ANESTHESIOLOGY

Postoperative Delirium after Dexmedetomidine *versus* Propofol Sedation in Healthy Older Adults Undergoing Orthopedic Lower Limb Surgery with Spinal Anesthesia: A Randomized Controlled Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Dexmedetomidine administration in the perioperative period has been associated with less postoperative delirium after general anesthesia.
- The incidence of delirium after cardiac surgery is lower when cardiac surgery patients are sedated with dexmedetomidine compared with propofol.

What This Article Tells Us That Is New

- A randomized double-blinded study of 732 patients 65 yr or older, scheduled for elective lower extremity orthopedic surgery under spinal anesthesia, were randomized to dexmedetomidine or propofol sedation.
- Patients receiving dexmedetomidine sedation had a lower incidence of delirium when compared to sedation with propofol, suggesting benefit of dexmedetomidine.

ABSTRACT

Background: Delirium is a critical postoperative complication in older patients. Based on the hypothesis that intraoperative dexmedetomidine sedation would lower postoperative delirium than propofol sedation would, the authors compared the incidence of postoperative delirium in older adults, using the mentioned sedatives.

Methods: This double-blinded, randomized controlled study included 748 patients, aged 65 yr or older, who were scheduled for elective lower extremity orthopedic surgery, between June 2017 and October 2021. Patients were randomized equally into two groups in a 1:1 ratio according to the intraoperative sedative used (dexmedetomidine *vs.* propofol). The postoperative delirium incidence was considered the primary outcome measure; it was determined using the confusion assessment method, on the first three postoperative days. The mean arterial pressure and heart rate were evaluated as secondary outcomes.

Results: The authors enrolled 732 patients in the intention-to-treat analyses. The delirium incidence was lower in the dexmedetomidine group than in the propofol group (11 [3.0%] *vs.* 24 [6.6%]; odds ratio, 0.42; 95% CI, 0.201 to 0.86; $P = 0.036$). During sedation, the mean arterial pressure (median [interquartile range] mmHg) was higher in the dexmedetomidine group (77 [71 to 84]) than in the propofol group (74 [69 to 79]; $P < 0.001$); however, it significantly fell lower (74 [68 to 80]) than that of the propofol group (80 [74 to 87]) in the postanesthesia care unit ($P < 0.001$). Lower heart rates (beats/min) were recorded with the use of dexmedetomidine than with propofol, both during sedation (60 [55 to 66] *vs.* 63 [58 to 70]) and in the postanesthesia care unit (64 [58 to 72] *vs.* 68 [62–77]; $P < 0.001$).

Conclusions: Dexmedetomidine showed a lower incidence of postoperative delirium than propofol in healthy older adults undergoing lower extremity orthopedic surgery.

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Postoperative delirium is an important complication of prolonged hospital stay, delayed functional recovery, and highly morbid conditions, particularly in older adults.[1,2] Furthermore, postoperative delirium is known to be a risk factor for dementia in old age.[3] However, healthcare planners and providers are not cognizant of its significance.[4] Numerous recent clinical trials have aimed to identify the factors contributing to postoperative delirium. With its multifactorial etiology, postoperative delirium is difficult to treat or prevent.[5]

The prevalence of postoperative delirium varies considerably with the patient's condition and the type of surgery. Currently, the main factors contributing to postoperative delirium are advanced age (greater than 65 yr) and

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orthopedic surgery.[6] Delirium is estimated to occur in 10 to 80% of inpatients;[7,8] the incidence of postoperative delirium after orthopedic surgery is reported to be 5 to 61%.[1,2,9]

In our previous retrospective study, dexmedetomidine, when infused as a sedative,[10] exhibited a lower incidence (2.5%) of postoperative agitation as compared to that of the propofol group (6.8%), with the latter group being 5.92 times more likely to experience it. However, to overcome the shortcomings of the retrospective study, we decided to clarify the results with a well-designed prospective trial.

The current study aimed to identify the effect of dexmedetomidine on the occurrence of postoperative delirium when used as a sedative during lower limb orthopedic surgery in healthy older adult patients under spinal anesthesia. Based on the hypothesis that intraoperative dexmedetomidine sedation would lower postoperative delirium more than that of propofol, the incidence of postoperative delirium was investigated for both the sedatives.

