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CLINICAL TRIAL REPORT

Preventive Effect of Preoperative Intranasal Dexmedetomidine for Postoperative Delirium in Elderly Patients with Sleep Disorders Undergoing Major Noncardiac Surgery: A Randomized, Triple-Blind, Placebo-Controlled Trial

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Purpose: Postoperative delirium (POD) is frequent and consequential in older adults, especially those with preexisting sleep disorders. While perioperative intravenous dexmedetomidine may lower POD risk, the benefit of preoperative intranasal administration is unknown. This study aimed to determine whether preoperative intranasal dexmedetomidine reduces POD in elderly patients with sleep disorders undergoing major noncardiac surgery.

Patients and Methods: In this randomized, triple-blind, placebo-controlled trial, 348 elderly patients (≥60 years) with a Pittsburgh Sleep Quality Index >7 undergoing major noncardiac surgery were enrolled between November 2023 and August 2024. Participants received either intranasal dexmedetomidine (n=174) or placebo (n=174) the night before surgery (20:30–00:00). Dexmedetomidine was administered using a weight-based regimen (≤45 kg: 45 μg; 45–75 kg: 60 μg; ≥75 kg: 75 μg), with a rescue dose of 30 μg allowed if sleep onset did not occur within 30 minutes. The primary outcome was the incidence of POD within 5 days postoperatively. Secondary outcomes included preoperative sleep quality, delayed neurocognitive recovery (dNCR) at 7 and 30 days postoperatively, and adverse events on the night before surgery.

Results: The incidence of POD was significantly lower in the dexmedetomidine group than in the placebo group (18.4% vs 32.8%, RR:0.56, 95% CI:0.38–0.82, P=0.002). Preoperative dexmedetomidine also improved sleep quality on the night before surgery, including total sleep time (6.2±1.5 hours vs 5.3±1.7 hours, mean difference:0.89, 95% CI:0.56–1.23, P<0.001), sleep efficiency (77.3% ±16.0% vs 66.3%±19.1%, mean difference:11.01%, 95% CI:7.3%-14.7%, P<0.001), and subjective sleep quality as assessed by the Richards-Campbell Sleep Questionnaire (68 ± 13 vs 59 ± 15, mean difference:9.31, 95% CI:6.35–12.27, P<0.001). There was no between-group difference in dNCR at day 7 or day 30 (both $P > 0.05$). Dexmedetomidine was associated with a higher incidence of bradycardia during the preoperative night (37.9% vs 16.7%; RR:2.28, 95% CI:1.55–3.34, $P < 0.001$), while the incidence of other adverse events was similar between groups (all $P > 0.05$).

Conclusion: Preoperative intranasal dexmedetomidine reduced the incidence of POD and enhanced preoperative sleep quality in elderly patients with sleep disorders undergoing major noncardiac surgery. Given the increased risk of bradycardia, these benefits should be weighed against the need for perioperative monitoring.

Keywords: geriatric anesthesia, sleep quality, neurocognitive disorders, delirium prevention, alpha-2 adrenergic agonists

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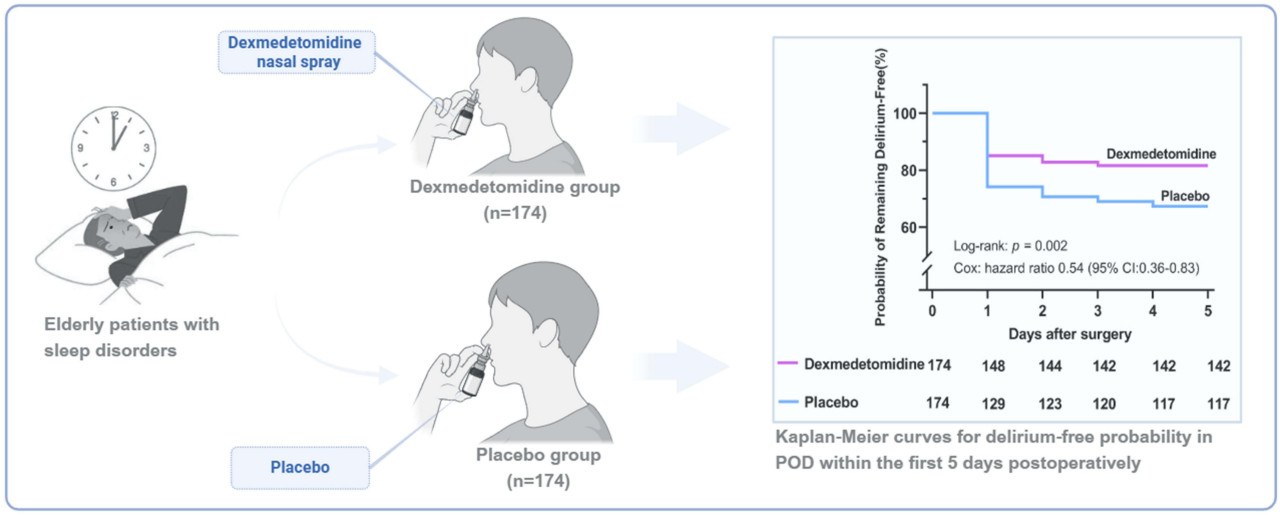
Graphical Abstract



Introduction

Postoperative delirium (POD) is a common and serious complication in elderly patients, characterized by acute disturbances in attention, awareness, cognition, and sleep-wake cycles.[1] Among individuals aged ≥60 years undergoing major noncardiac surgery, the incidence of POD can reach up to 23.8%.[2] POD is associated with a range of adverse outcomes, including prolonged hospitalization,[3], increased postoperative complications,[3] unplanned ICU admissions,[3] higher readmission rates,[4] long-term cognitive decline,[5] and elevated healthcare costs.[4]

POD is multifactorial in origin, with increasing evidence identifying preoperative sleep disturbances as a significant modifiable risk factor.[6,7] Sleep disorders are prevalent in surgical patients, with reported rates exceeding 60% in older adults prior to major procedures.[8,9] Poor sleep quality has been independently linked to heightened POD risk, yet interventions targeting this preoperative window remain limited.

