

Impact of Dexmedetomidine Infusion on Postoperative Acute Kidney Injury in Elderly Patients Undergoing Major Joint Replacement: A Retrospective Cohort Study

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Purpose: Postoperative acute kidney injury (AKI) is a frequent complication in elderly patients that increases morbidity and mortality. Approximately 1.7 million people die from AKI worldwide every year. Dexmedetomidine (Dex) is often used as an adjunct to multi-modal analgesia. Our study investigated whether Dex could safely decrease the incidence of AKI in elderly patients undergoing major joint replacement.

Methods: A single-center retrospective study was conducted in patients aged >65 years undergoing major joint replacement. Propensity score-matching analysis was used, and a total of 1,006 patients were matched successfully. The primary outcome was the incidence of postoperative AKI. Secondary outcomes included perioperative adverse complications, opioid consumption, time to extubation, and length of hospital stay.

Results: Among the 1,006 patients included, postoperative AKI occurred in 9.3% (n=94). The Dex group (perioperative Dex infusion) had lower incidence of postoperative AKI than the control group (7.2% vs 11.5%, $P=0.017$). Compared with the control group, the Dex group had less opioid consumption ($P<0.05$), reduced time to extubation ($P=0.004$), and shorter length of hospital stay ($P=0.001$). The Dex group also showed higher incidence of bradycardia (20.1% vs 15.1%, $P=0.038$). There were no differences in intraoperative hypotension (19.5% vs 17.5%), postoperative nausea and vomiting (4.2% vs 5.4%), time in PACU (45.0 ± 6.4 vs 45.5 ± 6.2 minutes), or rate of ICU admission (9.7% vs 11.1%) between the Dex group and control group (All $P>0.05$).

Conclusion: This retrospective study showed Dex infusion in elderly patients undergoing major joint replacement was associated with lower incidence of postoperative AKI, less opioid consumption, and shorter extubation time and hospital stay. However, the Dex group had higher incidence of bradycardia. We found no statistical differences in other perioperative adverse complications between the groups.

Keywords: dexmedetomidine, acute kidney injury, elderly patients, joint replacement

Introduction

Postoperative acute kidney injury (AKI) is a complex group of clinical syndromes. Elderly patients are especially in danger of developing AKI, given the presence of several comorbidities, including hypertension, diabetes, and chronic kidney disease.^{1,2} AKI has become a global issue, but has not attracted widespread attention. The occurrence of AKI after surgery leads to an increase in postoperative

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complications, which brings a heavy financial burden to families.³ A meta-analysis showed that the incidence of AKI and severe AKI requiring dialysis after total hip arthroplasty was 6.3% and 0.5%, respectively.⁴ Due to the different locations of joint replacement, the incidence of postoperative AKI is 0.5%–21.9%, and the incidence of renal failure caused by hip and knee replacement is 0.8%.⁵ At present, clinical research on AKI is mostly limited to cardiovascular surgery. There has been little research on AKI after joint replacement.

Dexmedetomidine (Dex) is a highly selective α_2 -adrenoceptor agonist with sympatholytic, analgesic, dose-dependent, sedative, and anxiolytic properties with minimal respiratory depression.⁶ Studies have shown that Dex provides neuroprotection and renoprotection in a dose-dependent manner.^{7,8} Perioperative Dex infusion can provide smooth and hemodynamically stable emergence.⁹ There has been no study to investigate the effects of Dex in preventing AKI in elderly patients undergoing major joint replacement due to its renal protection. Early identification and intervention of postoperative AKI is important, because there is no good therapy other than renal replacement when the disease becomes severe. We hypothesized that Dex infusion would lead to a reduced incidence of postoperative AKI safely.

