DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Thursday, 02 March, 2023
1800 HOURS

LOCATION:
HEIST Restaurant
168 Wellington St Suite 101

PRESENTING ARTICLES:
Dr. Mike Cummings & Dr. Jesse Chen

This program is possible by an educational grant from Edwards Lifesciences

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

ANESTHESIOLOGY

Spinal Anesthesia with Targeted Sedation based on Bispectral Index Values Compared with General Anesthesia with Masked Bispectral Index Values to Reduce Delirium: The SHARP Randomized Controlled Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- There are controversies about the value of processed electroencephalogram (*e.g.*, Bispectral Index [BIS]) guided anesthetic management for the prevention of postoperative delirium
- It is unclear whether reducing depth of anesthesia by the use of sedation with regional anesthesia decreases the risk of postoperative delirium compared to the use of general anesthesia

What This Article Tells Us That Is New

- This prospective single-center trial randomized patients undergoing spine surgery to spinal anesthesia with targeted sedation to BIS greater than 60 to 70 *versus* general anesthesia without BIS guidance
- There was no difference in the incidence of postoperative delirium between randomized groups in the trial
- Future studies are needed to determine whether these findings can be replicated at other centers and whether the results differ by cognitive status

ABSTRACT

Background: Reducing depth of anesthesia and anesthetic exposure may help prevent delirium, but trials have been conflicting. Most studies were conducted under general anesthesia or in cognitively impaired patients. It is unclear whether reducing depth of anesthesia beyond levels consistent with general anesthesia reduces delirium in cognitively intact patients. The authors' objective was to determine whether a bundled approach to reduce anesthetic agent exposure as determined by Bispectral Index (BIS) values (spinal anesthesia with targeted sedation based on BIS values) compared with general anesthesia (masked BIS) reduces delirium.

Methods: Important eligibility criteria for this parallel-arm randomized trial were patients 65 yr or greater undergoing lumbar spine fusion. The intervention group received spinal anesthesia with targeted sedation to BIS greater than 60 to 70. The control group received general anesthesia (masked BIS). The primary outcome was delirium using the Confusion Assessment Method daily through postoperative day 3, with blinded assessment.

Results: The median age of 217 patients in the analysis was 72 (interquartile range, 69 to 77). The median BIS value in the spinal anesthesia with targeted sedation based on BIS values group was 62 (interquartile range, 53 to 70) and in the general anesthesia with masked BIS values group was 45 (interquartile range, 41 to 50; $P < 0.001$). Incident delirium was not different in the spinal anesthesia with targeted sedation based on BIS values group (25.2% [28 of 111] *vs.* the general anesthesia with masked BIS values group (18.9% [20 of 106]; $P = 0.259$; relative risk, 1.22 [95% CI, 0.85 to 1.76]). In prespecified subgroup analyses, the effect of anesthetic strategy differed according to the Mini-Mental State Examination, but not the Charlson Comorbidity Index or age. Two strokes occurred among patients receiving spinal anesthesia and one death among patients receiving general anesthesia.

Conclusions: Spinal anesthesia with targeted sedation based on BIS values compared with general anesthesia with masked BIS values did not reduce delirium after lumbar fusion.

(ANESTHESIOLOGY 2021; 135:992–1003)

Postoperative delirium is common in older adults after surgery, with estimates of 10 to 50% depending on the type of surgery.[1–3] Although previously thought to be transient with few long-term effects, it is now recognized that postoperative delirium is associated with important sequelae, including increased duration of hospitalization,[4,5] decreased functional status,[6,7] and cognitive decline.[8,9] Despite its significance, there are few effective treatment strategies, and so prevention of delirium is paramount.[3]

In the intensive care unit, reducing the level of sedation has been associated with less delirium.[10] However, in the operating room, it is unclear whether a parallel strategy to reduce depth of anesthesia and anesthetic exposure is effective, as the results of previous trials have been promising, but conflicting.[11–16] One limitation is that most previous studies were conducted in patients undergoing general anesthesia with the goal of limiting excessive depth of anesthesia and anesthetic exposure,[11–14] and the effectiveness of strategies

to avoid general anesthesia and target lighter sedation has not been well studied. Although two additional trials did examine the benefits of lighter sedation during hip fracture surgery under spinal anesthesia, the results may not be generalizable to most older adults undergoing surgery, since a substantial number of patients were cognitively impaired.[15,16]

Thus, there is a clear need to establish whether reducing depth of anesthesia and anesthetic exposure (beyond levels consistent with general anesthesia) can reduce delirium after surgery in a representative population of older adults. This question is highly applicable since many of the most common surgeries in older adults can be performed using neuraxial/regional approaches.[17] Lumbar spine fusion surgery is one such surgery that is among the top five most frequent surgeries in older adults,[17] with an estimated incidence of postoperative delirium of 10 to 30%.[18–20] Therefore, we conducted a randomized pragmatic trial in older patients undergoing lumbar spine surgery, with the hypothesis that a bundled approach to reduce anesthetic agent exposure as determined by Bispectral Index [BIS] values (spinal anesthesia with targeted light sedation based on BIS values) compared with general anesthesia with masked BIS values would reduce the incidence of postoperative delirium.

Materials and Methods

Study Design

The research protocol was approved by the Mercy Medical Center (Baltimore, Maryland) Institutional Review Board (No. 2015-45). The trial was registered at ClinicalTrials.gov (NCT03133845, Principal Investigator Charles Brown). The initial protocol was released by the investigators to ClinicalTrials.gov on October 23, 2015. Due to quality control issues (in particular, the specificity of some outcomes, most notably post-discharge secondary outcomes that are not reported in this manuscript), the protocol was not formally registered and released to the public until April 2017, so the formal registration was retrospective to the start of the trial. The primary aim and outcome as reported in this manuscript have been unchanged since the initial submission to ClinicalTrials.gov on October 23, 2015. However, the secondary delirium outcomes (delirium severity and number of days of delirium) were not formally added to the trial registration until April 2017, although these outcomes were collected since the start of the trial as part of the study protocol. Other changes in enrollment criteria and sample size calculation are described below. Participants provided written informed consent. The SHaping Anesthetic techniques to Reduce Postoperative delirium (SHARP) study was conducted as a single-center prospective randomized controlled superiority trial with two parallel groups. The protocol was published near the end of the trial to summarize the conduct of the trial and provide the final statistical plan.[21]

