Effects of Intraoperative Dexmedetomidine Infusion on Postoperative Delirium in Elderly Patients Undergoing Total Hip Arthroplasty

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Objective: To investigate the effects of dexmedetomidine on postoperative delirium in elderly patients undergoing total hip arthroplasty.

Methods: A total of 100 patients, 42 male and 58 female, ages 60 to 85 years, American Society of Anesthesiologists grade I or II, who were undergoing total hip arthroplasty were randomly divided into 2 groups: a dexmedetomidine group (group D; n = 50) and a control group (group C; n = 50). Group D patients were infused with 0.3 μg · kg⁻¹ · h⁻¹ of dexmedetomidine from 5 minutes prior to anesthesia induction until the end of surgery. Group C patients received an equal volume of saline. Heart rate and mean arterial pressure (MAP) were recorded before anesthesia induction (T₀), 1 minute before extubation (T₁), and 30 minutes after extubation (T₂). The Visual Analog Score (VAS) at 1, 2, and 3 days after surgery, the incidence and duration of postoperative delirium, and the length of hospital stay were recorded. Adverse reactions, such as nausea, vomiting, and lethargy, were also recorded.

Results: The Visual Analog Scores in the 2 groups were similar. In group D, there was no significant difference in heart rate (P = 0.232) and MAP (P = 0.056) between T₀ and T₁. However, in group C, heart rate significantly increased by 15.3 bpm (P = 0.000) and MAP significantly increased by 10.7 mmHg (P = 0.001) at T₁ compared with those at T₀. The incidence of postoperative delirium in group D (10%) was significantly lower than that in group C (26%; P = 0.037). The duration of delirium in group D (1.3 ± 0.6 days) was shorter than that in group C (3.0 ± 0.5 days; P = 0.000). The length of hospital stay in group D (13.2 ± 0.9 days) was shorter than that in group C (16.1 ± 0.7 days; P = 0.000). No significant
differences were observed in adverse effects between the 2 groups.

**Conclusion:** Intravenous infusion of dexmedetomidine can not only reduce the incidence and duration of postoperative delirium, but also shorten the length of hospital stay in elderly patients undergoing total hip arthroplasty.

**Key words:** Elderly – Dexmedetomidine – Postoperative delirium – Total hip arthroplasty

Because of the increasing aging population, the number of elderly patients receiving hip arthroplasty is also increasing annually. Hip arthroplasty can be performed under either neuraxial or general anesthesia. Johnson *et al* investigated 29 studies involving 10,488 patients but found no statistically significant differences between neuraxial and general anesthesia with respect to mortality, surgical duration, surgical site or chest infection, nerve palsy, postoperative nausea and vomiting, or thromboembolic disease. The factors affecting the selection of anesthesia are patient characteristics, anesthetist’s experience, patient’s preference, surgeon’s preference, operation duration, and contraindications to general or neuraxial anesthesia.

Morbidity and mortality associated with anesthesia have significantly decreased during recent decades. Although the safety and efficacy of anesthesia procedures have improved, adverse events, such as delirium, have become an important target to further enhance the quality of care and to mitigate the negative consequences. Postoperative delirium is common and often associated with increased medical costs and increased long-term mortality. The incidence of delirium also differs for different types of surgery. Studies have reported that the highest incidence of delirium was associated with hip fracture surgery, followed by heart and macrovascular surgeries.

Dexmedetomidine is a highly selective α2- adrenoceptor agonist with anxiolytic, sedative, and modest analgesic effects that is associated with minimal respiratory depression. Moreover, dexmedetomidine is increasingly used in the intensive care unit (ICU), where it is associated with a decreased incidence of delirium. However, in each of these delirium studies, dexmedetomidine was compared to an active sedative drug that modulates the γ-aminobutyric-acid type A (GABA_A) receptors. These modulators of GABA_A receptors are represented by benzodiazepines, which are increasingly associated with the prevalence of delirium. A plausible explanation is that dexmedetomidine neither prevents the occurrence of delirium nor increases the incidence of delirium like the modulators of GABA_A receptors. Consequently, the protective effect of dexmedetomidine against delirium in other patient populations remains unclear.

Therefore, the present study was undertaken to investigate the effects of dexmedetomidine on delirium in elderly patients undergoing total hip arthroplasty. Further, we hypothesized that dexmedetomidine decreases the incidence of postoperative delirium, and this effect will provide a new method for the prevention and treatment of postoperative delirium in elderly patients undergoing total hip arthroplasty.