Materials and Methods

Study Setting

This double-blind randomized controlled study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (Seongnam, Korea; B-1704/391-304; June 2017) and was registered before patient enrollment at https://ClinicalTrials.gov (NCT03251651; principal investigator: Hyo-Seok Na; registered on August 16, 2017). Written informed consent was obtained from all participants. This study was conducted at Seoul National University Bundang Hospital from June 2017 to October 2021.

Participants, Study Design, and Randomization

Adult patients, aged 65 yr or older, who were scheduled for elective lower extremity orthopedic surgery with spinal anesthesia were screened. Patients with an American Society of Anesthesiologists (ASA) Physical Status I or II were included in this randomized study. Patients who refused intraoperative sedation, and those with visual, cognitive, language, or speech impairment, neuropsychiatric diseases including dementia, Parkinson's disease, or cerebrovascular accidents were excluded.

This study was a block-randomized, parallel-group trial with two equal-sized groups. A randomization chart was generated using a web-based randomization system, with a block size of four. The allocation ratio was set at 1:1. Randomization was performed by an anesthesiologist who prepared individual opaque, sealed envelopes for all participants, containing computer-generated instructions for group allocation. On the day of surgery, before entering the operation room, an anesthesiologist who was not involved in the patient's perioperative care opened the envelope and allocated participants.

As the two sedatives, propofol and dexmedetomidine, differ in color and infusion method, the anesthesiologist who attended to the patients' care during surgery was aware of the sedative used. A blinded investigator who did not directly participate in the patient's anesthetic care collected all postoperative data. In principle, the patients and orthopedic surgery team were blinded to the group allocation.

Preoperative Screening of Baseline Cognitive Status

Baseline cognitive function was evaluated using the Korean version of the Mini-Cog, validated in Korea.[11] This test consists of two components: a three-item recall test for memory, and a clock drawing test. Although it does not replace a complete diagnostic test, a total score of 3, 4, or 5 indicates a lower likelihood of dementia.

Spinal Anesthesia

The patients did not receive any premedication. Noninvasive arterial blood pressure, electrocardiogram, and pulse oximetry were monitored on arrival. Oxygen was supplied *via* a face mask at a rate of 5 l/min. After positioning the patient in the lateral decubitus position, a 25-gauge Quincke needle was inserted into L3–L4 or L4–L5, using a midline or paramedian approach. After confirming the free flow of cerebrospinal fluid through the needle, a mixture of 2.0 to 3.0 ml 0.5% hyperbaric bupivacaine and 10 to 20 μg fentanyl was intrathecally administered; the patient was instantly placed in a supine position, and a sensory

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check using a cold swab was performed every 1 to 2 min. A forced-air warming blanket was applied to the upper body to maintain normothermia during surgery.

Intraoperative Sedation

Sedation commenced after appropriate neuraxial block by spinal anesthesia, concurrently ensuring hemodynamic stability. Sedation was maintained to achieve a modified observer's assessment of alertness/sedation score of 3 or 4,[12] adhering to the standard sedation protocol of our institution.

While propofol was continuously infused *via* a target-controlled infusion device (Orchestra; Fresenius vial, France), adjusting the effect-site concentration within 1.0 to 2.0 μg/ml, 1 μg/kg dexmedetomidine was administered for more than 10 min as the loading dose, followed by continuous administration at 0.1 to 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$, in their respective groups. During the first 20 to 30 min after the drug infusion, the patient's sedation state was assessed by an anesthesiologist every 5 min to titrate the rate of drug infusion. Thereafter, the patient's sedative level was evaluated every 15 min. The propofol infusion was stopped when the final surgical dressing was applied. Administration of dexmedetomidine was stopped at the start of subcutaneous and skin closure, approximately 30 min earlier than the discontinuation of propofol.

Patients who developed hypotension (systolic blood pressure less than 80% of the baseline or less than 90 mmHg) were treated with intravenous ephedrine or phenylephrine. When the heart rate (HR) fell to less than 40 beats/min, atropine (0.5 mg) was administered.

