

Dexmedetomidine potential in attenuating postoperative delirium in elderly patients after total hip joint replacement

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SUMMARY

OBJECTIVE: This study aims to evaluate the effectiveness of dexmedetomidine in reducing the occurrence of postoperative delirium in elderly patients after total hip joint replacement.

METHODS: Patients who have undergone total hip joint replacement and who were admitted to the hospital from August 1, 2017, to August 1, 2020, were included in this study. After initial screening, 327 out of 385 patients were selected and randomly assigned to either dexmedetomidine (0.1 µg/kg/h, n=163) or placebo (n=164) groups. The occurrence of delirium was examined twice a day for one week by using the Confusion Assessment Method. Furthermore, 30-day all-cause mortality, hospitalization duration and costs, and the presence of any postoperative complications were also evaluated.

RESULTS: The postoperative delirium incidence was significantly lower in the dexmedetomidine group compared to that in the placebo group (13.8 vs. 29.3%, $p < 0.01$). The hospitalization duration (17.2 ± 6.3 vs. 15.6 ± 4.2 , $p = 0.006$) and cost (4.5 ± 0.9 vs. 4.9 ± 1.1 , $p = 0.001$) in the dexmedetomidine group were also lower than those in the placebo group. Meanwhile, no significant difference between the 30-day all-cause mortality of the two groups was observed ($p = 0.60$). In terms of safety, no significant differences between the occurrence of hypotension and bradycardia were also observed.

CONCLUSION: Our findings show that the dexmedetomidine medication can reduce the postoperative delirium incidence in older total hip joint replacement patients and can subsequently decrease the related hospitalization duration and cost of these patients.

KEYWORDS: Dexmedetomidine. Joint Replacement. Delirium.

INTRODUCTION

Postoperative delirium (POD) is a life-threatening clinical complication that is prevalent in elderly patients. It is associated with a higher risk of dementia and mortality¹. In most cases, POD often leads to prolonged treatment duration and high costs due to cognitive impairment and disability². Interestingly, a previous study has reported that POD has an incidence of around 11–51% in elderly patients who have received total hip arthroplasty (THA)³. In a similar study, it has been found that 23.33% of elderly patients undergoing THA due to hip fracture will develop POD⁴. Furthermore, POD can manifest in 60–80% of hospitalized elderly patients⁵. Alarming, in the United States, an 85% increase in total knee arthroplasty (TKA) procedure growth rate was observed within the last 14 years, and it is anticipated that THA procedures will increase to 71% by 2030⁶. Thus, it is important to prevent the development of POD to improve long-term outcomes and decrease the hospitalization duration and cost of affected patients.

Currently, there is no effective preventive drug against POD as well as proof from randomized controlled studies in post-THA elderly patients that has been reported yet.

Dexmedetomidine (DEX) is a highly selective agonist of the α -2-adrenergic receptor that causes adequate sedation with minimal respiratory depression⁷. Recent studies are increasingly providing evidence on the protective effects of DEX administration on various organ injuries^{7,8} and delirium^{2,9}. A previous study has also reported that DEX can potentially slow the course of delirium in critically ill patients¹⁰. Currently, there are no reports of any randomized controlled trials done to demonstrate the potency of DEX in preventing the development of POD in elderly patients following THA. Thus, the anti-delirium effectiveness of DEX has remained unclear and controversial. To bridge this knowledge gap, this study aims to explore the effectiveness of acute DEX treatment in reducing POD and improving post-THA operation clinical outcomes.

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METHODS

Study design and patient screening

A total of 385 patients who were admitted to the hospital from August 1, 2017 to August 1, 2020 were recruited for this study. Elderly patients who were scheduled for THA surgery were considered eligible to be included in the trial based on the following inclusion criteria:

1. over 60 years old,
2. amenable to a random treatment of DEX or placebo 72 h postsurgery, and
3. received general anesthetization for the surgery and was admitted in the Intensive Care Unit (ICU) after surgery.

