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CLINICAL TRIAL REPORT

Dexmedetomidine May Reduce the Incidence of Acute Kidney Injury in Elderly Patients Undergoing Orthopedic Surgery: A Randomized, Double-Blind Clinical Trial

Xiao-Yan Zheng[1,2,*], Zhe Su[1–3,*], Yang Zhang[1,2,*], Jing Yan[1,2], Xin-Yu Li[1,2], Ke Peng[1,2], Hong Liu[4], Xi-Sheng Shan[1,2], Fu-Hai Ji[1,2]

[1]Department of Anesthesiology, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, People's Republic of China; [2]Institute of Anesthesiology, Soochow University, Suzhou, Jiangsu, People's Republic of China; [3]Department of Anesthesiology, Affiliated Tongren Hospital of Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [4]Department of Anesthesiology and Pain Medicine, University of California Davis Health, Sacramento, CA, USA

*These authors contributed equally to this work

Correspondence: Fu-Hai Ji; Xi-Sheng Shan, Department of Anesthesiology, First Affiliated Hospital of Soochow University, 188 Shizi St, Suzhou, Jiangsu, 215006, People's Republic of China, Tel +86-13656207331; +86-15895551822, Email jifuhaisuda@163.com; xisheng83@sina.com

Background: Acute kidney injury (AKI) is a common complication in elderly patients undergoing orthopedic surgery, yet the renoprotective role of dexmedetomidine in this patient population remains unclear. This study aimed to evaluate the effect of dexmedetomidine on the incidence of AKI in elderly patients undergoing lower extremity orthopedic procedures.

Methods: In this randomized, double-blind, placebo-controlled trial, 300 patients aged ≥ 65 scheduled for lower extremity orthopedic surgery were randomized to receive either dexmedetomidine (0.4 μg/kg infused for 10 minutes before induction, followed by 0.4 μg/kg/h until 30 minutes before skin closure) or normal saline (control). The primary outcome was the incidence of AKI within 48 hours postoperatively, based on AKI Network criteria. Secondary outcomes included serum cystatin C and estimated glomerular filtration rate on postoperative day (POD) 1, 2, and 3, in-hospital complications (postoperative nausea and vomiting, delirium, pneumonia, stroke), intensive care unit admission, length of hospital stay, and in-hospital mortality.

Results: Of 295 patients who completed the study (62.7% female; mean age, 74 years), AKI occurred in 4.7% (7/149) of the dexmedetomidine group compared with 11.6% (17/146) of the control group (odds ratio = 0.37; 95% CI, 0.15 to 0.93; $P = 0.035$). This difference remained significantly after adjustment for baseline covariates (adjusted odds ratio = 0.36; 95% CI, 0.14 to 0.90; $P = 0.030$). All AKI cases were AKIN stage 1. Serum cystatin C on POD 1 were lower in the dexmedetomidine group (mean [SD], 1.06 [0.30] vs 1.17 [0.32] mg/L; $P = 0.003$). No significant between-group differences were observed in other secondary outcomes.

Conclusion: Dexmedetomidine administration was associated with a reduced incidence of AKI in elderly patients undergoing lower extremity orthopedic surgery. The renoprotective effects of dexmedetomidine in this patient population warrant validation in multicenter trials.

Clinical Trial Registration: Chinese Clinical Trial Registry (ChiCTR2400088225).

Keywords: acute kidney injury, elderly, orthopedic, dexmedetomidine, postoperative complications

Introduction

In the United States, elderly patients account for more than half of all inpatient orthopedic surgical procedures annually.[1] This patient population is particularly susceptible to perioperative acute kidney injury (AKI) owing to age-related renal alterations, including reduced renal mass, impaired renal perfusion and vascular sclerosis, and a substantial decline in renal functional reserve.[2,3] In addition, surgical stress, intraoperative position changes, and surgical bleeding, together with preexisting renal vulnerability, contribute to an elevated incidence of AKI observed in elderly orthopedic patients.[4] AKI in this setting is

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associated with delayed recovery, higher healthcare costs, and poorer long-term outcomes.[5] A retrospective study reported a 1-year mortality of 26.6% in patients who developed AKI after non-cardiac surgery, compared with 6.1% in those without AKI.[6] Despite its clinical significance, research on AKI in elderly orthopedic patients remains limited.

Dexmedetomidine is an α2 receptor agonist with multiple pharmacological effects, including sympatholytic, anti-inflammatory activity, renal arterial dilation, and renoprotective properties.[7–9] While adverse effects like bradycardia and hypotension have been reported, these events are typically transient and readily remedied.[10,11] Clinical studies evaluating the reno-protective effect of dexmedetomidine in cardiac and aortic surgery showed promising results.[12,13] A recent meta-analysis suggested that dexmedetomidine may confer protection against cardiac surgery–associated AKI, particularly for elderly patients.[14] Furthermore, a respective study of elderly patients undergoing major joint surgeries found that dexmedetomidine infusion was associated with a reduced incidence of AKI, lower opioid requirement and shorter hospital stay.[10] However, to date, no randomized controlled clinical study has specifically investigated the effect of dexmedetomidine on perioperative AKI in elderly patients undergoing orthopedic surgery.

We conducted this prospective, randomized, double-blinded, placebo-controlled trial to evaluate the impact of intraoperative dexmedetomidine infusion on the incidence of AKI in elderly patients undergoing lower extremity orthopedic surgery. We hypothesized that intraoperative dexmedetomidine infusion would be associated with a lower risk of postoperative AKI without compromising safety.

