

Low-Dose Perioperative Dexmedetomidine for the Prevention of Postoperative Delirium in Older Adults Undergoing Hip Fracture Surgery: A Randomized, Double-Blind, Placebo-Controlled Trial

Le Van Chung

Department of Anesthesiology and Intensive Care, Saigon ITO Phu Nhuan Hospital

Ta Duc Luan

bsluan.gmhs@gmail.com

Department of Anesthesiology and Intensive Care, Faculty of Medicine, Nguyen Tat Thanh University, Ho Chi Minh City, Vietnam

Lam Tri Duc

Department of Medical Laboratory Technology, Nguyen Tat Thanh University, Ho Chi Minh City, Vietnam, Ho Chi Minh City, Viet Nam

Research Article

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Abstract

Background

Postoperative delirium (POD) is a frequent neurocognitive complication in older adults undergoing surgery and is associated with delayed recovery, prolonged hospitalization, increased healthcare utilization, and poor clinical outcomes. Dexmedetomidine possesses sedative, analgesic, sympatholytic, and opioid-sparing properties that may reduce the risk of POD. This study evaluated the efficacy of perioperative low-dose dexmedetomidine for preventing postoperative delirium in older adults undergoing hip fracture surgery.

Methods

This prospective, randomized, double-blind, placebo-controlled trial was conducted at Saigon ITO Phu Nhuan Hospital, Vietnam, between December 2024 and April 2026. A total of 490 patients aged ≥ 65 years scheduled for hip fracture surgery under general anesthesia were randomly assigned (1:1) to receive either dexmedetomidine (Group D, $n = 245$) or 0.9% normal saline (Group C, $n = 245$). Patients in Group D received a loading dose of dexmedetomidine ($0.2 \mu\text{g/kg}$ over 10 minutes before induction of anesthesia), followed by a continuous infusion of $0.15 \mu\text{g/kg/h}$ throughout surgery and for a mean duration of 7.4 hours postoperatively. All patients received standardized multimodal analgesia, including continuous fascia iliaca compartment block with 0.2% ropivacaine for 48–52 hours. The primary outcome was the cumulative incidence of postoperative delirium within 7 postoperative days, assessed using the Confusion Assessment Method (CAM). Secondary outcomes included delirium severity (CAM-S), perioperative hemodynamic variables, postoperative pain scores, 24-hour rescue morphine consumption, and length of hospital stay. The trial was registered with the ISRCTN Registry (ISRCTN12589867) on 29 September 2026.

Results

Dexmedetomidine significantly reduced the incidence of postoperative delirium compared with placebo (21.2% [52/245] vs. 45.7% [112/245]; relative risk [RR] 0.46, 95% confidence interval [CI] 0.35–0.61; $P < 0.001$), corresponding to an absolute risk reduction of 24.5% and a number needed to treat (NNT) of 5. Severe delirium occurred less frequently in Group D than in Group C (1.9% vs. 66.1%, $P < 0.001$), and delirium duration was significantly shorter (15 ± 6 vs. 37 ± 8 hours). Patients receiving dexmedetomidine also had lower intraoperative heart rate (68 ± 10 vs. 73 ± 11 beats/min, $P < 0.001$), lower heart rate at 12 hours postoperatively (67 ± 11 vs. 75 ± 12 beats/min, $P < 0.001$), and lower intraoperative mean arterial pressure (69 ± 12 vs. 75 ± 13 mmHg, $P < 0.001$), whereas postoperative mean arterial pressure at 12 hours did not differ significantly ($P = 0.102$). Pain scores at rest and during movement were significantly lower in Group D (both $P < 0.001$), accompanied by lower 24-hour rescue morphine consumption (5 ± 0.1 vs. 30 ± 10 mg, $P < 0.001$). Length of hospital stay was reduced from 12 ± 0.8 to 8 ± 0.5 days ($P < 0.001$).

Conclusions

Perioperative administration of low-dose dexmedetomidine significantly reduced the incidence, severity, and duration of postoperative delirium in older adults undergoing hip fracture surgery. In addition, dexmedetomidine improved postoperative analgesia, reduced opioid requirements, and shortened hospital stay. These findings support the use of low-dose dexmedetomidine as part of a multimodal perioperative strategy for delirium prevention in high-risk older patients.

1. Introduction

Postoperative delirium (POD) is an acute neurocognitive disorder characterized by an abrupt onset, fluctuating clinical course, inattention, and disturbances in cognition or level of consciousness. According to the current nomenclature for perioperative cognitive disorders, delirium occurring after surgery is classified as a postoperative neurocognitive disorder within the spectrum of perioperative neurocognitive disorders (PNDs) [1]. POD is one of the most common postoperative complications in older adults but remains underdiagnosed, particularly in patients with hypoactive delirium.

The incidence of POD ranges from approximately 20% to 50% among older adults undergoing surgery for hip fracture [2, 7]. Advanced age, acute pain, prolonged immobilization, multiple comorbidities, pre-existing cognitive impairment, sleep disturbances, perioperative blood loss, and exposure to anesthetic and opioid medications are well-established risk factors for delirium. Current clinical practice guidelines recommend systematic preoperative risk assessment, routine postoperative delirium screening using validated assessment tools, and implementation of multidisciplinary, multimodal prevention strategies for patients at high risk [2, 3]. Postoperative delirium has consistently been associated with delayed functional recovery, prolonged hospitalization, increased dependency, higher healthcare costs, and increased short- and long-term mortality [7, 8].