In contrast, patients were excluded from the trial if they met any of the following criteria:

1. identified as probably unsalvageable at admission,
2. diagnosed with diabetes combined with high cholesterol levels, or
3. any history of brain injury, neurosurgery, severe sinus bradycardia, neurological disease, rhabdomyolysis, myopathy, mental illness, epilepsy, severe lung disease, and multiple organ dysfunction.

Using these criteria, 58 patients were excluded, while 327 patients were randomly assigned (1:1) to either the treatment or placebo group. The treatment group was treated with 0.1 µg/kg/h DEX, while the placebo group was administered with an equal amount of normal saline solution intravenously within 72 h following THA surgery. Assessment of delirium was performed twice a day for one week using the Confusion Assessment Method (CAM). One month after surgery, a final visit was conducted as a 30-day follow-up.

Randomization and masking

All patients and investigators involved in treatment delivery, data collection, or outcome assessment were kept blinded to the randomization detail. As previously discussed, the recruited subjects were randomly assigned to either the DEX or the placebo group. The drug appearance and packages of medical envelopes were all identical, and medications were delivered by a nurse adhering to the randomization sequence. To ensure that the safety of patients was maintained, two on-call experts or pharmacists were authorized to decide whether the grouping details could be revealed in any incidence of severe adverse events or unexpected deterioration in the patient's clinical status. All situations were documented in the case report forms.

Procedures

All patients were assigned to a subgroup based on the American Society of Anesthesiologists (ASA) classification following the evaluation of their medical comorbidities. In addition, they received no premedication, along with a standard preoperative evaluation and the same general anesthesia protocol using IV midazolam (1–2 mg) and fentanyl (50–100 mg) for preoperative sedation, and 3–6 mg/kg IV fentanyl for maintaining anesthesia. Electrocardiography, noninvasive blood pressure, pulse oximetry (SpO₂), and bispectral index were monitored routinely. Radial arterial pressure and central venous pressure were monitored as necessary.

Outcome assessment

As previously mentioned, all investigators were blinded to treatment allocation and were trained before the study. Those involved in data collection and outcome assessment did not participate in the treatment procedures. The POD incidence was evaluated postsurgery as the primary endpoint, with the first examination performed almost 24 h after surgery and continued twice a day during the first week⁹. POD assessment was conducted using CAM for the detection of four main features:

1. an acute change or a fluctuation in mental status,
2. inattention,
3. disorganization in thinking, and
4. alteration in consciousness levels.

Patients displaying features 1 and 2 with either 3 or 4 were diagnosed as developing delirium⁹. In case of death or discharge within the 1-week postsurgery period, the last delirium assessment was missing⁹. The 30-day all-cause mortality, hospital costs, and length of stay, as well as the occurrence of any nondelirium postoperative complications, were defined as the secondary endpoints.

Assessment of Dexmedetomidine-related adverse events

All related adverse events were subjected to evaluation. Hypotension and bradycardia were the most frequent adverse events. Patients were informed of their conditions when necessary.

Statistical analysis

To estimate the minimum appropriate sample size to be used in this study, an assumption of a 40% rate of POD for the DEX group and a 25% rate for the placebo group was made based on our preliminary trial. With these, we estimated that a sample size of 298 patients would be required for this study (80% power and 2-sided, $\alpha=0.05$, a 10% loss to follow-up),

and to account for our estimate, at least 300 patients were enrolled in our experimental design. The incidence and relative risk reduction of dichotomous variables were described for the DEX-treated group and were compared to the placebo group (95%CI). Normally distributed continuous data (mean±SD) and non-normally distributed data were analyzed using the unpaired t-test and independent-samples Mann-Whitney U test, respectively. In addition, the χ^2 test or continuity correction χ^2 test was used to compare the categorical data. Mean differences or risk ratios were calculated with two-sided 95%CI, considering a $p < 0.05$ as statistically significant. Statistical analyses were conducted using the SPSS statistics software (version 18, IBM, Chicago, IL). No interim analysis was included in the assessments. Data overseeing was performed by the Clinical Research Ethics Committee from the 904th Hospital of Joint Logistic Support Force of PLA.