Assessment of Postoperative Delirium

The confusion assessment method was used to determine the occurrence of postoperative delirium.[13] The confusion assessment method was developed as a delirium screening tool for nonpsychiatric clinicians, based on the elements of Diagnostic and Statistical Manual of Mental Disorders-III-R criteria; it is reported to be highly sensitive (94 to 100%) and specific (90 to 95%).[13] The assessments were performed by an investigator, who was blinded to the group assignment, using the confusion assessment method for three postoperative days; if one of the three days emerged as confusion assessment method positive, it was classified as postoperative delirium. Concurrently, investigators also reviewed the medical records, and interviewed their caregivers and nurses for evidence of suspicion of delirium, including confusion, agitation, hallucinations, delusions, or sedation.

Outcome Variables

The primary outcome was the incidence of postoperative delirium. Hemodynamic variables, including the mean arterial pressure (MAP) and HR, were considered for evaluation as secondary outcomes. MAP and HR were classified into three periods: (1) before sedation, after arriving at the operating room and before sedation; (2) during sedation, from start to end of sedative drug administration; and (3) at the postanesthesia care unit (PACU), during the stay in the PACU.

Although the trial was performed in adherence to the protocol, owing to the heterogeneity of surgery, it was expected that the outcomes regarding postoperative pain, patient-controlled analgesia, and rescue analgesics could exhibit considerable variability. Therefore, the plan was altered to exclude the collection of data on the postoperative pain and analgesic drugs.

Sample Size

In a previous study, the incidence of postoperative abnormal behavior after infusion of dexmedetomidine and propofol was reported as 2.3% and 6.8%, respectively.[10] To estimate the difference in incidence of postoperative delirium among the study groups, at a statistical power of 80% and a statistical significance of 5%, a total of 336 patients per group were required in the study; 748 patients were selected, estimating a dropout rate of 10%.

Statistical Analysis

The primary outcome, postoperative delirium rate, was analyzed using the chi-square test in both the intention-to-treat and per-protocol populations. For patients with missing data due to early hospital discharge, if they were evaluated as positive for the confusion assessment method even once during the postoperative admission period, they were classified as having postoperative delirium. For secondary outcomes, all continuous data were evaluated for normality using the Shapiro–Wilk test, and presented as median, interquartile range, and range; they were compared using Mann–Whitney U tests. Categorical data, expressed as numbers (percentages), were analyzed using chi-square or Fisher exact tests, at a 95% CI.

All analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corporation, USA). Statistical significance was set at a two-sided $P < 0.05$. The intention-to-treat analyses were presented as the main results, and the per-protocol analyses are shown in the Supplemental Digital Content.

Results

Of the 785 patients screened for eligibility, 37 were excluded (26 met the exclusion criteria, and 11 declined to participate). The remaining 748 patients were assigned to one of the two groups (374 patients in each group). After excluding 8 patients in each group, owing to withdrawal of consent or cancellation of the surgery, 732 patients were enrolled in the analysis of the intention-to-treat population. After 49 protocol deviations were further rejected, 683 patients were enrolled in the per-protocol population (fig. 1). Enrollment was stopped upon accrual of recruitment goals.

Table 1 presents the baseline patient characteristics. The perioperative variables related to surgery and anesthesia are listed in table 2. The sedative effect of dexmedetomidine (median [interquartile range]) lasted longer than that of propofol (37 [23 to 60] min *vs.* 27 [20 to 43] min, respectively; $P < 0.001$), and thus with a lower modified observer's assessment of alertness/sedation score (5 [4 to 5] *vs.* 5 [5 to 5], respectively; $P < 0.001$) at PACU.

The baseline cognitive function did not differ between the two groups (table 3). We found that postoperative delirium was significantly lower in the dexmedetomidine group than in the propofol group (3.0% *vs.* 6.6%; odds ratio, 0.42; 95% CI, 0.201 to 0.86; $P = 0.036$). Postoperative delirium was most frequently reported on the first postoperative day in both the groups.