Methods

Study Design

This prospective, randomized, double-blind, placebo-controlled trial was approved by the Institutional Review Board of The First Affiliated Hospital of Soochow University (Approved No. 2022026) on January 08, 2022. Prior to the first patient enrollment, this study was registered at the Chinese Clinical Trial Registry (ChiCTR2400088225). Written informed consent was obtained from all participants prior to any study-related procedures. The study was conducted in accordance with the Declaration of Helsinki and reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[15]

Inclusion and Exclusion Criteria

The inclusion criteria were: patients aged ≥ 65 years, scheduled for lower extremity orthopedic surgeries under general anesthesia, with an expected surgical duration exceeding 1 hour. The exclusion criteria included: (1) emergency surgery; (2) uncontrolled grade III hypertension; (3) sick sinus syndrome, atrioventricular block, or bradycardia; (4) severe anemia (Hb < 7.0 g/dl); (5) preoperative systemic infection; (6) hepatic disease (Child-Pugh classification C); (7) undergoing renal replacement therapy.

Randomization and Blinding

An independent assistant, who was not involved in the study, utilized an online tool (https://www.sealedenvelope.com/simple-randomiser/v1/lists) to generate random numbers in a 1:1 ratio with permuted block sizes of 2 and 4. Patients were randomized into either the dexmedetomidine group or the control group based on the randomly generated sequence. The allocation sequence was secured in identical opaque envelopes and stored in locked cabinet until allocation. An independent nurse, blinded to the study objectives, prepared the study medications as per the allocation sequence. All medications were all stored in identical 50 mL syringes and packaged in bags labeled solely with the patient number. Patients, surgeons, anesthesiologists, and postoperative outcome evaluators were all blinded to group allocation until final data analysis was completed.

Perioperative Management

Baseline mean blood pressure (MBP) and heart rate (HR) were recorded in the anesthesia preparation room. No sedative medications were administered prior to surgery. Upon arrival in the operating room, patients underwent standard

monitoring, including non-invasive blood pressure measurement, electrocardiography, pulse oximetry, end-tidal carbon dioxide, temperature, and bispectral index (BIS; Medtronic, Minneapolis, MN, USA). After induction of anesthesia, the radial artery was cannulated to facilitate continuous arterial blood pressure monitoring. Hemodynamic parameters, including stroke volume (SV), cardiac output (CO), and stroke volume variation (SVV), were continuously assessed using the FloTrac/Vigileo system (Edwards Lifesciences, Irvine, CA).

Anesthesia was induced with sufentanil (0.2–0.4 μg/kg), propofol (1.5–2.0 mg/kg), and cisatracurium (0.15 mg/kg). After intubation patients received mechanically ventilation with a tidal volume of 6–8 mL/kg ideal body weight, a positive end-expiratory pressure of 5 cmH_2O, and 50% inspired oxygen fraction (FiO2). Respiratory rate and FiO2 were adjusted to maintain an end-tidal carbon dioxide concentration of 35–45 mmHg and peripheral oxygen saturation ≥ 95%. General anesthesia was maintained with sevoflurane (1–3%), titrated to BIS 40–60. Intraoperative analgesia was supplemented with sufentanil (0.1–0.2 μg/kg), and additional doses of cisatracurium were given as indicated.

All patients were covered with a forced-air blanket to maintain a nasopharyngeal temperature of 36–37°C. Lactated Ringer's solution was used as the default fluid for volume replacement, whereas hydroxyethyl starch 130/0.4 was administered at the discretion of the anesthesia team to support hemodynamic stability. MAP, CO, and SVV were continuously monitored throughout the procedure. Hemodynamic optimization was guided by an SVV-based goal-directed fluid therapy protocol, with a therapeutic target of maintaining SVV < 10%, a threshold previously applied in patients undergoing major orthopedic surgery.[16] Hypotension (defined as MAP < 65 mmHg or a decrease ≥ 20% from baseline) was managed with intravenous ephedrine or phenylephrine. Bradycardia (HR < 50 beats/min) was treated with intravenous atropine, or with ephedrine in cases with hypotension.

At the end of surgery, all patients received intravenous ondansetron (8 mg) for prophylaxis against postoperative nausea and vomiting (PONV). Patients were transferred to the post-anesthesia care unit (PACU) for recovery and subsequently returned to surgical ward. Following perioperative evaluation, high-risk patients were admitted to the surgical intensive care unit (ICU) for enhanced monitoring and management. Postoperative analgesia was provided with intravenous morphine (5–10 mg) or alternative opioid analgesics (oxycodone, tramadol) as required.

AKI Prevention Strategy

The risk of AKI was assessed preoperatively using the AKI risk index, which is determined by the number of risk factors: age ≥ 56 years, male, hypertension, diabetes mellitus (oral or insulin therapy), emergency surgery, abdominal surgery, ascites, heart failure, and renal dysfunction (preoperative serum creatinine [SCr] >106.1 μmol/L).[17] Patients were stratified into five classes: class I (0–2 risk factors), class II (3 risk factors), class III (4 risk factors), class IV (5 risk factors), and class V (≥ 6 risk factors), with class ≥ III representing a moderate to high risk of postoperative AKI.[18] To mitigate the risk of perioperative AKI for all patients in this study, a preventative bundle protocol was implemented, which included hemodynamic optimization guided by SVV-based goal-directed fluid therapy, glycemic control; avoidance of nephrotoxic medication exposure, and monitoring of novel AKI biomarkers such as serum cystatin C.

Study Intervention

In the dexmedetomidine group, patients received an intravenous loading dose of dexmedetomidine (0.4 μg/kg) administered over 10 minutes before induction, followed by a continuous infusion at 0.4 μg/kg/h until 30 minutes prior to skin closure. This dosing regimen was established based on previous studies conducted in elderly patients.[19,20] In the control group, an equivalent volume saline was administered at the same rate as dexmedetomidine.