RESULTS

Out of the 385 initially assessed patients, 327 patients were recognized as eligible to be included in the study. The enrolled patients were randomly assigned to either the DEX (n=163) or placebo (n=164) groups (Figure 1). No patient withdrew their consent; however, four patients in the DEX group and two patients in the control group gave up the treatment. Furthermore, seven patients from the DEX group and five patients from the placebo group had to adjust their doses as shedding cases. Therefore, a total of 309 patients were ultimately included in the final intention-to-treat analysis (Figure 1), with all patients completing the 30-day follow-up.

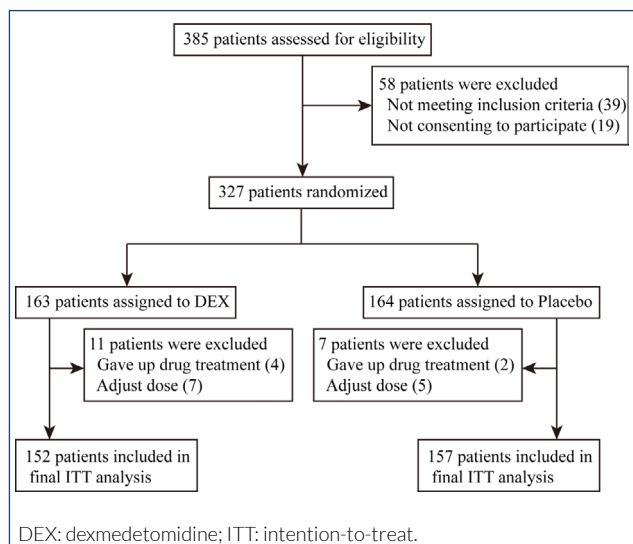


Figure 1. Trial profile.

Comparison of the baseline patient characteristics between the Dexmedetomidine and placebo groups

The baseline patient characteristics of 152 DEX-treated patients and 157 placebo-treated patients were compared at the end of the intervention period. The demographics, characteristics, and postoperative medication and management of patients were similar between the two groups (Table 1).

Postoperative delirium incidence

A lower POD incidence was observed in the DEX (21 cases; 13.8% of total) group compared to that in the placebo (46 cases; 29.3% of total) group ($p < 0.01$; Table 2).

Secondary endpoint parameters

A lower 30-day all-cause mortality of 3.3% (n=5 out of 152) was observed in the DEX group compared to 4.5% (n=7 out of 157) in the placebo group ($p = 0.60$; Table 2). Meanwhile, hospitalization duration in the placebo group was significantly higher than that in the DEX group (17.2 ± 6.3 vs. 15.6 ± 4.2 ; $p = 0.006$; Table 2). Similarly, the hospitalization costs in the placebo group were also significantly higher than that in the DEX group (4.9 ± 1.1 vs. 4.5 ± 0.9 ; $p = 0.001$; Table 2).

Safety evaluation

The occurrence of hypotension and bradycardia were evaluated as drug-related complications. Signs of hypotension were observed in 8.3% of the placebo group and 14.5% of the DEX group, while bradycardia was observed in 5.7% of the placebo group and 10.5% of the DEX group. However, no significant difference in the occurrence of these complications was seen in both groups (Table 2). Nonetheless, a relative increase in the incidence of postoperative complications was observed in the DEX group compared to the placebo group, which requires attention to minimize the development of serious complications.

DISCUSSION

Based on our findings, DEX treatment can significantly decrease POD in elderly patients who have undergone THA surgery. Furthermore, the use of DEX can also reduce hospitalization duration and costs. However, the 30-day all-cause mortality rates were not improved by the DEX administration. There was also no significant difference in the occurrence of postoperative complications, such as hypotension and bradycardia, between the treatment and placebo groups.