Dexmedetomidine, a selective α 2-adrenergic receptor agonist, has shown promise in reducing POD when administered intravenously during or after surgery,[10] possibly due to its sedative and sleep-promoting properties.[11,12] However, the clinical utility of intravenous dexmedetomidine in the preoperative setting is constrained by the need for venous access, monitoring, and logistical complexity. Intranasal dexmedetomidine, recently developed for noninvasive delivery, offers a convenient alternative with favorable pharmacokinetics, including high nasal mucosal absorption and bioavailability.[11,13] Its ease of administration makes it a potentially suitable option for improving preoperative sleep quality and mitigating delirium risk in elderly patients.

This study aims to investigate whether intranasal dexmedetomidine administered on the night before surgery reduces the incidence of POD in elderly patients with preexisting sleep disorders undergoing major noncardiac surgery. Secondary outcomes include preoperative sleep quality, delayed neurocognitive recovery (dNCR) on postoperative days 7 and 30, and adverse events.

Methods

Trial Design and Registration

The randomized, triple-blind, placebo-controlled trial conducted at The Affiliated Hospital of Guizhou Medical University from November 2023 to August 2024, was approved by the Medical Ethics Committee (Approval No. 2023169K) on October 13, 2023. It adhered to the Helsinki Declaration and clinical trial management standards.

Informed consent was obtained from all participants. The trial was registered with the China Clinical Trial Registry (Registration No. ChiCTR2300077614) on November 14, 2023, and followed CONSORT guidelines.

Trial Participants

Inclusion Criteria

1) Scheduled to undergo major noncardiac surgery under general anesthesia;
2) Expected surgical duration of at least 2 hours;
3) Age ≥ 60 years;
4) Pittsburgh Sleep Quality Index (PSQI) score > 7;
5) Ability to understand and sign the informed consent form;
6) Mini-Mental State Examination (MMSE) score > 24.

Exclusion Criteria

1) Known allergy to dexmedetomidine or any component of the study drug;
2) Baseline heart rate < 60 bpm, sick sinus syndrome, or atrioventricular block;
3) Diagnosed with central or obstructive sleep apnea;
4) American Society of Anesthesiologists (ASA) physical status classification of IV or higher;
5) Unsuitability for intranasal administration (eg, severe nasal pathology or history of nasal surgery);
6) Presence of severe neurological or psychiatric disorders, or current use of antipsychotic medications;
7) Scheduled for day surgery or intracranial surgery;
8) Patient withdrawal from the study during the research period.

Randomization and Blinding

Participants were randomly assigned (1:1) in this triple-blind trial to the placebo or dexmedetomidine group using computer-generated randomization prepared by an independent biostatistics expert. The randomization sequence was sealed in opaque, consecutively numbered envelopes, held and opened by pharmacy personnel who were otherwise uninvolved in the trial, who prepared and dispensed the assigned study spray (dexmedetomidine nasal spray or placebo). The placebo was sterile 0.9% saline delivered in nasal spray bottles identical in appearance, viscosity, smell, spray pattern, and packaging to the commercial dexmedetomidine spray. No distinguishable differences existed between the two. Group assignments were blinded to participants, the perioperative care team, and outcome assessors. The pre-operative instruction/administration team was operationally separate from the postoperative assessment team, who remained unaware of group allocation throughout the study.

Intervention Measures

The investigational drug used was either placebo or dexmedetomidine hydrochloride nasal spray (Shanghai HengRui Pharmaceutical Co., Ltd., Shanghai). On the night before surgery (20:30~00:00), all participants were in the hospital ward and instructed to clean and dry their nasal cavities before bedtime. The researcher administered the drug according to the instructions.[11] To determine an appropriate dosing regimen for improving sleep quality, we referred to studies suggesting effective sedation with intranasal dexmedetomidine doses of 1–2 μg/kg in elderly populations.[12,14] To balance efficacy and minimize hemodynamic side effects, we adopted an initial dose plus a rescue dose strategy. Each spray of the nasal formulation delivers 15 μg, allowing for practical dosing adjustments based on body weight: Patients weighing ≤45 kg: 45 μg (3 sprays); 45kg<Patients weighing<75kg: 60 μg (4 sprays); Patients weighing ≥75 kg: 75 μg (5 sprays). A rescue dose of 30 μg (2 sprays) was given if patients did not fall asleep within 30 minutes, as the peak plasma concentration of intranasal dexmedetomidine occurs within this timeframe.[11] To maintain blinding, the placebo group received identically labeled sprays and followed the same dosing schedule, including the rescue dose. After administration of the study drug, patients were required to remain in a quiet, darkened environment. Lights were turned off, noise and staff movement were minimized, and visitors were restricted to promote undisturbed sleep and reduce external interference.

From drug administration until awakening the next morning, sleep parameters, heart rate (HR), and peripheral oxygen saturation (SpO_2) were continuously monitored using portable devices. Non-invasive blood pressure (NIBP) was measured for 6 hours post-administration—every 30 minutes during the first 3 hours and then hourly—to minimize disturbance during sleep. Adverse events were monitored during the night of drug administration, from dosing until the next morning. Adverse event criteria included bradycardia (heart rate [HR] <55 bpm), tachycardia (HR >100 bpm), hypotension (systolic blood pressure [SBP] <90 mmHg or >20% decrease in mean arterial pressure [MAP] from baseline), hypertension (SBP >160 mmHg or >30% increase in MAP from baseline), hypoxemia (SpO_2 <90%), and occurrence of nasal congestion/sneezing, headache, nausea/vomiting, or allergic reactions. When any threshold was met, the rescue dose was withheld, the patient was aroused and reassessed, and predefined treatments were applied: atropine for bradycardia; crystalloid bolus followed by a vasopressor (eg, phenylephrine or ephedrine) for hypotension; a short-acting antihypertensive with concurrent assessment of pain/anxiety for hypertension; airway repositioning with stepwise oxygen escalation (nasal cannula → face mask) for hypoxemia; saline spray/supportive care for nasal symptoms; acetaminophen for headache; and standard antiemetics for nausea/vomiting. Suspected allergy prompted immediate discontinuation of study medication and protocolized anti-allergic treatment.