Methods

Study Design and Participants

This retrospective study (Jiangsu, China; XYFY2020-KL050-01) was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. We used propensity score-matching analysis, and 1,006 elderly patients who had undergone major joint replacement at the Affiliated Hospital of Xuzhou Medical University from October 2013 to October 2019 were included finally. The study was registered in the American Clinical Trial Registry (NCT04132921) and the requirement for informed consent waived, because this retrospective trial was limited to preexisting data without intervention. Inclusion criteria were age ≥ 65 years and unilateral joint replacement. Exclusion criteria were lack of clinically relevant data, patients who had undergone emergency surgery, patients with severe liver/kidney dysfunction, heart failure, or severe arrhythmia.

Data Collection

All information was obtained from the electronic medical record and anesthesia systems. Researchers were trained

before data collection, and two independent investigators verified all data. We mainly collected demographic data (sex, age, BMI, American Society of Anesthesiologists [ASA] classification, and preoperative comorbidities), general conditions during the operation, laboratory-examination results, incidence of AKI, postoperative outcomes, including nausea and vomiting, length of hospitalization, time to extubation (time from end of operation to removal of tracheal tube), time in the postanesthesia care unit (PACU), and whether the patient had been admitted to the ICU after surgery.

Dex administration was defined as a loading dose of 0.5–1.0 $\mu\text{g/kg}$ within 10–15 minutes or intraoperative continuous infusion at a rate of 0.2–0.7 $\mu\text{g/kg/h}$. The primary outcome variable was prevalence of postoperative AKI defined according to the criteria from Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. AKI can be diagnosed if one of the following conditions is met: increase in serum creatinine ≥ 0.3 mg/dL within 48 hours or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days. Baseline serum creatinine was defined as

Table 1 Weighted scores for each item of the 20-item Charlson Comorbidity Index

Comorbidity	Score
Age	Score of 1 for every decade >40 years of age
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective-tissue disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes mellitus without end-organ damage	1
Moderate–severe chronic kidney disease	2
Hemiplegia	2
Diabetes with end-organ damage	2
Tumour without metastasis	2
Leukemia (acute or chronic)	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
AIDS	6

the most recent value prior to surgery, and the peak value was defined as the highest serum creatinine within 7 days following surgery. A simplified MDRD formula was used to calculate the estimated glomerular filtration rate (eGFR): $186 \times \text{serum creatinine value}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (female). Low eGFR was defined as eGFR <60 mL/min/1.73m², hypotension as mean arterial pressure <65 mmHg for >5 minutes, bradycardia as heart rate <50 beats per minute, hypoproteinemia as albumin <35 g/L and thrombocytopenia as platelet count <100×10⁹ L.

Elderly patients >65 years old often have accompanying basic diseases, and the impact of comorbidities on disease outcomes can be measured by a well-established and validated 20-item risk-scoring tool: the Charlson Comorbidity Index (CCI). The second edition of the CCI is a combined age-comorbidity score that adds the factor of age (Table 1). Based on their scores, patients were divided into two groups in our study: those with scores ≤3 and those with scores of >3. This work was completed by two members of the team reviewing the

surgical medical record system. All enrolled patients were anesthetized by general anesthesia at the discretion of the attending anesthesiologist, and intraoperative monitoring was performed with electrocardiography, pulse oximetry, invasive surveillance of arterial blood pressure, and bispectral index. In order to reduce the use of anesthetic drugs and postoperative complications, most patients underwent general anesthesia combined with femoral nerve block, sciatic nerve block, or lumbar plexus block. All invasive operations were performed by senior anesthesiologists.

Statistical Analyses

For continuous variables, the Kolmogorov–Smirnov test was used to assess normality, normally distributed continuous variables as means ± SD, and abnormally distributed continuous variables as medians (IQR). Categorical variables are summarized as frequencies and proportions. Unpaired *t*-tests were used normally distributed continuous variables, Mann–Whitney *U*-test for variables without