Study Outcomes

The primary outcome was the incidence of AKI within 48 hours after surgery, diagnosed according to the AKI Network (AKIN) criteria.[21] The SCr levels were measured daily at 07:00 am on postoperative day (POD) 1–3. Urine output was recorded hourly using either a urinary catheter or a urine collection container if the catheter had been removed. The secondary outcomes included serum cystatin C and eGFR measured on POD 1, 2 and 3. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (http://ckdepi.org/equations/gfr-calculator). Additional secondary outcomes comprised in-hospital complications (PONV, delirium, pneumonia, stroke), postoperative ICU

admission, length of hospital stay, and in-hospital mortality. Delirium assessment was conducted twice daily (06:00–-09:00 and 16:00–19:00) during the first 3 postoperative days by trained physicians using either the 3-Minute Diagnostic Interview for confusion assessment method (3D-CAM) or the confusion assessment method for the intensive care unit (CAM-ICU), as appropriate.[19,22] Definitions of postoperative complications are provided in Table S1.

Sample Size Calculation

Studies have shown that the incidence of AKI in elderly patients following lower extremity orthopedic surgeries ranged from 8.4% to 28.4%.[23–25] In our previous study, we observed that dexmedetomidine significantly reduced the incidence of postoperative AKI in patients undergoing endovascular aortic repair for Stanford type B aortic dissection.[26] Based on these findings, we estimated an approximate 20% incidence of postoperative AKI in elderly orthopedic surgery patients and hypothesized that dexmedetomidine could potentially reduce this incidence by 12%. To detect such a difference with 80% statistical power and a significance level of 0.05, we planned to enroll 150 patients in each group (300 patients in total), allowing for an anticipated dropout rate of 10%. The sample size was calculated using PASS software (version 15; NCSS, Kaysville, UT, USA).

Statistical Analyses

Data distribution was evaluated using the Shapiro–Wilk test. Normally distributed data are reported as mean (standard deviation [SD]), and non-normally distributed data as median (interquartile range, [IQR]). Categorical data are expressed as number (%). Data analysis was conducted using the independent *t*-test, Mann–Whitney *U*-test, Chi-squared test, or Fisher's exact test, as appropriate. The treatment effect was quantified as odds ratio (OR) or difference, with its 95% confidence interval (CI).

Data analysis was conducted in the modified intention-to-treat population, which included all randomized patients who underwent the procedure and had available data for the primary outcome. No interim analyses were performed, and no imputation methods were planned for missing data. Subgroup analyses of the primary outcome were conducted based on sex, BMI, hypertension and diabetes history, and surgery type. In addition, we performed several post hoc analyses, including: (1) adjusted analysis of AKI incidence, serum cystatin C changes, and the proportion of patients with eGFR decrease for relevant baseline covariates (hypertension, diabetes, eGFR, and serum cystatin C) using multivariate logistic regression or generalized linear models; (2) changes in serum cystatin C from baseline to POD 1, 2, and 3; and (3) the number of patients with a >25% decrease in eGFR from baseline to POD 1, 2, and 3.

For the primary outcome, statistical significance was defined as a two-sided $P < 0.05$. For secondary outcomes, adjustments for multiple comparisons were made using the Benjamini-Hochberg method, with a false discovery rate (FDR) threshold of $q < 0.05$ indicating significance. All statistical analyses were carried out using R software (version 4.3.3, R Foundation for Statistical Computing).

Results

Study Flow

From August 2024 to August 2025, 350 patients were screened for eligibility. Of these, 50 were excluded, and 300 were randomized to receive either dexmedetomidine or placebo. After randomization, surgery was postponed or canceled in 3 patients, and 2 patients withdrew the consent prior to anesthesia. Finally, 295 patients completed this study (dexmedetomidine group, n = 149; control group, n = 146). Data for both the primary and secondary outcomes were complete (Figure 1).

Baseline and Perioperative Data

Baseline characteristics were comparable between the two groups (Table 1). The mean (SD) age was 74.0 (6.0) years in the dexmedetomidine group and 74.6 (7.1) years in the control group. Females accounted for 62.3% of patients in the dexmedetomidine group and 63.1% in the control group. The majority of patients (approximately 68%) were classified as American Society of Anesthesiologists (ASA) physical status II. According to the AKI risk index, 17.4% of patients in