Dexmedetomidine, a highly selective α_2 -adrenergic receptor agonist, produces sedation that closely resembles natural sleep while providing analgesic, sympatholytic, and opioid-sparing effects with minimal respiratory depression. These pharmacological properties have made dexmedetomidine an attractive candidate for delirium prevention in older surgical patients. Several randomized controlled trials and meta-analyses have demonstrated that perioperative dexmedetomidine may reduce the incidence of postoperative delirium. However, the magnitude of its benefit has been inconsistent across studies because of differences in patient populations, dosing regimens, timing and duration of administration, anesthetic techniques, and perioperative care pathways [12–17]. Moreover, evidence specifically addressing older patients undergoing hip fracture surgery remains limited, and data from low- and middle-income countries, including Vietnam, are scarce.

Therefore, the present randomized, double-blind, placebo-controlled trial was conducted to evaluate whether perioperative low-dose dexmedetomidine reduces the incidence of postoperative delirium during the first 7 postoperative days in older adults undergoing hip fracture surgery. Secondary

objectives were to compare delirium severity and duration, postoperative pain intensity, 24-hour rescue morphine consumption, perioperative anesthetic and analgesic requirements, hemodynamic parameters, and length of hospital stay between the two study groups.

2. Methods

Study Design

This prospective, randomized, double-blind, placebo-controlled clinical trial was conducted at Saigon ITO Phu Nhuan Hospital, Ho Chi Minh City, Vietnam, between December 2024 and April 2026. The study was designed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2025 statement.

Participants

Patients aged 65 years or older who were diagnosed with either femoral neck fracture or intertrochanteric femoral fracture and scheduled to undergo surgical repair within 48 hours of hospital admission were eligible for inclusion. Written informed consent was obtained from all participants or their legally authorized representatives before enrollment. Exclusion criteria were preoperative delirium, Mini-Mental State Examination (MMSE) score < 18, Parkinson's disease, severe dementia, second- or third-degree atrioventricular block without a permanent pacemaker, resting heart rate < 50 beats/min, systolic blood pressure < 100 mmHg, Child–Pugh class C liver disease, or known hypersensitivity to dexmedetomidine.

Randomization and Blinding

Participants were randomly assigned in a 1:1 ratio to either the dexmedetomidine group (Group D) or the placebo group (Group C) using block randomization with variable block sizes of four and six generated by Random Allocation Software. The allocation sequence was concealed throughout the enrollment process. Participants, anesthesiologists responsible for postoperative outcome assessment, surgeons, ward staff, and data analysts remained blinded to treatment allocation. Dexmedetomidine and placebo solutions were prepared in identical syringes with the same appearance and volume to ensure allocation concealment throughout the study.

Perioperative Intervention

Patients assigned to Group D received dexmedetomidine (Y-Med Pharmaceutical Co., Ltd., Vietnam) as a loading dose of 0.2 µg/kg administered intravenously over 10 minutes before induction of anesthesia, followed by a continuous infusion of 0.15 µg/kg/h during surgery (mean duration, 68 ± 10 minutes) and continued postoperatively for a mean duration of 7.4 ± 0.8 hours. Patients in Group C received an equivalent volume of 0.9% normal saline administered at the same infusion rate.

All patients underwent standardized general anesthesia with endotracheal intubation according to institutional protocols. Standard intraoperative monitoring included electrocardiography, invasive arterial blood pressure monitoring, pulse oximetry, and routine anesthetic monitoring. Surgical procedures included hemiarthroplasty, total hip arthroplasty, or proximal femoral nail antirotation (PFNA) fixation.

Postoperative analgesia was standardized in both groups using a multimodal analgesic protocol consisting of continuous fascia iliaca compartment block with 0.2% ropivacaine for 48–52 hours, celecoxib 200 mg administered the evening before surgery, intravenous paracetamol 1 g every 12 hours, intravenous nefopam 20 mg every 12 hours, and ketorolac 30 mg every 8 hours after surgery. Intravenous morphine was administered as rescue analgesia according to institutional protocols when pain control was inadequate.

Antimicrobial prophylaxis consisted of intravenous cefazolin 1 g administered within 60 minutes before skin incision and repeated every 12 hours for 48 hours postoperatively. Venous thromboembolism prophylaxis included subcutaneous enoxaparin 40 mg initiated 4 hours after surgery, followed by oral rivaroxaban 10 mg once daily for four weeks.

Outcomes and Assessments

The primary outcome was the cumulative incidence of postoperative delirium during the first seven postoperative days. Delirium was assessed twice daily using the Confusion Assessment Method (CAM). A diagnosis of delirium required the presence of acute onset or fluctuating course and inattention, together with either disorganized thinking or an altered level of consciousness, according to the validated CAM diagnostic algorithm [4].

Delirium severity was quantified using the short-form Confusion Assessment Method Severity (CAM-S) score (range, 0–7), with higher scores indicating greater delirium severity [5]. Delirium severity was categorized as mild (1–2 points), moderate (3–5 points), or severe (6–7 points).

Postoperative pain was assessed using the 5-point Verbal Rating Scale (VRS; score 0–4) at rest and during movement for up to 72 hours after surgery in communicative patients. In patients with delirium or impaired communication, pain was evaluated using the Pain Assessment in Advanced Dementia (PAINAD) scale (score range, 0–10), with scores categorized as no pain (0), mild pain (1–3), moderate pain (4–6), and severe pain (7–10) [6].

Secondary outcomes included delirium duration, 24-hour rescue morphine consumption, cumulative perioperative dexmedetomidine dose, intraoperative anesthetic and analgesic requirements, perioperative heart rate, mean arterial pressure (MAP), estimated cumulative ropivacaine dose administered through the fascia iliaca catheter, and length of hospital stay.

