Int J Clin Exp Med 2018;11(5):4984-4990
www.ijcem.com /ISSN:1940-5901/IJCEM0075571

Original Article

A study of dexmedetomidine in the prevention of postoperative delirium in elderly patients after vertebral osteotomy

Fengyong He[1*], Lili Shen[1*], Jiang Zhong[2]

[1]Department of Anesthesiology, Nanxiang Hospital of Shanghai Jiading District, Shanghai, China; [2]Department of Anesthesiology, Jinshan Hospital Fudan University, Shanghai, China. [*]Equal contributors and co-first authors.

Received March 7, 2018; Accepted April 4, 2018; Epub May 15, 2018; Published May 30, 2018

Abstract: Objective: To study the preventive effect of dexmedetomidine (DEX) on the postoperative delirium (POD) in elderly patients aged over 75 years old after vertebral fracture operation, and its regulating effect on the depth of anesthesia during operation. Methods: A total of 90 patients aged 75-90 years old with vertebral fractures surgically treated under general anesthesia in Nanxiang Hospital of Shanghai Jiading District from January 2015 to December 2017 were enrolled in this study. They were randomly divided into the DEX group (group A, n=30), the midazolam group (group B, n=30) and the control group (group C, n=30). Group A was injected with DEX (0.5 μg/kg) through a pump for 10 min before anesthesia induction, and then the drug was maintained at 0.4 μg/(kg·h) until the end of operation; group B received intravenous injection of 0.03 mg/kg midazolam; group C was given the same dose of normal saline. During operation, the bispectral index (BIS) was used to monitor the depth of anesthesia, which was maintained by adjusting the inspired concentration of sevoflurane (BIS value: 55-60). The operation time, intraoperative blood loss, extubation time, Richmond Agitation-Sedation Scale at extubation, intraoperative sevoflurane dosage, statuses of postoperative nausea, vomiting, dizziness and other adverse reactions, and delirium assessment at 1-5 days after operation (confusion assessment method) were recorded and compared. Results: There were no significant differences in general condition, operation time, intraoperative blood loss and fracture site among the three groups of patients (all P>0.05). Extubation time in group B was longer than those in group A and C (P<0.05), and there was no significant difference in extubation time between group A and C (P>0.05). The agitation rates at extubation of patients in group B and C were significantly higher than that in group A (P<0.05). The intraoperative dosage of sevoflurane in group A was obviously less than those in group B and C (P<0.05). There were no significant differences in the incidence rate of postoperative adverse reactions among the three groups of patients (P>0.05). The incidence rate of POD in group A was apparently lower than those in group B and C (P<0.05); the incidence rate of POD at 1-2 days after operation in group B was higher than that in group C (P<0.05); there was no significant difference in the incidence rate of POD at 3-5 days after operation between group B and C (P>0.05). Conclusion: DEX not only had a good sedative effect, but also could be used in combination with sevoflurane to control the depth of anesthesia, reduce the dosage of sevoflurane, and lower the incidence rate of POD in elderly patients after vertebral fracture operation and the agitation rate at extubation under general anesthesia.

Keywords: Dexmedetomidine, fracture, postoperative delirium, sevoflurane

Introduction

Postoperative delirium (POD) is an acute encephalopathy syndrome that often occurs in elderly patients aged over 65 years old at 3-5 days after operation [1]. It is mainly manifested as mental disorders in consciousness, thinking, orientation, cognition, memory, sleep, etc., typically characterized by more serious syndrome in the daytime than that at night, that is, the above mental disorder symptoms are more obvious at night [2]. The mechanism of POD is not clear. A study has confirmed that POD in the elderly may be associated with the advanced age, preoperative combination with hypertension, postoperative high body temperature, high postoperative Visual Analogue Scale, and the advanced age may be an independent risk factor for POD [3, 4]. In addition, studies have revealed that the incidence rate of POD in patients aged over 70 years old significantly increases, based on which the occurrence risk