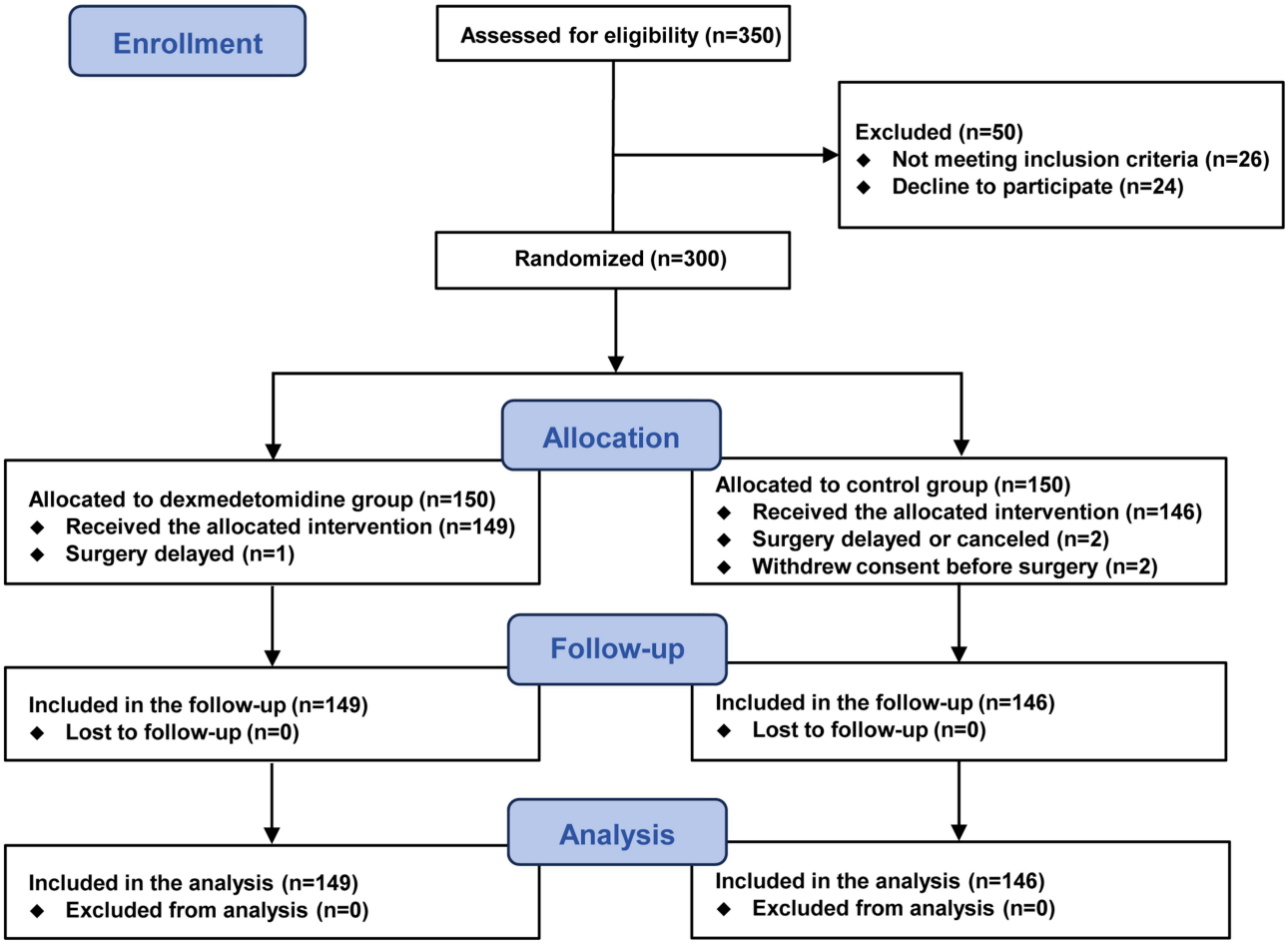

Figure 1 Study flow diagram.

the dexmedetomidine group and 19.1% of patients in the control group were at class III or IV, with no patients classified as class V.

Perioperative medication use, hemodynamic parameters, and fluid balance are summarized in Table 2. Compared to the control group, dexmedetomidine did not increase the incidence of hypotension but was associated with a higher incidence of bradycardia (25.5% vs 15.8%), with a greater proportion of individuals in the dexmedetomidine group

Table 1 Baseline Characteristics

	Dexmedetomidine (n=149)	Control (n=146)
Demographics		
Age (years)	74.0 (6.0)	74.6 (7.1)
Female sex	91 (62.3%)	94 (63.1%)
BMI (kg/m^2)	23.8 (3.8)	23.1 (3.3)
Smoking	47 (31.5%)	43 (29.5%)
Alcohol intake	21 (14.1%)	17 (11.6%)
ASA physical status		
I	8 (5.4%)	6 (4.1%)
II	104 (69.8%)	97 (66.4%)
III	37 (24.8%)	43 (29.5%)

(*Continued*)

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Table 1 (Continued).

	Dexmedetomidine (n=149)	Control (n=146)
Comorbidities		
Hypertension	50 (33.6%)	45 (30.8%)
Diabetes	10 (6.7%)	16 (11%)
Coronary artery disease	7 (4.7%)	10 (6.9%)
Cerebral vascular disease	11 (7.4%)	13 (8.9%)
Surgical procedure		
Total knee replacement	65 (43.6%)	57 (39%)
Total hip replacement	65 (43.6%)	76 (52.1%)
ORIF	19 (12.8%)	13 (8.9%)
Preoperative laboratory data		
Hemoglobin (g/L)	118.1 (16.9)	117.7 (18.5)
Serum creatinine (μmol/L)	59.8 (49.4, 72.7)	61.3 (51.3, 72.6)
eGFR (mL/min/1.73m^2)	103.2 (30.5)	101.3 (27.6)
Serum cystatin C (mg/L)	1.04 (0.24)	1.04 (0.30)
Lactic acid (mmol/L)	0.90 (0.70, 1.21)	0.90 (0.70, 1.21)
Preoperative hemodynamic variables		
Heart rate (beat/min)	67.0 (64.5, 75.0)	67.0 (63.0, 70.0)
Mean blood pressure (mmHg)	95.0 (82.0, 111.0)	89.0 (82.0, 112.0)
AKI Risk Index class [a]		
I	63 (42.3%)	59 (40.4%)
II	60 (40.3%)	59 (40.4%)
III	20 (13.4%)	24 (16.4%)
IV	6 (4.0%)	4 (2.7%)

Notes: Data are shown as mean (SD), median (interquartile range) or number of patients (%). [a] Acute Kidney Injury (AKI) Risk Index class (I to IV, with higher class indicating greater postoperative AKI risk).
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ORIF, open reduction and internal fixation.