The MAP and HR were comparable between the two groups before sedation (fig. 2, A and B; table 2). During sedation, the MAP was higher in the dexmedetomidine group ($P < 0.001$) when relatively lesser concentrations of phenylephrine were used (1.06 $\mu g \cdot kg^{-1} \cdot h^{-1}$ *vs.* 1.76 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively; $P = 0.049$). However, the MAP of the dexmedetomidine group was significantly lower in the PACU ($P < 0.001$; fig. 2A; table 2), thus requiring a higher quantity of phenylephrine than the propofol group (0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ *vs.* 0.21 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively; $P = 0.002$). Moreover, the HR was lower in the dexmedetomidine group, both during sedation and in the PACU ($P < 0.001$; fig. 2B; table 2).

A MAP of less than 60 mmHg was recorded during sedation in 6 (1.6%) and 13 (3.6%) patients in the dexmedetomidine and propofol groups, respectively, while only 10 patients (2.7%) of the former group recorded similar values at PACU.

The results of per-protocol analyses can be found in the Supplemental Digital Content (table S1, table S2, and table S3; http://links.lww.com/ALN/C971).

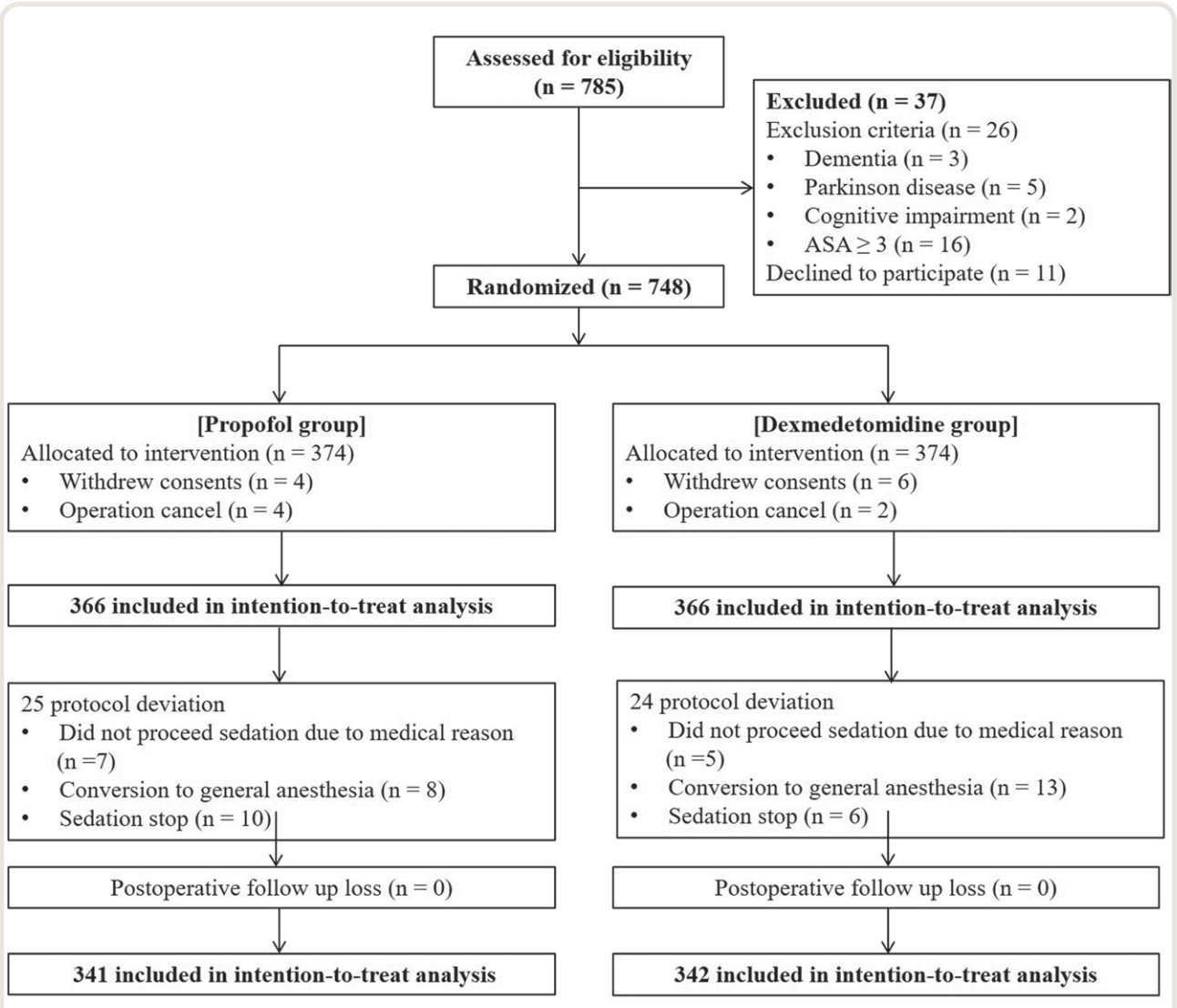

Fig. 1. CONsolidated Standards of Reporting Trials diagram. ASA, American Society of Anesthesiologists.

Table 1. Characteristics of Patients

	Propofol (n = 366)	Dexmedetomidine (n = 366)
Age (yr)	71 (67–75)	72 (68–76)
Sex		
Male	77 (21%)	78 (21%)
Female	289 (79%)	288 (79%)
Weight (kg)	63 (56–69)	61 (56–69)
Height (cm)	154 (150–159)	153 (149–159)
ASA Physical Status classification		
I	66 (18%)	52 (14%)
II	300 (82%)	314 (86%)
Underlying disease		
Hypertension	223 (61%)	232 (64%)
Diabetes mellitus	77 (21%)	101 (28%)
Chronic kidney disease	7 (1.9%)	8 (2.2%)
Chronic liver disease	3 (0.8%)	4 (1.1%)
Chronic pulmonary disease	8 (2.2%)	2 (0.5%)