Participants

Patients were approached before scheduled surgery by a research coordinator to evaluate eligibility and obtain informed consent. Inclusion criteria were (1) age 65 yr or greater; (2) undergoing lumbar spine fusion; (3) expected surgery duration less than 3 h; (4) under the care of a participating surgeon; and (5) ability to understand and comply with study procedures. Exclusion criteria were (1) contraindications to spinal anesthesia (*e.g.*, severe aortic stenosis, anticoagulant therapy); (2) body mass index greater than 40 kg/m^2; (3) previous L2–L5 full lumbar fusion; (4) communication issues precluding baseline assessments; (5) baseline dementia or Mini-Mental State Examination less than 24; (6) psychiatric disease precluding cooperation with sedation; and (7) surgeon or anesthesiologist preference for either anesthetic approach for any reason due to clinical considerations. Delirium was not formally assessed, although all patients were assessed for capacity to consent. Patients were enrolled between September 2015 to May 2019. Eligibility criteria were expanded after the study began to allow slightly younger patients, a higher body mass index, and longer duration of surgery. The specific criteria that were changed were a decrease in the lower age limit from 70 yr to 65 yr, an increase in the upper limit of body mass index (from 35 kg/m^2 to 40 kg/m^2), and an increase in the upper limit of anticipated surgery duration (from 2 h to 3 h).

Randomization and Assignment of Intervention

A computer-generated simple randomization list with 1:1 allocation was created by a research nurse before the study. For allocation concealment, assignments were placed in sealed opaque envelopes, which were sequentially handed to clinicians after randomization, before entering the operating room.

Intervention and Control

The intervention group received spinal anesthesia with targeted depth of anesthesia based on BIS values. The BIS monitor is approved to monitor depth of anesthesia and displays a unitless number (0 to 100) derived from processed electroencephalogram waveforms. BIS values between 40 and 60 are consistent with general anesthesia.[22] In the

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 940. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version.

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intervention group, spinal anesthesia was obtained using intrathecal injection of bupivacaine (10 to 15 mg) or lidocaine. Patients received sedation with propofol (25 to 150 mcg · kg^{-1} · min^{-1}), targeted to a BIS greater than 60 to 70. However, the anesthesiologist was instructed to prioritize clinical concerns if depth of sedation needed to be increased.

In the control group, patients received general anesthesia with an endotracheal tube. Anesthesia induction was with propofol (1 to 2 mg/kg) or etomidate, maintenance with a volatile anesthetic, muscle relaxation with a nondepolarizing muscle relaxant, and analgesia with fentanyl (generally 2 to 5 mcg/kg titrated) or hydromorphone and/or morphine. Patients on baseline opioids could receive additional opioids based on clinical criteria. For patients under general anesthesia, the anesthetic provider was masked to BIS values unless there was a clinical need.

Masking

Delirium outcome assessors were masked to the intervention. Postoperative data were abstracted from the electronic medical record by staff masked to the intervention. Patients, surgeons, and anesthesiologists were not masked, because it is impossible for the anesthetic technique to be masked to treating physicians or patients. Statisticians and investigators involved in data analysis were masked.

Perioperative Management

Perioperative care was based on established clinical protocols. Patients could receive intrathecal morphine during spinal anesthesia at the discretion of the anesthesiologist, or by direct intraoperative injection at the discretion of the surgeon. Postoperative analgesia was with fentanyl or hydromorphone patient-controlled analgesia, with transition to oxycodone or other oral opioids as tolerated.

Outcomes and Other Covariates

Delirium was assessed once daily during the first 3 postoperative days in the hospital using the validated Confusion Assessment Method[23] (sensitivity, 94 to 100%; specificity, 90 to 95%). For purposes of missing data, daily in-hospital assessments were not considered missing if the patient was discharged from the hospital on that day and not available for assessment. The Confusion Assessment Method included formal tests of cognition (Mini-Mental State Examination,[24] Calendar Reverse Months, Shortened Digit Span Forward/Reverse, and Delayed Word Recall tests) as well as questions for nurses, clinicians, and family. Patients who refused an assessment and no delirium assessment could be made were considered to not have delirium for that assessment. The primary outcome was incident delirium as defined by any positive assessment during hospitalization. A chart review for delirium was also conducted using validated methods to supplement in-person assessments.[25] Secondary outcomes included delirium duration and severity (Delirium Rating Scale-Revised 98).[26] Covariate information was collected from baseline assessments, patient report, and the medical record. Instrumental activities of daily living were measured at baseline.[27] Number of surgical levels included the range of involved vertebrae.

Sample Size

At the start of the trial, we assumed a delirium incidence of 40% in the control group (general anesthesia with masked BIS values) and a 50% reduction in the intervention group, based on previous studies.[15,18] Further, we assumed a 4 to 6% dropout or crossover. With these assumptions, 190 patients would be needed to show a difference in incidence of delirium at a 0.05 significance level with a power of 0.8. After the first year of data collection, the delirium incidence was noted to be less than predicted, and so the sample size was increased to at least 218, based on a revised assumption of delirium incidence (40% to 35% in the control arm) and similar assumptions regarding 50% reduction in delirium in the intervention group and 4 to 6% dropout.

Statistical Analysis

The primary analysis was based on the intention to treat principle (patients included in the group to which randomized). For the primary outcome, incident delirium, both the absolute difference and relative change were computed. The chi-square test was used to compare proportions with the primary outcome between groups. Secondary outcomes were compared using Wilcoxon rank sum tests. Normally distributed variables are reported using mean ± SD, and nonnormally distributed variables are reported using mean and interquartile range. Adjusted analyses were conducted with multivariable logistic regression to account for potential confounding, first with prespecified adjustment for age, education, and cognitive score[28] and second with adjustment for additional variables associated with delirium in bivariate analyses. As-treated analyses were also conducted (patients included in the group to which they received treatment). Standard diagnostics, including goodness of fit, influence, and collinearity, were examined for all regression models. BIS data were downloaded from the monitor after surgery and were analyzed in several ways, including the mean ± SD and minutes below or above clinically relevant cutoffs (BIS less than 40 and BIS greater than 55), based on the methodology of previous studies.[11,16]

Prespecified subgroup analyses were conducted based on stratification by age (less than 75 *vs.* 75 yr old or greater), Charlson Comorbidity Index (0 *vs.* 1 or greater), and baseline cognition (Mini-Mental State Examination less than 27 *vs.* 27 or greater), with cutoffs chosen based on biologic relevance and/or to have anticipated sufficient number of patients in the subgroups.[16,29,30] *Post hoc*, we examined four subgroups identified based on differences in bivariate analyses. Relative risks were calculated within each subgroup, and 95% CIs were generated using the percentile method *via* a bootstrap procedure (5,000 bootstrap samples). The hypothesis that the intervention would have differential effect based on subgroups was formally tested using a *P* value for interaction, without adjustment for other covariates. SAS v9.4 (USA) was used. Formal interim analyses were to assess

recruitment, safety events, and dropout, but not efficacy, and a Data Safety and Monitoring Board monitored study conduct and safety. There were no prespecified stopping criteria, and enrollment ceased when the target sample size was obtained. In all analyses, $P < 0.05$ was considered significant, and all hypothesis testing was two-tailed.