in elderly patients at the age of more than 75 years old greatly increases [5-7]. Therefore, the prevention and treatment of POD in elderly patients are extremely important for strengthening postoperative recovery, shortening the hospital stay, reducing hospitalization costs, and lowering postoperative mortality rate in elderly patients [8]. A study has evidenced that elderly patients are more likely to suffer from POD after orthopedic surgery compared with other visceral organ surgeries [9]. Elderly people are prone to fractures due to osteoporosis, while vertebral fractures can cause severe pain, concurred with nerve damage or dyspnea [10]. The curative effect of conservative treatment and the patient's prognosis are very poor [11]. Therefore, surgical treatment has been more frequently used in recent years, and thoracolumbar fractures are more common among vertebral fractures in elderly patients [12, 13]. As a result, elderly patients with thoracolumbar fractures were selected in this study. Dexmedetomidine (DEX) is a new type of highly selective α_2 adrenergic receptor agonist. A study has manifested that DEX plays a certain role in the prevention and treatment of POD [14]. It has been found in a study on a sevoflurane-induced operation under general anesthesia for children that the application of DEX can reduce the incidence of POD, and will not prolong postoperative tracheal extubation time and the length of stay in anesthesia recovery room [15]. Additionally, a study has confirmed that the continuous intravenous infusion of DEX in patients with POD in the Intensive Care Unit can well sedate patients, so that POD can be satisfactorily controlled and does not produce adverse respiratory reactions [16]. Due to the unclear mechanism of POD, DEX can only be observed clinically to be effective in POD. However, the mechanism of DEX in the treatment and prevention of POD is still not clear, which needs to be confirmed by further studies. Moreover, little is known about DEX in the prevention of POD in elderly patients after major operations. In consequence, DEX was selected to study the prevention of POD in elderly patients after vertebral fracture operation in this study.

Materials and methods

General data

The study was approved by the Medical Ethics Committee of Nanxiang Hospital of Shanghai Jiading District, and the patients were informed of the possible treatment risks and other treatment options if the curative effect was poor. All the patients signed informed consent. A total of 90 elderly patients undergoing vertebral fracture operation in Nanxiang Hospital of Shanghai Jiading District from January 2015 to December 2017 were selected.

Inclusion criteria: (1) Patients aged 75-90 years old; (2) Patients receiving selective operation at grade I-III in the American Society of Anesthesiologists (ASA) classification [17]; (3) Patients with thoracic or lumbar vertebral fractures.

Exclusion criteria: (1) Patients with diseases in the central nervous system and mental illness, and those who cannot effectively communicate with the psychiatrist; (2) Patients gaining ≤23 points in the Mini-Mental State Examination [18]; (3) Patients taking sedatives or antipsychotics; (4) Patients suffering from severe diseases in the heart, lung, brain, liver, kidney or other important organs; (5) Patients who have severe vision or hearing impairment and cannot complete POD assessment; (6) Patients who are allergic to the drugs used in this study or those who are not suitable for this study.

Study objects

A total of 90 patients were selected, including 52 males and 38 females. According to the number random table method, the patients were divided into the DEX group (group A, n=30), the midazolam group (group B, n=30) and the control group (group C, n=30).

Anesthesia methods

All the patients were fasted for 8 h before operation, and their venous accesses were opened up. Radial artery puncture was performed under local anesthesia for invasive artery monitoring, and the monitored indicators included blood pressure (BP), mean arterial pressure, heart rate (HR), respiratory rate (RR), blood oxygen saturation (SpO_2). After 75% alcohol was used to wipe the forehead skin, the bispectral index (BIS) sensor electrode was pasted for continuous monitoring of BIS. Before anesthesia, patients fully inhaled oxygen at 5 L/min using a mask. Group A received the pump injection of 0.5 μg/kg DEX for 10 min before anesthesia induction. Then the

Table 1. Comparison of general data among the three groups of patients

	Group A	Group B	Group C	P	F/H
Age (year)	82.5±5.4	81.9±6.2	83.2±5.1	0.618	4.533
Gender					
Male	16	19	17	0.614	4.856
Female	14	11	13	0.327	3.435
ASA classification					
I	4	3	5	0.254	5.047
II	15	18	14	0.331	4.872
III	11	9	11	0.638	3.861

Note: ASA, American Society of Anesthesiologists.

