

Effect of intraoperative dexmedetomidine on postoperative delirium after kidney transplantation: a randomised, double-blind, placebo-controlled trial

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Abstract

Background

Patients with end-stage renal disease frequently present with preoperative electrolyte disturbances and concomitant polypharmacy, factors associated with an increased incidence of postoperative delirium (POD) after allogeneic kidney transplantation. This study aimed to evaluate whether dexmedetomidine reduces the incidence of POD in kidney transplant recipients.

Methods

This prospective, single-centre, randomised, double-blind, placebo-controlled trial enrolled adult patients undergoing kidney transplantation between January 2018 and December 2021. Participants were randomly assigned in a 1:1 ratio to receive dexmedetomidine 0.4 µg/kg or an equal volume of normal saline immediately after tracheal intubation. The primary outcome was postoperative delirium within the first 5 postoperative days, assessed every 12 h using the Confusion Assessment Method for the Intensive Care Unit.

Results

A total of 180 participants were randomised into the dexmedetomidine group (DEX, n = 90) and the control group (CON, n = 90). In the primary complete-case analysis of 174 participants, POD occurred in 4 of 88 participants (4.5%) in the DEX group and 13 of 86 participants (15.1%) in the CON group (risk ratio, 0.30; 95% CI, 0.10–0.89; P = 0.019). Acute graft rejection was less frequent in the DEX group than in the CON group (0/88 [0.0%] vs 7/86 [8.1%]; Fisher's exact P = 0.006).

Conclusions

Intraoperative dexmedetomidine was associated with a lower incidence of postoperative delirium within 5 days after kidney transplantation, without an observed increase in intraoperative hypotension or bradycardia. Fewer acute graft rejection events were observed in the DEX group, although this exploratory finding requires confirmation.

Trial registration

ClinicalTrials.gov, NCT02509949. First submitted on 24 July 2015.

Introduction

Postoperative delirium is a common central nervous system complication following surgery and is widely recognized as a form of acute brain dysfunction. It typically occurs within 24–72 hours after surgery and is characterized by fluctuating disturbances in consciousness, inattention, disorganized thinking, cognitive decline, memory impairment, disorientation, and disruption of the sleep–wake cycle [1]. Postoperative delirium has been strongly associated with prolonged hospital stay, increased

healthcare costs, higher rates of hospital readmission, persistent cognitive impairment or dementia, and increased mortality [2]. Patients with end-stage renal disease frequently present with fluid and electrolyte imbalances, neurological dysfunction, anaemia, hypertension, and secondary hyperparathyroidism. Consequently, individuals undergoing kidney transplantation are at an elevated risk of developing postoperative delirium in the postoperative period, reported at approximately 6% [3], the incidence rate can be as high as 20.0% in some populations [2, 4].

Dexmedetomidine, a highly selective α_2 -adrenergic receptor agonist, exerts its pharmacological effects through suppression of sympathetic activity and enhancement of vagal tone, thereby providing sedation, analgesia, anxiolysis, and amnestic effects [5]. In addition, accumulating evidence suggests that dexmedetomidine confers protective effects across multiple organ systems [6]. Notably, dexmedetomidine has been shown to reduce the incidence of postoperative delirium [7].

A multicentre randomised controlled trial by Su et al. demonstrated that prophylactic administration of dexmedetomidine not only significantly reduced the incidence of postoperative delirium but also decreased perioperative complications such as hypertension and tachycardia [8]. Some views suggest that dexmedetomidine is one of the effective perioperative interventions for postoperative delirium [9]. However, not all studies have yielded consistent findings. Large randomised trials by Deiner et al. and Turan et al. failed to demonstrate a significant preventive effect of intraoperative dexmedetomidine on postoperative delirium, suggesting that its efficacy may vary according to patient population, surgical type, dosing regimen, and timing of administration [10, 11]. Therefore, the role of dexmedetomidine in postoperative delirium prevention remains a subject of ongoing debate. Importantly, many of these studies have focused on heterogeneous surgical populations or patients admitted to the intensive care unit, with substantial variability in surgical procedures.

Therefore, we conducted a prospective, single-centre randomised controlled trial to evaluate the efficacy of dexmedetomidine in preventing postoperative delirium in patients undergoing kidney transplantation, and to further assess its effects on other postoperative complications in this population. Evidence regarding the effect of dexmedetomidine on postoperative delirium specifically in kidney transplant recipients remains limited.

Methods

Study design

This study was a prospective, single-centre, randomised, parallel-group, double-blind trial conducted at The First Affiliated Hospital of Sun Yat-sen University. The study protocol was approved by the institutional ethics committee (approval number: [2015] No. 17). The trial was registered at ClinicalTrials.gov (registration number: NCT02509949). No important changes were made to the study methods after trial commencement.

The anesthesiologists responsible for drug administration, outcome assessors, and participants were all blinded to group assignment. To ensure patient safety, unblinding was permitted in cases of serious adverse events or other unforeseen circumstances that could compromise patient safety.

Inclusion criteria

Participants were eligible for enrolment if they met all of the following criteria:

1. Age between 18 and 75 years,
2. Diagnosis of renal failure of any cause and scheduled to undergo allogeneic kidney transplantation,
3. Provision of written informed consent.