Table 2 Perioperative Data

	Dexmedetomidine (n=149)	Control (n=146)	*P* value
Intraoperative hemodynamic events			
Hypotension	61 (40.9%)	57 (39%)	0.739
Bradycardia	38 (25.5%)	23 (15.8%)	0.039
Medications for intraoperative hemodynamic events			
Ephedrine	35 (23.5%)	40 (27.4%)	0.441
Phenylephrine	22 (14.7%)	25 (17.1%)	0.580
Atropine	29 (19.5%)	16 (11.0%)	0.042
Intraoperative intake and output			
Lactated Ringer's solution (mL)	850 (700, 1000)	800 (600, 950)	0.056
Hydroxyethyl starch 6% 130/0.4 (mL)	500 (300, 500)	500 (300, 700)	0.301
Urine output (mL)	350 (250, 500)	300 (250, 500)	0.080
Intraoperative bleeding (mL)	200 (100, 300)	200 (100, 300)	0.798
Transfusion (%)	15 (10.1%)	21 (14.4%)	0.257
Anesthetics and analgesics			
Sufentanil (μg)	35 (30, 40)	40 (35, 45)	<0.001
Sevoflurane (%)			
Skin incision	1.5 (1.0, 2.0)	2.0 (1.0, 2.0)	0.022
0.5 h in surgery	1.5 (1.0, 2.0)	2.0 (1.0, 2.0)	0.061
1 h in surgery	1.5 (1.0, 2.0)	1.5 (1.0, 2.0)	0.209

(*Continued*)

Table 2 (Continued).

	Dexmedetomidine (n=149)	Control (n=146)	*P* value
SVV at the end of surgery (%)	8 (7, 9)	8 (7, 9)	0.099
CO at the end of surgery (L/min)	4.2 (3.5, 4.4)	4.2 (3.4, 4.4)	0.515
Duration of surgery (min)	105 (90, 128)	100 (80, 125)	0.068
Time to extubation (min)	24 (16, 35)	25 (16, 36)	0.263
Postoperative medications on POD 1			
Oxycodone	77 (51.7%)	79 (54.1%)	0.676
Tramadol	59 (39.6%)	56 (38.4%)	0.827
Morphine	4 (2.7%)	5 (3.4%)	0.748
Flurbiprofen axetil	11 (7.4%)	12 (8.2%)	0.789
Cefazolin sodium	138 (92.6%)	131 (89.7%)	0.381
Clindamycin	11 (7.4%)	15 (10.3%)	0.381
Diuretic	1 (0.7%)	2 (1.4%)	0.620
Postoperative medications on POD 2			
Oxycodone	54 (36.2%)	57 (39.0%)	0.620
Tramadol	37 (24.8%)	31 (21.2%)	0.463
Morphine	3 (2.0%)	3 (2.1%)	0.999
Flurbiprofen axetil	5 (3.4%)	7 (4.8%)	0.570
Cefazolin sodium	138 (92.6%)	131 (89.7%)	0.381
Clindamycin	11 (7.4%)	15 (10.3%)	0.381
Diuretic	0	1 (0.7%)	0.495

Notes: Data are presented as median (interquartile range), or number of patients (%).
Abbreviations: CO, cardiac output; POD, postoperative day, SVV, stroke volume variation.

requiring atropine (19.5% vs 11.0%). The sufentanil dose (35 μg vs 40 μg) and sevoflurane concentration at skin incision (1.5% vs 2.0%) were both lower in the dexmedetomidine group compared with the control group. No significant between-group differences were observed in the intraoperative use of ephedrine or norepinephrine.

Oxycodone and tramadol were the primary analgesics administered during the first two postoperative days. Flurbiprofen axetil was administered to 23 patients on POD 1 and to 12 patients on POD 2. Cefazolin sodium was the most frequently prescribed antibiotic. Diuretics were administered to three patients on POD 1 and to one patient on POD 2. The use of analgesics, antibiotics, and diuretics on PODs 1 and 2 were comparable between the groups.

Primary Outcome

During the first 48 h after surgery, AKI occurred in 7 of 149 patients (4.7%) who received dexmedetomidine infusion, compared with 17 of 146 patients (11.6%) who received normal saline (OR = 0.37, 95%Cl: 0.15–0.93; $P = 0.035$) (Table 3). All AKI cases were classified as AKIN stage 1. Renal function impairment in patients with AKI was transient across both groups, no patients required renal replacement therapy. Of the patients transferred to the ICU postoperatively, AKI occurred in 2 out of 16 patients in the dexmedetomidine group and in 3 out of 15 patients in the control group. Collectively, these post-ICU transfer cases constituted 20.8% of all AKI cases in the study. The details of postoperative AKI are shown in Table S2.

The renal protective effect of dexmedetomidine was consistent across all subgroups, including sex (female vs male), BMI (< 25 vs ≥ 25), history of hypertension (no vs yes), history of diabetes (no vs yes), and type of surgery (open reduction and internal fixation [ORIF] of fracture, total hip replacement, and total knee replacement) (Figure 2).

