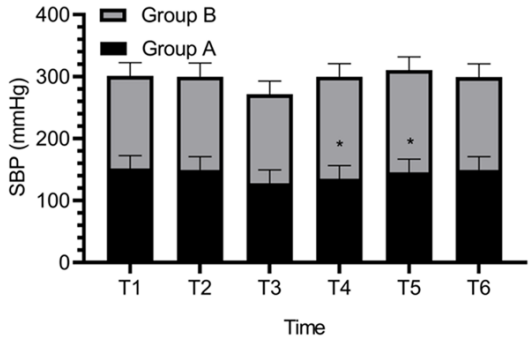

Figure 3. SBP of patients in both groups. SBP at T1, T2, and T3 showed little differences between the two groups, *P*>0.05; The same was true for SBP reported at T6. SBP at T4 and T5 in group A were smaller than those in group B, *P*<0.05. * indicates *P*<0.05 as compared with group B.

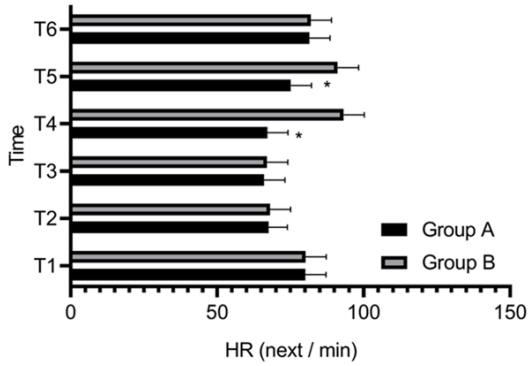

Figure 4. HR of patients in both groups. HR at T1, T2, and T3 showed little differences between the two groups, *P*>0.05; The same was true for HR reported at T6. HR at T4 and T5 in group A were smaller than those in group B, *P*<0.05. * indicates *P*<0.05 as compared with group B.

Dexmedetomidine reduces the fluctuation of HR

HR at T1, T2, and T3 in group A were 75.15±8.16 beats/min, 62.98±6.12 beats/min, and 61.08±8.15 beats/min respectively. HR at T1, T2, and T3 in group B were 75.19±8.22 beats/min, 63.05±6.09 beats/min and 62.01±8.13 beats/min respectively. By contrast, HR at T4 and T5 in group A: 62.13±5.12 beats/min and 70.15±4.52 beats/min, were notably lower than those in group B: 88.18±6.68 beats/min and 86.12±7.58 beats/min. At T6, HR in group A was 76.52±2.12 beats/min, which was not different from that in group B (76.98±2.18 beats/min) (P>0.05). Overall, the fluctuation of

Table 2. Price-Henry pain scores of patients in both groups ($\bar{x}$ ± sd)

Group	10 min after surgery	1 h after surgery	6 h after surgery	24 h after surgery	48 h after surgery
Group A (n=62)	0.96±0.08*	1.32±0.05*	1.96±0.03#,*	2.42±0.21#	2.69±0.25#
Group B (n=58)	2.78±0.32	2.68±0.15	2.85±0.36	2.58±0.63	2.72±0.29
t	30.675	47.749	13.722	1.338	0.430
P	0.000	0.000	0.000	0.786	0.689

Note: #indicates *P*<0.05 as compared with that reported 10 min after surgery; *indicates *P*<0.05 as compared with that in group B.

Table 3. Ramsay score for sedation of patients in both groups ($\bar{x}$ ± sd)

Group	10 min after surgery	1 h after surgery	6 h after surgery	24 h after surgery	48 h after surgery
Group A (n=62)	2.96±0.25	2.63±0.22	2.15±0.19#	2.05±0.16#	1.96±0.12#
Group B (n=58)	2.92±0.28	2.55±0.28	2.09±0.13#	1.98±0.18#	1.92±0.15#
t	0.584	1.235	1.418	1.594	1.144
P	0.561	0.222	0.162	0.116	0.257

Note: #indicates *P*<0.05 as compared with that reported 10 min after surgery.

Table 4. Incidence of postoperative delirium in both groups [n (%)]

Group	Cases	Incidence
Group A	62	4 (6.45)*
Group B	58	24 (41.37)
X^2		10.218
P		0.001

Note: *indicates *P*<0.05 as compared with that in group B.

HR in group A was smaller than that in group B with significant differences (P<0.05) (**Figure 4**).