Rheumatoid arthritis	4 (1.1%)	13 (3.6%)

Data expressed as median (interquartile range) or n (%).
ASA, American Society of Anesthesiologists.

Table 2. Perioperative Surgical and Anesthetic Variables

	Propofol (n = 366)	Dexmedetomidine (n = 366)	*P* Value
Type of surgery			
Hip and femur	92 (25%)	89 (24%)	0.667
Knee and tibia/fibula	248 (68%)	247 (68%)	0.937
Ankle and foot	26 (7%)	30 (8%)	0.472
Surgery time (min)	85 (75–105)	85 (75–105)	0.244
Anesthesia time (min)	125 (115–150)	130 (115–155)	0.413
Estimated blood loss (ml)	50 (50–250)	50 (50–200)	0.336
Crystalloid (ml)	450 (300–600)	400 (300–550)	0.258
Colloid (ml)	0 (0–0)	0 (0–100)	0.651
Urine (ml)	244 (130–400)	250 (150–380)	0.778
Erythrocyte (unit)			
Before surgery	0 (0–0)	0 (0–0)	> 0.999
During surgery	0 (0–0)	0 (0–0)	0.799
After surgery	0 (0–0)	0 (0–0)	0.635
Modified observer's assessment of alertness/sedation score at PACU	5 (5–5)	5 (4–5)	< 0.001
PACU stay (min)	27 (20–43)	37 (23–60)	< 0.001
Length of stay (d)			
Before surgery	1 (1–1)	1 (1–1)	0.870
After surgery	6 (6–7)	6 (6–7)	0.778
Total	7 (7–8)	6 (6–7)	0.821
ICU care, postoperatively	1 (0.3%)	0 (0%)	> 0.999
Ephedrine, total (mg)	5 (0–5)	5 (0–10)	0.179
Phenylephrine, total (μg)	0 (0–30)	0 (0–20)	0.411
Atropine, total (mg)	0 (0–0)	0 (0–0)	0.314
MAP (mmHg)			
Before sedation	94 (87–102 [61–122])	92 (83–101 [61–121])	0.098
During sedation	74 (69–79 [41–119])	77 (71–84 [53–103])	< 0.001
At PACU	80 (74–87 [60–112])	74 (68–80 [55–112])	< 0.001
HR (beats/min)			
Before sedation	74 (67–82 [46–112])	74 (65–82 [45–125])	0.194
During sedation	63 (58–70 [45–125])	60 (55–66 [44–104])	< 0.001
At PACU	68 (62–77 [44–100])	64 (58–72 [43–99])	< 0.001

Data expressed as median (interquartile range), median (interquartile range [range]), or n (%).
ICU, intensive care unit; HR, heart rate; MAP, mean arterial pressure; PACU, postanesthesia care unit.