Exclusion criteria

Participants were excluded if they met any of the following criteria:

1. Second-degree or higher atrioventricular block,
2. Sick sinus syndrome or Wolff–Parkinson–White syndrome,
3. Resting heart rate < 50 beats per minute before surgery,
4. Use of dexmedetomidine within 30 days prior to surgery,
5. Severe heart failure or left ventricular ejection fraction < 30%,
6. Preoperative shock,
7. Severe hepatic dysfunction (bilirubin level > 2 times the upper limit of normal),
8. Known or suspected allergy to dexmedetomidine,
9. Preoperative serum potassium > 5.5 mmol/L,
10. Pregnancy,
11. Body mass index ≥ 35 kg/m²,
12. Documented history of severe psychiatric illness, delirium, or severe dementia confirmed by the patient or family members,
13. Visual, auditory, speech, or other communication impairments that could interfere with assessment.

Anaesthesia and Perioperative Management

After fasting overnight for at least 8 hours, participants continued their usual antihypertensive medications. No routine anaesthetic premedication was administered by the study team before surgery. Upon arrival in the operating room, standard monitoring was established, including non-invasive blood pressure, electrocardiography, body temperature, pulse oxygen saturation (SpO₂), and depth of anaesthesia monitoring using Narcotrend. A peripheral venous line was inserted for intravenous infusion of lactated Ringer's solution.

All patients underwent combined intravenous–inhalational general anaesthesia with endotracheal intubation. Anaesthesia was induced with target-controlled infusion (TCI) of propofol (target plasma concentration, 4 µg/mL), sufentanil (0.3 µg/kg), and cisatracurium (0.2 mg/kg) administered as a single intravenous bolus. Following adequate depth of anaesthesia and neuromuscular blockade, endotracheal intubation was performed. Mechanical ventilation was initiated in volume-controlled mode with a tidal volume of 6–8 mL/kg, respiratory rate of 10–12 breaths per minute, inspiratory-to-expiratory ratio of 1:2, and end-tidal carbon dioxide maintained at 35–45 mmHg. The propofol target concentration was subsequently reduced to 2 µg/mL. A central venous catheter was placed via the internal jugular vein for continuous monitoring of central venous pressure (CVP).

Anaesthesia was maintained with sevoflurane at 0.5–1.0 minimum alveolar concentration (MAC), propofol TCI at 1–2 µg/mL, continuous infusion of remifentanyl (effect-site concentration 3–5 ng/mL), and intermittent administration of cisatracurium to maintain neuromuscular blockade. Anaesthetic depth was titrated to maintain a Narcotrend index between 40 and 60. Anaesthesiologists were permitted to adjust drug dosing according to anaesthetic depth and haemodynamic stability.

Haemodynamic Management

Before reperfusion of the transplanted kidney, blood pressure was maintained within $\pm 20\%$ of baseline values, heart rate was kept above 50 beats per minute, and CVP was gradually increased to 8–12 mmHg. Immediately prior to graft reperfusion, furosemide (100 mg) was administered. Mean arterial pressure (MAP) was maintained at ≥ 80 mmHg using fluid administration and vasoactive agents such as dopamine as required.

Fluid and Transfusion Management

Intraoperative fluid requirements, including maintenance needs and preoperative fasting deficits, were met with lactated Ringer's solution. Human albumin (0.6–1.0 g/kg) was administered to expand intravascular volume, with a target CVP of approximately 10 mmHg at the time of graft reperfusion to facilitate renal perfusion and urine output. In patients without coronary artery disease, red blood cell transfusion was administered when haemoglobin levels decreased below 70 g/L.

Postoperative Management

All patients received a standardized postoperative analgesia regimen consisting of intravenous patient-controlled analgesia (PCA) with hydromorphone (9 mg diluted in 150 mL normal saline), with no background infusion and a bolus dose of 0.15 mg per demand.

At the end of surgery, patients remained intubated and were transferred to the post-anaesthesia care unit (PACU) for monitoring. Tracheal extubation was performed according to standard PACU protocols, after which patients were transferred to a specialized transplant care unit.

Randomisation

After obtaining written informed consent, eligible participants were enrolled by a study investigator and randomly assigned in a 1:1 ratio to the dexmedetomidine (DEX) group or the control (CON) group. Simple randomisation was performed using a computer-generated random number sequence. An independent research assistant who was not involved in participant enrolment, treatment administration, outcome assessment, or data analysis generated the random sequence. Allocation assignments were placed in sequentially numbered, opaque, sealed envelopes and remained concealed until enrolment. After enrolment, the next sequentially numbered envelope was opened, and a separate research assistant prepared the study medication according to the allocation. The anaesthesiologist administered the prepared study medication but remained blinded to group allocation.

After tracheal intubation, participants in the DEX group received dexmedetomidine 0.4 µg/kg diluted in 100 mL of 0.9% normal saline and infused intravenously at 10 mL/min. Participants in the CON group received 100 mL of 0.9% normal saline at the same time and infusion rate.