Sample Size Calculation

Sample size estimation was based on an expected postoperative delirium incidence of 30% in the placebo group and 18% in the dexmedetomidine group. Assuming a two-sided α level of 0.05, 80% statistical power, and a 1:1 allocation ratio, a minimum of 198 participants per group was required. After allowing for an anticipated 10% dropout or loss to follow-up, at least 220 participants were required in each group. Therefore, a total sample size of 490 participants (245 per group) was planned.

Statistical Analysis

All analyses were performed according to the intention-to-treat principle. Categorical variables are presented as frequencies and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables are presented as mean $\pm$ standard deviation (SD) and were compared using Welch's independent-samples t test when appropriate. Treatment effects for the primary outcome are reported as relative risk (RR), absolute risk reduction (ARR), and corresponding 95% confidence intervals (CIs). No outcome data were missing; therefore, no imputation procedures were performed. Analyses of secondary outcomes were considered exploratory and were not adjusted for multiple comparisons. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

This randomized controlled trial was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

3. Results

Study population and baseline characteristics

Between December 2024 and April 2026, a total of 490 older adults undergoing surgery for hip fracture were enrolled and randomly assigned in a 1:1 ratio to receive dexmedetomidine (Group D, $n = 245$) or placebo (Group C, $n = 245$). All randomized participants received the allocated intervention, with no loss to follow-up or discontinuation of intervention. All 490 participants were included in the intention-to-treat analysis (Fig. 1).

Baseline demographic and perioperative characteristics are presented in Table 1. Mean age was 72 ± 12 years in Group D and 71 ± 11 years in Group C ($P = 0.337$). Mean body weight was 55 ± 11 kg and 54 ± 10 kg, respectively ($P = 0.293$). Male participants accounted for 42.4% of Group D and 42.9% of Group C ($P = 0.927$). Mean duration of surgery was 95 ± 11 minutes in Group D and 93 ± 12 minutes in Group C ($P = 0.055$), while the corresponding duration of general anesthesia was 110 ± 19 and 113 ± 21 minutes, respectively ($P = 0.098$). Postoperative blood transfusion volume was 850 ± 22 mL in Group D and 855 ± 18 mL in Group C ($P = 0.006$).

Table 1
Baseline characteristics and perioperative data

Variable	Dexmedetomidine group (n = 245)	Control group (n = 245)	P value
Age, years	72 ± 12	71 ± 11	0.337
Body weight, kg	55 ± 11	54 ± 10	0.293
Male sex, n (%)	104 (42.4)	105 (42.9)	0.927
Duration of surgery, min	95 ± 11	93 ± 12	0.055
Duration of general anesthesia, min	110 ± 19	113 ± 21	0.098
Postoperative blood transfusion volume, mL	850 ± 22	855 ± 18	0.006
Type of surgery, n (%)			0.888†
Hemiarthroplasty	111 (45.3)	108 (44.1)	
Total hip arthroplasty	59 (24.1)	57 (23.3)	
Proximal femoral nail antirotation (PFNA) fixation	75 (30.6)	80 (32.7)	
Continuous fascia iliaca compartment catheter, n (%)	245 (100)	245 (100)	
Hypertension, n (%)	198 (80)	200 (82)	> 0.05
Ischemic heart disease, n (%)	214 (87)	218 (89)	> 0.05
Diabetes mellitus, n (%)	125 (50)	111 (45)	> 0.05
Chronic kidney disease, n (%)	112 (46)	126 (51)	> 0.05

Data are presented as mean ± standard deviation or n (%). †Overall P value for the distribution of the three surgical procedures. PFNA, proximal femoral nail antirotation. P values for continuous variables were calculated using Welch's t-test.

The distribution of surgical procedures is shown in Table 1. Hemiarthroplasty was performed in 111 (45.3%) participants in Group D and 108 (44.1%) in Group C; total hip arthroplasty in 59 (24.1%) and 57 (23.3%), respectively; and proximal femoral nail antirotation (PFNA) fixation in 75 (30.6%) and 80 (32.7%), respectively. The overall distribution of the three surgical procedures did not differ significantly between groups (P = 0.888). Continuous fascia iliaca compartment catheterization was performed in all participants in both groups.

The prevalence of hypertension was 80% in Group D and 82% in Group C, ischemic heart disease 87% and 89%, diabetes mellitus 50% and 45%, and chronic kidney disease 46% and 51%, respectively. No statistically significant between-group differences were reported for these comorbidities (P > 0.05).

Educational attainment is presented in Supplementary Table S1. Completion of high school was reported in 52% of participants in Group D and 51% in Group C, followed by university education (20% in both groups), education below high school (18% and 21%, respectively), and postgraduate education (10% and 8%, respectively). The distribution of educational attainment did not differ significantly between groups ($P > 0.05$).

Perioperative anesthetic and analgesic drug use

Perioperative anesthetic and analgesic drug use is presented in Table 2.

Table 2
Perioperative anesthetic and analgesic drug use

Variable	Dexmedetomidine group (n = 245)	Control group (n = 245)	P value
Propofol, mg	108.1	120.12	< 0.001
Sufentanil, μg	11.3	15.5	< 0.001
Rocuronium, mg	55.7	54.9	0.442
Ropivacaine concentration, %	0.2	0.2	
Infusion duration, h	49 $\pm$ 0.9	49 $\pm$ 0.9	
Infusion rate, mL/h	4.5 $\pm$ 0.8	5.8 $\pm$ 0.7	< 0.001
Ropivacaine dose, mg/h	9.0 $\pm$ 1.6	11.6 $\pm$ 1.4	< 0.001
Total infusion volume, mL	220.5 $\pm$ 39.4	284.2 $\pm$ 34.7	< 0.001
Estimated cumulative ropivacaine dose, mg	441.0 $\pm$ 78.8	568.4 $\pm$ 69.4	< 0.001

The total doses of propofol and sufentanil were 108.1 mg and 11.3 μg , respectively, in Group D, compared with 120.12 mg and 15.5 μg in Group C. The between-group differences were statistically significant for both propofol and sufentanil ($P < 0.001$ for both). Total rocuronium use was 55.7 mg in Group D and 54.9 mg in Group C ($P = 0.442$).