Table 3. Basal Cognitive Status and Postoperative Delirium

	Propofol (n = 366)	Dexmedetomidine (n = 366)	Odds Ratio (95% CI)	*P* Value
Mini-Cog score	5 (3–5)	5 (3–5)		0.102
Delirium*	24 (6.6%)	11 (3.0%)	0.42 (0.201–0.86)	0.036
Delirium onset				0.802
Postoperative 1 day	15 (4.1%)	7 (1.9%)		
Postoperative 2 day	5 (1.4%)	3 (0.8%)		
Postoperative 3 day	4 (1.1%)	1 (0.3%)		
Delirium period†				Not applicable
Postoperative 1 to 2 days	6 (1.6%)	0 (0%)		
Postoperative 2 to 3 days	1 (0.3%)	1 (0.3%)		
Postoperative 1 to 3 days	1 (0.3%)	0 (0%)		

Data expressed as median (interquartile range), n (%), or odd ratio (95% CI).

*For patients with missing data due to early hospital discharge, if they were evaluated as positive for the confusion assessment method even once during the postoperative admission period, they were classified as having postoperative delirium: in the propofol group, 8 and 16 patients discharged at 2 and 3 days after surgery, respectively. In the dexmedetomidine group, 4 and 18 patients discharged at 2 and 3 days after surgery, respectively. †Only patients with delirium lasting more than 2 days were included.

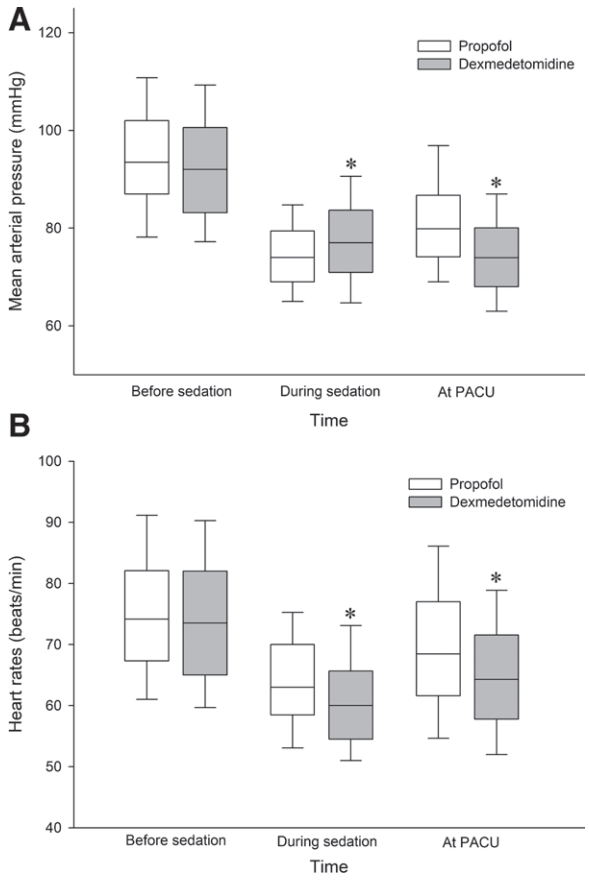

Fig. 2. Hemodynamic variables across three time periods, compared between the two study groups. (*A*) Mean arterial pressure and (*B*) heart rate, measured before and during sedation, and at the PACU. *$P < 0.001$. PACU, postanesthesia care unit.

Discussion

In this randomized study, older patients operated on for lower extremity orthopedic surgeries under spinal anesthesia demonstrated a lower incidence of postoperative delirium with the use of dexmedetomidine for sedation than with propofol.