**Materials and Methods**

This study was approved by the hospital ethics committee, and written informed consent was obtained from all patients and their families. A total of 100 patients who underwent unilateral total hip arthroplasty under general anesthesia were enrolled in the study. Of these, 42 were men and 58 were women, ages between 60 and 85 years, weighing between 47 and 81 kg, and American Society of Anesthesiologists scores I to II. Patients were excluded based on the following criteria: (1) preoperative diagnosis of dementia, schizophrenia, or depression; (2) recent use of psychotropic drugs; (3) history of stroke within the past 6 months; (4) preoperative alcoholism, smoking, long-term insomnia, and severe physical decline; (5) preoperative serum sodium <130 or >150 mmol · L⁻¹, and serum potassium <3 or >6 mmol · L⁻¹; and (6) preoperative blood glucose <60 or >300 mg · dL⁻¹ and serum albumin <34 g · L⁻¹. The patients were randomly divided into the dexmedetomidine group (group D) and the control group (group C).

**Anesthesia procedure**

All patients received an intravenous catheter puncture on arrival in the operating room. Routine monitoring of SpO₂, heart rate (HR), and ECG was conducted. Invasive arterial pressure was monitored...
by left radial artery puncture under local anesthesia. Group D patients were infused with 0.3 μg · kg⁻¹ · h⁻¹ dexmedetomidine from 5 minutes before anesthesia induction until the end of surgery. Group C patients were intravenously infused with an equal volume of normal saline. Anesthesia was induced by intravenous infusion of midazolam (0.03 mg · kg⁻¹), propofol (1.5 mg · kg⁻¹), cisatracurium besilate (0.2 mg · kg⁻¹), and sufentanil (0.3 μg · kg⁻¹). Tracheal intubation was performed 3 minutes after anesthesia induction. An additional 0.3 μg · kg⁻¹ sufentanil was infused before the skin incision. Anesthesia was maintained with intravenous injection of propofol (4.0–6.0 mg · kg⁻¹ · h⁻¹), remifentanil (0.1–0.25 μg · kg⁻¹ · h⁻¹), and cisatracurium besilate (0.15–0.2 mg · kg⁻¹). A patient-controlled intravenous analgesia pump was connected when the skin was sutured. Cisatracurium besilate infusion was discontinued 15 minutes before the end of the surgery, and the other infusion was terminated at the end of the procedure. The patients were transferred to the postanesthesia resuscitation room. During the entire procedure, if the HR was <50 bpm, the patients received an intravenous injection of 5 mg of atropine, and if the mean arterial pressure (MAP) was below 60 mmHg, the patients received an intravenous injection of 5 mg of ephedrine.

**Observation**

The Mini-Mental State Examination (MMSE)⁹ score was calculated using a simple mental state measurement scoring form (a maximum of 30 points, fewer than 24 indicated cognitive dysfunction). The VAS score was calculated as follows: 0 points indicates no pain, and 10 points indicates unbearable pain. MMSE score, VAS score, hemoglobin value, and albumin value were recorded before the operation. The HR and MAP were recorded 5 minutes before anesthesia induction (T₀), 1 minute before extubation (T₁), and 30 minutes after extubation (T₂). The operation time, intraoperative blood loss, and intraoperative blood transfusion were recorded. The VAS scores at rest and motion were recorded at 1, 2, and 3 days after surgery, and the incidence and duration of delirium within 7 days after surgery, length of hospital stay, and adverse reactions, such as nausea, vomiting, and lethargy, were also recorded. Consciousness assessment method was used to diagnose delirium. Delirium was confirmed based on the following criteria: (1) acute onset and course of fluctuation, (2) inattention, and (3) mental disorder or abnormal level of consciousness.

**Statistical analysis**

SPSS 13.0 statistical software was used for analysis. Multiple-group comparisons were performed by analysis of variance followed by a Scheffe test. The difference between different time points was analyzed using paired t-test. P < 0.05 was considered statistically significant. Count data were compared using χ² test.

The incidence of postoperative delirium after hip surgery in elderly patients ranges between 4% and 53%,¹⁰ but we thought that 53% was too high an incidence of delirium in patients in the control group would be half the upper limit (i.e., 26%), and the incidence in those receiving dexmedetomidine would be the lower limit (4%). To enable detection of differences, we set the statistical power as 1 – β = 90% and the sensitivity as α = 5%. Through power analysis, we consequently set the required number of patients at 50 patients per group.

**Results**

There were no significant differences in sex, age (P = 0.373), body weight (P = 0.302), MMSE score (P = 0.103), VAS score (P = 0.227), hemoglobin value (P = 0.962), albumin value (P = 0.615), operation time (P = 0.556), and intraoperative blood loss (P = 0.174) between the 2 groups (Tables 1 and 2).

There was no statistically significant difference in VAS scores between the 2 groups at rest (day 1, P = 0.185; day 2, P = 0.136; day 3, P = 0.124) and motion (day 1, P = 0.263; day 2, P = 0.367; day 3, P = 0.389) on days 1, 2, and 3 after surgery (Figs. 1 and 2).