Continuous postoperative analgesia was provided using 0.2% ropivacaine through a fascia iliaca compartment catheter in both groups. The infusion duration was 49 $\pm$ 0.9 hours in both groups. The infusion rate was 4.5 $\pm$ 0.8 mL/h in Group D and 5.8 $\pm$ 0.7 mL/h in Group C ($P < 0.001$). The corresponding hourly ropivacaine doses were 9.0 $\pm$ 1.6 and 11.6 $\pm$ 1.4 mg/h, respectively ($P < 0.001$). Total infusion

volume was 220.5 ± 39.4 mL in Group D and 284.2 ± 34.7 mL in Group C ($P < 0.001$), while the estimated cumulative ropivacaine dose was 441.0 ± 78.8 and 568.4 ± 69.4 mg, respectively ($P < 0.001$).

Postoperative delirium

Incidence of postoperative delirium

The incidence of postoperative delirium within 7 days was 52/245 (21.2%) in Group D and 112/245 (45.7%) in Group C (Table 3). The relative risk was 0.46 (95% CI, 0.35–0.61; $P < 0.001$), with a relative risk reduction of 53.6% and an absolute risk reduction of 24.5 percentage points (95% CI, 16.4–32.6). The number needed to treat was 5.

Table 3
Incidence of postoperative delirium within 7 days

Outcome	Dexmedetomidine group (n = 245)	Control group (n = 245)	RR (95% CI)	Relative risk reduction	Absolute risk reduction (95% CI)	NNT	P value
Delirium within 7 days, n (%)	52 (21.2)	112 (45.7)	0.46 (0.35–0.61)	53.6%	24.5 percentage points (16.4–32.6)	5	< 0.001

RR, relative risk; CI, confidence interval; NNT, number needed to treat.

The incidence of postoperative delirium in the two groups is shown in Fig. 2.

Delirium severity and duration

Among participants who developed postoperative delirium, the distribution of CAM-S severity categories differed between groups ($P < 0.001$) (Table 4 and Fig. 3). In Group D, 47/52 (90.4%) cases were classified as mild, 4/52 (7.7%) as moderate, and 1/52 (1.9%) as severe. In Group C, 22/112 (19.6%) cases were mild, 16/112 (14.3%) were moderate, and 74/112 (66.1%) were severe.

Among participants who developed postoperative delirium, the mean duration of delirium was 15 ± 6 hours in Group D and 37 ± 8 hours in Group C. The mean between-group difference was $- 22.0$ hours (95% CI, $- 24.2$ to $- 19.8$; $P < 0.001$).

Table 4
Delirium severity and duration A. CAM-S severity

CAM-S severity	Dexmedetomidine	Control
Mild	47 (90.4)	22 (19.6)
Moderate	4 (7.7)	16 (14.3)
Severe	1 (1.9)	74 (66.1)
Overall P < 0.001		
B. Delirium duration		

Outcome	Dexmedetomidine	Control	Mean difference (95% CI)	P
Duration of delirium, h	15 ± 6	37 ± 8	-22.0 (- 24.2 to - 19.8)	< 0.001

Postoperative pain and rescue morphine use

Postoperative pain scores and rescue morphine use are presented in Table 5. Mean VRS scores at rest were 0.3 ± 0.1 in Group D and 1.1 ± 0.5 in Group C, with a mean between-group difference of -0.8 (95% CI, -0.86 to -0.74 ; $P < 0.001$). During movement, the corresponding values were 0.8 ± 0.3 and 1.8 ± 0.9 , respectively, with a mean difference of -1.0 (95% CI, -1.12 to -0.88 ; $P < 0.001$).

Mean rescue morphine consumption during the first 24 hours was 5 ± 0.1 mg in Group D and 30 ± 10 mg in Group C. The mean between-group difference was -25.0 mg (95% CI, -26.26 to -23.74 ; $P < 0.001$).

Table 5
Postoperative pain, rescue morphine use, and length of hospital stay

Outcome	Dexmedetomidine group (n = 245)	Control group (n = 245)	Mean difference (95% CI)	P value
Mean VRS score at rest	0.3 ± 0.1	1.1 ± 0.5	-0.8 (- 0.86 to - 0.74)	< 0.001
Mean VRS score during movement	0.8 ± 0.3	1.8 ± 0.9	-1.0 (- 1.12 to - 0.88)	< 0.001
Rescue morphine during the first 24 h, mg	5 ± 0.1	30 ± 10	-25.0 (- 26.26 to - 23.74)	< 0.001
Length of hospital stay, days	8 ± 0.5	12 ± 0.8	-4.0 (- 4.12 to - 3.88)	< 0.001

Data are presented as mean ± standard deviation. VRS, Verbal Rating Scale.

Among participants who developed postoperative delirium, pain severity assessed using the PAINAD scale is presented in Supplementary Table S2 and Supplementary Figure S1. In Group D, 47/52 (90.4%)

participants had a PAINAD score indicating no pain, 5/52 (9.6%) had mild pain, and none had moderate pain. In Group C, 28/112 (25.0%) participants had no pain, 18/112 (16.1%) had mild pain, and 66/112 (58.9%) had moderate pain. No participant had a PAINAD score of 7–10. The overall distribution differed between groups ($P < 0.001$).