Preoperative cognitive assessment, delirium assessment and data collection

Before surgery, participants' baseline cognitive status was assessed once using the culturally adapted Chinese version of the original 30-point Mini-Mental State Examination (MMSE) [12, 13]. During the first 5 postoperative days, participants were assessed for postoperative delirium at the bedside every 12 hours. Each assessment began with the Richmond Agitation–Sedation Scale (RASS) [14, 15]. Participants with a RASS score of – 3 or higher were subsequently evaluated using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [16, 17]. For participants with a RASS score of – 4 or – 5, the CAM-ICU assessment was deferred and repeated when the level of arousal permitted assessment. Outcome assessors were blinded to treatment allocation.

In addition to the standardised scale-based assessments, outcome assessors reviewed medical records and obtained unstructured collateral clinical information from participants and their family members regarding possible clinical features of delirium. No separate study-specific interview questionnaire or interview schedule was developed or administered.

The duration of postoperative delirium was recorded for affected participants. Additional data collected included 24-hour urine output on postoperative days 1–5, the occurrence of nausea, vomiting, headache, dizziness, vertigo, hiccups, as well as postoperative sleep quality and oral intake. The incidence of postoperative complications, requirement for temporary bedside dialysis, and length of hospital stay were also documented.

Perioperative variables included the duration of surgery and the occurrence of intraoperative haemodynamic events, specifically bradycardia and hypotension. Postoperative adverse events, including graft rejection, nausea, vomiting, and shivering, were also recorded.

Primary outcome

The primary outcome was the incidence of postoperative delirium (POD) within the first 5 postoperative days.

Secondary outcomes

Secondary outcomes included the duration of postoperative delirium, intraoperative haemodynamic stability, incidence of graft rejection, postoperative renal resistive index (RI), postoperative urine output, and length of hospital stay.

Additional postoperative complications were recorded, including perirenal haematoma, infection, perirenal fluid collection, delayed wound healing, delayed graft function, nausea and vomiting, headache, dizziness, vertigo, hiccups, insomnia, resting visual analogue scale (VAS) pain scores, and time to resumption of oral intake. Intraoperative hypotension was defined as blood pressure more than 20% below the preoperative baseline. Bradycardia was defined as a transient or sustained intraoperative heart rate below 50 beats/min. Delayed graft function was defined as the requirement for dialysis within the first postoperative week.

No changes were made to the prespecified primary or secondary outcomes after trial commencement.

Statistical analysis

The primary outcome was the incidence of postoperative delirium (POD). A pilot study involving 60 patients undergoing allogeneic kidney transplantation at our institution was used to estimate the incidence of POD for sample-size calculation. In the pilot study, POD occurred in 1 of 30 patients (3.33%) in the dexmedetomidine (DEX) group and in 5 of 30 patients (16.67%) in the control (CON) group.

Based on these preliminary data, the sample size was calculated using a two-sided α level of 0.05 and a statistical power of 80%. Calculations performed with PASS software (version 11) indicated that 71 participants were required per group. Assuming a dropout rate of up to 20%, the final sample size was increased to 90 participants per group. Patients without complete delirium assessments were excluded from the primary outcome analysis because standardized delirium evaluation could not be performed after ICU transfer.

Continuous variables were expressed as mean (standard deviation) and categorical variables as counts (percentages). Normality of continuous data was assessed using the Shapiro–Wilk test.

Between-group comparisons of continuous variables, including age, body weight, serum creatinine, duration of delirium, and length of hospital stay, were performed using the independent-samples t-test for normally distributed data. Categorical variables, including sex, comorbidities, American Society of Anesthesiologists (ASA) physical status classification, and incidence of postoperative delirium, were compared using the chi-square test or Fisher's exact test, as appropriate.

Postoperative urine output was analysed using two-way analysis of variance. Post hoc sensitivity analyses were performed by separately excluding participants aged ≥ 65 years and participants with a body mass index ≥ 30 kg/m². In each sensitivity analysis, the incidence of postoperative delirium was compared between groups using the chi-square test or Fisher's exact test, as appropriate, and the duration of postoperative delirium was compared using the independent-samples t-test or Mann-Whitney U test, depending on data distribution. No adjusted analyses were performed. Descriptive analyses and statistical tests were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Effect estimates are reported with two-sided 95% confidence intervals. For binary outcomes, risk ratios or odds ratios were calculated using the log-transformed Wald method, as appropriate. For sparse binary outcomes or outcomes with a zero cell, risk differences and 95% confidence intervals were calculated using the Newcombe method. For continuous outcomes, between-group mean differences and corresponding 95% confidence intervals were calculated using the t distribution. No adjustment was made for multiple secondary comparisons; therefore, secondary outcome findings were considered exploratory. A two-sided P value of < 0.05 was considered statistically significant.

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) for English-language editing and manuscript formatting. The authors reviewed and revised all generated content and take full responsibility for the final manuscript.

This trial was reported in accordance with the CONSORT 2010 guidelines. The CONSORT flow diagram is provided as Fig. 1, and the completed CONSORT 2010 checklist is provided as Additional file 1.