Secondary Outcomes

Serum cystatin C on POD 1 was significantly lower in the dexmedetomidine group compared to the control group (1.06 [0.3] mg/L vs 1.17 [0.32] mg/L; difference = −0.11 mg/L, 95%Cl: −0.18 to −0.04; $P = 0.003$) (Table 3). Serum cystatin C on POD 2 and 3 and eGFR during the first three postoperative days were comparable between groups. There were also

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Table 3 Postoperative Outcomes

	Dexmedetomidine (n=149)	Control (n=146)	Odds Ratio or Difference (95% CI)	*P* value	*q* value
Primary outcome					
Acute kidney injury	7 (4.7%)	17 (11.6%)	0.37 (0.15 to 0.93)	0.035	–
Secondary outcomes [a]					
Serum cystatin C at POD1 (mg/L)	1.06 (0.30)	1.17 (0.32)	−0.11 (−0.18 to −0.04)	0.003	0.039
Serum cystatin C at POD2 (mg/L)	1.07 (0.28)	1.14 (0.36)	−0.07 (−0.14 to 0.01)	0.074	0.315
Serum cystatin C at POD3 (mg/L)	1.05 (0.29)	1.10 (0.33)	−0.05 (−0.12 to 0.02)	0.146	0.353
eGFR at POD1 (mL/min/1.73m^2)	99.3 (26.1)	93.9 (29.3)	5.37 (−0.96 to 11.69)	0.097	0.315
eGFR at POD2 (mL/min/1.73m^2)	98.6 (29.1)	93.3 (35.1)	5.24 (−2.11 to 12.60)	0.163	0.353
eGFR at POD3 (mL/min/1.73m^2)	101.4 (29.4)	96.7 (34.8)	4.62 (−2.72 to 11.97)	0.219	0.406
PONV	40 (26.9%)	43 (29.5%)	0.88 (0.53 to 1.46)	0.619	0.894
Delirium	16 (10.7%)	26 (17.8%)	0.56 (0.28 to 1.09)	0.096	0.315
Pneumonia	1 (0.7%)	0 (0%)	–	1.000	1.000
Stroke	0 (0%)	0 (0%)	–	1.000	1.000
Postoperative ICU admission	16 (11%)	15 (10%)	1.05 (0.50 to 2.21)	0.897	1.000
Length of hospital stay (day)	6 (5–8)	6 (5–8)	−0.13 (−0.60 to 0.34)	0.586	0.894
In-hospital mortality	0 (0)	0 (0)	–	1.000	1.000

Notes: Data are presented as mean (SD), median (interquartile range), or n (%). [a] For secondary outcomes, multiple comparisons were corrected using the Benjamini-Hochberg approach to control for false discovery ($q < 0.05$ was applied).
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; POD, postoperative day.

no significant between-group differences in the incidence of PONV, delirium, pneumonia, or stroke either (Table 3). Postoperative ICU admission occurred in 11% of patients in dexmedetomidine group and 10% of those in the control group. The median length of hospital stay was 6 days in both groups, and no patients died during hospitalization.

Post Hoc Analyses

After adjusting for relevant baseline covariates, dexmedetomidine was still associated with a significantly reduced incidence of AKI (adjusted OR = 0.36, 95% CI: 0.14 to 0.90; $P = 0.030$) (Table 4). On POD 1, the median change in serum cystatin C was 0.02 mg/L (IQR, −0.07 to 0.09) in the dexmedetomidine group and 0.08 mg/L (IQR, (−0.10 to 0.39) mg/L in the control group. The between-group difference was −0.08 mg/L (95% Cl, −0.17 to −0.01 mg/L; $P = 0.043$) in unadjusted analysis and −0.09 mg/L (95% Cl, −0.16 to −0.02 mg/L; $P = 0.012$) after adjustment. The dexmedetomidine group had lower number of patients with eGFR decline > 25% on POD 1 (5 of 149 vs 8 of 146), POD 2 (6 of 149 vs 10 of 146), and POD 3 (4 of 149 vs 5 of 146). No patients in either group experienced an eGFR decrease exceeding 50%.

Discussion

This study revealed that perioperative dexmedetomidine infusion (0.40 μg/kg bolus followed by 0.4 μg/kg/h infusion) may reduce the incidence of postoperative AKI in elderly patients undergoing lower extremity orthopedic surgeries. This protective effect remained statistically significant after adjustment for baseline covariates. In addition, the dexmedetomidine group had lower serum cystatin C levels and smaller postoperative increases on POD 1 compared with controls. To our knowledge, this is the first randomized controlled trial to show the association between dexmedetomidine use and a reduced AKI incidence in elderly patients undergoing lower extremity orthopedic surgery.

AKI is a common complication in elderly patients undergoing lower extremity orthopedic surgeries, with an incidence ranging from 8.4% to 28.4%.[23–25] As the elderly population continues to grow, many are affected by chronic conditions such as hypertension and diabetes, which impose an increased burden on kidney. Moreover, the physiological characteristics of elderly patients–including reduced renal adaptability to hemodynamic fluctuations and diminished responsiveness to vasodilatory factors–further heighten their susceptibility to postoperative renal dysfunction.[27,28] Lower extremity