Results

A patient flow diagram is shown in figure 1. Of 799 patients screened from September 8, 2015, to May 6, 2019, 111 patients were randomized to spinal anesthesia with targeted sedation based on BIS values, and 108 patients were randomized to general anesthesia with masked BIS values. Reasons that patients were not enrolled and randomized are listed in figure 1. Enrollment was stopped upon accrual of enrollment goals. Among patients randomized to spinal anesthesia with targeted sedation based on BIS values, an adequate level of spinal anesthesia could not be obtained in seven patients, and these patients crossed over to receive general anesthesia. Among patients randomized to general anesthesia with masked BIS values, two patients withdrew after randomization, and one patient crossed over to receive spinal anesthesia.

Baseline Patient Characteristics

The median age of patients in this study was 72 yr (interquartile range, 69 to 77), 38% were male, and the median Mini-Mental State Examination score was 29 (interquartile range, 27 to 29). Patients rated their average preoperative pain as a median of 7 (interquartile range, 5 to 8) and their current pain as a median of 3 (interquartile range, 1 to 6). Patient characteristics were generally similar in the two arms of the study (table 1). However, the Charlson Comorbidity Index was slightly higher and there were more patients with a previous myocardial infarction and atrial fibrillation in the spinal anesthesia with targeted sedation based on BIS values group.

Perioperative Characteristics and Separation in BIS Values

Intra- and postoperative characteristics are described in table 2 (intention to treat) and Supplemental Digital Content table 1 (http://links.lww.com/ALN/C700; as treated). Overall, the median length of surgery was 128 min (interquartile range, 106 to 159), the median number of spinal levels was 3 (interquartile range, 2 to 4), and the median estimated blood loss was 300 ml (interquartile range, 200 to 460). In the spinal anesthesia with targeted sedation based on BIS values group, the median dose of bupivacaine was 14 mg (interquartile range, 12.5 to 15), and the maximum propofol infusion rate was a median of 80 mcg · kg^{-1} · min^{-1} (interquartile range, 75 to 100). Among patients who received general anesthesia, desflurane was predominantly utilized. Patients in the general anesthesia with masked BIS values group received more fentanyl and less IV fluids.

The average BIS value in the spinal anesthesia with targeted sedation based on BIS values group was higher than in the general anesthesia with masked BIS values group (median of 62 [interquartile range, 53 to 70] *vs.* 45 [interquartile range, 41 to 50]; $P < 0.001$). The median duration of BIS less than 40 was substantially lower in the spinal anesthesia with targeted sedation based on BIS values group compared to the general anesthesia with masked BIS values group (3 min [interquartile range, 0 to 22] *vs.* 68 min [interquartile range, 22 to 102]; $P < 0.001$).

Effect of the Intervention on Postoperative Delirium and Other Outcomes

The overall incidence of delirium was 22% (48 of 217). Out of 544 opportunities for delirium assessments for nondischarged patients, 509 in-person assessments were completed, and 24 assessments were refused by patients. Two patients refused all assessments. In the intention to treat analysis, there was no significant difference in the incidence of delirium in the spinal anesthesia with targeted sedation based on BIS values group (25.2% [28 of 111]) compared with the general anesthesia with masked BIS values group (18.9% [20 of 106]; $P = 0.259$), absolute difference, 6.4% (95% CI, –4.6 to 17.4%), and relative risk, 1.22 (95% CI, 0.85 to 1.76). When a chart review delirium method was used to supplement the in-person assessments, there was no significant difference in the incidence of delirium in the spinal anesthesia with targeted sedation based on BIS values group (27.9% [31 of 111]) compared with the general anesthesia with masked BIS values group (23.6% [25 of 106]; $P = 0.465$). Similarly, there was no difference by group in the incidence of delirium for each individual postoperative day or in maximum delirium severity score (table 3 [intention to treat]; Supplemental Digital Content table 2, [http://links.lww.com/ALN/C700; as treated]). The incidence of delirium was also not different between groups when adjusted for variables associated with delirium in bivariate analyses (Supplemental Digital Content table 3, http://links.lww.com/ALN/C700).

Duration of recovery in the postanesthesia care unit was similar between the two groups, but pain at postanesthesia care unit discharge was lower in the spinal anesthesia with targeted sedation based on BIS values group compared with the general anesthesia with masked BIS values group (median, 4 [interquartile range, 1 to 5] *vs.* median, 5 [interquartile range, 3 to 7]; $P = 0.004$). There were two strokes in the spinal anesthesia with targeted sedation based on BIS values group, and there was one death in the general anesthesia with masked BIS values group. Other complications by randomization group are listed in table 2 (intention to treat) and Supplemental Digital Content table 1 (http://links.lww.com/ALN/C700; as treated).

Prespecified Subgroup Analyses

There were three prespecified subgroup analyses, based on cutoffs of the Mini-Mental State Examination, the Charlson Comorbidity Index, and age, with forest plot results by the primary intention to treat analysis shown in figure 2. (The forest plot for the as treated analysis, as well as an expanded description of the numbers of events in each subgroup, are shown in Supplemental Digital Content figure 1 and Supplemental Digital Content table 4, respectively, http://