Results

Of the 213 individuals assessed for eligibility, 33 were excluded: 11 had second-degree or higher atrioventricular block, 8 had a resting heart rate below 50 beats/min before surgery, 5 declined to participate, and 9 patients had previously participated in other interventional clinical studies. The remaining 180 participants were randomised in a 1:1 ratio, with 90 participants randomly assigned to the control (CON) group and 90 to the dexmedetomidine (DEX) group, between 2018 and 2021.

In the DEX group, two participants were transferred to the ICU postoperatively and did not complete the scheduled delirium assessments. In the CON group, one participant died from an acute postoperative myocardial infarction and three were transferred to the ICU; these four participants did not complete the scheduled delirium assessments. Consequently, 88 participants in the DEX group and 86 in the CON group were included in the primary complete-case analysis. The participant flow is shown in Fig. 1.

Baseline demographic and clinical characteristics, including donor source, are presented in Table 1.

Table 1
Baseline demographic and clinical characteristics of the study participants

Characteristic	CON group (n = 86)	DEX group (n = 88)
Sex, male/female, n	63/23	64/24
Age, years	44 ± 12	43 ± 12
Body weight, kg	61 ± 11	63 ± 11
Body mass index, kg/m ²	22 ± 3	23 ± 3
Education, years	12 ± 4	14 ± 3
Comorbidities, n (%)		
Coronary heart disease	4 (4.6)	5 (5.7)
Previous cerebral infarction	1 (1.2)	1 (1.1)
Diabetes mellitus	12 (14.0)	20 (22.7)
Charlson Comorbidity Index, points	2.8 ± 1.3	3.0 ± 1.4
MMSE score, points	27.6 ± 1.1	28.0 ± 1.2
NYHA functional class, n (%)		
I	73 (84.9)	75 (85.2)
II	11 (12.8)	13 (14.8)
III	2 (2.3)	0 (0.0)
ASA physical status, n (%)		
III	71 (82.6)	79 (89.8)
IV	15 (17.4)	9 (10.2)
History of sedative-hypnotic or antipsychotic medication use, n (%)		
Alprazolam	2 (2.3)	1 (1.1)
Estazolam	2 (2.3)	2 (2.3)
Diazepam	0 (0.0)	2 (2.3)
Zopiclone	1 (1.2)	0 (0.0)
Haemoglobin, g/L	115 ± 20	112 ± 20
Preoperative serum creatinine, µmol/L	946 ± 319	958 ± 276
Blood urea nitrogen, mmol/L	22 ± 9	22 ± 8

Characteristic	CON group (n = 86)	DEX group (n = 88)
Dialysis modality, n (%)		
None	7 (8.1)	9 (10.2)
Haemodialysis	63 (73.3)	65 (73.9)
Peritoneal dialysis	16 (18.6)	14 (15.9)
Donor source, n (%)		
Living donor	6 (7.0)	13 (14.8)
Deceased donor	80 (93.0)	75 (85.2)

Data are presented as mean $\pm$ standard deviation or n (%), unless otherwise indicated.

ASA, American Society of Anesthesiologists; CON, control; DEX, dexmedetomidine; MMSE, Mini-Mental State Examination; NYHA, New York Heart Association.

Primary outcome

POD occurred in 4 of 88 participants (4.5%) in the DEX group and 13 of 86 participants (15.1%) in the CON group (risk ratio, 0.30; 95% CI, 0.10–0.89; $P = 0.019$). There was no significant difference between the groups in the duration of POD (1.5 ± 0.6 days vs 1.3 ± 0.5 days; $P = 0.512$).

After excluding the four participants aged ≥ 65 years (two in each group), POD occurred in 3 of 86 participants (3.5%) in the DEX group and 12 of 84 participants (14.3%) in the CON group (OR, 0.22; 95% CI, 0.06–0.80; $P = 0.013$). There was no significant between-group difference in the duration of POD (1.3 ± 0.6 days vs 1.3 ± 0.5 days; $P = 1.000$).

After excluding the five participants with obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), POD occurred in 4 of 85 participants (4.7%) in the DEX group and 13 of 84 participants (15.5%) in the CON group (OR, 0.27; 95% CI, 0.08–0.87; $P = 0.015$). There was no significant between-group difference in the duration of POD (1.5 ± 0.6 days vs 1.3 ± 0.5 days; $P = 0.512$).

Sensitivity analyses excluding elderly and obese patients yielded consistent results.

Secondary outcomes

Acute graft rejection occurred in none of the 88 patients in the DEX group and in 7 of the 86 patients in the CON group (0.0% vs 8.1%). The absolute risk difference was -8.1 percentage points (95% CI, -15.9 to -2.3 ; Fisher's exact $P = 0.006$). Because acute graft rejection was a secondary outcome with a small number of events, this finding should be interpreted as exploratory.

Two-way analysis of variance showed a significant main effect of time on postoperative urine output in kidney transplant recipients ($F = 4.62$, $P = 0.001$), indicating that urine output decreased over time. There was no significant main effect of dexmedetomidine on postoperative urine output ($F = 0.27$, $P = 0.60$), and no significant interaction between time and dexmedetomidine was observed ($F = 0.37$, $P = 0.83$).