However, patients in group D were more tolerant of tracheal intubation. In group D, there were no

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**Table 1 The general condition of the patients before surgery**

|               | n  | Age, y | Body weight, kg | MMSE score | VAS score | Hemoglobin value, g · L⁻¹ | Albumin value, g · L⁻¹ |
|---------------|----|--------|-----------------|------------|-----------|--------------------------|------------------------|
| C group       | 50 | 72.7 ± 4.3 | 61.5 ± 14.3    | 29.2 ± 0.3 | 2.3 ± 0.5 | 121.5 ± 11.2             | 40.1 ± 3.2             |
| D group       | 50 | 73.2 ± 5.8 | 62 ± 13.8      | 29.5 ± 0.2 | 2.4 ± 0.4 | 119.6 ± 13.8             | 41 ± 2.9               |
| P value       |    | 0.373   | 0.302           | 0.103      | 0.227     | 0.962                     | 0.615                  |

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significant differences in HR ($P = 0.232$) and MAP ($P = 0.056$) between T\textsubscript{0} and T\textsubscript{1}. In group C, the HR significantly increased by 15.3 bpm ($P = 0.000$), and the MAP significantly increased by 10.7 mmHg ($P = 0.001$) in T\textsubscript{1} compared with those in T\textsubscript{0} (Figs. 3 and 4). The incidence of delirium in group D was found to be 10%, which was significantly lower than that in group C (26%) within 7 days ($P = 0.037$). The duration of delirium in group D (1.3 ± 0.6 days) was significantly shorter than that in group C (3.0 ± 0.5 days; $P = 0.000$). The average length of hospital stay in group D (13.2 ± 0.9 days) was significantly lower than that in group C (16.1 ± 0.7 days; $P = 0.000$; Table 3).

In group C, 3 patients had nausea, 2 patients had vomiting, and 4 patients had lethargy. In group D, 4 patients had nausea, 2 patients had vomiting, and 5 patients had lethargy; however, there were no statistically significant differences between the 2 groups (nausea, $P = 0.695$; vomiting, $P = 1$; lethargy, $P = 0.727$; Table 4).

Discussion

Total hip arthroplasty is an effective treatment used frequently to treat late-stage hip osteoarthritis and, rarely, to treat delayed hip fracture.$^{11}$ Total hip arthroplasty is performed either using neuraxial anesthesia or general anesthesia; however, the question of which anesthetic procedure is better is still controversial.$^{1,12,13}$ The selection of anesthesia is dependent on the anesthesiology team’s discretion, surgeon’s preference, and patient’s choice. Because the patient is conscious during operation under neuraxial anesthesia, the surgical environment may negatively influence the patient. These effects may be more obvious during orthopedic interventions because of the noise of the tools being used, the long duration of tourniquet use, the position given, and the manipulation of patient extremities during the surgery. To eliminate the possibility of such effects, general anesthesia is preferred. Moreover, neuraxial anesthesia has not shown any benefit with respect to postoperative delirium.$^{14}$ In this study, we evaluated the use of dexmedetomidine in patients under general anesthesia.

Delirium is a common postoperative complication; its incidence peaks 1 to 3 days after surgery. Postoperative delirium is associated with prolonged hospital stay and also increases in in-hospital mortality and long-term mortality. The current pathogenesis of delirium is multifactorial, including neurotransmitter theory, stress response hypothesis, sleep-wake cycle disorders, brain metabolism level theory, etc.$^{15}$ Many studies have been conducted on the prevention and treatment of postoperative delirium. However, if postoperative delirium occurs, immediate treatment of both causative factors and symptoms has a major impact in reducing its duration.$^{16-18}$ Some studies have demonstrated that haloperidol$^{19,20}$ or atypical neuroleptics$^{21,22}$ could reduce the incidence of postoperative delirium or reduce its severity and duration. However, these findings remain uncertain because of inconsistent

| Table 2 Operation time and intraoperative blood loss in the 2 groups |
|-------------------------------------------------------------|
| n | Operation time, min | Intraoperative blood loss, mL |
|----------------|----------------------|-------------------------------|
| C group | 50 | 70 ± 12.5 | 210 ± 43.5 |
| D group | 50 | 68 ± 13.4 | 201 ± 50.2 |
| P value | 0.556 | 0.174 |

**Fig. 1** VAS scores at rest status on days 1, 2, and 3. Data are expressed as the mean ± SD. There were 50 patients in each group.
results of aggregated evidence. Perioperative \( \alpha_2 \) agonists, such as dexmedetomidine or clonidine, might be considered to decrease the incidence of postoperative delirium after cardiac or vascular surgery. 