Perioperative dexmedetomidine dose and hemodynamic parameters

The dexmedetomidine doses administered in Group D are presented in Table 6. The mean loading dose was $11.0 \pm 2.2 \mu\text{g}$. The mean intraoperative maintenance dose was $9.35 \pm 2.34 \mu\text{g}$ over 68 ± 10 minutes, and the mean postoperative maintenance dose was $61.05 \pm 13.94 \mu\text{g}$ over 7.4 ± 0.8 hours. The mean total maintenance dose was $70.40 \pm 15.67 \mu\text{g}$, and the mean total perioperative dose was $81.40 \pm 17.67 \mu\text{g}$ per participant.

Perioperative hemodynamic parameters are also presented in Table 6. Mean intraoperative heart rate was 68 ± 10 beats/min in Group D and 73 ± 11 beats/min in Group C, with a mean difference of -5.0 beats/min (95% CI, -6.87 to -3.13 ; $P < 0.001$). At 12 hours postoperatively, mean heart rate was 67 ± 11 beats/min in Group D and 75 ± 12 beats/min in Group C, with a mean difference of -8.0 beats/min (95% CI, -10.04 to -5.96 ; $P < 0.001$).

Mean intraoperative MAP was 69 ± 12 mmHg in Group D and 75 ± 13 mmHg in Group C, with a mean difference of -6.0 mmHg (95% CI, -8.22 to -3.78 ; $P < 0.001$). At 12 hours postoperatively, mean MAP was 71 ± 13 mmHg in Group D and 73 ± 14 mmHg in Group C, with a mean difference of -2.0 mmHg (95% CI, -4.40 to 0.40 ; $P = 0.102$).

Table 6
Perioperative dexmedetomidine dose and hemodynamic parameters
A. Perioperative dexmedetomidine dose

Dexmedetomidine dose	Mean dose per patient
Loading dose, μg	11.0 ± 2.2
Intraoperative maintenance dose, μg	9.35 ± 2.34
Postoperative maintenance dose, μg	61.05 ± 13.94
Total maintenance dose, μg	70.40 ± 15.67
Total perioperative dose, μg	81.40 ± 17.67
B. Hemodynamic parameters	

Parameter	Dexmedetomidine group (n = 245)	Control group (n = 245)	Mean difference (95% CI)	P value
Intraoperative heart rate, beats/min	68 ± 10	73 ± 11	-5.0 (- 6.87 to - 3.13)	< 0.001
Intraoperative MAP, mmHg	69 ± 12	75 ± 13	-6.0 (- 8.22 to - 3.78)	< 0.001
Heart rate at 12 h postoperatively, beats/min	67 ± 11	75 ± 12	-8.0 (- 10.04 to - 5.96)	< 0.001
MAP at 12 h postoperatively, mmHg	71 ± 13	73 ± 14	-2.0 (- 4.40 to 0.40)	0.102
Note: Data are presented as mean ± standard deviation. CI, confidence interval; MAP, mean arterial pressure. P values were calculated using Welch's <i>t</i> -test.				

Length of hospital stay

The mean length of hospital stay was 8.0 ± 0.5 days in Group D and 12.0 ± 0.8 days in Group C (Table 5). The mean between-group difference was - 4.0 days (95% CI, - 4.12 to - 3.88; *P* < 0.001).

4. Discussion

In this randomized, double-blind, placebo-controlled trial involving 490 older adults undergoing hip fracture surgery, perioperative administration of low-dose dexmedetomidine significantly reduced the incidence of postoperative delirium during the first seven postoperative days compared with placebo. In addition, dexmedetomidine was associated with lower delirium severity, shorter delirium duration, improved postoperative pain control, reduced opioid and anesthetic requirements, and shorter hospital stay. These findings suggest a potential clinical benefit of perioperative low-dose dexmedetomidine in this high-risk population. The relatively high delirium incidence observed in the placebo group (45.7%) is consistent with previous reports in elderly patients with hip fracture and may reflect the high baseline vulnerability of older adults with acute hip fracture, together with perioperative factors such as pain, immobilization, and exposure to general anesthesia [2, 7, 20]. For comparison, the REGAIN trial reported an overall delirium incidence of approximately 20% and found no significant difference between spinal and general anesthesia [24], highlighting the influence of population characteristics and perioperative management on observed delirium rates

Our findings are generally consistent with previous randomized controlled trials and recent meta-analyses demonstrating a protective effect of dexmedetomidine against postoperative delirium [12, 16, 22, 23]. Su et al. reported a significant reduction in delirium following postoperative low-dose dexmedetomidine infusion in older adults undergoing major non-cardiac surgery [12], whereas Shin et al. observed similar benefits during lower-limb orthopedic surgery under spinal anesthesia [16]. Furthermore, a recent meta-analysis including 3,159 elderly orthopedic patients demonstrated a pooled

relative risk of 0.55, supporting a potential preventive effect of perioperative dexmedetomidine on postoperative delirium [22]. Nevertheless, not all studies have reported consistent benefits. Deiner et al. and Hong et al. found no statistically significant reduction in postoperative delirium [13, 21]. These discrepancies probably reflect differences in patient populations, anesthetic techniques, dexmedetomidine dosage, timing and duration of administration, comparator interventions, and implementation of multimodal delirium prevention protocols. In the present study, dexmedetomidine was administered throughout both the intraoperative and early postoperative periods within a standardized multimodal analgesic protocol, which may partly explain the magnitude of the observed treatment effect.