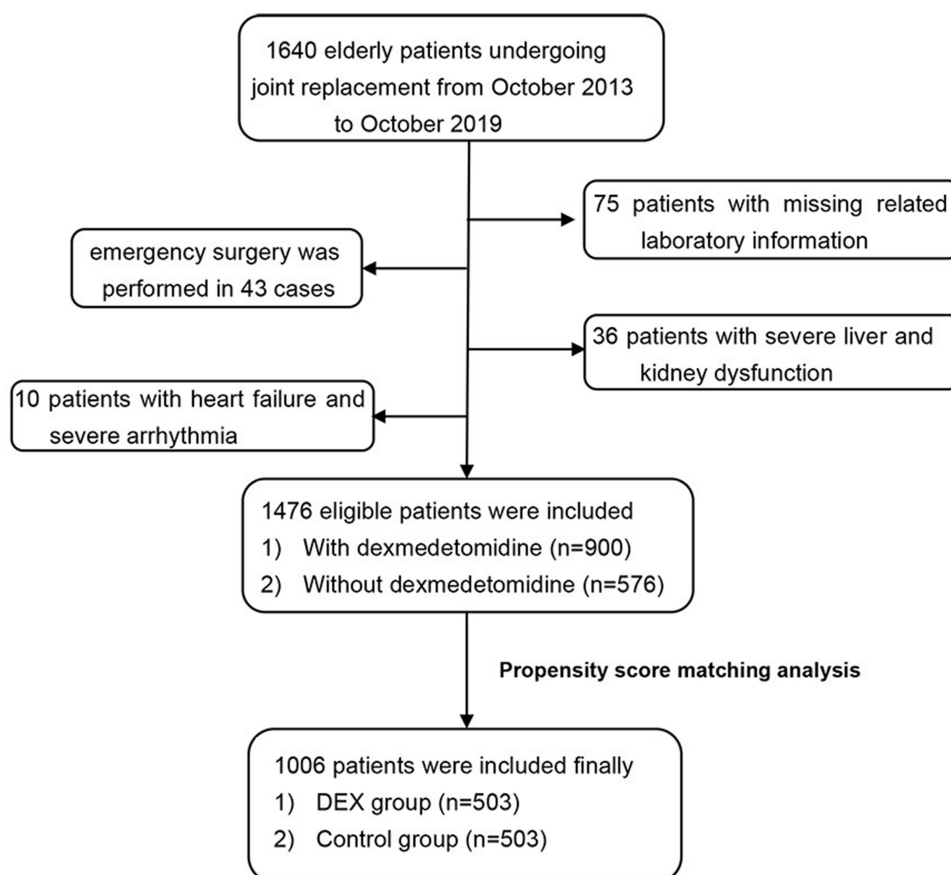


Figure 1 Study flowchart.

Abbreviation: Dex, Dex (perioperative infusion).

Table 2 Baseline variables of patients with or without dexmedetomidine infusion

	Dex group (n=503)	Control group (n=503)	P-value
Sex, n (%)			
Male	206 (41.0)	200 (39.8)	0.700
Female	297 (59.0)	303 (60.2)	
Age (years), mean (SD)	73 (7)	74 (7)	0.787
BMI, mean (SD)	21.4 (3.0)	21.7 (3.1)	0.132
ASA classification, n (%)			
Class I–II	357 (71.0)	368 (73.2)	0.440
Class III–IV	146 (29.0)	135 (26.8)	
CCI score ≥ 4, n (%)	64 (12.7)	60 (11.9)	0.701
Comorbidities, n (%)			
Hypertension	78 (15.5)	74 (14.7)	0.725
Diabetes	28 (5.6)	23 (4.6)	0.472
Low eGFR	27 (5.4)	30 (6.0)	0.682
Anemia	234 (46.5)	222 (44.1)	0.447
Cardiac disease	46 (9.1)	60 (11.9)	0.151
Thrombocytopenia	10 (2.0)	17 (3.4)	0.172
Hypoproteinemia	87 (17.3)	79 (15.7)	0.497
Chronic smoking	94 (18.7)	89 (17.7)	0.683
Alcoholism	29 (5.8)	19 (3.8)	0.139

Abbreviations: BMI, body-mass index; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate.

normal distribution, and χ^2 or Fisher's exact tests for categorical data as appropriate. Propensity-score methods can effectively control for baseline confounding by balancing measured baseline confounders and risk factors. We identified 900 patients who had been treated with Dex and 576 who had not. Finally, we successfully matched 503 pairs who had propensity score within 0.02, based on age, sex, BMI, ASA classification, and CCI score. Propensity-score matching was successful in achieving balance across all measured covariates.