Dexmedetomidine is a highly selective \( \alpha_2 \) adrenergic receptor agonist that exhibits central antisypathetic effects and can induce natural sleep sedation. Dexmedetomidine is commonly used in patients under ICU sedation. A randomized controlled trial of intraoperative dexmedetomidine, midazolam, or propofol revealed that dexmedetomidine reduced the incidence of postoperative delirium. Chen and Chen studied hemodynamic changes in patients with intracranial tumors and demonstrated that dexmedetomidine can effectively prevent patients from reaching serum S100\( \beta \) levels. The S100\( \beta \) protein is considered a sensitive marker of Alzheimer disease and delirium. Furthermore, studies have confirmed that serum S100\( \beta \) levels were associated with postoperative cognitive dysfunction and delirium. Wang et al demonstrated that serum S100\( \beta \) levels were significantly lower in the postoperative dexmedetomidine group compared with those in the midazolam group. 

Deng and Liu indicated that dexmedetomidine can improve HR variability, effectively regulate the tension of the sympathetic vagus nerve, and stabilize cardiovascular function in elderly patients under general anesthesia. Hu et al demonstrated that dexmedetomidine as spinal anesthesia adjuvant therapy can significantly inhibit the stress response. A study of cognitive dysfunction in elderly patients after general anesthesia revealed that dexmedetomidine could improve hemodynamics in elderly patients and protect postoperative cognitive function. Moreover, Fang et al demonstrated that dexmedetomidine could reduce the incidence of delirium.

Fig. 2  VAS scores in motion status on days 1, 2, and 3. Data are expressed as the mean ± SD. There were 50 patients in each group.

Fig. 3  Heart rate at different time points. Data are expressed as the mean ± SD. There were 50 patients in each group. *\( P < 0.05 \) versus T0; #\( P < 0.05 \) versus C group.
postoperative cognitive dysfunction in elderly patients undergoing hip arthroplasty.

The results of the present study showed that intravenous infusion of dexmedetomidine before anesthesia induced hemodynamic stability before and after extubation, significantly decreased incidence of postoperative delirium, and significantly shortened duration of delirium and length of hospital stay. In the ICU, a previously reported incidence of postoperative delirium ranged from 10% to 74%, and 87% of patients developed delirium. In the present study, the incidence of postoperative delirium in the control group was 26%, which is consistent with the reported range, but the incidence was still high. Age is a risk factor for postoperative delirium. In total hip arthroplasty surgery, increased pressure within the bone marrow cavity leads to the release of fat particles into the blood, which may result in cerebrovascular microfat embolism that affects brain tissue perfusion, resulting in postoperative delirium. In our study, the incidence of postoperative delirium was 10% in group D patients, which was significantly lower than that in group C patients. The mechanism may be that dexmedetomidine can reduce sympathetic nerve activity, reduce stress-induced abnormal blood pressure increase, lower the heart rate, and reduce the synthesis of cortisol release, thereby improving the stability of hemodynamics during operation and maintaining good cerebral perfusion in elderly patients undergoing total hip arthroplasty by highly selective activation of the α2 adrenergic receptor.

In summary, intravenous infusion of dexmedetomidine before anesthesia induction can stabilize hemodynamics in elderly patients undergoing total hip arthroplasty, reduce the incidence of postoperative delirium, shorten the duration of delirium, and reduce the length of hospital stay. Small sample size and the inability to conduct a long-term follow-up of patients are the shortcomings of this study. The MMSE is the most commonly used instrument for the assessment of cognitive function in both clinical and research settings. The assessment of the patient’s preoperative state using MMSE scores has some limitations; educational level, age, and sex are known to have strong influences on the MMSE score. It is highly recommended to consider eliminating the impact of these confounding factors in future follow-up studies. In addition, it is unclear whether dexmedetomidine has the same effect on patients undergoing epidural anesthesia, and further studies are warranted.

| Table 3  | The incidence of delirium, duration of delirium, and hospital days in the 2 groups |
|----------|----------------------------------------------------------------------------------|
|          | Delirium incidence, n (%) | Delirium duration, days | Hospital days |
| C group  | 50 | 13 (26) | 3.0 ± 0.5 | 16.1 ± 0.7 |
| D group  | 50 | 5 (10)* | 1.3 ± 0.6* | 13.2 ± 0.9* |
| P value  | 0.037 | 0.000 | 0.000 |

*P < 0.05 versus C group.

| Table 4  | Adverse reactions in the 2 groups |
|----------|----------------------------------|
|          | n Nausea, n Vomiting, n Lethargy, n |
| C group  | 50 3 2 4 |
| D group  | 50 4 2 5 |
| P value  | 0.695 1 0.727 |
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