Anesthesia Protocol

A standardized anesthesia protocol was used for all participants. Anesthesia induction involved the administration of etomidate (0.2 $mg•kg^{-1}$ to 0.3 $mg•kg^{-1}$), sufentanil (0.3 $\mu g•kg^{-1}$ to 0.5 $\mu g•kg^{-1}$), and rocuronium (0.6 $mg•kg^{-1}$ to 1 $mg•kg^{-1}$) for neuromuscular blockade. After intubation, mechanical ventilation was initiated, and the tidal volumes, respiratory rate and FiO_2 were adjusted to maintain the end-tidal carbon dioxide $ETCO_2$ at 35–45 mmHg and $SpO_2 \geq$ 97%. Anesthesia was maintained with sevoflurane, remifentanil, and propofol, and the bispectral index was maintained between 40 and 60. No dexmedetomidine or benzodiazepines were administered intraoperatively or postoperatively. Additional doses of sufentanil and rocuronium were administered as needed. Vasoactive drugs, fluids, or blood products were adjusted to maintain the HR and blood pressure within ±20% of baseline and temperature within ±0.5°C using forced-air warming blankets. Preemptive analgesia and antiemetic prophylaxis were administered 30 minutes before the end of surgery NSAIDs/sufentanil and palonosetron.

Following surgery, patients were transferred to the post-anesthesia care unit (PACU) for recovery, with neuromuscular reversal agents not routinely administered unless deemed necessary by the attending physician. Comprehensive documentation included all medications and their doses administered intraoperatively and in the PACU, as well as anesthesia and surgery duration, primary surgical procedures, types and quantities of intravenous fluids and blood products administered, blood loss, and urine output. Postoperative pain management comprised sufentanil (2 $\mu g•kg^{-1}$) combined with palonosetron (0.5 mg) and flurbiprofen ester (2 $mg•kg^{-1}$, if no contraindications), which were diluted in normal saline to achieve a total volume of 100 mL for intravenous administration. Patient-controlled analgesia was initiated at a rate of 2 mL/h with a bolus dose of 0.5 mL, and a lockout period of 15 minutes was implemented.

Primary Outcome

The primary outcome was the incidence of POD within the first 5 days after surgery. POD was assessed twice daily (08:00–10:00 and 15:00–18:00) using the 3-Minute Diagnostic Interview for Confusion Assessment Method-defined Delirium (3D-CAM) for patients in the general ward and the Confusion Assessment Method for the ICU (CAM-ICU) for patients in the ICU.[15] Delirium severity was evaluated using the Confusion Assessment Method-Severity (CAM-S) scale, with scores ranging from 0–19 points; scores were categorized as mild (2 points), moderate (3–4 points), or severe (5–19 points).[16] The type of delirium was classified as hyperactive Richmond Agitation-Sedation Scale (RASS) scores of +1 to +4), hypoactive (RASS scores of −3 to 0), or mixed (varying RASS scores).[15] Delirium assessment followed the evaluation of patient agitation and sedation using the RASS, with delirium assessment performed only if the RASS score was >-4.[15] If hospitalization was <5 days, assessments continued until the day before discharge; classification used an observed-case rule without carrying forward values after discharge: any observed CAM/CAM-ICU positive within days 1–5 defined POD, whereas participants with ≥1 negative and no positive assessments prior to discharge were classified as non-POD. POD was defined as present if a patient had a positive delirium assessment at any point during the 5-day

postoperative period. Assessors underwent structured training and inter-rater calibration for RASS, 3D-CAM/CAM-ICU, and CAM-S prior to study initiation, with periodic cross-checks to ensure consistency.

Delirium duration was calculated as the total number of calendar days with a positive delirium assessment. The time to delirium onset was defined as the first day a positive delirium assessment occurred. The count of delirium episodes was defined by discrete CAM-positive calendar days. For example, if a patient exhibited positive delirium assessments on non-consecutive days, such as days 2 and 4 postoperatively, it was counted as two separate episodes. However, if delirium was detected on consecutive days (eg, days 1, 2, and 3), it was counted as a single episode.

Secondary Outcomes

Sleep data were recorded the night before surgery, with drug administration marking the starting point (T_1). Smart wearables (huawei watch, HUAWEI Technologies Co. Ltd, China) tracked sleep onset (T_2), deep sleep duration, light sleep duration, rapid eye movement (REM) sleep duration, the number of awakenings, and wake-up time (T_3). Total sleep time was the sum of deep, light, and REM sleep. Sleep latency was defined as T_2 minus T_1, bed rest time was defined as the duration between T3 and T1, and sleep efficiency was defined as the total sleep time divided by the bed rest time. The Richards Campbell Sleep Questionnaire (RCSQ) was used to determine subjective sleep scores before surgery nights, covering sleep depth, latency, awakenings, efficiency, quality. Higher scores indicated better sleep.

Cognitive function was evaluated on postoperative days 7 and 30 (±2 days) using the Montreal Cognitive Assessment (MoCA) for hospitalized patients and the Telephone-MoCA (T-MoCA) for discharged patients. Scores <26 points for the MoCA or ≤18 points for the T-MoCA indicated dNCR.[17,18]

Postoperative pain scores were assessed from postoperative day 1 to day 5 using the Numerical Rating Scale (NRS) at rest and during movement (0–10 scale), with rescue analgesia administered if the rest NRS score was ≥4 points. Adverse events to dexmedetomidine were recorded, and postoperative recovery quality was assessed on the 3rd day using the Quality of Recovery-15 (QoR-15) scale.[19] Non-delirium complications during hospitalization were assessed (including postoperative infection, unplanned reoperation, postoperative major bleeding, and unplanned ICU admission). Clinically significant differences were defined as changes ≥2 points in the pain NRS score, ≥7 points in the RCSQ score, and ≥8 points in the QoR-15 score.[15] Additionally, the total and postoperative length of hospital stay, and 30-day all-cause mortality rates were documented.