Table 3 Preoperative laboratory information

	Dex group (n=503)	Control group (n=503)	P-value
Cystatin C (mg/L), median (IQR)	1.5 (1.2–1.5)	0.7 (0.6–1.8)	0.144
Lactic acid (mmol/L), median (IQR)	2.1 (1.8–2.1)	2.0 (1.4–2.1)	0.100
Albumin (g/L), mean (SD)	39.3 (5.9)	38.5 (5.6)	0.026
Creatinine ($\mu\text{mol/L}$), median (IQR)	89.0 (41.0–89.0)	48.0 (36.0–48.0)	0.638
BUN (mmol/L), median (IQR)	6.3 (5.9–6.7)	4.8 (3.8–4.8)	0.162
Glu (mmol/L), median (IQR)	7.1 (7.0–8.2)	8.4 (8.3–9.4)	0.993
Platelet ($10^9/\text{L}$), median (IQR)	240 (122–255)	298 (298–324)	0.025
CRP (mg/L), median (IQR)	16.0 (16.0–116.0)	35.5 (15.0–76.4)	0.733

Sample size was based on a 23.2% incidence of AKI in hospitalized patients according to KDIGO criteria.¹⁰ We assumed a 35% reduction in postoperative AKI incidence in the Dex group. Sample size was calculated using PASS11 software, and 736 patients were required to provide 80% power to detect a two-sided difference, with a type I error probability of 0.05. Ultimately, we included 1,006 patients for analysis. Statistical analysis was performed using SPSS version 23.0 (IBM, Armonk, NY, USA). All statistical tests were two-tailed, and $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 1,640 elderly patients who had been scheduled to undertake elective major joint replacement surgery were screened from October 2013 to October 2019 at the Affiliated Hospital of Xuzhou Medical University. There were 164 patients excluded according to our exclusion criteria and 1,476 eligible patients included. In order to balance measured baseline confounders and risk factors, propensity score-matching analysis was used and 1,006 matched successfully. The specific flow diagram for patient selection is presented in [Figure 1](#).

Baseline Characteristics

There were no significant differences in sex, age, BMI, ASA classification, CCI scores, comorbidities (hypertension, diabetes, low eGFR, anemia, cardiac disease), chronic smoking, or alcoholism between the two groups (All $P > 0.05$). We analyzed preoperative laboratory information and found significant differences in albumin and platelet counts. For ease of analysis and interpretation, we represented these related risk factors as binary predictor variable. There was no difference for hypoproteinemia or thrombocytopenia ([Tables 2 and 3](#)).

Outcomes

Our study showed no differences in surgery or anesthesia procedure (Table 4). However, there were significant differences in sufentanil and remifentanyl consumption between the groups ($P<0.05$). No differences were seen in propofol, rocuronium, cisatracurium, sevoflurane, or NSAID use. We compared the choice of nerve block, and no differences were found for femoral nerve block (37.0% vs 40.0%, $P=0.331$), sciatic nerve block (20.1% vs 22.9%, $P=0.282$), or lumbar plexus block (11.7% vs 9.3%, $P=0.218$) (Table 4). Postoperative AKI occurred in 9.3% ($n=94$) of all patients, and the Dex group was associated with lower incidence of postoperative AKI than the control group (7.2% vs 11.5%, $P=0.017$; Table 5).