anesthesia induction began, while DEX was maintained at 0.4 μg/(kg·h) until the end of operation. Group C was given the normal saline at the same amount of DEX in group A, and group B was slowly intravenously injected with 0.03 mg/kg midazolam before anesthesia induction. Afterwards, the three groups were given conventional intravenous anesthesia induction with 1-1.5 mg/kg propofol, 2-3 μg/kg fentanyl and 0.8 mg/kg rocuronium bromide, and the specific dose was adjusted according to the patient's general situation before operation. In the case of patients suffering from abnormal BP, diabetes mellitus and other underlying diseases, the drug dosage should be reduced in order to avoid greater volatility caused by hemodynamics. In the case of patients suffering from obesity and no significant underlying diseases before operation existing, the drug dosage should be increased to achieve certain blood concentration. Three min later, mechanical ventilation was conducted after the endotracheal intubation. The tidal volume was 6-10 mL/kg, RR was 10-15 times/min, and the specific tidal volume and RR were adjusted according to the CO_2 partial pressure at the end of the respiration so that this pressure was maintained at 35-45 mmHg, respiratory ratio at 1:2, and oxygen flow at 1.5 L/min. In the two groups, anesthesia was maintained with the inhalation of sevoflurane and the pump infusion of 0.1 μg/(kg·min) remifentanil, the concentration of sevoflurane was adjusted, making the BIS value ranged 50-60, and rocuronium was continuously injected to maintain muscle relaxation. If the intraoperative BP dropped more than 30% of the base value, 5-10 mg ephedrine would be given intravenously, and if HR <50 beat/min, 0.5 mg atropine was injected intravenously. At 5 min before the end of operation, all anesthetics were disabled, and no antagonisms were used during the recovery. After vital signs became stable and extubation indications were clear, the endotracheal tube was removed.

Operation methods

The current operation method for spinal fractures is mainly achieved using more posterior pedicle screw fixation combined with vertebroplasty, which was also used in this study [19]. Patients were placed in the prone position and the middle longitudinal incision behind the injured vertebra was taken. The injured vertebra, adjacent lamina, spinous processes and other structures were exposed, so as to determine vertebral pedicles in the upper and lower vertebral body; the vertebral pedicle bolt was screwed accurately to restored the vertebral body to the normal height. Then the bone cement was implanted into the vertebral body and pedicle via the injured vertebral pedicle, then the articular cartilage, articular process and lamina cortex were polished, and vertebroplasty was conducted.

Monitoring indicators

Main indicators: Delirium assessment results were observed and recorded at 1-5 days after operation in patients (confusion assessment method): (1) Acute onset and the fluctuation of the disease; (2) Impaired concentration or inattention; (3) Disorganized thinking; (4) Changes in the awareness level. If patients memt (1), (2) and (3) or (4), they can be diagnosed with POD; the incidence rate of delirium = the number of delirium patients/the total number of people [20].

Secondary indicators: (1) Operation time and intraoperative blood loss were observed and recorded; (2) The extubation time, the Richmond Agitation-Sedation Scale (RASS) at extubation (RASS >1 point represents agitation at extubation, and agitation rate at extubation = the number of agitate patients/the total number of patients), and the number of patients suffering from postoperative nausea, vomiting, dizziness and other adverse reactions were recorded

Table 2. Comparison of fracture site, operation time and intraoperative blood loss among the three groups of patients

Group	Group A	Group B	Group C	P	F
Fracture site					
Thoracic segments	11	13	14	0.617	4.751
Lumbar segments	19	17	16	0.372	6.422
Operation time (min)	158.0±18.9	163.0±17.2	154.0±21.4	0.715	4.495
Intraoperative blood loss (mL)	345.0±33.0	329.0±42.7	344.0±31.5	0.827	4.036

Table 3. Comparison of extubation time, agitation rate at extubation and intraoperative dosage of sevoflurane among the three groups of patients

	Extubation time (min)	Agitation rate (%)	Dosage of sevoflurane (μg)
Group A	15.3±5.4★★	37.0	25.3±6.8
Group B	24.6±7.2	63.0△△△	39.8±5.4☆☆
Group C	14.9±6.5★★	70.0△△△	45.3±4.9☆☆☆,◆

Note: Group A and group C compared with group B, ★★P<0.01; group B and group C compared with group A, △△△P<0.001; group B compared with group A, ☆☆P<0.01; group C compared with group A, ☆☆☆P<0.001; group C compared with group B, ◆P<0.05.

[21, 22]; (3) The amount of sevoflurane dosage in the operation was recorded.

Safety evaluation

If intraoperative uncontrollable factors appeared in patients, such as bleeding and unstable vital signs leading to the failure of the operation, the operation should be stopped immediately to implement rescue, and these patients were included in the invalid cases; if the patients needed re-operation because of a variety of reasons such as postoperative changes in the disease or were unable to accomplish the target due to critical illness, other treatment methods should be adopted to rescue patients, and these patients were included in the invalid cases.

