Effect of dexmedetomidine on postoperative delirium in elderly patients undergoing hip fracture surgery

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Abstract: Dexmedetomidine is a highly selective central α2 adrenergic receptor agonist, which has anti sympathetic, sedative and analgesic effects. The aim of this study was to investigate the effect of dexmedetomidine on postoperative delirium in elderly patients undergoing hip fracture surgery. The results showed that the dosage of sufentanil and propofol decreased significantly in the experimental group (P<0.05). The price-henry pain scores of 10min, 1H and 6h in the experimental group were significantly reduced after the operation. At the same time, there were 3 cases (4.28%) of postoperative delirium in the experimental group, which were significantly less than 12 cases (17.14%) in the control group. The dosage of propofol in the operation is a risk factor for postoperative delirium. Dexmedetomidin can significantly reduce the amount of propofol in the operation and it has a neuroprotective effect, which can reduce the incidence of postoperative delirium in the elderly. In the elderly patients with hip surgery, its adjuvant to general anesthesia can effectively reduce narcotic drug dosage and reduce the incidence of postoperative delirium.

Keywords: Dexmedetomidine, postoperative delirium, hip surgery, induction of anesthesia, fentanyl.

INTRODUCTION

Hip fracture is a common fracture in the elderly. At present, surgical treatment is the main treatment for hip fracture in the elderly (Deiner *et al.,* 2017; Liu *et al.,* 2017). Postoperatively delirium (POD) is one of the common postoperative complications of elderly hip fractures, which not only increases the incidence of bedsore, pulmonary infection, and venous thrombosis (Hauser *et al.,* 2015). It can also increase complications such as artificial prosthesis, internal fixation loosening and breakage, fall injury, and even lead to depression or self-mutilation. Studies have found that dexmedetomidine can prevent and treat delirium associated with ICU (Kang *et al.,* 2013). The aim of this study was to investigate the effect of dexmedetomidine on POD (postoperative delirium) in elderly patients undergoing hip fracture surgery.

The incidence of postoperative delirium in elderly patients with hip fracture is high, and has high risk. It is extremely unfavorable to the treatment effect and prognosis of the patients (Djaiani *et al.,* 2016). Delirium induced factors are more complicated. Sedation drugs, electrolyte disorders, cerebral ischemia and hypoxia may induce those (Kan *et al.,* 2003). Dexmedetomidine is a highly selective central α2 adrenergic receptor agonist, which has anti sympathetic, sedative and analgesic effects (Leng *et al.,* 2004). The activation of presynaptic membrane α2 receptor can inhibit the release of noradrenaline and terminate the conduction of pain signal. At the same time, it can also stimulate the receptors of the postsynaptic membrane, inhibit sympathetic activity, thereby reducing blood pressure and heart rate, and relieving anxiety (Li *et al.,* 2015). Dexmedetomidin can also increase the oxygen uptake of brain tissue, stabilize the microcirculation hemodynamics of the nerve tissue, and stimulate the *α2* adrenergic receptor in the locus coeruleus nucleus, that is, inhibiting the increase of cAMP level, blocking the protein kinase A and the downstream phosphorylation, thus reducing the amount of nociceptive neurotransmitter release in the brain (Ostojic *et al.,* 2015).

MATERIALS AND METHODS

General information

140 elderly patients undergoing hip surgery in Tiantai people's hospital in 2016-2017 were selected, ASA grade I to III, 74 males and 66 females, aged 62~85 years The scores of all patients with simple preoperative mental state examination (MMSE) were more than 24 points, no serious respiratory system disease, no serious cardio cerebral vascular disease (the patients with hypertension were treated with SBP not higher than 160mmHg, DBP was not higher than 90mmHg). Severe impairment of liver and kidney function, including AST and ALT exceeding 1.5 times the upper limit of normal value, Creatinine and / or urea nitrogen exceed the upper limit of normal value. Those who took sedative drugs for a long time had a history of abnormal anesthesia. As well as the existence of mental and neurologic diseases, unanticipated massive bleeding in the operation, prolonged operation time, serious drug allergy events and other causes that are not easy to collaborate. All patients were approved by ethics committee of Tiantai People's

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Hospital, ethical approval number as 2014TPHTD2 and all patients signed on the informed consent.