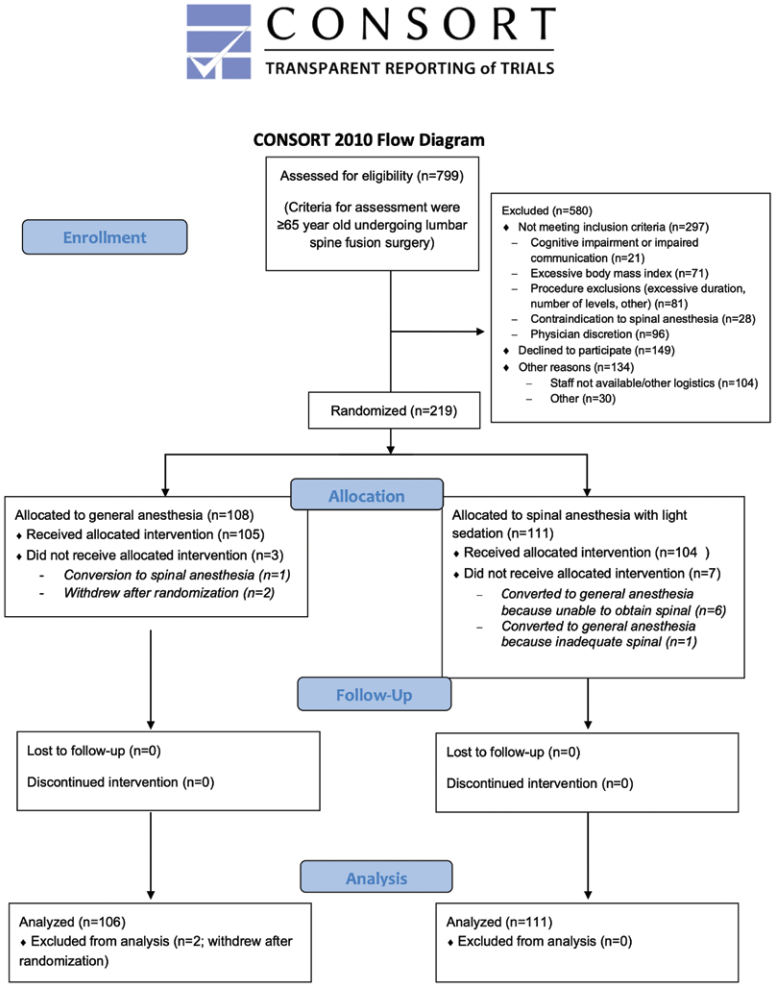

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. A patient flow diagram is shown.

links.lww.com/ALN/C700). Baseline Mini-Mental State Examination did moderate the effect of the intervention (P interaction = 0.009). Specifically, for patients with Mini-Mental State Examination less than 27, the incidence of delirium was less in the spinal anesthesia with targeted sedation based on BIS values group compared to the general anesthesia with masked BIS values group (17.7% [3 of 17] *vs.* 43.5% [10 of 23]). On the other hand, for patients with Mini-Mental State Examination 27 or greater, the incidence of delirium was greater in the spinal anesthesia with targeted sedation based on BIS values group *versus* the general anesthesia with masked BIS values group (26.6% [25 of 94] *vs.* 12.1% [10 of 83]). There was no difference in the effect of the intervention (*i.e.*, no interaction) based on the other prespecified subgroups of age strata (less than 75 *vs.* 75 yr old or greater) or Charlson Comorbidity Index (0 *vs.* 1 or greater). Several other subgroup analyses were chosen *post hoc* (sex, education, use of short-acting opioids at baseline, and administration of intrathecal morphine during surgery; fig. 2). Intrathecal morphine did modify the effect of the intervention in the intention to treat analysis (P interaction = 0.029) but not in the as treated analysis (P interaction = 0.088). Specifically, for patients who did not receive intrathecal morphine, the incidence of delirium in the intention to treat analysis was less in the spinal anesthesia with targeted sedation based on BIS values group compared to the general anesthesia with masked BIS values group (8.8% [3 of 34] *vs.* 20.4% [10 of 49]). On the other hand, for patients who did receive intrathecal morphine, the incidence of delirium was greater in the spinal anesthesia with targeted sedation based on BIS values group *versus* the general anesthesia with masked BIS values group (32.5% [25 of 77] *vs.* 17.5% [10 of 57]).

Risk Factors for Delirium

In bivariate analyses, male sex, lower Mini-Mental State Examination score, higher Charlson Comorbidity Index, preoperative short-acting opioid medication, longer surgery, and increased postoperative pain were among the variables associated with delirium (Supplemental Digital

Table 1. Baseline Patient Characteristics

	Total (n = 217)*	General Anesthesia with Masked BIS Values (n = 106)	Spinal Anesthesia with Targeted Sedation Based on BIS Values (n = 111)
Age (yr), median (interquartile range)	72 (69–77)	72 (69–76)	73 (69–78)
Male, n (%)	83 (38.2)	35 (33.0)	48 (43.2)
Race, n (%)			
White	197 (90.8)	93 (87.7)	104 (93.7)
Black	20 (9.2)	13 (12.3)	7 (6.3)
Education college or higher, n (%)	104 (47.9)	49 (46.2)	55 (49.5)
Living arrangement, at home, n (%)	203 (94.4)	95 (91.3)	108 (97.3)
Mini-Mental State Examination,† median (interquartile range)	29 (27–29)	28 (27–29)	29 (27–29)
Instrumental Activities of Daily Living,‡ median (interquartile range)	13 (12–14)	13 (12–14)	13 (12–14)
Comorbidities, n (%)			
Previous stroke	3 (1.4)	2 (1.9)	1 (0.9)
Hypertension	157 (72.4)	74 (69.8)	83 (74.8)
Atrial fibrillation	12 (5.5)	2 (1.9)	10 (9.0)
Congestive heart failure	1 (0.5)	0 (0)	1 (0.9)
Myocardial infarction	20 (9.2)	5 (4.7)	15 (13.5)
Peripheral vascular disease	9 (4.1)	1 (0.9)	8 (7.2)
Chronic obstructive pulmonary disease	22 (10.1)	10 (9.4)	12 (10.8)
Tobacco (previous)	73 (33.6)	33 (31.1)	40 (36)
Diabetes	54 (24.9)	25 (23.6)	29 (26.1)
Chronic kidney disease	38 (17.5)	15 (14.2)	23 (20.7)
ASA Status,§ median (interquartile range)	II (II–III)	II (II–III)	II (II–III)
Charlson Comorbidity Index,‖ median (interquartile range)	1 (0–1)	0 (0–1)	1 (0–1)
Hemoglobin (g/dl), mean ± SD	13.5 ± 1.3	13.6 ± 1.2	13.5 ± 1.4
Baseline medications			
Aspirin, n (%)	21 (9.8)	12 (11.5)	9 (8.1)
β-Blockers, n (%)	56 (26)	21 (20.2)	35 (31.5)
Calcium channel blockers, n (%)	51 (23.7)	22 (21.2)	29 (26.1)
Angiotensin-converting enzyme inhibitors, n (%)	43 (20)	17 (16.3)	26 (23.4)
Angiotensin II-receptor blockers, n (%)	49 (22.8)	26 (25)	23 (20.7)
Statin, n (%)	109 (50.7)	55 (52.9)	54 (48.6)
Selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors, n (%)	39 (18.1)	20 (19.2)	19 (17.1)
Other psychotropic medication, n (%)	23 (10.7)	9 (8.7)	14 (12.6)
Short-acting opioids, n (%)	106 (49.3)	44 (42.3)	62 (55.9)
Current pain,# median (interquartile range)	3 (1–6)	3 (1–7)	3 (0–5)
Average pain,# median (interquartile range)	7 (5–8)	7 (5–8)	8 (5–8)