The incidence of POD following a THA operation was 29.3% in the DEX group and 13.8% in the placebo group.

Table 1. Demographic and baseline characteristics of the study population in the two groups.

	Placebo (%)	DEX (%)	p-value
Number	157	152	
Age			0.50
Mean±SD	68.4±6.6	67.9±5.9	
Sex			0.88
Male	74 (47.1)	73 (48.0)	
Female	83 (52.9)	79 (52.0)	
BMI	20.14±0.89	20.25±0.92	0.29
Weight	63.4±10.9	64.8±11.3	0.27
Type 2 DM			0.56
Yes	23 (14.6)	26 (17.1)	
No	134 (85.4)	126 (82.9)	
History of hypertension			0.75
Yes	51 (32.5)	52 (34.2)	
No	106 (67.5)	100 (65.8)	
Smoking history			0.23
Yes	41 (26.1)	31 (20.4)	
No	116 (73.9)	121 (79.6)	
Duration of operation (min)	2.3±0.4	2.3±0.3	0.45
Blood transfusion			0.40
Yes	12 (7.6)	8 (5.3)	
No	145 (92.4)	144 (94.7.0)	
Bleeding (mL)	435±108	382±93	0.07
ICU stays (day)	2.2±1.4	2.2±1.5	0.96
Intraoperative medication			>0.05
Midazolam	81 (51.6)	77 (50.7)	
Fentanyl	157 (100)	152 (100)	
Propofol	157 (100)	152 (100)	
Atropine	22 (14.0)	18 (11.8)	
Analgesic (within 7 days)			>0.05
Diclofenac sodium	55 (35.0)	49 (32.2)	
Diclofenac sodium dose (mg)	284±92	229±113	
Morphine	40 (25.5)	34 (22.4)	
Morphine dose (mg)	24.4±5.8	23.12±9.4	
Midazolam	13 (8.3)	9 (5.9)	
Midazolam (mg)	37.3±9.5	36.1±8.2	

DEX: dexmedetomidine; Mean±SD: Mean±Standart Deviation; BMI: Body mass index; DM: diabetes.

These results are consistent with the findings of previous studies^{4,11}. In one study, an overall POD incidence of 44% was observed in 144 patients undergoing major abdominal, thoracic, and vascular operations with an average onset time of 2.1±0.9 days and a mean duration of 4.0±5.1 days¹². Another recent study has shown that delirium in elderly patients undergoing major thoracic and abdominal surgeries decreased by one-third upon using a combined epidural and general anesthesia procedure¹³. Similarly, our findings indicated that POD increases hospitalization duration and costs, which emphasizes efficient medications as the major therapy. In relation to this, treatment with haloperidol or ziprasidone did not elicit any significant change in the POD duration in ICU patients with acute respiratory failure or shock, as well as in the presence of hypoactive or hyperactive delirium in these patients¹⁴. Another similar trial showed that treatment with simvastatin did not reduce the incidence nor the duration of delirium in treated patients¹⁵. Hence, it is necessary to explore new drugs that can be beneficial for ameliorating delirium.

Delirium is a multifactorial disorder that can be induced or aggravated by many factors, such as the use of sedatives or hypnotic drugs, sleep deprivation, brain trauma, and coma¹. The pathophysiologic underlying mechanisms of delirium are extremely complicated and can include systemic neuroinflammation and micro-thrombosis processes, oxidative stress and endothelial damage, various neurotransmitters, cerebral hypoperfusion, and an injured blood-brain barrier^{1,16}. Previous studies have reported elevated expression levels of C-reactive protein, interleukins (IL) 1, 6, 8, and 10, as well as tumor necrosis

Table 2. The results between two groups.