Numerous clinical studies have validated a lesser frequency of delirium in patients sedated with dexmedetomidine compared to propofol in the intensive care unit; one such study by Djaiani *et al.* reported a lower incidence and duration and delayed onset of postoperative delirium after cardiac surgery in older patients.[14] A recent systematic review and meta-analysis presented similar findings with dexmedetomidine, without a significant difference in drug-related adversities.[15]

In addition to intensive care unit sedation, intraoperative dexmedetomidine elicits preventive effects against postoperative delirium in older orthopedic patients.[10,16] In a recent study involving older patients undergoing hip arthroplasty under nerve block, Mei *et al.*[17] presented results that were consistent with our findings;[17] however, a higher overall postoperative delirium incidence was observed when compared to our study (7% *vs.* 3% in the dexmedetomidine group; 16% *vs.* 7% in the propofol group). This difference can be substantiated by the fact that we included only ASA Physical Status I and II patients who were relatively healthy when compared to those with ASA Physical Status III or greater. Second, it is generally known that the incidence of postoperative delirium is higher in hip surgery than in other types of surgery.[10,18] Our study included various types of lower extremity orthopedic surgeries including hip surgery.

The definitive mechanism underlying the delirium-reducing effects of dexmedetomidine remains unclear. Although the neuroprotective effect of dexmedetomidine was attributed to the attenuation of

ketamine-induced neuroapoptosis in the rat brain,[19,20] it has not been confirmed in humans with respect to postoperative delirium. Other suggested mechanisms include the lack of inhibitory effect on acetylcholine release,[21,22] reduction of postoperative hypoxemia without respiratory depression,[23] and avoidance of postoperative delirium–related drugs such as benzodiazepines and opioids.[24] We recommend further research involving the pharmacologic properties of dexmedetomidine to clarify the underlying process.

Hypotension and bradycardia are among the most common hemodynamic changes, secondary to dexmedetomidine use.[25] Interestingly, dexmedetomidine-induced hypotension was observed in the PACU, but not during sedation. During the intraoperative sedation period, the proportion of patients who received a vasoconstrictor or an inotropic agent was similar between the two groups (40.9% in the dexmedetomidine group; 40.6% in the propofol group); conversely, 23.3% of the former required medications in the PACU, whereas only 7.2% of the latter received treatment for hypotension. Although hypotension in the PACU is not clinically significant, persistent postoperative hypotension must be assessed when using dexmedetomidine. Since our cohort consisted of healthy older patients, severe hypotension is unlikely; however, when associated with an illness, hypotension may persist for a considerable period postsedation with dexmedetomidine.

Despite using a randomized controlled design and a large sample size, the evaluation method for the degree of sedation was disadvantageous. Although sedation was maintained to achieve a score of 3 or 4 on the modified observer's assessment of alertness/sedation scale, objective monitoring, such as the Bispectral Index, could have determined a more precise degree of sedation. However, mild to moderate sedation was the target level of this study, which was reported to elicit a linear correlation between the Bispectral Index and the Modified Observer's Assessment of Alertness and Sedation scale.[26] Furthermore, a recent clinical study did not show a significant difference in the incidence of delirium pertaining to the depth of sedation.[27] Second, patients who did not receive intraoperative sedation were excluded, thus making it impossible to demonstrate the potential benefits and limited risks to patients receiving dexmedetomidine compared to those unsedated. In the current study, most patients desired sedation for their elective surgery under spinal anesthesia. Further studies are needed in this regard to evaluate the effectiveness of dexmedetomidine. Finally, postoperative pain and analgesic requirements, perceived as risk factors for the occurrence of postoperative delirium, were not evaluated in the current study.[6] If these data were obtained and analyzed, the possible mechanism of the delirium-sparing effect of dexmedetomidine would be explained more precisely.

In conclusion, dexmedetomidine was associated with a lower incidence of postoperative delirium than propofol when used as an intraoperative sedative in healthy older patients undergoing lower extremity orthopedic surgery under spinal anesthesia.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: hsknana@gmail.com. Raw data available at: hsknana@gmail.com.

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Supplemental Digital Content

Supplemental Tables, http://links.lww.com/ALN/C971
Supplemental Table S1. Characteristics of patients.
Supplemental Table S2. Perioperative surgical and anesthetic variables.
Supplemental Table S3. Basal cognitive status and postoperative delirium.

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