Sample Size Calculation

Based on previous studies, the incidence of POD in elderly patients with SD was 35.6%.[20] Meta-analyses have shown that dexmedetomidine can reduce the risk of POD in patients undergoing noncardiac surgery, with a relative risk ranging from 0.47 to 0.60.[10,21] Accordingly, we assumed a POD incidence of 35% in the placebo group and a 40% reduction in POD incidence in the dexmedetomidine group, yielding a POD incidence of 21%. To detect this difference with a two-sided α level of 0.05 and a statistical power of 80%, and assuming a 1:1 allocation ratio, a sample size of 158 participants per group was required. Considering a 10% dropout rate, the final target sample size was increased to 174 participants per group, for a total of 348 participants.

Statistical Analysis

All statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9.5 (GraphPad Software Inc., Boston, MA) for graphical representation. Analyses were performed according to the intention-to-treat (ITT) principle.

Categorical variables are presented as counts and percentages. Group comparisons were performed using the chi-square test or Fisher's exact test as appropriate. Risk ratios (RRs) and 95% confidence intervals (CI) were calculated to quantify between-group differences.

Continuous variables are expressed as means ± standard deviations (SD) for normally distributed data or as medians with interquartile ranges (IQR) for non-normally distributed data. Normality was assessed using the Shapiro–Wilk test. Between-group comparisons were made using independent-sample t-tests or Mann–Whitney *U*-tests, as appropriate. Differences in means or medians are reported with corresponding 95% CIs. For repeated measurements of physiological parameters (eg, mean arterial pressure, heart rate, and peripheral oxygen saturation) over time, repeated-measures

ANOVA was used to evaluate group-by-time interactions. To control for type I error inflation due to multiple comparisons among primary and secondary outcomes, Bonferroni correction was applied where appropriate. Two-sided *P*-values < 0.05 were considered statistically significant.

Results

Participant Characteristics

Between November 2023 and August 2024, 471 patients were assessed for eligibility, with 123 excluded (55 Met exclusion criteria, 68 declined). A total of 348 patients were randomized into the dexmedetomidine (n=174) and placebo (n=174) groups.

During the 5-day postoperative follow-up period for the primary outcome (POD), 67 patients were discharged early: 29 in the dexmedetomidine group (16 on postoperative day 4 and 13 on day 5), and 38 in the placebo group (5 on day 3, 12 on day 4, and 21 on day 5). All of these patients underwent twice-daily POD assessments during hospitalization and had four consecutive negative evaluations prior to discharge. Therefore, the last available observation was carried forward to impute the remaining assessments.

In addition, 14 patients (4.0%) were lost to follow-up. For these cases, missing data for the primary outcome (<5%) were addressed using multiple imputation by chained equations (MICE), under the assumption of missing at random (MAR). The imputation model included baseline covariates such as age, sex, PSQI, ASA physical status, type of surgery, and observed POD patterns. All randomized participants (n = 174 per group) were included in the intention-to-treat (ITT) analysis (Shown in Figure 1).

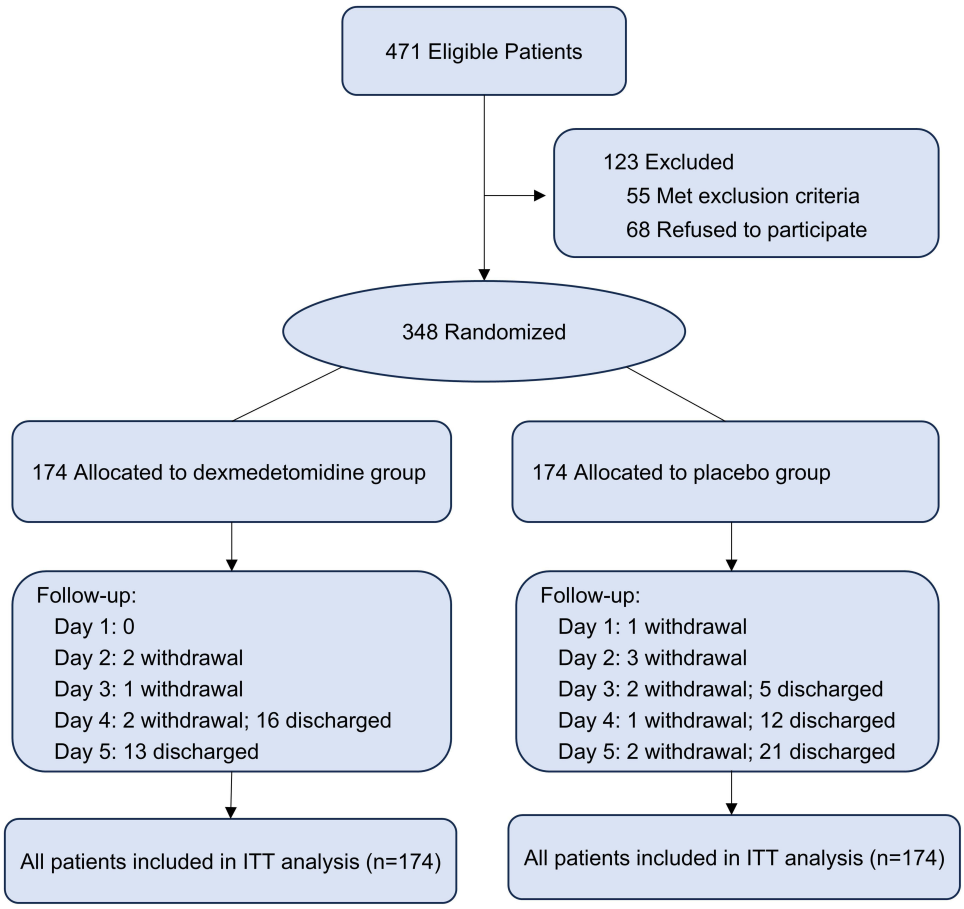


Figure 1 Study Flow Diagram. 471 patients were assessed for eligibility, with 123 excluded (55 met exclusion criteria; 68 refused to participate). A total of 348 patients were randomized into the dexmedetomidine (n=174) and placebo (n=174) groups. All randomized participants were included in the intention-to-treat (ITT) analysis.