Among participants who developed postoperative delirium, the distribution of CAM-S severity categories differed between the two groups, with a greater proportion of mild delirium and a lower proportion of severe delirium observed in the dexmedetomidine group. Because this analysis was restricted to participants who developed delirium after randomization, these findings should be interpreted as exploratory rather than as evidence of a treatment effect on delirium severity. Patients receiving dexmedetomidine also had lower postoperative pain scores, lower rescue morphine consumption, and lower intraoperative requirements for propofol and sufentanil. These findings are consistent with the established analgesic- and anesthetic-sparing properties of dexmedetomidine. Because uncontrolled postoperative pain and excessive opioid exposure have been associated with postoperative delirium [2, 9, 20], the observed reductions in pain and rescue morphine consumption may have contributed to the lower delirium incidence observed in the dexmedetomidine group. However, the present study was not designed to determine whether these factors mediated the effect of dexmedetomidine on delirium.

Dexmedetomidine acts through selective α_2 -adrenergic receptor activation within the locus coeruleus, suppressing central noradrenergic activity while producing a sleep-like sedative state. In addition to its sedative and analgesic effects, dexmedetomidine attenuates sympathetic activation and may modulate neuroinflammatory pathways implicated in postoperative delirium [2, 20]. These complementary mechanisms likely contribute to improved perioperative recovery. Nevertheless, dexmedetomidine should be regarded as one component of a comprehensive multimodal delirium prevention strategy rather than a replacement for established non-pharmacological interventions [2, 3, 9, 10].

An additional clinically relevant finding was the significant reduction in hospital length of stay among patients receiving dexmedetomidine. Although improved delirium prevention, better pain control, and reduced opioid exposure may facilitate earlier mobilization and functional recovery, hospital stay is influenced by numerous factors beyond the intervention itself, including discharge policies, postoperative complications, rehabilitation resources, and institutional practice. Therefore, this outcome should be interpreted cautiously. An additional clinically relevant finding was the significant reduction in hospital length of stay among patients receiving dexmedetomidine. Although improved delirium prevention, better pain control, and reduced opioid exposure may facilitate earlier mobilization and functional recovery, hospital stay is influenced by numerous factors beyond the intervention itself, including discharge policies, postoperative complications, rehabilitation resources, and institutional

practice. Therefore, this outcome should be interpreted cautiously. Perioperative dexmedetomidine was associated with lower heart rate during surgery and at 12 hours postoperatively, as well as lower intraoperative mean arterial pressure. In contrast, postoperative mean arterial pressure at 12 hours did not differ significantly between groups. These findings are consistent with the sympatholytic effects of dexmedetomidine. However, because clinically significant bradycardia, hypotension requiring intervention, and vasopressor use were not prospectively assessed, the hemodynamic safety profile of the intervention cannot be fully evaluated in the present study.

This study has several strengths, including its randomized double-blind placebo-controlled design, relatively large sample size, complete follow-up, intention-to-treat analysis, standardized perioperative management, and systematic delirium assessment using validated CAM and CAM-S instruments. However, several limitations should be acknowledged. This was a single-center study, which may limit generalizability. Important delirium-related variables, including frailty, ASA physical status, baseline cognitive function, depth of anesthesia, and perioperative complications, were not systematically evaluated. Furthermore, detailed safety outcomes such as clinically significant bradycardia, hypotension requiring intervention, or vasopressor use were not prospectively collected. Despite these limitations, the present study provides additional evidence that perioperative low-dose dexmedetomidine may reduce postoperative delirium in older adults undergoing hip fracture surgery. Future multicenter randomized controlled trials are warranted to confirm these findings, optimize dosing strategies, and further define the safety profile of dexmedetomidine in this high-risk population.

5. Conclusions

In older adults undergoing surgery for hip fracture, perioperative administration of low-dose dexmedetomidine significantly reduced the incidence of postoperative delirium within the first seven postoperative days compared with placebo. Dexmedetomidine was also associated with lower delirium severity, shorter delirium duration, improved postoperative pain control, reduced opioid and anesthetic requirements, and a shorter hospital stay.

These findings support the use of low-dose perioperative dexmedetomidine as a valuable adjunct to multimodal perioperative care for older adults undergoing hip fracture surgery. Nevertheless, given the single-center design of this study, further large-scale multicenter randomized controlled trials are warranted to confirm these findings, establish the optimal dosing strategy, and further characterize the safety profile of dexmedetomidine in this high-risk population.

Declarations

Ethics approval and consent to participate

The study was approved by the Scientific and Technical Ethics Committee of the Saigon ITO Hospital System (Approval No. 24/HĐKHKT-SGITO; May 7, 2024). Written informed consent was obtained from all participants or their legally authorized representatives before enrollment. The study was conducted in

accordance with the ethical principles of the Declaration of Helsinki and relevant ethical guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The de-identified datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request and with approval from the institutional ethics committee.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Le Van Chung: Conceptualization, methodology, investigation, data curation, formal analysis, writing-original draft.

Ta Duc Luan: Study supervision, methodology, validation, manuscript review and editing.

Lam Tri Duc: Statistical analysis, data interpretation, visualization, writing-review and editing.

All authors read and approved the final manuscript.