There was no significant difference between the groups in the incidence of intraoperative hypotension (29.5% [26/88] vs 31.4% [27/86]; odds ratio [OR] 0.91, 95% CI 0.48–1.72; $P = 0.791$).

Similarly, no significant difference was observed in the incidence of intraoperative bradycardia (21.6% [19/88] vs 20.9% [18/86]; OR 1.04, 95% CI 0.50–2.16; $P = 0.915$).

A range of postoperative adverse events and complications were observed, including nausea, vomiting, dizziness, pain, infection, graft rejection, perirenal hemorrhage, delayed graft function, and poor wound healing.

Except for graft rejection, there were no significant differences between the groups in the incidence of postoperative complications (all $P > 0.05$).

There was no significant difference in the length of hospital stay between the CON and DEX groups (26 ± 12 vs 25 ± 12 days; $P = 0.573$).

After excluding patients with postoperative complications that could prolong hospitalization (e.g., delayed graft function or other surgical complications), sensitivity analysis showed that the length of hospital stay remained comparable between the groups ($P = 0.320$), indicating the robustness of the findings. The primary, secondary, and sensitivity outcomes are summarized in Table 2.

Table 2
Primary, secondary, and sensitivity outcomes

Outcome	CON group	DEX group	Effect estimate (95% CI)	P value
Primary outcome				
Postoperative delirium within 5 postoperative days	13/86 (15.1%)	4/88 (4.5%)	RR 0.30 (0.10 to 0.89)	0.019
Key secondary outcomes				
Duration of postoperative delirium, days	1.3 ± 0.5	1.5 ± 0.6	Mean difference 0.20 days (– 0.44 to 0.84)	0.512
Acute graft rejection	7/86 (8.1%)	0/88 (0.0%)	Risk difference – 8.1 percentage points (– 15.9 to – 2.3)	0.006
Length of hospital stay, days	26 ± 12	25 ± 12	Mean difference – 1.0 days (– 4.6 to 2.6)	0.573
Postoperative urine output, postoperative days 1–5	—	—	Treatment effect: F = 0.27; time×treatment: F = 0.37	0.600
Sensitivity analyses				
POD after excluding participants aged ≥ 65 years	12/84 (14.3%)	3/86 (3.5%)	OR 0.22 (0.06 to 0.80)	0.013
POD after excluding participants with BMI ≥ 30 kg/m ²	13/84 (15.5%)	4/85 (4.7%)	OR 0.27 (0.08 to 0.87)	0.015

Data are presented as n/N (%), mean ± standard deviation, or effect estimate (95% confidence interval). Effect estimates were calculated for the DEX group relative to the CON group.

The duration of postoperative delirium was calculated among participants who developed delirium (CON, n = 13; DEX, n = 4).

For postoperative urine output, the P value represents the overall treatment effect. The time effect was significant (F = 4.62, P = 0.001), whereas the time-by-treatment interaction was not significant (F = 0.37, P = 0.830).

BMI, body mass index; CI, confidence interval; CON, control; DEX, dexmedetomidine; OR, odds ratio; POD, postoperative delirium; RR, risk ratio.

The denominators differ across sensitivity analyses because participants aged ≥ 65 years and those with BMI ≥ 30 kg/m² were excluded separately. Four participants aged ≥ 65 years were excluded (two from each group), and five participants with BMI ≥ 30 kg/m² were excluded (two from the CON group and three from the DEX group).

Safety outcomes

Two patients in the DEX group required postoperative admission to the intensive care unit (ICU) for further management. In the CON group, one participant died following postoperative acute myocardial infarction. This death was included in the safety analysis, but the participant was excluded from the primary complete-case analysis because scheduled postoperative delirium assessments could not be completed. Adverse events and safety outcomes are summarized in Table 3. There were no statistically significant between-group differences in intraoperative hypotension, intraoperative bradycardia, postoperative ICU admission, or death.