The baseline characteristics and intraoperative data of the patients are detailed in (Table 1 and Table 2). Intraoperative factors were also balanced between the groups (Table 2). No significant differences were observed in terms of surgery site, surgery type, intraoperative medications and anesthetic drugs (all $P > 0.05$).

Primary Outcomes

Dexmedetomidine significantly reduced the incidence of POD compared to placebo (18.4% vs 32.8%; RR: 0.56; 95% CI: 0.38–0.82; $P=0.002$) (Table 3). Specifically, it markedly reduced the incidence of moderate to severe POD (8.6% vs 20.7%; RR: 0.42; 95% CI: 0.24–0.73; $P = 0.004$). In addition, we conducted an exploratory analysis of POD subtypes. Trends toward lower incidence were observed in the dexmedetomidine group across all delirium subtypes: hypoactive delirium (6.9% vs 11.5%; RR: 0.60, 95% CI: 0.30–1.19; $P=0.414$), hyperactive delirium (8.1% vs 15.0%; RR: 0.54, 95% CI: 0.29–1.00; $P=0.132$), mixed delirium (3.4% vs 6.3%; RR: 0.55, 95% CI: 0.21–1.44, $P=0.642$). Given the limited number of cases in each subtype, these analyses were exploratory and underpowered, and the findings should be interpreted with caution. Most cases of delirium occurred only once and were concentrated between postoperative days 1 and 3 (Table 3).

Table 1 Baseline Clinical Characteristics of Participants

Characteristic	Dexmedetomidine (n=174)	Placebo (n=174)
Age, median (IQR), years	66 (62–72)	67 (63–72)
BMI, mean ± SD, $kg \cdot m^{-2}$	23.9 ± 3.2	23.8 ± 3.6
PSQI, median (IQR)	11 (10–14)	12 (9–15)
MMSE, median (IQR)	28 (27–30)	28 (26–30)
Female, n (%)	96 (55.2)	95 (54.6)
Educational level, n (%)		
1-6 years	68 (39.1)	64 (36.8)
7-12 years	77 (44.3)	91 (52.3)
>12 years	29 (16.6)	19 (10.9)
Comorbidities, n (%)		
Hypertension	80 (46.0)	77 (44.3)
Coronary artery disease	14 (8.0)	11 (6.3)
Diabetes mellitus	35 (20.1)	27 (15.5)
Thyroid dysfunction	7 (4.0)	5 (2.9)
Liver dysfunction	3 (1.7)	6 (3.4)
Kidney dysfunction	0	3 (1.7)
Medical history, n (%)		
Allergic history	1 (0.5)	0
Surgery history	96 (55.2)	93 (53.4)
Smoking history	39 (22.4)	52 (29.9)
Drinking history	19 (10.9)	27 (15.5)
NYHA functional classification, n (%)		
1	4 (2.3)	1 (0.6)
2	166 (95.4)	166 (95.4)
3	4 (2.3)	7 (4.0)
Haemoglobin, mean ± SD, $g \cdot l^{-1}$	133.6 ±18.1	132.4 ± 18.7
Albumin, mean ± SD, $g \cdot l^{-1}$	42.3 ± 6.2	41.6 ± 5.4
Age-adjusted Charlson Comorbidity Index, median (IQR)	4 (3–5)	4 (3–5)
ASA physical status, n (%)		
2	133 (76.4)	144 (82.8)
3	41 (23.6)	30 (17.2)

Abbreviations: IQR, interquartile range; BMI, Body mass index; PSQI, Pittsburgh Sleep Quality Index Score; MMSE, Mini-Mental State Examination score; NYHA, New York Heart Association; ASA, American Society of Anesthesiologists.

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Table 2 Intraoperative Characteristics of Participants

Characteristic	Dexmedetomidine (n=174)	Placebo (n=174)	*P* Value
Surgery site, n (%)			0.441
Abdomen	69 (39.7)	63 (36.2)	/
Thoracics	46 (26.5)	55 (31.6)	/
Spine or limbs	57 (32.8)	51 (29.3)	/
Others	2 (1.0)	5 (2.9)	/
Surgery type, n (%)			0.569
Minimally invasive surgery[a]	114 (65.5)	119 (68.4)	/
Open Surgery[b]	60 (34.5)	55 (31.6)	/
Intraoperative medications			
Duration of surgery, median (IQR), h	3.0 (2.2–3.8)	3.1 (2.4–4.0)	0.169
Duration of anesthesia, median (IQR), h	3.4 (2.6–4.3)	3.5 (2.8–4.4)	0.135
Infusion of artificial colloid solution, median (IQR), mL	500 (0–500)	500 (0–500)	0.350
Infusion of crystalloid solution, median (IQR), mL	1355 (1100–1700)	1500 (1100–1700)	0.562
Estimated blood loss, median (IQR), mL	40 (20–100)	50 (20–100)	0.674
Urine, median (IQR), mL	300 (200–600)	350 (200–600)	0.946
Allogeneic red blood cell infusion, n (%)	13 (7.5)	9 (5.2)	0.378
Vasopressor, n (%)	135 (77.6)	143 (82.2)	0.285
Anesthetic drugs, median (IQR)			
Etomidate, mg	18 (16–20)	18 (15–20)	0.808
Rocuronium, mg	53 (40–65)	50 (36–70)	0.635
Sufentanil, μg	35 (30–45)	35 (25–45)	0.177
Propofol, mg	391 (300–532)	390 (292–524)	0.907
Remifentanil, μg	761 (534–1000)	744 (557–980)	0.828
Sevoflurane, mL	61 (46–75)	63 (51–76)	0.434

Notes: [a] Minimally invasive surgery refers to surgical procedures primarily performed using techniques such as laparoscopy, thoracoscopy, arthroscopy and endoscopic spine surgery. [b] Open surgery refers to surgical techniques performed through larger incisions or by direct exposure of target tissues or organs, such as total hip replacement, knee replacement, and procedures performed through abdominal or thoracic incisions.