Statistical methods

Experimental data were analyzed and plotted by SPSS 19.0 and Graphpad Prism 5 software. Measurement data are expressed as mean ± standard deviation ($\bar{x}$ ± sd). If the data were not normally distributed, the rank-sum test was applied for the pairwise comparison, and the Kruska-Wallis test for comparisons among the three groups. If the data were normally distributed, the independent samples t-test or repeated measures analysis of variance (ANOVA) was used for the pairwise comparison, the Bonferroni post hoc test for the differences in the pairwise comparison of measurement data at each time point, and ANOVA for comparisons among the three groups. Count data were expressed as percentage, the χ^2 test was used for intergroup comparisons, and the rank-sum test was applied for rank variables. P<0.05 represented that the difference was statistically significant.

Results

Comparisons of general data among the three groups of patients

There was no significant difference in general data, including gender, age, ASA classification, fracture site, operation time and intraoperative blood loss among the three groups of patients (all P>0.05) as shown in **Tables 1**, **2**.

Extubation and postoperative status as well as the dosage of sevoflurane in the three groups of patients

The extubation time of patients in group B was significantly longer than those of patients in group A and C (P=0.005, t=11.421; P=0.006, t=10.342), and there was no significant difference in the extubation time between group A and C (P=0.638, t=4.725). The agitation rates at extubation of patients in group B and C were significantly higher than that in group A (P<0.001, t=15.362; P<0.001, t=16.381), and there was no significant difference in the agitation rate between group B and C (P=0.825, t=3.615). There was no significant difference in the incidence rate of postoperative adverse reactions among the three groups of patients (P>0.05). The intraoperative dosage of sevoflu-

Table 4. Comparison of postoperative adverse reactions among the three groups of patients (n, %)

	Nausea and vomiting	Dizziness	Fatigue	Muscular tremors
Group A	6 (20.0)	5 (16.7)	11 (36.7)	7 (23.3)
Group B	8 (26.7)	8 (26.7)	9 (30.0)	6 (20.0)
Group C	9 (30.0)	6 (20.0)	13 (43.3)	9 (30.0)
P	0.634	0.558	0.329	0.715
χ^2	4.674	5.262	6.828	4.155

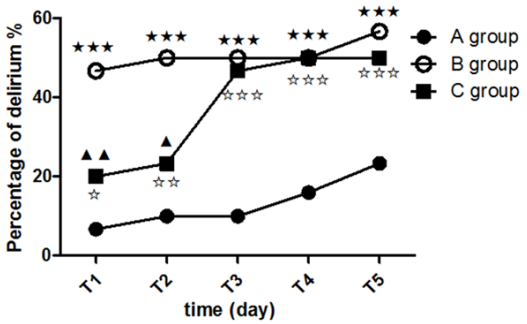

Figure 1. Comparison of postoperative delirium rate among the three groups of patients. Abscissa T1, T2, T3, T4 and T5 indicated 1-5 days after surgery, respectively; ordinate indicated postoperative delirium rate (%). Group B compared with group A, ★★★P<0.001; group C compared with A, ☆P<0.05; group C compared with group A, ☆☆P<0.01; group C compared with group A, ☆☆☆P<0.001; group C compared with group B, ▲P<0.05; group C compared with group B, ▲▲P<0.01.

rane in group A was obviously less than those in group B and C (P=0.006, t=12.644; P<0.001, t=15.176), and the dosage in group B was less than that in group C (P=0.036, t=12.511) as shown in **Tables 3**, **4**.

Comparisons of POD among the three groups of patients

In this study, the number of patients with delirium at 1-5 days after operation was observed and recorded, and the incidence rate of delirium was calculated. The incidence rate of delirium in group A was significantly lower than those in group B and C (P<0.001, F=38.731). The incidence rate of delirium in group B was higher than that in group C at 1-2 days after operation (P=0.003, F=26.759; P=0.031, F=17.685), and there was no significant difference in the incidence rate of delirium between group B and C at 3-5 days after operation (P=0.528, F=4.716; P=0.815, F=3.681; P=0.482, F=6.257) as shown in **Figure 1**.