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Figures

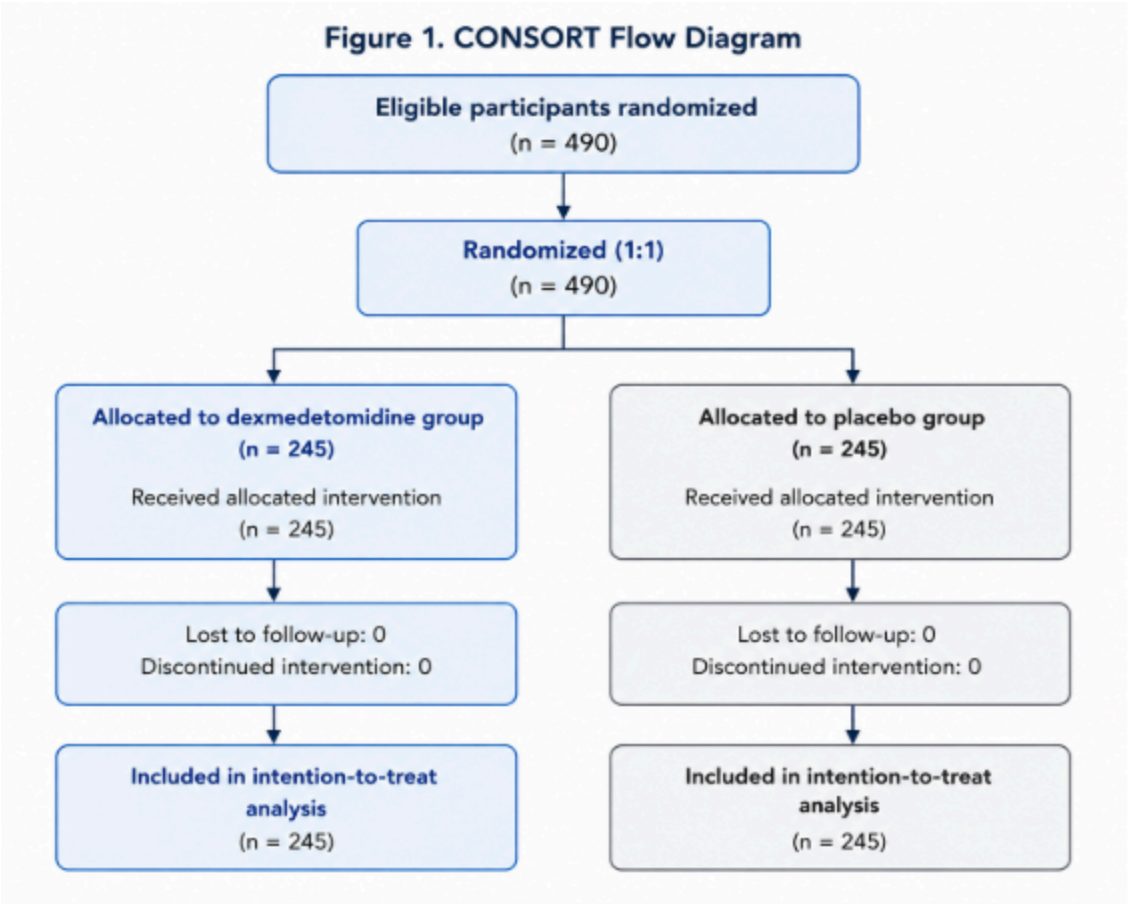


Figure 1
CONSORT flow diagram

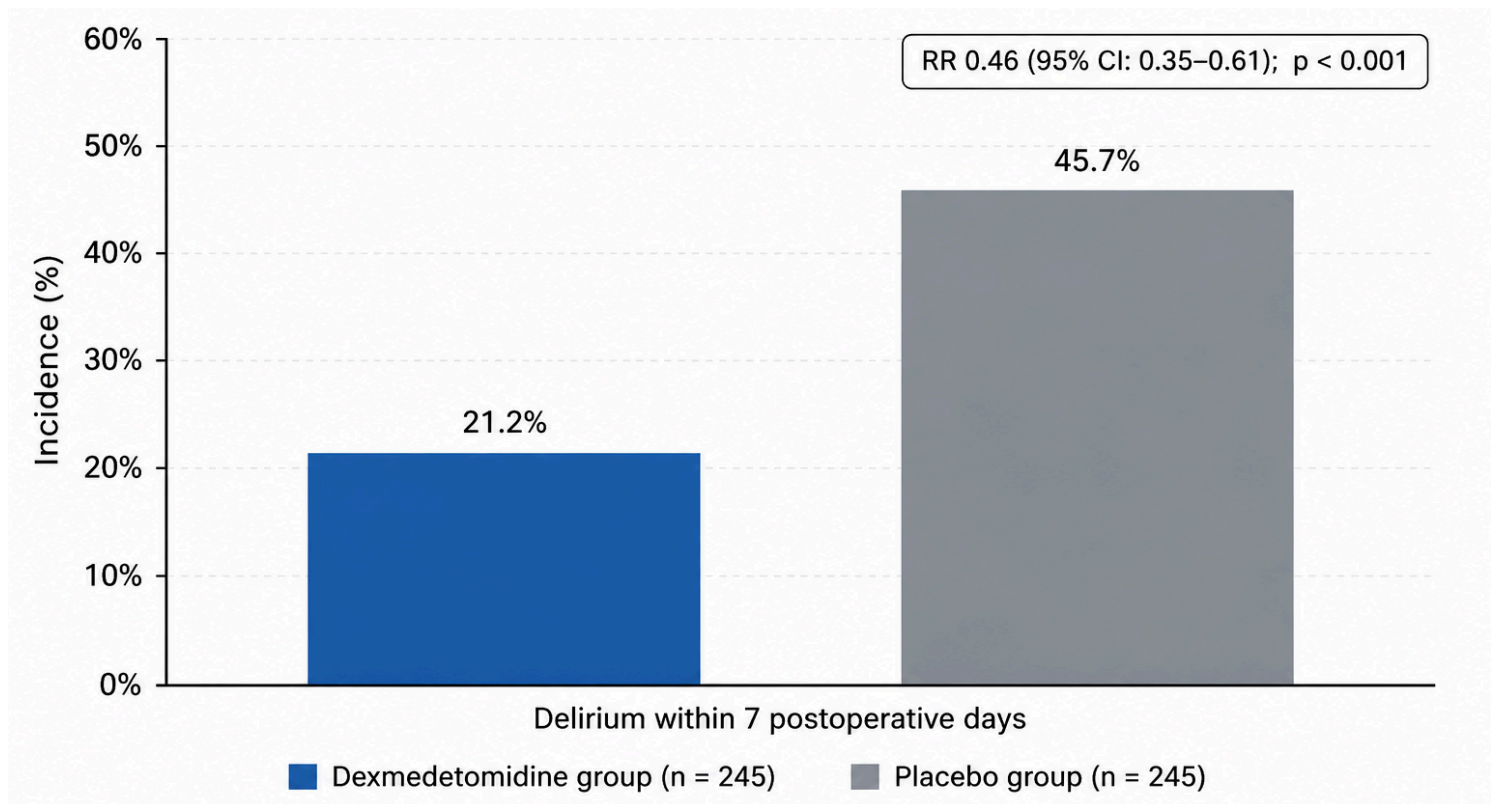


Figure 2

Cumulative incidence of postoperative delirium within the first 7 postoperative days in the dexmedetomidine and placebo groups. The cumulative incidence of