Dexmedetomidine increases the Price-Henry pain score

The scores in group A were lower than those in group B at 10 min, 1 h, and 6 h after operation (P<0.05). Little difference was found in scores at 24 h and 48 h after operation between the two groups (P>0.05). As compared with the score recorded 10 min after surgery, those reported 6 h, 24 h, and 48 h after surgery increased (P<0.05). As compared with the score recorded 10 min after surgery, there was no significant change in the pain score of group B at 6 h, 24 h and 48 h after surgery (**Table 2**).

Dexmedetomidine decreases Ramsay score for sedation

As compared with the score recorded 10 min after surgery, those reported 6 h, 24 h, and 48 h after surgery decreased for both groups (P<0.05). Overall the Ramsay scores for sedation in the two groups did show remarkable differences (P>0.05) (**Table 3**).

Dexmedetomidine reduces postoperative delirium

The incidence of postoperative delirium in group A was 6.45% (4/62), lower than 41.37% (24/58) in group B (P<0.05) (**Table 4**).

Discussion

Although the specific mechanism of postoperative delirium has not been fully explicated in clinic, some studies have shown that the basal forebrain cholinergic system plays a very important role in the regulation of cognitive functions such as attention, learning and memory, and pathogenesis of postoperative delirium may be the dysfunction of neurotransmitter [15, 16]. Damages to different cholinergic channels may cause various symptoms. Impaired cholinergic function, for example, in the brainstem and frontal cortex leads to disturbance of consciousness, while impaired cholinergic system in the basal ganglia causes memory loss [17]. Clinical studies have also shown that inflammatory responses and cholinergic systems may be the common pathways in delirium [18]. In addition, parasecretion of melatonin and glutamate, excess dopamine, and cholinergic defi-

ciency are also related to delirium [19, 20]. Elderly people are prone to postoperative delirium due to poor body resistance, weakened functions of various organs, combined with basic diseases such as diabetes and hypertension, in addition to the unsatisfactory postoperative pain control effects and insufficient sleep [21]. Patients of advanced age or combined with cerebral disease that causes declined central acetylcholine and therefore poorer bioclock, alertness, learning and memory also are prone to postoperative delirium [22].

Hip fractures are common in the elderly. However, the often used surgical treatment gives rise to post-operative delirium which has a significant impact on recovery. By scholars in general anesthesia studies, BIS monitoring the depth of anesthesia reduces the dose of propofol by 21% and lowers the incidence of postoperative delirium as well as cognitive dysfunction [23]. Postoperative delirium caused by circulatory instability was ruled out.

Dexmedetomidine, considered as an imidazole derivative, is the dextroisomer of medetomidine that serves in stable hemodynamics, antisympathetic, anti-stress response, analgesia, anti-anxiety, and sedation, with slight respiratory depression [24, 25]. In this study, the overall fluctuations of DBP, SBP and HR in group A were less than those in group B ($P<0.05$), suggesting that dexmedetomidine could have effectively held the hemodynamics in patients. This may be explained by the fact that dexmedetomidine imposes two-way regulation on the cardiovascular system, that is, the initial dose of dexmedetomidine affects directly α2 adrenoreceptor to give rise to temporary increased blood pressure and reduced heart rate reflex, and following the continuous low-dose maintenance dosage, the heart rate and blood pressure can be reduced by actions on sympathetic nerves and nervi vagus. In general, dexmedetomidine holds stable hemodynamics without respiratory depression. It is safe in anesthesia maintenance, induction and analepsia related to middle-aged and elderly patients [26]. The results showed that Price-Henry pain scores in group A were lower than those in group B at 10 min, 1 h, and 6 h after surgery ($P<0.05$), suggesting that dexmedetomidine is beneficial for reducing postoperative pain. Postoperative pain is one of the causes of postoperative sleep dysfunction, which is closely correlated with postoperative delirium and irritability. The incidence of postoperative delirium in group A in the study was 6.45% (4/62), lower than 41.37% (24/58) in group B ($P<0.05$). This further demonstrates the effectiveness of dexmedetomidine in the treatment of hip fracture in the elderly and helps to reduce the incidence of postoperative delirium. The underlying mechanism could be the analgesic effect of dexmedetomidine when it binds with central and spinal dorsal horn α2 adrenoreceptors. Besides, dexmedetomidine exerted synergistic effect with sufentanil so as to improve the analgesic effects, which reduced the dosage of sufentanil.

To sum up, dexmedetomidine is conducive to reducing the incidence of post-operative delirium in elderly patients undergoing hip fracture surgery, which keeps hemodynamics and therefore ideal analgesic and sedative effects.

The small sample size in this study determined the bias in the results. Further studies with larger sample size and more comprehensive analyses are warranted.

Disclosure of conflict of interest

None.

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