*All variables were complete (n = 217) except the following: Instrument Activities of Daily Living, ASA score (n = 211), current and average pain (n = 212), living status (n = 203), all baseline medications (n = 215), hemoglobin (n = 216). †Mini-Mental State Examination scores range from 0 to 30, with higher scores indicating better performance. ‡Instrumental Activities of Daily Living scores range from 0 to 14 with higher scores indicating better functional status. §For non–brain dead surgical patients, ASA scores range from I to V with higher scores indicating greater comorbidities. ‖The Charlson Comorbidity Index ranges from 0 to 33, with higher scores indicating greater risk of long-term mortality. #Pain is rated on a scale of 0 to 10, with higher scores indicating more pain.

ASA, American Society of Anesthesiologists; BIS, Bispectral Index.

Content tables 5 and 6, http://links.lww.com/ALN/C700). In adjusted models (Supplemental Digital Content table 3, http://links.lww.com/ALN/C700), only lower Mini-Mental State Examination score remained independently associated with delirium. The administration of intrathecal morphine was also associated with delirium in the adjusted model, but not in the bivariate comparison.

Discussion

The results of this trial demonstrate that spinal anesthesia with targeted sedation based on BIS values compared with general anesthesia with masked BIS values does not reduce the incidence of delirium in lumbar spine surgery patients.

The results of this study add to several studies examining whether titrating depth of anesthesia and anesthetic exposure compared with usual care can reduce delirium. Early trials in general anesthesia patients suggested that a strategy to reduce anesthetic exposure based on BIS values could reduce delirium.[11,12] Based on these and other studies, delirium guidelines have recommended depth of anesthesia monitoring may be considered.[1] However, the recent large trial reported no difference in delirium in patients randomized to a strategy of avoiding excessive anesthetic exposure and burst suppression on the electroencephalogram.[14] Similarly, the results of the current study demonstrate that a bundled approach to reduce anesthetic agent exposure as determined by BIS values does not reduce the

Table 2. Perioperative and Postoperative Characteristics by Randomization Group

	Overall (n = 217)*	General Anesthesia with Masked BIS Values (n = 106)	Spinal Anesthesia with Targeted Sedation Based on BIS Values (n = 111)	*P* Value
Intraoperative				
Duration of surgery (min), median (interquartile range)	128 (106–159)	130 (110–163)	123 (102–154)	0.262
Number of levels, median (interquartile range)	3 (2–4)	3 (2–3)	3 (2–4)	0.425
Anesthetic management				
Spinal anesthesia arm				
Bupivacaine dose (mg), median (interquartile range)	14 (12.5–15)	Not applicable	14 (12.5–15)	Not applicable
Maximum propofol infusion (mcg · kg^{-1} · min^{-1}), median (interquartile range)	80 (75–100)	Not applicable	80 (75–100)	Not applicable
General anesthesia arm				
Desflurane, n (%)	82 (37.8)	77 (72.6)	Not applicable	Not applicable
Intrathecal morphine, n (%)	134 (61.8)	57 (53.8)	77 (69.4)	0.018
Intrathecal morphine (mg), median (interquartile range)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.019
Fentanyl, n (%)	203 (93.5)	100 (94.3)	103 (92.8)	0.643
Fentanyl (mcg), median (interquartile range)	150 (100–250)	200 (150–250)	100 (100–100)	< 0.001
Hydromorphone, n (%)	43 (19.8)	40 (37.7)	3 (2.7)	< 0.001
Hydromorphone (mg), median (interquartile range)	1.5 (1–2)	1.3 (1–2)	2 (1–2)	0.449
Midazolam, n (%)	69 (31.8)	33 (31.1)	36 (32.4)	0.837
Midazolam (mg), median (interquartile range)	2 (2–2)	2 (2–2)	2 (2–2)	0.554
Phenylephrine, n (%)	50 (23.0)	23 (21.7)	27 (24.3)	0.646
Phenylephrine (mcg), median (interquartile range)	300 (200–650)	300 (50–450)	250 (150–750)	0.611
Ephedrine, n (%)	140 (64.5)	68 (64.2)	72 (64.9)	0.913
Ephedrine (mg), median (interquartile range)	20 (10–33)	25 (13–40)	20 (10–30)	0.055
Fluids administered (ml), median (interquartile range)	2,000 (1,700–2,700)	2,000 (1,400–2,600)	2,050 (1,900–2,950)	0.006
Estimated blood loss (ml), median (interquartile range)	300 (200–460)	300 (200–500)	300 (200–400)	0.648
Packed erythrocyte transfusion, n (%)	4 (1.8)	1 (0.9)	3 (2.7)	0.622
Lowest MAP (mm Hg), median (interquartile range)	59 (52–64)	59 (51–64)	60 (52–64)	0.672
Average BIS, median (interquartile range)	51 (44–63)	45 (41–50)	62 (53–70)	< 0.001
Duration of BIS < 40 (min), median (interquartile range)	22 (1–76)	68 (22–102)	3 (0–22)	< 0.001
Duration of BIS > 55 (min), median (interquartile range)	31 (16–92)	20 (13–30)	87 (34–110)	< 0.001
Duration of PACU (min), median (interquartile range)	119 (75–164)	119 (75–169)	118 (75–160)	0.530
Pain score at PACU discharge, median (interquartile range)	4 (2–6)	5 (3–7)	4 (1–5)	0.004
Postoperative				
ICU admission, n (%)	4 (1.8)	0 (0)	4 (3.6)	0.122
Duration of hospitalization (days), median (interquartile range)	3 (2–3)	3 (2–3)	3 (2–3)	0.087
Maximum pain on postoperative day 1 (0–10), median (interquartile range)	8 (7–10)	8 (7–10)	8 (7–10)	0.413
Complications,† n (%)				
Stroke	2 (0.9)	0 (0)	2 (1.8)	0.498
Atrial fibrillation	1 (0.5)	0 (0)	1 (0.9)	1.000
Congestive heart failure	0 (0)	0 (0)	0 (0)	Not applicable
Myocardial infarction	1 (0.5)	0 (0)	1 (0.9)	1.000
Sepsis	0 (0)	0 (0)	0 (0)	Not applicable
Pneumonia	2 (0.9)	0 (0)	2 (1.8)	0.498
Urinary tract infection	18 (8.3)	9 (8.5)	9 (8.1)	0.919
Pulmonary embolism or deep venous thrombosis	2 (0.9)	1 (0.9)	1 (0.9)	1.000
Acute kidney injury	1 (0.5)	0 (0)	1 (0.9)	1.000
Fall	0 (0)	0 (0)	0 (0)	Not applicable
Reoperation	1 (0.5)	0 (0)	1 (0.9)	1.000
In-hospital death	1 (0.5)	1 (0.9)	0 (0)	0.488