Discussion

A study has shown that DEX has certain anti-sympathetic activity, can produce dose-dependent sedative, analgesic, and anti-anxiety effects, and protects the heart, brain, kidney and other important organs [2]. The preventive effect of DEX on POD has been deeply researched in recent years, which may be related to the following aspects. First, DEX can bind to the spinal cord, brain and other norepinephrine receptors in the whole body and studies have revealed that changes in the noradrenergic system may be associated with POD in patients [23]. Second, studies have manifested that application of opioids or other general anesthetics increases the incidence rate of POD, while the existing studies have indicated that DEX can reduce the dosage of opioids so as to prevent opioid-induced POD [24]. Third, propofol and benzodiazepines such as midazolam have a high affinity to γ-aminobutyric acid receptor, and changes in γ-aminobutyric acid receptors result in a variety of neurotransmitter changes, thus leading to the occurrence of POD. Studies have confirmed that the affinity of DEX to γ-aminobutyric acid receptors decreases, and the binding also declines [25]. Fourth, some scholars hold that delirium was an acute stress reaction, and operation and trauma can rapidly increase the blood cortisol level. Many studies have evidenced that the elevation of cortisol concentration after the stimulation can increase the incidence rate of POD, while DEX can reduce hemodynamic changes during anesthesia and operations and the stress response [26]. Fifth, it has been reported that DEX has certain neuroprotective effects, probably through the regulation of pro-apoptotic and anti-apoptotic proteins [27]. Finally, DEX has a strong anti-inflammatory effect, and studies have demonstrated that cytokines such as interleukins, tumor necrosis factors and interferons can cause POD by increasing blood-brain barrier permeability and altering the delivery of neurotransmitters [28].

The decreased blood supply to the brain of elderly patients reduces the cerebral blood flow, cerebral metabolism, drug metabolism, and the sensitivity to hypoxia, which are postoperative risk factors for delirium [29]. It can be seen from the above that DEX can reduce the dosage, stress response, and inflammatory response, thus lowering the incidence rate of

POD in elderly patients. In this paper, the effect of DEX on the incidence rate of POD in patients receiving vertebral fracture operation was explored, and it could be known from the conclusion that compared with midazolam group and normal saline control group, DEX could significantly reduce the incidence rate of POD in patients at 1-5 days after operation, the incidence rate of POD in midazolam group at 1-2 days after operation was higher than that in normal saline control group, and there was no significant difference in the incidence rate of POD at 3-5 days after operation, which proved that midazolam might increase the incidence rate of POD in the short term, but this was not confirmed by any studies. This study revealed that DEX and midazolam could reduce the dosage of sevoflurane in patients under general anesthesia compared with that in control group, but the variation degree was more obvious in the DEX group than the midazolam group. In addition, general anesthetics can increase the incidence rate of POD in patients, so the declined POD incidence rate in patients after vertebral fracture operation in this study might be caused by the decreased dosage of sevoflurane. Although midazolam can also reduce the dosage of sevoflurane, but the above conclusion evidenced that midazolam could increase the incidence rate of short-term POD, which might be because this drug triggered other changes in the body such as reduced cerebral blood flow and brain metabolism so as to increase the incidence rate of POD [30]. Due to the limited time and the number of objects in this study, this conclusion needs to be further confirmed. Compared with the midazolam group and the normal saline control group, DEX could also significantly shorten the extubation time and reduce the agitation rate at extubation without increasing postoperative nausea, vomiting, dizziness, fatigue, amyostasia and other adverse reactions, while midazolam, on the contrary, increased the extubation time.

There are many deficiencies in this study due to limited time and study objects. For example, only the incidence rate of delirium at 1-5 days after operation was investigated in this study. Although POD often occurs at 3-5 days after operation, this study could only confirm the preventive effect of DEX on short-term POD, and there is no evidence proving this effect at 5 days after operation, which needs to be confirmed by further experiments.

In summary, DEX is a good anesthetic and sedative drug, especially for elderly patients, which can not only prevent the occurrence of POD, but also reduce the dosage of general anesthetics. Additionally, it can control the depth of anesthesia in elderly patients in coordination with other general anesthetics, thus reducing hemodynamic fluctuations and adverse reactions caused by general anesthetics and operations.

Acknowledgements

This work was supported by Shanghai Science and Technology Committee of Jiading District (KW2015027).

Disclosure of conflict of interest

None.

Address correspondence to: Lili Shen, Department of Anesthesiology, Nanxiang Hospital of Shanghai Jiading District, No.495 Zhongren Road, Nanxiang Town, Jiading District, Shanghai 201802, China. Tel: +86-13916405125; E-mail: lilishen8s74j@126.com

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