	Placebo (%)	DEX (%)	p-value
Number	157	152	
POD	21 (13.8)	46 (29.3)	<0.01
All-cause 30-day mortality	5 (3.3)	7 (4.5)	0.60
Hospitalization duration	17.2±6.3	15.6±4.2	0.006
Hospitalization costs	4.5±0.9	4.9±1.1	0.001
Hypotension			0.086
Yes	13 (8.3)	52 (14.5)	
No	144 (91.7)	100 (85.5)	
Bradycardia			0.122
Yes	9 (5.7)	16 (10.5)	
No	148 (94.3)	136 (89.5)	

DEX: dexmedetomidine; POD: postoperative delirium.

factor- α (TNF- α) in patients developing delirium during acute medical hospitalizations¹⁷. Interestingly, DEX treatment has been shown to significantly increase the neurological score and suppress the expression of other factors such as IL-1 β , IL-6, and TNF- α in patients, which suggests that DEX can alleviate neuroinflammation¹⁸.

DEX is frequently used as an adjuvant in general anesthesia because of its potency and specific affinity to α -2-adrenergic receptors. It also serves as a sedation agent against delirium for ICU patients receiving mechanical ventilation^{9,19}. It has been shown that the effects of DEX on POD were dose-dependent, as low doses could significantly decrease POD with no enhancement in the risk of adverse events^{9,20}. We also observed that a low dose of DEX was safe and did not aggravate drug-related complications, such as hypotension and bradycardia. Consistent with our findings, previous studies have reported that intraoperative DEX treatment can reduce the delirium risk in elderly patients following a major noncardiac surgery²¹. To our knowledge, no evidence-based medical investigation has been done to determine the effectiveness of DEX in THA patients. This is the first large-sample randomized, double-blind, placebo-controlled trial that explored the effectiveness of low-dose DEX in elderly patients who received

THA. Because of the limitations in the availability of treatment options for established delirium, risk assessment and perioperative risk reduction have been suggested to be the most effective approaches to managing POD^{22,23}.

CONCLUSION

Postoperative DEX administration has the potential to reduce the incidence of POD in elderly patients who have undergone THA. Furthermore, although we have not observed any benefit of the DEX treatment in reducing the 30-day all-cause mortality rate, our analyses showed that it can decrease the length of ICU stay and hospital costs for patients. Moving forward, we recommend that a larger population of elderly patients who have undergone THA surgery should be investigated using a variety of DEX doses to achieve a more comprehensive understanding of its potential for preventing POD.

AUTHORS' CONTRIBUTIONS

YL: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **LG:** Data curation, Writing – original draft.