postoperative delirium was significantly lower in the dexmedetomidine group than in the placebo group (21.2% vs. 45.7%; RR, 0.46; 95% CI, 0.35–0.61; $P < 0.001$).

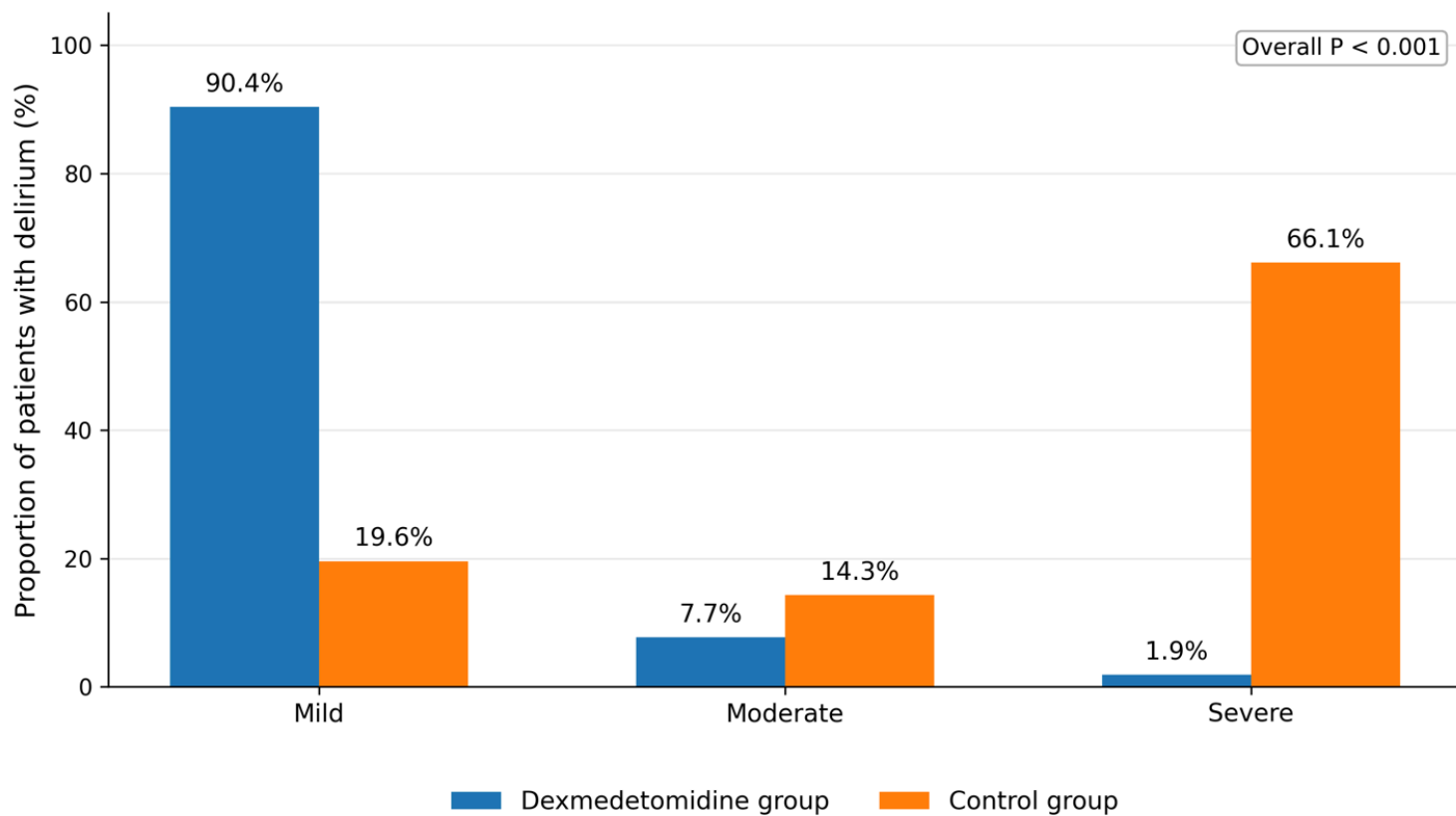


Figure 3

Delirium severity according to CAM-S

Postoperative pain and rescue morphine use

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