*All variables were complete except bupivacaine and propofol dose in the spinal anesthesia group (n = 101), BIS values (n = 192), and postoperative day 1 pain (n = 216). †Some patients experienced multiple complications, apart from urinary tract infections. One patient in the general anesthesia group had a pulmonary embolism and died. One patient in the spinal anesthesia group had a stroke, myocardial infarction, and pneumonia.

BIS, Bispectral Index; ICU, intensive care unit; MAP, mean arterial pressure; PACU, postanesthesia care unit.

incidence of delirium in older adults undergoing lumbar spine fusion surgery.

An important consideration in interpreting previous studies is that in most trials, all patients received general anesthesia. The pertinent comparisons were general anesthesia *versus* deeper general anesthesia, and the benefits of lighter anesthesia could not be examined. This is an important gap since critical care guidelines recommend that mechanically ventilated patients in the intensive care unit benefit from light sedation,[31] a level of consciousness that is substantially more alert than general anesthesia. Two trials in hip fracture surgery patients under spinal anesthesia examined benefits

Table 3. Effect of the Intervention on Postoperative Delirium

	General Anesthesia with Masked BIS Values (n = 106)	Spinal Anesthesia with Targeted Sedation Based on BIS Values (n = 111)	*P* Value
Any delirium, n (%)*	20 (18.9)	28 (25.2)	0.259
Number of days of delirium, among delirious patients, median (interquartile range)	1 (1–3)	1 (1–2)	0.224
Delirium by postoperative day*			
Day 1, n (%)	7 (6.6)	15 (13.5)	0.092
Day 2, n (%)	15 (14.2)	22 (19.8)	0.267
Day 3, n (%)	11 (10.4)	14 (12.6)	0.606
Maximum delirium severity score as measured by Delirium Rating Scale–Revised-98,† median (interquartile range)*	4 (3–6)	5 (3–8)	0.276
Maximum delirium severity score as measured by Delirium Rating Scale–Revised-98 by postoperative day*			
Day 1, median (interquartile range)	3 (2–6)	4 (3–7)	0.088
Day 2, median (interquartile range)	3 (1.5–5)	3 (2–6)	0.354
Day 3, median (interquartile range)	3 (1–5)	3 (1–6)	0.960

*Out of 544 opportunities for delirium assessments for nondischarged patients at assessment, 509 in-person assessments were completed, and 24 assessments were refused by patients. A total of 215 patients had a postoperative assessment with the Confusion Assessment Method and Delirium Rating Scale-Revised-98 (two patients refused all assessments and were considered to not have delirium). For each postoperative day, the number of patients with a Confusion Assessment Method and Delirium Rating Scale-Revised-98 evaluation among the number of nondischarged patients at assessment was 199/217 (postoperative day 1), 190/198 (postoperative day 2), and 120/129 (postoperative day 3).

†Delirium Rating Scale–Revised-98 severity scores range from 0 to 39, with higher scores indicating greater severity of delirium.

of intraoperative "light" sedation.[15,16] However, the results of these two studies were conflicting, and moreover, the elderly, frail, and cognitively impaired populations may not be generalizable to most older adults undergoing surgery. Thus, there has been a clear need to determine whether reducing depth of anesthesia beyond general anesthesia could reduce delirium in a generalizable population of older adults. This question is highly relevant since many surgeries can be performed with neuraxial or regional approaches. The SHARP study addressed this question in a pragmatic manner and demonstrated no delirium reduction in patients treated with spinal anesthesia with targeted sedation based on BIS values compared with general anesthesia with masked BIS values.

One of three preplanned subgroup analyses showed different effects of the intervention according to baseline cognition. Specifically, for patients with Mini-Mental State

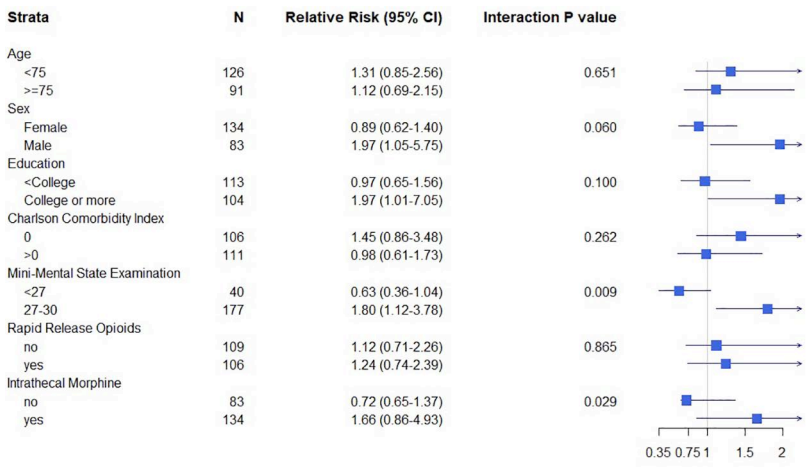

Fig. 2. Subgroup analyses of the primary outcome of incident delirium. Subgroup analyses based on intention to treat analyses with the primary outcome of incident delirium. Prespecified subgroup analyses were conducted based on stratification by age, Charlson Comorbidity Index, and baseline cognition. *Post hoc*, four subgroups were identified based on differences in bivariate analyses. The effect of anesthetic approach (relative risk [95% CI]) is presented separately in each subgroup to define the effect of the intervention in that particular subgroup. The interaction term is a test of significance for whether the effect of anesthetic approach is statistically different between subgroups. Rapid release opioids refer to baseline opioids. Relative risk less than 1 favors spinal anesthesia with targeted sedation based on Bispectral Index values. Relative risk greater than 1 favors general anesthesia with masked Bispectral Index values.