Medication method

All patients did not use preoperatively. After entering the room, the right upper limb vein was open, and SBP, DBP, SpO2, ECG, BIS were monitored. The left radial artery was used to monitor the invasive blood pressure after local anesthesia. In the experimental group, the dexmedetomidine 2mg was diluted to 50ml with saline to 0.5μg/kg. After the 10min pump, the anesthesia was induced to be induced at the same time as 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and the control group was given equal amount of saline.

The two groups were induced in the same way. Midazolam 0.02mg/kg, sufentanil 0.4μg/kg, propofol 1.5mg/kg, vecuronium 0.08mg/kg were slowly induced, and 5 to 10min were completed. The hemodynamic stability was maintained during the induction period. BP was lower than the basal blood. Ephedrine was given 0.1mg/kg for 30% hours, and HR for atropine 0.2 to 0.5mg below 50 times/minute.

When BP was higher than the basic blood pressure at 30%, the nitroglycerin $0.5\mu g \cdot kg^{-1} \cdot min^{-1}$ began to pump. The dosage of nitroglycerin was adjusted according to the change of blood pressure. When HR was slower than 90 times / time, then give esmolol load 0.5mg/kg and dose adjusted according to HR. After successful placement of a disposable general laryngeal mask anesthesia machine, the volume of respiration was controlled and RR and V_T were adjusted to maintain $P_{ET}CO_2$ 30 to 40mmHg. The value of propofol was adjusted to maintain BIS value at 40~60: Intermittent intravenous injection of sufentanil 0.3μg/kg and vecuronium 2mg to maintain analgesia and muscle relaxation. The BP maintained within the range of the baseline range of ±30% and HR55 to 80 times/ minutes.

The two groups before skin incision and suture were routinely given flurbiprofen axetil 50mg intravenously, and 30min stopped pumping dexmedetomidine before the end of operation. After removal of the laryngeal mask airway after resuscitation, the patient should return to the ward with Steward score of 4 or more. The patient did not use an analgesic pump after the operation.

Observation index

(1) Record the intraoperative lens volume, intraoperative colloid volume, intraoperative dose, and extubation time of all patients. (2) Recording SBP, DBP, HR, SpO_2, BIS values, PETCO2 and nasal temperature at different time periods. The patient was admitted into the room (T1), Dexmedetomidine load or after saline infusion (T2), after placing a laryngeal mask airway (T3), after operation, 10min (T4) and laryngeal mask airway were removed after operation (T5), after the operation (T6). (3) Record the drug use in two groups of patients. (4) Observe and record the two groups of patients after the operation of 10min, 1H, 6h, 24h, 48h Ramsay sedation score (1 points, fidgety uneasiness; 2 points, quiet cooperation; 3 points, sleepiness, quick response to the instructions but vague pronunciation; 4 points, sleep state, can wake up; 5 points. The response to the call is slow; 6 points, deep sleep or anesthesia, call no response). Price - Henry pain score (0 points, no pain in coughing; 1 points, cough with pain; 2, quiet, no pain, deep breathing pain; 3, quiet state of mild pain, tolerable; 4, quiet state of severe pain, unbearable). (5) Observe and record the occurrence of postoperative bradycardia, hypertension, hypotension and other adverse reactions.

Each patient was evaluated with delirium assessment (CAM): (1) Acute onset, disease fluctuation; (2) lack of attention or attention; (3) disorder of thinking; (4) change of consciousness level. Delirium can be diagnosed if there are 1 and 2 of the patients and 3 or 4 of them are found, and the occurrence of delirium first to 4 days after operation can be recorded.

STATISTICAL ANALYSIS

The SPSS13.0 statistical software was used to analyze the data, and the measured data were expressed as x±s, and the single factor analysis of variance was used. Count data using $\chi 2$ test.

RESULTS

General data comparison

There was no significant difference in gender, age, height, weight and BMI between the two groups (table 1). Compared with the control group, the dosage of sufentanil and propofol in the experimental group decreased significantly ($P<0.05$), and there was no significant difference in the amount of other drugs (table 2).