Table 3
Adverse events and safety outcomes

Outcome	CON group	DEX group	Effect estimate (95% CI)	P value
Intraoperative haemodynamic events				
Intraoperative hypotension	27/86 (31.4%)	26/88 (29.5%)	OR 0.92 (0.48 to 1.75)	0.791
Intraoperative bradycardia	18/86 (20.9%)	19/88 (21.6%)	OR 1.04 (0.50 to 2.15)	0.915
Postoperative complications and adverse events				
Perirenal haematoma	4/86 (4.7%)	1/88 (1.1%)	RD - 3.5 pp (- 10.3 to 2.2)	0.208
Infection	1/86 (1.2%)	1/88 (1.1%)	RD - 0.0 pp (- 5.2 to 5.1)	1.000
Perirenal fluid collection	2/86 (2.3%)	1/88 (1.1%)	RD - 1.2 pp (- 7.0 to 4.1)	0.618
Delayed wound healing	2/86 (2.3%)	1/88 (1.1%)	RD - 1.2 pp (- 7.0 to 4.1)	0.618
Acute graft rejection	7/86 (8.1%)	0/88 (0.0%)	RD - 8.1 pp (- 15.9 to - 2.3)	0.006
Postoperative cerebral infarction	0/86 (0.0%)	1/88 (1.1%)	RD 1.1 pp (- 3.2 to 6.2)	1.000
Delayed graft function	12/86 (14.0%)	8/88 (9.1%)	OR 0.62 (0.24 to 1.59)	0.315
Nausea and vomiting	30/86 (34.9%)	25/88 (28.4%)	OR 0.74 (0.39 to 1.41)	0.358
Headache	12/86 (14.0%)	8/88 (9.1%)	OR 0.62 (0.24 to 1.59)	0.315
Dizziness	25/86 (29.1%)	17/88 (19.3%)	OR 0.58 (0.29 to 1.18)	0.133
Vertigo	5/86 (5.8%)	3/88 (3.4%)	OR 0.57 (0.13 to 2.47)	0.494
Hiccups	10/86 (11.6%)	10/88 (11.4%)	OR 0.97 (0.38 to 2.47)	0.956
Insomnia	18/86 (20.9%)	19/88 (21.6%)	OR 1.04 (0.50 to 2.15)	0.915
Serious postoperative events				
Postoperative ICU admission	3/90 (3.3%)	2/90 (2.2%)	RD - 1.1 pp (- 7.3 to 4.8)	1.000

Outcome	CON group	DEX group	Effect estimate (95% CI)	P value
Intraoperative haemodynamic events				
Postoperative death	1/90 (1.1%)	0/90 (0.0%)	RD – 1.1 pp (– 6.0 to 3.1)	1.000

Data are presented as n/N (%). Effect estimates compare the DEX group with the CON group.

ORs are reported for outcomes with sufficient events. For sparse outcomes (≤ 5 total events) or outcomes with a zero cell, risk differences (RDs) are reported in percentage points (pp), with 95% confidence intervals calculated using the Newcombe method.

P values were calculated using Pearson's chi-square test or Fisher's exact test, as appropriate.

Intraoperative hypotension was defined as blood pressure $> 20\%$ below the preoperative baseline. Bradycardia was defined as a transient or sustained intraoperative heart rate < 50 beats/min. Delayed graft function was defined as a requirement for dialysis within the first postoperative week.

All outcomes except postoperative ICU admission and death are reported for the primary complete-case population (CON, $n = 86$; DEX, $n = 88$). ICU admission and death are reported for all randomised participants ($n = 90$ per group). The death in the CON group was caused by postoperative acute myocardial infarction.

CI, confidence interval; CON, control; DEX, dexmedetomidine; ICU, intensive care unit; OR, odds ratio; RD, risk difference.

Discussion

In this prospective, randomised, double-blind trial, intraoperative administration of dexmedetomidine significantly reduced the incidence of postoperative delirium (POD) in kidney transplant recipients. Compared with the control group, the incidence of POD decreased from 15.1% to 4.5% in patients receiving dexmedetomidine, representing an approximately 70% relative risk reduction and suggesting a potential perioperative neuroprotective effect of dexmedetomidine in this high-risk population. In addition, no acute graft rejection events occurred in the DEX group, whereas seven occurred in the CON group. Because acute graft rejection was a secondary outcome with few events, this finding should be considered exploratory, whereas no significant differences were found in postoperative urine output, length of hospital stay, or other common postoperative complications. Importantly, dexmedetomidine administration was not associated with an increased incidence of intraoperative hypotension or bradycardia, supporting the safety of the dosing regimen used in the present study.

The incidence of postoperative delirium in the control group was consistent with previous reports involving kidney and other solid-organ transplant recipients[2–4]. Patients with ESRD are exposed to

uremic toxin accumulation and CKD-related cognitive impairment, which may reduce cerebral reserve and increase vulnerability to perioperative stressors [18, 19]. Consequently, kidney transplant recipients represent a population at particularly high risk of POD, in whom delirium may result from the interaction between pre-existing neurological vulnerability and acute perioperative insults [2–4].

Our findings are broadly consistent with previous randomised and meta-analytic evidence in older patients undergoing non-cardiac surgery [8, 20]. However, evidence regarding the efficacy of dexmedetomidine for postoperative delirium prevention remains heterogeneous [10, 11, 20]. Differences in patient characteristics, timing of administration, dosing strategies, and delirium assessment tools may partially explain the variability among studies [21]. Unlike previous investigations, the present study focused specifically on kidney transplant recipients, a population with a particularly high baseline risk of delirium.

Older age is an established risk factor for postoperative delirium. However, only four participants aged ≥ 65 years were included in the present study, with two participants in each treatment group. Among these four participants, one participant in each group developed POD. After excluding these four participants, the incidence of POD remained lower in the DEX group than in the CON group. In addition, five participants had a BMI ≥ 30 kg/m², and none developed POD. After excluding these participants, the between-group difference in POD incidence also remained statistically significant. These post hoc sensitivity analyses yielded results consistent with the primary analysis, suggesting that the observed association was unlikely to be explained solely by the small number of older or obese participants. Nevertheless, because these analyses were post hoc and included very few older and obese participants, residual confounding cannot be excluded. In addition, donor characteristics may influence graft recovery and perioperative inflammatory burden. However, donor type was comparable between groups, reducing the likelihood that donor-related factors confounded the observed findings.