Examination less than 27, there was less delirium in the spinal anesthesia with targeted sedation based on BIS values group, while for patients with Mini-Mental State Examination 27 or greater, there was less delirium in the general anesthesia with masked BIS values group. The results of this subgroup analysis are qualitatively similar to a subgroup analysis reported in a trial of depth of sedation in hip fracture surgery patients.[16] In this trial in which the median Mini-Mental State Examination score was 24, the subgroup of healthy patients with a Charlson Comorbidity Index score of 0 to 1 (but not higher) had less delirium with a light *versus* deep sedation strategy. Thus, in both the hip fracture trial and the current trial, patients who were relatively healthy but with impaired cognition derived benefit from lighter sedation. These results need to be considered hypothesis-generating since they were subgroup analyses. One potential explanation is that cognitively impaired patients are more sensitive to anesthetic depth, perhaps due to underlying neurodegenerative disease.[32–35] On the other hand, it is not entirely clear why cognitively intact patients benefited from general anesthesia with masked BIS values. The overall risk of delirium was less in these patients, as would be expected. Future studies should examine anesthetic strategies to reduce depth of anesthesia in cognitively impaired older adults, although the logistics of enrolling a sufficient number of eligible patients would be challenging. A *post hoc* analysis also showed that the administration of intrathecal morphine was independently associated with delirium and modified the effects of the intervention such that in patients who received intrathecal morphine, there was less delirium in the general anesthesia with masked BIS values group. Previous work has suggested that intrathecal morphine was associated with less postoperative delirium,[36] while in our study, patients who received intrathecal morphine had more delirium, and the finding of this *post hoc* analysis should also be considered exploratory.

In the current study, the strongest and most consistent delirium risk factor was lower Mini-Mental State Examination score. These results are consistent with other studies examining risk factors for delirium[3] and highlight the importance of cognitive testing for risk stratification. Overall, pain and pain treatment were important, with baseline short-acting opioids and maximum postoperative pain being associated with delirium. These results highlight the balance of treating pain while minimizing deliriogenic opioid medication.[3,37]

There are several strengths of this study. The SHARP trial used a unique study design to compare spinal anesthesia with targeted sedation based on BIS values *versus* general anesthesia with masked BIS values in cognitively intact older adults. The intervention was pragmatic, conducted at a community-based hospital, and achieved a separation in BIS values. The research group is experienced in assessing postoperative delirium. Although the study sample was older adults undergoing spine surgery, results are likely generalizable to a number of surgeries for which general or neuraxial/regional anesthesia is appropriate.

There are several limitations. The intervention was bundled, and it is unclear which aspect (light sedation, spinal anesthesia, or propofol) was most responsible for the subgroup effect. The doses of propofol that were used were relatively high, the sedation protocol was pragmatic, and a formal observer assessment of sedation was not used. Thus, a number of patients in the spinal anesthesia with targeted sedation based on BIS values group had BIS values below the target of 60 to 70, and this may have biased the results toward the null. Additionally, BIS may not be an accurate measure of depth of anesthesia in older adults. However, the majority of patients had BIS values that exceeded the upper limit of 55 that has been advocated to prevent awareness during general anesthesia.[38,39] The bundled approach also did not permit the use of other sedative agents, such as dexmedetomidine, and future studies are needed to examine potentially beneficial effects of dexmedetomidine in this population. The study was powered for a large effect size, based on a previous study,[15] and we revised the estimate of delirium incidence due to a lower incidence than originally expected. However, the overall incidence of delirium was still below the expected incidence in the power calculation, and so the study was underpowered. Nevertheless, given the observed effect, it is unlikely that a larger study would demonstrate a benefit in the intervention group. We assessed delirium only once daily, and some cases may have been missed. Thus, imprecision of the outcome assessment and/or misclassification may have biased the results. Patients in the spinal anesthesia with targeted sedation based on BIS values had more cardiac and vascular disease at baseline, although the baseline Mini-Mental State Examination was slightly higher than the general anesthesia with masked BIS values group. Perioperative management aside from the intervention was based on established protocols, and this introduced heterogeneity into the study. There was crossover between study arms in eight patients, largely due to obtaining adequate spinal anesthesia in patients with degenerative spine disease, and this is a source of bias. However, results were similar in intention to treat and as treated analyses. The Mini-Mental State Examination is a general screen of cognition and is limited by ceiling effect and educational biases.[40] Further, the distinction between a Mini-Mental State Examination score above and less than 27 may not be clinically meaningful, and so the results of the subgroup analyses should be considered hypothesis-generating. Finally, the trial was not formally registered in ClinicalTrials.gov until 2017 due to quality control issues, although the initial protocol with the aim and primary outcome of this manuscript was submitted in October 2015.

In conclusion, the results of the SHARP study demonstrate that spinal anesthesia with targeted sedation based on BIS values does not reduce delirium in older adults undergoing lumbar spine surgery. Further studies are needed to examine optimal anesthetic strategies in cognitively impaired patients, who are at high risk for delirium.

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Competing Interests

Dr. Brown has consulted for and received grant funding from Medtronic Inc. (Minneapolis, Minnesota). Dr. Neufeld has received grant funding from Hitachi Inc. (Tokyo, Japan) and consulted for Merck Inc. (Kenilworth, New Jersey). Dr. Hogue has received payment for advisory board membership from Medtronic Inc. and Edwards Lifesciences (Irvine, California). He serves on a data safety monitoring committee for Merck Inc. Dr. Cha has consulted for Avania LLC (Marlborough, Massachusetts) and MC3 Corp (Dexter, Michigan). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: cbrownv@jhmi.edu. Raw data may be available with the appropriate institutional agreements at: cbrownv@jhmi.edu.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Dr. Alan Van Poznak Slides the Musical into the Medical Syringe!

Gentleman, scholar, and lifelong Cornellian, Alan Van Poznak, M.D. (hugging Dr. Kathryn McGoldrick, *upper left*), famously developed methoxyflurane in the 1960s with longtime colleague Joseph Artusio, M.D. Proving his inventive mind was not limited to the lab bench, he combined pieces from two precisely cut syringes and created a musical masterpiece—the syringe slide whistle (*right)*! Once again, fortune favored the prepared mind. Apprenticed to a pipe-organ builder in his teens, Dr. Van Poznak was able to recognize the instrumental potential in the cylindrical syringe. While serenading pediatric patients at the New York Hospital, he taught anesthesia residents both Bernoulli and Venturi principles just before closing lectures with Cornell's school song (*bottom*). To learn how this little whistle sang its way into the hearts of the Big Apple Circus and Late Night TV hosts, watch the full interview of Dr. Van Poznak by former student Kathryn McGoldrick, M.D. (hugging Dr. Van Poznak, *upper left*), in the Wood Library-Museum's John W. Pender Collection of the Living History of Anesthesia (https://www.woodlibrarymuseum.org/library/living-history). (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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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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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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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.