Comparison of drug use

Compared with the control group, the SBP and DBP decreased significantly at T4 and T5 in the experimental group, and the HR in T2, T4 and T5 decreased significantly ($P<0.05$).Compared with T1, SBP and DBP in the experimental group decreased significantly at T3 and T4 and the SBP and DBP in the control group increased significantly when T4 and T5 were found. At the time of T2 to T4, the HR in the experimental group was significantly slowed and the HR in the control group decreased significantly at T3, and the BIS in the two groups decreased significantly ($P<0.05$) at T3 and T4 ($P< 0.05$) (table 3). All patients took oxygen inhalation, SpO_2 was more than 94.2%. There was no significant difference in SpO_2, $P_{ET}CO_2$ and nasal temperature between the two groups at different time points.

Table 1: General data comparison of patients

Group	Cases	Male/female	Age	Height (CM)	Weight (kg)	BMI (kg / m2)	MMSE score
Experience group	70	38/32	68.2±5.6	163.7±6.5	64.2±10.2	23.1±4.6	27.6±0.5
Control group	70	36/34	69.7±5.3	165.1±6.9	62.7±9.6	22.7±4.8	27.3±0.7

Table 2: Comparison of drug use

Group	Midazolam (mg)	Vecuronium (mg)	Sufentanil (μ g)	Propofol (mg)	Ephedrine (mg)	Atropine (mg)	Nitroglycerin (mg)	Esmolol (mg)
Experience group	1.4±0.5	8.1±4.2	26.1±2.7	319.5±15.3	5.7±1.2	0.7±0.4	0.25±0.04	8.4±1.7
Control group	1.6±0.7	8.2±4.5	29.6±3.1	382.4±18.2	5.4±1.6	0.6±0.3	0.28±0.08	8.7±1.3

Table 3: Comparison of BP, HR and BIS at different time points

Index	Group	T1	T2	T3	T4	T5	T6
SBP	Experience group	138.2±15.2	135.2±14.8	109.2±9.1	118.3±10.8	132.7±10.8	128.2±13.9
	Control group	133.7±12.8	133.6±12.7	118.3±10.8	136.7±14.2	145.2±13.5	142.7±11.3
DBP	Experience group	71.3±6.5	66.2±8.4	62.3±9.8	62.3±8.9	65.4±8.4	71.3±8.4
	Control group	69.5±7.2	67.5±9.1	61.8±10.1	75.2±9.3	79.3±7.2	75.4±7.9
HR	Experience group	71.5±13.6	59.2±6.4	61.2±5.7	64.2±8.3	72.3±8.9	74.3±12.3
	Control group	75.2±14.8	68.1±7.8	63.7±8.1	79.1±9.4	81.3±9.5	78.6±13.5
BIS	Experience group	89.3±2.4	84.3±3.2	55.2±6.5	51.2±6.1	83.6±5.3	91.3±2.7
	Control group	91.6±2.3	90.1±4.1	57.8±7.3	52.7±6.9	89.2±6.2	92.5±3.1

Table 4: Ramsay sedation score and price pain score

Index	Group	Postoperative 10min	Postoperative 1h	Postoperative 6h	Postoperative 24h	Postoperative 48h
Ramsay sedation score	Experience group	3.1±1.2	2.7±0.6	2.2±0.5	2.1±0.2	1.8±0.4
	Control group	3.2±1.5	2.5±0.8	2.0±0.3	2.0±0.4	1.9±0.3
Price-Henry pain score	Experience group	0.8±0.3	1.4±0.5	1.8±0.5	2.2±0.5	2.5±0.4
	Control group	2.1±0.5	2.3±0.6	2.6±0.8	2.6±0.7	2.7±0.3

Table 5: Incidence of postoperative delirium

Group	First day	Second day	Third day	Fourth day	Total incidence
Experience group	0	2	1	0	4.28%
Control group	1	5	4	2	17.14%

Comparison of pain score

Compared with the control group, the pain scores of 10min, 1h and 6h in the experimental group were significantly lower ($P<0.05$). Compared with postoperative the two groups in 10min, 6h, 24h and 48h after operation were significantly lower in the sedative score, and the pain score in the experimental group was significantly higher ($P<0.05$) (table 4).

Occurrence of delirium

Postoperative delirium in 3 cases (4.28%) of the experimental group was significantly lower than that in the control group (12 cases (17.14%) ($P<0.05$) (table 5). There was no significant difference between the two groups in intraoperative intraoperative lens, colloid fluid intake, intraoperative stool volume and extubation time. There was no significant difference in incidence of postoperative bradycardia and other adverse reactions.