REFERENCES

- Chen J, Wang Y, Hu X, Li M, Xiong K, Zhang Z, et al. The role of statins in the management of delirium: recent advances. *CNS Neurol Disord Drug Targets*. 2021;20(3):203-15. <https://doi.org/10.2174/1871527319666200720111318>
- Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-22. [https://doi.org/10.1016/S0140-6736\(13\)60688-1](https://doi.org/10.1016/S0140-6736(13)60688-1)
- Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med*. 2010;38(7):1513-20. <https://doi.org/10.1097/CCM.0b013e3181e47be1>
- Redelmeier DA, Manzoor F, Thiruchelvam D. Association Between Statin Use and Risk of Dementia After a Concussion. *JAMA Neurol*. 2019;76(8):887-96. <https://doi.org/10.1001/jamaneurol.2019.1148>
- Sloan M, Premkumar A, Sheth NP. Projected Volume of Primary Total Joint Arthroplasty in the U.S., 2014 to 2030. *J Bone Joint Surg Am*. 2018;100(17):1455-60. <https://doi.org/10.2106/JBJS.17.01617>
- He R, Wang F, Shen H, Zeng Y, Lijuan Zhang. Association between increased neutrophil-to-lymphocyte ratio and postoperative delirium in elderly patients with total hip arthroplasty for hip fracture. *BMC Psychiatry*. 2020;20(1):496. <https://doi.org/10.1186/s12888-020-02908-2>
- Yang T, Feng X, Zhao Y, Zhang H, Cui H, Wei M, et al. Dexmedetomidine enhances autophagy via α 2-AR/AMPK/mTOR pathway to inhibit the activation of nlrp3 inflammasome and subsequently alleviates lipopolysaccharide-induced acute kidney injury. *Front Pharmacol*. 2020;11:790. <https://doi.org/10.3389/fphar.2020.00790>
- Li H, Lu C, Yao W, Xu L, Zhou J, Zheng B. Dexmedetomidine inhibits inflammatory response and autophagy through the circLrp1b/miR-27a-3p/Dram2 pathway in a rat model of traumatic brain injury. *Aging (Albany NY)*. 2020;12(21):21687-705. <https://doi.org/10.18632/aging.103975>
- Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;388(10054):1893-902. [https://doi.org/10.1016/S0140-6736\(16\)30580-3](https://doi.org/10.1016/S0140-6736(16)30580-3)
- Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301(5):489-99. <https://doi.org/10.1001/jama.2009.56>
- O'Gara BP, Mueller A, Gasangwa DVI, Patxot M, Shaefi S, Khabbaz K, et al. Prevention of Early Postoperative Decline: A Randomized, Controlled Feasibility Trial of Perioperative Cognitive Training. *Anesth Analg*. 2020;130(3):586-95. <https://doi.org/10.1213/ANE.0000000000004469>
- Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M. Postoperative delirium in the elderly: risk factors and outcomes. *Ann Surg*. 2009;249(1):173-8. <https://doi.org/10.1097/SLA.0b013e31818e4776>
- Li YW, Li HJ, Li HJ, Zhao BJ, Guo XY, Feng Y, et al. Delirium in Older Patients after Combined Epidural-General Anesthesia or General Anesthesia for Major Surgery: A Randomized Trial. *Anesthesiology*. 2021;135(2):218-32. <https://doi.org/10.1097/ALN.0000000000003834>
- Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, et al. Haloperidol and Ziprasidone for Treatment of Delirium in

- Critical Illness. *N Engl J Med.* 2018;379(26):2506-16. <https://doi.org/10.1056/NEJMoa1808217>
15. Page VJ, Casarin A, Ely EW, Zhao XB, McDowell C, Murphy L, et al. Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med.* 2017;5(9):727-37. [https://doi.org/10.1016/S2213-2600\(17\)30234-5](https://doi.org/10.1016/S2213-2600(17)30234-5)
 16. Alam A, Hana Z, Jin Z, Suen KC, Ma D. Surgery, neuroinflammation and cognitive impairment. *EBioMedicine.* 2018;37:547-56. <https://doi.org/10.1016/j.ebiom.2018.10.021>
 17. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry.* 2013;21(12):1190-222. <https://doi.org/10.1016/j.jagp.2013.09.005>
 18. Feng X, Ma W, Zhu J, Jiao W, Wang Y. Dexmedetomidine alleviates early brain injury following traumatic brain injury by inhibiting autophagy and neuroinflammation through the ROS/Nrf2 signaling pathway. *Mol Med Rep.* 2021;24(3):661. <https://doi.org/10.3892/mmr.2021.12300>
 19. Alexopoulou C, Kondili E, Diamantaki E, Psarologakis C, Kokkini S, Bolaki M, et al. Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot study. *Anesthesiology.* 2014;121(4):801-7. <https://doi.org/10.1097/ALN.0000000000000361>
 20. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics.* 2009;50(3):206-17. <https://doi.org/10.1176/appi.psy.50.3.206>
 21. Li CJ, Wang BJ, Mu DL, Hu J, Guo C, Li XY, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. *Br J Surg.* 2020;107(2):e123-32. <https://doi.org/10.1002/bjs.11354>
 22. Alam A, Ma D. Is it time to Assess Neurological Status Before Surgery to Improve Postoperative Outcomes? *Ann Surg.* 2022;275(4):644-5. <https://doi.org/10.1097/sla.0000000000005287>
 23. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth.* 2020;125(4):492-504. <https://doi.org/10.1016/j.bja.2020.06.063>