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).

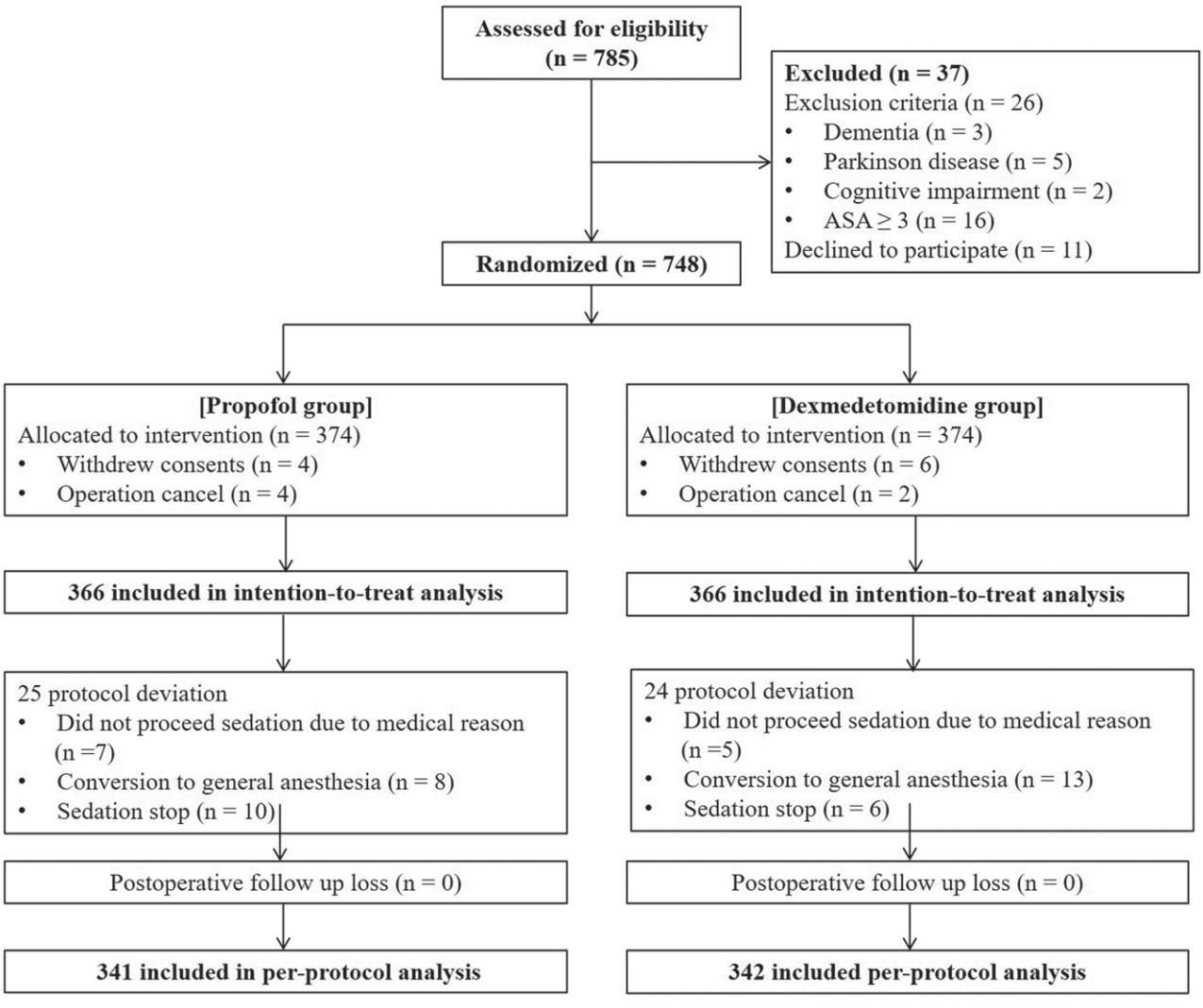

Fig. 1. CONsolidated Standards of Reporting Trials diagram. ASA, American Society of Anesthesiologists.

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.

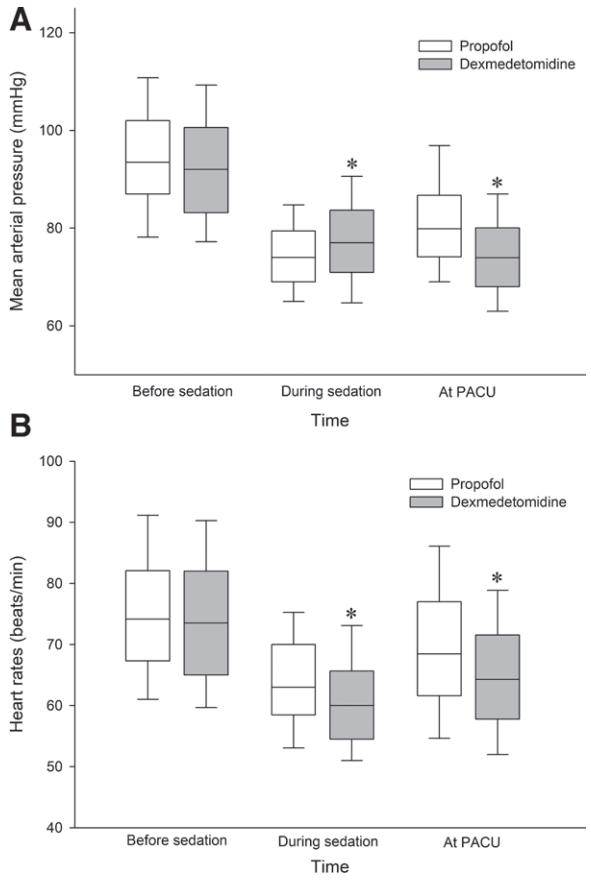

Fig. 2. Hemodynamic variables across three time periods, compared between the two study groups. (*A*) Mean arterial pressure and (*B*) heart rate, measured before and during sedation, and at the PACU. *$P < 0.001$. PACU, postanesthesia care unit.

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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