DISCUSSION

It is reported that the incidence of delirium in the elderly patients is up to 10% to 50%, which is closely related to ischemic anoxia, electrolyte disturbance, the use of diazepam, infection, organ failure and so on (Park *et al.*, 2017). Studies have suggested that dexmedetomidine (DEX) is effective in the prevention and treatment of postoperative delirium (Pasin *et al.*, 2014). The study found that 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ after intravenous injection of DEX 1μg/ kg in a small surgical operation for spinal

anesthesia could effectively reduce the chills of the patients and have no serious adverse reactions (Piro *et al.,* 2002). Therefore, DEX 0.5 μg/kg was injected before anesthesia induction. After the 10min pump was completed, the maintenance of $0.4\mu g \cdot kg^{-1} \cdot h^{-1}$ was maintained to 30min before the operation.

The use of BIS to monitor the depth of anesthesia in general anesthesia can reduce the dosage of propofol by 21%, reduce the amount of inhalation narcotic drugs by 30%, and reduce postoperative cognitive impairment and postoperative delirium (Sheng *et al.,* 2015). The reason is that BIS can accurately anesthetized medication and reduces anesthetic exposure (Schreuder *et al.,* 2017). The study found that children with isoflurane anesthesia had higher postoperative delirium rate than remifentanil group (Shin *et al.,* 2015). In this study, BIS was used to monitor the depth of anesthesia for accurate anesthesia. Intravenous anesthesia was used to avoid the effect of inhalation anesthesia on postoperative delirium; laryngeal mask tube was used to reduce the probability of hemodynamic fluctuations after induction of anesthesia in order to exclude postoperative delirium caused by circulatory instability (Seshiah *et al.,* 2002).

The residual effect of narcotic drugs should be considered on the same day after surgery. There may be some deviations in delirium determination. After the follow-up, it was found that the patients who had postoperative delirium were most of the patients who were not good at talking, introverted or more worried about the preoperative visit (Santos *et al.,* 2003). It may be that these patients are not good at communicating with the doctors and their families and it is difficult to relieve the doubts and worries of the heart, which causes the patients to increase their postoperative hair in the state of anxiety before operation. The rate of postoperative delirium in the experimental group (4.28%) was significantly lower than that of the control group (17.14%), and the dosage of propofol and sufentanil in the experimental group was significantly lower than that of the control group. This may be the effect of DEX and the central α2A receptor in the combination of sedative, hypnotic and anti anxiety effects and reduced the operation (Xiao *et al.,* 2015). The use of sedative drugs; the combination of DEX with the α2A receptor in the posterior horn of the spinal cord produces analgesic effects, and may also be a synergistic effect of DEX on sufentanil to enhance the analgesic effect and reduce the amount of sufentanil (Vincent *et al.,* 2011). The dosage of propofol in the operation is a risk factor for postoperative delirium. DEX can significantly reduce the amount of propofol in the operation, and it has a neuroprotective effect (Webster *et al.,* 2017). Therefore, it can reduce the incidence of postoperative delirium in the elderly patients. In addition, by observing the vital signs at each time point of the two groups, DEX has a biphasic function on the cardiovascular system. The initial dose directly acts on the alpha 2 beta receptor (mainly on the vascular smooth muscle), which can produce a transient rise in blood pressure and a decrease in heart rate reflex (Wollheim, 2000). Continuous small dose maintenance can reduce blood pressure and heart rate through the excitation of the vagus and central sympathetic responses. During the treatment, DEX can maintain relatively stable hemodynamics and do not lead to respiratory depression. Therefore, it is safe for the induction, maintenance and waking phase of the middle and old patients (Zhang *et al.,* 2015).

CONCLUSION

After the comparison of the two groups of postoperative sedation score and pain score, the pain degree of the patients in the 6h group was significantly lower than that in the control group, and the postoperative pain was the main factor causing the patient's irritability and sleep dysfunction. The study showed that there was a close relationship between the disorder of sleep and the occurrence of delirium. It can be seen that DEX can alleviate postoperative dysphoria and improve sleep quality of patients, which may play a preventive role in the occurrence of delirium.

Dexmedetomidin has a sedative and analgesic effect. It can effectively reduce the dosage of sufentanil and propofol in the general anesthesia in the elderly hip surgery, and make the hemodynamics stable during the perioperative period, reduce the incidence of postoperative delirium, and have a definite value in clinical application.

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