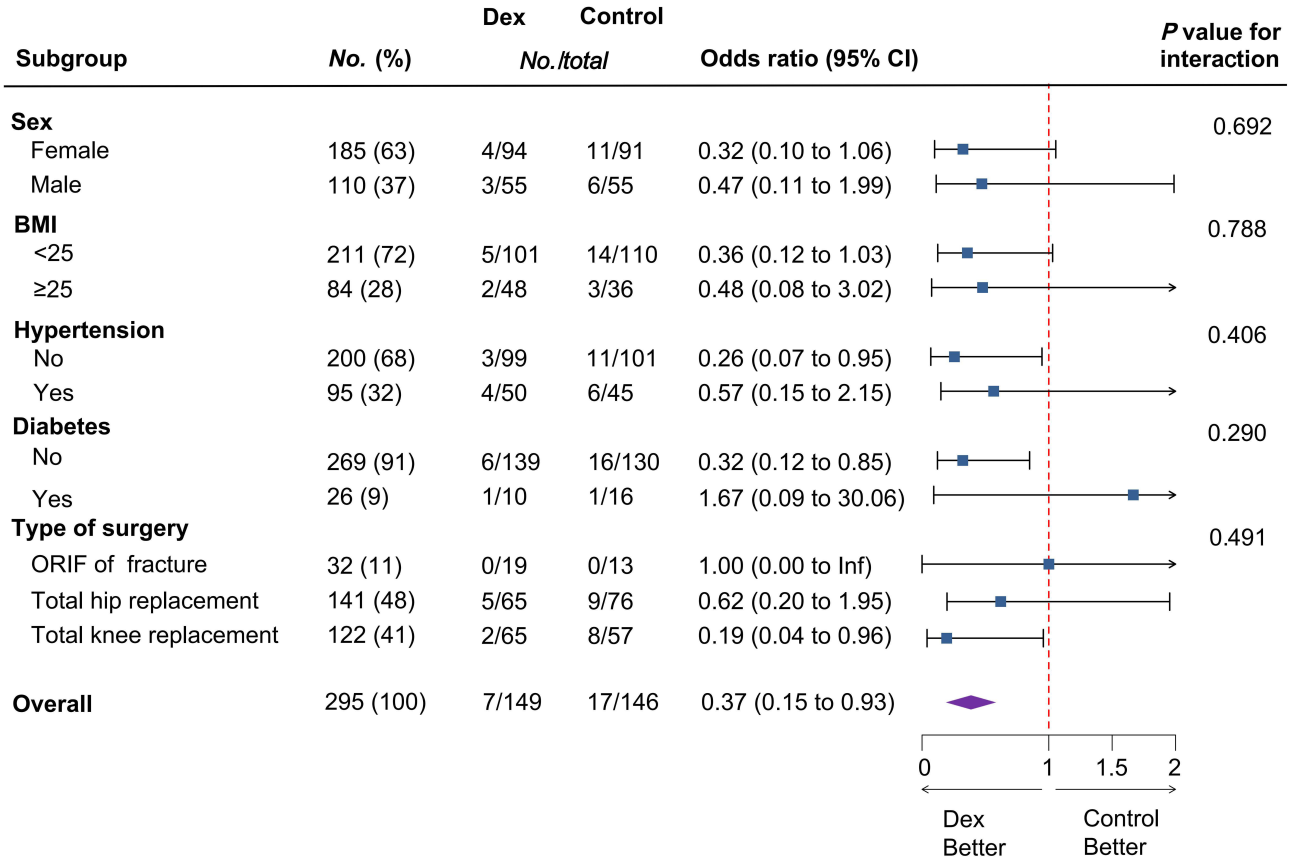

Figure 2 Subgroup analysis for the incidence of AKI.
Notes: Red colored dotted lines are the demarcation lines for an odds ratio of 1.
Abbreviations: BMI, body mass index; ORIF, open reduction and internal fixation.

orthopedic surgery itself is typically accompanied by considerable surgical stress, position change and bleeding risk. Anesthetic considerations are also relevant, as evidence suggests that sevoflurane may increase renal sympathetic activity, reduce urine output and sodium excretion, particularly among elderly patients.[29,30] Collectively, these factors trigger sympathetic activation and inflammatory cytokine upregulation, leading to renal arteriolar constriction, impaired renal perfusion, and ultimately an increased likelihood of developing AKI.[31–33] Given the critical role of perioperative fluid management in preventing AKI,[5] we implemented SVV–guided goal-directed fluid therapy to optimize hemodynamic status and mitigate renal insult.

As a highly selective α2 receptor agonist, dexmedetomidine can effectively attenuate sympathetic hyperexcitability, stabilize hemodynamics, induce renal artery vasodilation and enhance renal blood flow.[7,34,35] A recent meta-analysis reported that dexmedetomidine reduced the incidence of AKI from 18.3% to 10.9% in patients undergoing cardiac surgery, with the greatest benefit observed when administered before and during surgery, particularly in elderly patients.[14] In another randomized controlled trial, dexmedetomidine significantly decreased the incidence of postoperative AKI from 31% to 13% (an absolute reduction of 18%) following aortic surgery with cardiopulmonary bypass, without clinically relevant sedative or sympatholytic effects.[13] Our previous study demonstrated that administering 24-h dexmedetomidine infusion reduced the incidence of AKI from 22% to 6.3% (an absolute reduction of 15.7%) following endovascular repair for Stanford type B aortic dissection.[26] Although elderly patients undergoing orthopedic surgery experience different physiological stress and surgical complexity compared with those undergoing cardiac or aortic procedures, dexmedetomidine has also shown a potential renoprotective profile in this population. In a retrospective study of 1,006 elderly patients undergoing major joint replacement, dexmedetomidine infusion was associated with a reduction in AKI incidence from 11.5% to 7.2%.[10] In this study, dexmedetomidine reduced AKI incidence from 11.6%

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Table 4 Results of Post Hoc Analyses