Table 3 Primary Outcomes

Measurement	Dexmedetomidine (n=174)	Placebo (n=174)	Risk Ratio (95% CI)	Adjusted *P*
Postoperative delirium within 5 day, n (%)	32 (18.4)	57 (32.8)	0.56 (0.38–0.82)	0.002
Duration of delirium, n (%), days				
1	15 (8.6)	25 (14.4)	0.60 (0.33–1.10)	0.279
2	13 (7.5)	25 (14.4)	0.52 (0.28–0.98)	0.117
≥3	4 (2.3)	7 (4.0)	0.57 (0.17–1.92)	1.62
Types of delirium, n (%)				
Hypoactive	12 (6.9)	20 (11.5)	0.60 (0.30–1.19)	0.414
Hyperactive	14 (8.1)	26 (15.0)	0.54 (0.29–1.00)	0.132
Mixed	6 (3.4)	11 (6.3)	0.55 (0.21–1.44)	0.642
Severity of delirium, n (%)				
Mild	17 (9.8)	21 (12.1)	0.81 (0.44–1.48)	0.984
Moderate to severe[a]	15 (8.6)	36 (20.7)	0.42 (0.24–0.73)	0.004
Number of delirium episodes[b], n (%)				
1	30 (17.4)	57 (32.8)	0.53 (0.36–0.78)	<0.001
2	2 (1.0)	0	/	0.998

(*Continued*)

Table 3 (Continued).

Measurement	Dexmedetomidine (n=174)	Placebo (n=174)	Risk Ratio (95% CI)	Adjusted *P*
Time to onset of delirium, n (%)				
Postoperative Day 1	26 (17.2)	45 (31.0)	0.58 (0.37–0.89)	0.044
Postoperative Day 2	4 (2.6)	6 (4.3)	0.67 (0.19–2.32)	>0.999
Postoperative Day 3	2 (1.7)	3 (1.7)	0.67 (0.11–3.94)	>0.999
Postoperative Day 4	0	3 (1.7)	/	0.992

Notes: [a] Moderate to severe, combined count of moderate and severe delirium; [b]Postoperative delirium episodes were identified based on discrete Confusion Assessment Method-positive days, non-consecutive positive days, such as on both days 2 and 4, were counted as separate episodes, Consecutive positive days, like days 1, 2, and 3, were counted as a single episode.

Secondary Outcomes

Sleep quality (Table 4). On the preoperative night, dexmedetomidine improved the primary objective sleep metrics: total sleep time (6.2 ± 1.5 vs 5.3 ± 1.7 h; mean difference 0.89 h, 95% CI 0.56–1.23; adjusted $P < 0.001$), sleep efficiency (77.3% ± 16.0% vs 66.3% ± 19.1%; difference 11.01 %, 95% CI 7.3–14.7; adjusted $P < 0.001$), and sleep latency (0.8 vs 1.2 h; median difference −0.33 h, 95% CI −0.50 to −0.19; adjusted $P < 0.001$). Stage-specific outputs were analyzed

Table 4 Secondary Outcomes

Measurement	Dexmedetomidine (n=174)	Placebo (n=174)	Difference or Risk Ratio (95% CI)	Adjusted *P*
Sleep data				
Total sleep, mean ± SD, h	6.2 ± 1.5	5.3 ± 1.7	0.89 (0.56–1.23)	<0.001
Sleep efficiency, mean ± SD, %	77.3 ± 16.0	66.3 ± 19.1	11.01 (7.3–14.7)	<0.001
Sleep latency, median (IQR), h	0.8 (0.4–1.3)	1.2 (0.6–1.8)	−0.33 (−0.50 to −0.19)	<0.001
Bed rest time, mean ± SD, h	8.1 ± 1.2	8.1 ± 1.3	0.01 (−0.26 to 0.27)	>0.999
Deep sleep, mean ± SD, h	2.0 ± 0.8	1.4 ± 0.7	0.55 (0.41–0.70)	<0.001
Light sleep, mean ± SD, h	2.9 ± 0.8	2.8 ± 1.0	0.10 (−0.09 to 0.29)	>0.999
REM sleep, mean ± SD, h	1.4 ± 0.5	1.1 ± 0.6	0.25 (0.14–0.36)	<0.001
Number of awakenings, median (IQR), times	3 (2–3)	3 (2–4)	0 (−1 to 0)	0.570
Preoperative day 1 RCSQ, mean ± SD	68 ± 13	59 ± 15	9.31 (6.35–12.27)	<0.001
Trial drug consumption, median (IQR), $\mu g \cdot kg^{-1}$	1.1 (1.0–1.2)	0	/	/
Postoperative cognitive function recovery delay, n (%)				
Postoperative day 7	51 (29.3)	68 (39.1)	0.75 (0.56–1.01)	0.110
Postoperative day 30	40 (23.0)	48 (27.6)	0.82 (0.57–1.18)	0.586
Postoperative days 1–5 rest NRS score, median (IQR)				
Day 1	4 (2–4)	4 (2–4)	0 (0–0)	>0.999
Day 2	2 (1–3)	2 (2–4)	0 (0–0)	>0.999
Day 3	2 (1–3)	2 (1–4)	0 (−1 to 0)	0.015
Day 4	1 (1–2)	1 (1–2)	0 (0–0)	>0.999
Day 5	1 (1–2)	1 (1–2)	0 (0–0)	>0.999
Postoperative days 1–5 movement NRS score, median (IQR)				
Day 1	6 (5–7)	6 (5–6)	0 (0–0)	>0.999
Day 2	4 (3–5)	5 (4–6)	0 (0–0)	>0.999
Day 3	4 (3–4)	4 (3–5)	0 (0–0)	0.755
Day 4	3 (2–4)	3 (2–4)	0 (0–0)	>0.999
Day 5	3 (2–4)	3 (3–4)	0 (0–0)	>0.999

Abbreviations: NRS, numeric rating scale; RCSQ, Richards Campbell sleep questionnaire. REM, rapid eye movement.

exploratorily given the limited staging accuracy of wearables in older adults and potential algorithm interference by α2-agonist sedation; these showed directionally higher values with dexmedetomidine (deep sleep: difference 0.55 h, 95% CI 0.41–0.70; adjusted $P < 0.001$; REM sleep: difference 0.25 h, 95% CI 0.14–0.36; adjusted $P < 0.001$) but are interpreted cautiously. Subjective sleep quality also improved (RCSQ mean difference 9.31, 95% CI 6.35–12.27; adjusted $P < 0.001$).