The mechanisms through which dexmedetomidine reduces postoperative delirium are likely various. As a highly selective α_2 -adrenoceptor agonist, dexmedetomidine produces a sedative state resembling physiological non-rapid eye movement sleep through activation of the locus coeruleus, thereby improving perioperative sleep architecture and preserving circadian rhythm [22, 23]. Furthermore, dexmedetomidine attenuates sympathetic nervous system activation and perioperative stress responses, reducing neuroendocrine activation and cerebral metabolic demand.

Accumulating evidence suggests that neuroinflammation plays a central role in the development of postoperative delirium. In kidney transplantation, surgical trauma, ischemia–reperfusion injury, and perioperative immunomodulatory therapies may collectively trigger systemic inflammatory responses [24]. These processes can disrupt blood–brain barrier integrity, activate microglia, and promote the release of pro-inflammatory cytokines, thereby contributing to delirium development. Experimental studies suggest that dexmedetomidine may exert anti-inflammatory effects through inhibition of NF- κ B signalling and suppression of pro-inflammatory mediators [25, 26]. These mechanisms may partially

explain the reduced incidence of postoperative delirium observed in our study. However, because inflammatory biomarkers were not measured, this hypothesis remains speculative.

Although dexmedetomidine significantly reduced the incidence of postoperative delirium, it did not shorten delirium duration among affected patients. This observation suggests that dexmedetomidine may primarily influence the initiation of delirium-related pathophysiological processes, thereby reducing the likelihood of postoperative delirium occurrence. Once delirium develops, however, its clinical course may be determined by multiple factors, including baseline comorbidities, postoperative complications, and subsequent therapeutic interventions, potentially limiting the impact of dexmedetomidine on delirium duration.

Another noteworthy finding of the present study was the significantly lower incidence of acute graft rejection in the dexmedetomidine group. The mechanism underlying the reduced incidence of acute rejection remains uncertain. A retrospective propensity-adjusted cohort study previously reported an association between perioperative dexmedetomidine administration and lower risks of delayed graft function and acute rejection after kidney transplantation [27]. Experimental evidence suggests that dexmedetomidine may attenuate renal ischemia–reperfusion injury through α_2 -adrenoceptor-mediated activation of the PI3K/Akt-eNOS signalling pathway [28]. These observations provide biological plausibility for the association observed in our study. Nevertheless, acute rejection after kidney transplantation is influenced by numerous factors, including donor and recipient characteristics, HLA matching, immunosuppressive regimens, infectious complications, and delayed graft function. Acute graft rejection was a secondary outcome, and the trial was not powered to evaluate this endpoint. Only seven rejection events were observed, and no adjustment was made for multiple secondary comparisons. Therefore, this finding should be considered exploratory and hypothesis-generating rather than definitive evidence that dexmedetomidine prevents acute graft rejection.

In contrast, no significant effect on postoperative urine output was observed. Two-way analysis of variance demonstrated that postoperative urine output was primarily influenced by time, whereas neither the main effect of dexmedetomidine nor the interaction between dexmedetomidine and time reached statistical significance. Although experimental studies have suggested that dexmedetomidine may improve renal perfusion and attenuate ischemia–reperfusion injury, our findings did not demonstrate a measurable effect on early postoperative urine output [28, 29]. The routine administration of high-dose furosemide during transplantation and perioperative fluid management strategies may have masked potential renal effects of dexmedetomidine.

Bradycardia and hypotension remain important concerns during clinical use of dexmedetomidine, particularly when high loading doses or prolonged infusions are employed. In the present study, a single intravenous dose of $0.4 \mu\text{g}\cdot\text{kg}^{-1}$ was administered, and no significant differences in the incidence of hypotension or bradycardia were observed between groups [8, 20]. These findings suggest that the dosing strategy used in this study may provide potential neuroprotective benefits without increasing clinically significant haemodynamic adverse events.

Several limitations should be acknowledged. First, this was a single-centre study, which may limit the generalizability of our findings. Second, the sample size calculation was based on the primary outcome, and the study may have been underpowered to detect differences in relatively infrequent outcomes such as acute rejection. Third, delirium assessment was limited to the first five postoperative days, and long-term cognitive outcomes were not evaluated. Finally, inflammatory and neuronal injury biomarkers were not measured, preventing direct investigation of the mechanisms underlying the observed clinical effects.

Conclusions

Intraoperative dexmedetomidine was associated with a lower incidence of postoperative delirium within 5 days after kidney transplantation, without an observed increase in intraoperative hypotension or bradycardia. Dexmedetomidine use was also associated with a lower incidence of acute graft rejection.