Compared with the control group, the Dex group had higher incidence of bradycardia (20.1% vs 15.1%,

$P=0.038$). We found that the Dex group had shorter time (minutes) to extubation (18.6 ± 2.2 vs 19.0 ± 2.3 , $P=0.004$) and shorter length (days) of hospital stay (19.5 ± 2.0 vs 19.9 ± 1.9 , $P=0.001$). Nausea and vomiting are the most common complications after general anesthesia, and 21 patients in the Dex group and 27 in the control group experienced mild nausea and vomiting upon checking the anesthesia record. No significant difference was observed between the two groups (4.2% vs 5.4%, $P=0.375$). There were no differences in intraoperative hypotension (19.5% vs 17.5%), time (minutes) in PACU (45.0 ± 6.4 vs 45.5 ± 6.2), or rate of ICU admission (9.7% vs 11.1%) between the Dex group and control group (all $P>0.05$, Table 5).

Discussion

AKI has become a global issue, however, attention paid to it is still not enough. Elderly patients are growing in numbers and often have such diseases as hypertension and diabetes, which increase the burden on the kidneys.^{11,12} Therefore, for elderly patients, a comprehensive anesthesia and surgical evaluation should be performed before surgery. A study has shown that Dex infusion in pediatric patients after congenital heart surgery is associated with decreased incidence of AKI.¹³ However, the impact of Dex on AKI after major joint replacement is still unknown, and our study showed that Dex infusion decreased the incidence of postoperative AKI safely in elderly patients after total knee or hip arthroplasty.

AKI is a common complication caused by multiple factors, and its risk factors include older age, high BMI, hypo-proteinemia, anemia, decrease in GFR, use of colloids, and decreased mean arterial pressure.^{14–17} Many factors are still controversial, and one possible mechanism is hemodynamic changes leading to an imbalance of oxygen supply and demand in organs, with ischemia–reperfusion injury eventually leading to AKI.^{18,19} Si et al²⁰ recently demonstrated that Dex appears to act, at least in part, by upregulating SIRT3 to inhibit mitochondrial damage and cell apoptosis and thereby protect against renal ischemia–reperfusion injury, which is consistent with our study. However, Oh et al found no significant association between Dex use and AKI after joint replacement, and a possible explanation that should be considered is this retrospective observational study included only patients who received spinal anesthesia.

Analysis of perioperative adverse outcomes showed no significant differences in intraoperative hypotension, nausea and vomiting, time in PACU, or rate of ICU admission. The Dex group had higher incidence of bradycardia than

Table 4 Surgery- and anesthesia-related information

	Dex group (n=503)	Control group (n=503)	P- value
Type of surgery			
Knee replacement, n (%)	165 (32.8)	174 (34.6)	0.548
Hip replacement, n (%)	338 (67.2)	329 (65.4)	
Surgery and anesthesia			
Surgery time (minutes), mean (SD)	113.3 (43.2)	114.5 (41.8)	0.638
Anesthesia time (minutes), mean (SD)	150.6 (51.3)	150.2 (46.6)	0.897
Duration of hypotension (minutes), median (IQR)	9 (6–14)	10 (7–13)	0.249
Times of hypotension, median (IQR)	2 (1–3)	3 (1–3)	0.261
Phenylephrine, n (%)	53 (10.5)	46 (9.1)	0.459
Ephedrine, n (%)	21 (4.2)	17 (3.4)	0.508
Bleeding (mL), median (IQR)	300 (200–600)	300 (250–500)	0.814
Colloid (mL), median (IQR)	500 (500–1,000)	500 (500–1,000)	0.807
Crystal (mL), median (IQR)	1,250 (1,000–1,500)	1,250 (1,000–1,500)	0.687
Urine (mL), median (IQR)	400 (300–400)	350 (300–400)	0.158
Blood transfusion, n (%)	47 (9.3)	62 (12.3)	0.128
Choice of anesthetic			
Sufentanil (μg), mean (SD)	51.7 (6.1)	52.8 (6.6)	0.007
Propofol (mg), mean (SD)	364.1 (46.0)	366.8 (44.2)	0.346
Rocuronium (mg), mean (SD)	51.7 (9.4)	50.8 (9.9)	0.141
Cisatracurium (mg), mean (SD)	14.9 (2.2)	15.0 (2.2)	0.425
Remifentanyl (mg), mean (SD)	2.0 (0.3)	2.1 (0.9)	0.012
Sevoflurane	358 (71.2)	370 (73.6)	0.398
NSAIDs	251 (50.0)	271 (53.9)	0.207
Nerve block			
Femoral, n (%)	186 (37.0)	201 (40.0)	0.331
Sciatic, n (%)	101 (20.1)	115 (22.9)	0.282
Lumbar, n (%)	59 (11.7)	47 (9.3)	0.218