The incidence of dNCR on postoperative day 7 was lower in the dexmedetomidine group compared to the placebo group, but this difference was not statistically significant (29.3% vs 39.1%; P=0.110). By postoperative day 30, the incidence of dNCR remained similar between the dexmedetomidine group (23.0%) and the placebo group (27.6%), P=0.586 (Table 4).

Postoperative NRS pain scores at rest and during movement on postoperative days 1–5 were generally similar between the two groups (Table 4). A statistically significant difference was observed in the resting NRS score on day 3 (median 2 vs 2; $P = 0.015$); however, this difference did not exceed the clinically meaningful threshold of 2 points.

Adverse Events

In terms of adverse events (Table 5), the incidence of bradycardia was significantly greater in the dexmedetomidine group 37.9% than in the placebo group16.7% (RR: 2.28; 95% CI: 1.55–3.34; P<0.001). There were no significant differences

Table 5 Adverse Events and Complications

Measurement	Dexmedetomidine (n=174)	Placebo (n=174)	Difference or Risk Ratio (95% CI)	*P*-Value
Adverse events on the night before surgery, n (%)				
Bradycardia	66 (37.9)	29 (16.7)	2.28 (1.55–3.34)	<0.001
Hypotension	46 (26.4)	34 (19.5)	1.35 (0.92–2.00)	0.126
Hypoxemia	51 (29.3)	37 (21.3)	1.38 (0.96–1.99)	0.084
Hypertension	0	0	/	/
Tachycardia	0	0	/	/
Nasal congestion or sneezing	16 (9.2)	21 (12.1)	0.76 (0.41–1.41)	0.358
Nausea or vomiting	4 (2.3)	9 (5.2)	0.44 (0.14–1.42)	0.258
Headache	0	0	/	/
Allergies	0	0	/	/
NonDelirium Complications, n (%)				
Postoperative infection[a]	9 (5.2)	7 (4.0)	1.29 (0.49–3.38)	0.609
Unplanned reoperation[b]	1 (0.6)	2 (1.1)	0.5 (0.05–5.46)	>0.999
Postoperative major bleeding[c]	0	0	/	/
Unplanned ICU admission[d]	1 (0.6)	1 (0.6)	1 (0.06–15.80)	>0.999
Postoperative nausea or vomiting	28 (16.1)	27 (15.5)	1.04 (0.64–1.68)	0.883
Postoperative data				
Sufentanil consumption for postoperative analgesia, median (IQR), μg	120 (100–140)	115 (105–140)	5 (−0.88 to10.88)	0.101
Quality of recovery-15 item, mean ± SD	121 ± 13	122 ± 13	1.39 (−3.20 to 2.25)	0.731
Hospital length of stay, median (IQR), day	13 (10–17)	12 (8–16)	1.00 (0–2.00)	0.129
Hospital length of stay after surgery, median (IQR), day	8 (6–11)	8 (5–11)	0 (0–1.00)	0.381
Hospital stay ≥30 days, n (%)	6 (3.4)	6 (3.4)	1.00 (0.33–3.04)	>0.999
Death within 30 days after surgery, n (%)	2 (1.1)	5 (2.9)	0.40 (0.08–2.03)	0.445

Notes: [a] Postoperative infection refers to newly acquired infections after surgery. [b] Unplanned reoperation indicates surgeries performed outside of the planned schedule due to surgical complications; [c] Postoperative major bleeding denotes postoperative bleeding equal to or exceeding 10% of total blood volume or requiring surgical intervention for hemostasis; [d] Unplanned ICU admission refers to unexpected transfer to the ICU due to post-surgical complications or sudden deterioration.

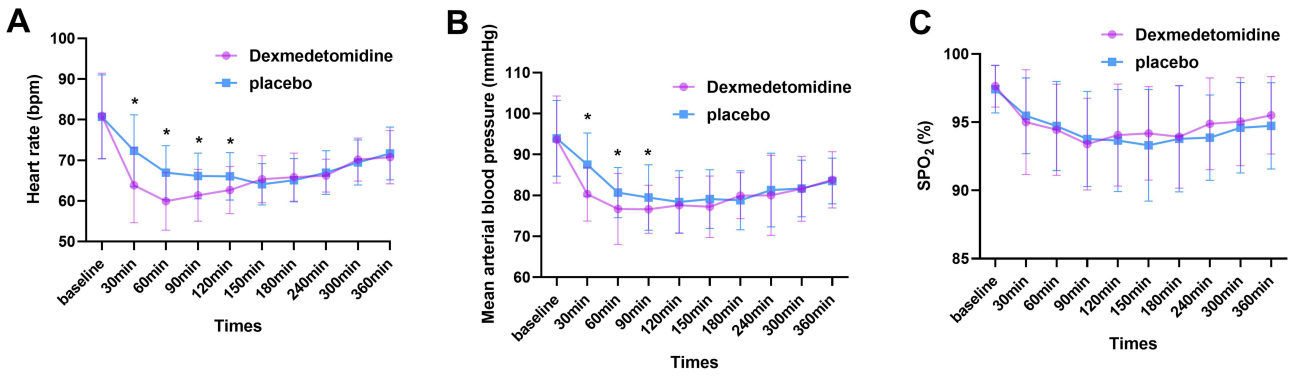

Figure 2 Vital signs data within 6 hours after administration of investigational drug. Date are described as means and SD. (**A**) Heart rate; (**B**) Mean arterial pressure; (**C**) Peripheral capillary oxygen saturation (SpO_2); n=174; *Indicates statistical significance compared to the placebo group ($P < 0.05$).

between the groups in terms of the incidence of hypotension or hypoxemia. Additionally, no significant differences were observed in the incidence of hypertension, tachycardia, nasal congestion or sneezing, nausea or vomiting, headache, or allergies between the groups, all $P > 0.05$. Compared to the placebo group, the dexmedetomidine group exhibited a decrease in heart rate at 30, 60, 90, and 120 minutes after drug administration. Similarly, the mean arterial pressure was lower at these time points (30, 60, 90, 120 minutes). No significant effect on peripheral oxygen saturation (SpO_2) was observed (Shown in Figure 2).