Abbreviations

ASA	American Society of Anesthesiologists
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CON	control
CVP	central venous pressure
DEX	dexmedetomidine
DGF	delayed graft function
ESRD	end-stage renal disease
ICU	intensive care unit
MAC	minimum alveolar concentration
MAP	mean arterial pressure
MMSE	Mini-Mental State Examination
PACU	post-anaesthesia care unit
POD	

postoperative delirium
RASS
Richmond Agitation–Sedation Scale
RI
resistive index
TCI
target-controlled infusion
VAS
visual analogue scale.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of The First Affiliated Hospital, Sun Yat-sen University (approval number: [2015] No. 17). Written informed consent was obtained from all participants before enrolment. All methods were performed in accordance with the Declaration of Helsinki and relevant guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

HW and QW contributed equally to this work. HW collected the data, performed the statistical analyses, interpreted the results, and drafted the manuscript. QW performed the statistical analyses, interpreted the results, and critically revised the manuscript. WX, HX, and XS contributed to participant recruitment, perioperative management, and data collection. JY contributed to the study design, supervised the implementation of the trial, and critically reviewed the manuscript. TZ conceived and designed the study, supervised the overall conduct of the trial, interpreted the results, and critically revised the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Data Availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request, subject to institutional and ethical requirements for the protection of participant confidentiality.

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Figures

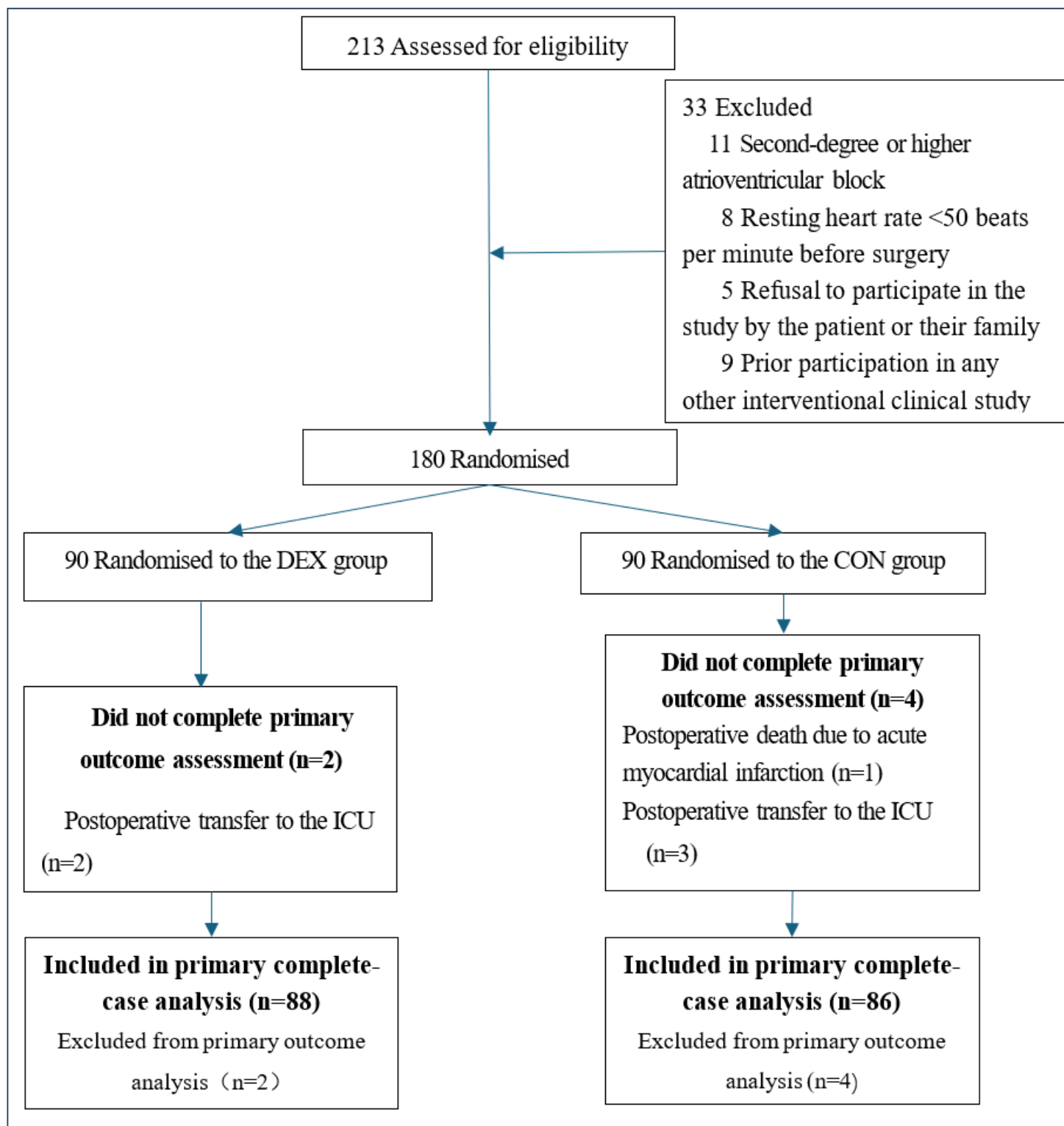


Figure 1

CONSORT flow diagram of participant enrolment, allocation, follow-up, and analysis.

DEX, dexmedetomidine; CON, control; ICU, intensive care unit.

Supplementary Files

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