Abbreviation: NSAIDs, nonsteroidal antiinflammatory drugs.

Table 5 Perioperative outcomes

	Dex group (n=503)	Control group (n=503)	P-value
AKI, n (%)	36 (7.2)	58 (11.5)	0.017
Intraoperative hypotension, n (%)	98 (19.5)	88 (17.5)	0.417
Bradycardia, n (%)	101 (20.1)	76 (15.1)	0.038
Nausea and vomiting, n (%)	21 (4.2)	27 (5.4)	0.375
Time in PACU (minutes), mean (SD)	45.0 (6.4)	45.5 (6.2)	0.189
Time to extubation (minutes), mean (SD)	18.6 (2.2)	19.0 (2.3)	0.004
ICU admission, n (%)	49 (9.7)	56 (11.1)	0.470
Hospital stay (days), mean (SD)	19.5 (2.0)	19.9 (1.9)	0.001

Abbreviations: PACU, postanesthesia care unit; ICU, intensive care unit.

the control group, but the occurrence of bradycardia was transient and the percentage of patients requiring intervention very low. Compared with the control group, the Dex group had shorter time to extubation and shorter length of hospital stay, meaning an optimal dose of Dex infusion was not associated with obvious residual sedation, which is similar to a recent study.²¹

Total hip or knee arthroscopy is a common orthopedic procedure, and postoperative pain delays discharge and increases medical cost.^{22,23} From the perspective of enhanced recovery after surgery, we have to achieve significant clinical and economic benefits after surgery.²⁴ According to Sun et al,²⁵ elderly patients in a Dex group reported significantly lower numeric rating-scale pain scores at 3, 12, 24, and 48 hours after surgery and significantly improved Richards–Campbell Sleep Questionnaire results during the first 3 days after major elective noncardiac surgery. Studies have shown satisfactory analgesic effects of Dex in total hip or knee arthroscopy, but some experimental conclusions are controversial.^{26–28} The dose of Dex we chose was similar to previous research: the Dex administration was a loading dose of 0.5–1.0 µg/kg within 10–15 minutes or intraoperative continuous infusion at 0.2–0.7 µg/kg/h according to anesthesia system records. Consistently with previous research results,²⁹ intraoperative Dex was associated with a small but clinically important reduction in opioid consumption. Due to the limitations of retrospective studies, we could not collect additional postoperative opioid-use data, which may limit the accuracy of our conclusions.

Additionally, this was a single-center retrospective study, which has some limitations. Demographic, anesthesia-, and surgery-related data were collected from electronic medical records and doses and infusion rate of Dex cannot be accurately assessed; therefore, large-sample randomized controlled trials are still needed. We also noticed the impact of

tourniquets on postoperative AKI, but as this was a retrospective experiment, we could not accurately assess the use of tourniquets in knee arthroplasty.

Conclusion

Our study showed that Dex infusion was associated with lower incidence of postoperative AKI, less opioid consumption, and shorter extubation time and length of hospital stay. Except for transient bradycardia during the operation, Dex infusion did not produce any severe adverse complications.

Data-Sharing Statement

Individual participant data underlying published results reported in this study can be accessed with approval from the corresponding author after 6 months of publication of the main results. The study protocol, statistical analysis plan, and clinical study report will also be available.

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Disclosure

The authors report no conflicts of interest in this work.

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