There were no significant differences between the groups in postoperative non-delirium complications (including postoperative infection, unplanned reoperation, postoperative major bleeding, and unplanned ICU admission), QoR-15 scores on postoperative day 3, hospital length of stay, hospital length of stay after surgery, the number of patients with hospital stays ≥30 days, or death within 30 days after surgery (all $P > 0.05$) (Table 5).

Discussion

Preoperative intranasal dexmedetomidine in older adults with preexisting sleep disorders undergoing major noncardiac surgery was associated with a lower 5-day incidence of postoperative delirium and better preoperative-night sleep quality. This benefit was accompanied by a higher incidence of bradycardia, consistent with the drug's pharmacology. Taken together, the findings indicate a clinically meaningful reduction in delirium that should be balanced against the increased need for heart-rate monitoring and potential intervention in appropriate candidates and settings.

SD are known to increase POD risk through central neuroinflammation, circadian disruption, and impaired clearance of brain metabolic waste.[22,23] Consistent with systematic reviews identifying preoperative SD as a major risk factor,[6,24] the placebo group in our cohort—prospectively enriched for SD—showed a higher POD incidence than typically reported in unselected elderly noncardiac populations.[6,24] Prior work has established that perioperative dexmedetomidine can reduce POD, with postoperative intravenous regimens generally outperforming intraoperative use.[21,25] Building on this evidence, our trial intentionally intervened during the preoperative night—a practical, modifiable window before surgery—and used a ward-feasible intranasal route, while deliberately enrolling older adults with preexisting SD to target a high-risk yet potentially modifiable subgroup. Although preoperative dexmedetomidine has been less studied. Fang et al[26] reported benefit in elderly cardiac patients with sleep disturbances. Extending these observations beyond cardiac surgery, our SD-enriched, major noncardiac cohort demonstrated a lower POD risk with preoperative intranasal dexmedetomidine (RR 0.56 vs placebo), suggesting that who is treated and when the intervention occurs may be as consequential as the agent itself.

Regarding sleep, preoperative dexmedetomidine significantly improved sleep quality by increasing total sleep time sleep efficiency and enhanced subjective sleep quality, these are critical for brain recovery and function.[27] Studies have shown that sleep plays a crucial role in the clearance of inflammatory factors, metabolic waste, β-amyloid, and tau proteins, all of which are essential for maintaining brain health. Thus, the sleep-promoting effects of dexmedetomidine may be a key mechanism underlying its reduction in POD incidence.[28,29] By contrast, stage-specific sleep findings (deep

and REM sleep) were derived from a wearable on a single preoperative night and may be influenced by α2-agonist–related sedation; these results are therefore exploratory and should be interpreted with caution.

The effect of dexmedetomidine on dNCR and postoperative cognitive dysfunction varies across different populations. While systematic reviews and meta-analyses suggest that dexmedetomidine can reduce the incidence of dNCR in cardiac surgery patients,[30] its effects in noncardiac surgery patients remain less clear.[31,32] In our study, preoperative dexmedetomidine tended to reduce the incidence of dNCR in elderly noncardiac surgery patients with SD, although this difference was not statistically significant. Given the limited evidence on preoperative dexmedetomidine and neurocognitive outcomes, further studies are needed to explore this potential benefit.

Safety deserves a balanced reading. Prior intranasal studies in older adults using doses around 1–2 $\mu g \cdot kg^{-1}$ reported improved sedation/sleep but relatively frequent hypotension and bradycardia.[12,14] To mitigate hemodynamic liability, we used a weight-based initial dose with a symmetrical rescue protocol timed to the expected absorption peak (~30 min).[11] The average final dose was ~1.1 $\mu g \cdot kg^{-1}$. In our trial, bradycardia was more common than with placebo—as anticipated—but managed under predefined algorithms; serious adverse events did not differ significantly between groups. Taken together, these data support the feasibility of preoperative intranasal dexmedetomidine in carefully selected, monitored patients while reinforcing the need for vigilant cardiovascular surveillance.

Limitations

Our study has several limitations: First, the study was conducted at a single center, limiting the generalizability of the findings, as the population and surgical practices at other centers may differ. Second, we did not monitor plasma concentrations of dexmedetomidine after nasal spray administration, which could affect the understanding of its bioavailability and pharmacokinetics in elderly patients. This lack of pharmacokinetic data may have influenced the accuracy of dosing and the assessment of its duration of action. Only a single preoperative dose was administered, which did not improve sleep from postoperative days 1 to 5, suggesting the need for further research on postoperative dexmedetomidine use. Finally, we did not monitor biomarkers or explore the mechanisms underlying the reduction in delirium incidence.

Conclusions

Preoperative intranasal dexmedetomidine strategy was associated with a lower five-day incidence of delirium and improved objective/subjective sleep metrics, at the cost of increased bradycardia requiring monitoring and potentially treatment; confirmation in multicentre trials with robust handling of missingness, adjudicated harms, and appropriate cognitive endpoints is necessary before recommending routine adoption.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are not publicly available due to privacy policies protecting human subjects but are available from Jing Shi (shijing81@gmc.edu.cn), upon reasonable request.

Ethics Approval

This study was approved by the Medical Ethics Committee of the affiliated hospital of guizhou medical university (Approval No. 2023169K) on October 13, 2023.

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An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com). The authors thank those who assisted with the non-blinded packaging of randomized envelopes in the anesthesia pharmacy and the Clinical Research Center staff at the participating hospital for their contributions to participant randomization.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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