	Dexmedetomidine (n=149)	Control (n=146)	Odds Ratio or Difference (95% CI)	*P* value	Adjusted Odds Ratio or Difference (95% CI) [a]	Adjusted *P* value [a]
Primary outcome						
Acute kidney injury	7 (4.7%)	17 (11.6%)	0.37 (0.15 to 0.93)	0.035	0.36 (0.14 to 0.90)	0.030
Other renal outcomes						
Changes of serum cystatin C on POD 1 (mg/L)	0.02 (−0.07, 0.09)	0.08 (−0.10, 0.39)	−0.08 (−0.17 to −0.01)	0.043	−0.09 (−0.16 to −0.02)	0.012
Changes of serum cystatin C on POD 2 (mg/L)	0.04 (−0.12, 0.27)	0.09 (−0.12, 0.36)	−0.05 (−0.15 to 0.04)	0.278	−0.05 (−0.12 to 0.03)	0.211
Changes of serum cystatin C on POD 3 (mg/L)	0.01 (−0.16, 0.20)	0.04 (−0.14, 0.27)	−0.06 (−0.16 to 0.03)	0.179	−0.06 (−0.14 to 0.02)	0.148
eGFR decrease >25% on POD 1	5 (3.4%)	8 (5.5%)	0.60 (0.19 to 1.88)	0.379	0.64 (0.20 to 2.10)	0.462
eGFR decrease >25% on POD 2	6 (4.0%)	10 (6.9%)	0.57 (0.20 to 1.61)	0.290	0.58 (0.20 to 1.66)	0.312
eGFR decrease >25% on POD 3	4 (2.7%)	5 (3.4%)	0.78 (0.20 to 2.96)	0.712	1.13 (0.26 to 4.87)	0.868

Notes: Data are median (interquartile range) or number of patients (%). [a]Adjusted for baseline covariates (hypertension, diabetes, eGFR, and serum cystatin C) using multivariate logistic regression or generalized linear model.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; POD, postoperative day.

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to 4.7% in elderly patients undergoing lower extremity orthopedic surgeries, as defined by the AKIN criteria. This finding suggested a potentially strong renoprotective effect in this high-risk patient population. In this study, the overall incidence of AKI was 8.1%, lower than that reported in prior lower extremity orthopedic surgery cohorts,[10,24] which may attribute to the adoption of a preventative bundle protocol for AKI.

In post hoc analysis, we applied the Risk, Injury, Failure, Loss of kidney function, End-stage renal disease (RIFLE) criteria, incorporating a >25% decline in estimated GFR as an additional marker of AKI. Although fewer patients in the dexmedetomidine group showed a >25% decrease in GFR on POD 1–3, the between-group difference did not reach statistical significance. It is important to note that the RIFLE criteria may underestimate AKI incidence, as they did not account for minor elevations in SCr that have been shown to contribute to postoperative morbidity and mortality.[36] While the AKIN criteria, which incorporate even small increases in SCr (≥ 26.5 μmol/L), has been more widely adopted.[21]

Serum cystatin C, secreted by all nucleated cells, is freely filtered by the glomeruli and fully reabsorption by the renal tubules before being catabolized.[37] Unlike SCr, its concentration is less influenced by factors such as age, muscle mass, and diet.[38] Previous studies have established serum cystatin C as a reliable marker for assessing renal function and for the early detection of AKI.[39,40] In this study, perioperative monitoring serum cystatin C was incorporated into the preventative AKI bundle protocol. The dexmedetomidine group demonstrated lower serum cystatin C levels and smaller increases from baseline on POD 1, whereas SCr and eGFR remained comparable between groups. These findings suggest that dexmedetomidine infusion may help preserve early renal function in elderly patients undergoing orthopedic surgery.

This dexmedetomidine infusion protocol showed a favorable safety profile in elderly patients, without increasing intraoperative hypotension, time to extubation, postoperative admission to ICU during perioperative period. The only notable adverse effect was a higher incidence of bradycardia. This phenomenon appeared to be transient and did not result in obvious adverse outcomes, which aligns with previous studies.[10,11] Conventionally, dexmedetomidine is administered with a loading dose (eg, 1 μg/kg bolus over 10 min) followed by a maintenance infusion for sedation; however, this regimen is frequently associated with intraoperative hypotension, which is a well-recognized risk factor for postoperative renal dysfunction.[41,42] Base on prior research conducted in elderly patients,[19,20] we adopted a modified dexmedetomidine dosing regimen consisting of 0.4 μg/kg bolus followed by 0.4 μg/kg/h infusion.

There are several limitations in this study. First, as a single-center study, the findings may be less generalizable compared to those from multi-center clinical trials. Second, hydroxyethyl starch 6% 130/0.4 was administered as part of SVV-guided fluid management strategy, and its impact on renal function remains controversial.[43,44] Nonetheless, recent studies indicated that HES 6% 130/0.4, when used for volume replacement, may provide superior hemodynamic stability compared with crystalloids alone, without increasing the risk of renal injury in major surgery.[45–48] Third, the relative short follow-up periods did not allow for an assessment of long-term renal function recovery. Therefore, further multi-center studies with longer follow-up periods are needed to validate our findings and assess the long-term benefits of dexmedetomidine in elderly orthopedic surgical patients. Fourthly, the majority of patients in this study were classified as ASA I-II, which represents a relatively low-risk cohort; therefore, the results may not be generalizable to more frail or higher-risk elderly populations.

In conclusion, this randomized controlled clinical trial found that perioperative dexmedetomidine infusion was associated with a reduced incidence of AKI in elderly patients following lower extremity orthopedic surgery. Multicenter trials are warranted to validate the renoprotective effects of dexmedetomidine in this patient population.

Data Sharing Statement

Data are available to researchers on request for the purpose of reproducing the results or replicating the procedure by directly contacting the corresponding author, Xi-Sheng Shan.

Ethical Approval

Ethical approval for this study (Approved No. 2022026) was provided by the Ethical Committee of the First Affiliated Hospital of Soochow University, Suzhou, China. The study protocol was registered at the Chinese Clinical Trial Registry (identifier: ChiCTR2400088225). Written informed consent was obtained from all participants prior to any study-related procedures.

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All authors have read and approved the final manuscript.

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

No potential competing interest was reported by the authors.

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