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ARTICLE

Perioperative Dexmedetomidine Improves Outcomes of Kidney Transplant

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Graft function is crucial for successful kidney transplantation. Many factors may affect graft function or cause delayed graft function (DGF), which decreases the prognosis for graft survival. This study was designed to evaluate whether the perioperative use of dexmedetomidine (Dex) could improve the incidence of function of graft kidney and complications after kidney transplantation. A total of 780 patients underwent kidney transplantations, 315 received intravenous Dex infusion during surgery, and 465 did not. Data were adjusted with propensity scores and multivariate logistic regression was used. The primary outcomes are major adverse complications, including DGF and acute rejection in the early post-transplantation phase. The secondary outcomes included length of hospital stay (LOS), infection, overall complication, graft functional status, post-transplantation serum creatinine values, and estimated glomerular filtration rate (eGFR). Dex use significantly decreased DGF (19.37% vs. 23.66%; adjusted odds ratio, 0.744; 95% confidence interval, 0.564–0.981; $P = 0.036$), risk of infection, risk of acute rejection in the early post-transplantation phase, the risk of overall complications, and LOS. However, there were no statistical differences in 90-day graft functional status or 7-day, 30-day, and 90-day eGFR. Perioperative Dex use reduced incidence of DGF, risk of infection, risk of acute rejection, overall complications, and LOS in patients who underwent kidney transplantation.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Graft function is crucial for successful kidney transplantation. Dexmedetomidine (Dex) has been shown to have renal protective effect in preclinical and other surgeries.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ The objective of this study was to evaluate whether the perioperative Dex administration was associated with improved graft kidney function or decreased complications after kidney transplantation.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ This study demonstrated that perioperative Dex administration was associated with improved kidney function and outcomes in patients who underwent kidney transplantation.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ The results from this study suggest perioperative Dex administration could be beneficial to donor kidney grafts.

The cost to care for patients with chronic kidney disease and endstage renal disease (ESRD) is significant with total spending over US $120 billion for Medicare beneficiaries alone representing 33.8% of total Medicare fee-for-service spending according to the United States Renal Data System 2019 annual data report.[1] There were nearly 500,000 patients receiving maintenance dialysis treatments and well over 200,000 living with a kidney transplant in the United States by the end of 2015.[2] Thus, ESRD is a major public health problem due to its high morbidity and mortality as well as social and financial implications.[3] Treatment outcomes vary depending on different modalities like hemodialysis, peritoneal dialysis, and renal transplantation. Renal transplantation has an obvious survival advantage over dialysis treatments for patients with ESRD along with better quality of life.[4–6] However, the 5-year graft survival rate was 74.4% in deceased-donor transplants and 85.6% in living-donor transplants.[7] The etiology of graft kidney dysfunction is multifactorial and involves immunologic factors, surgical techniques, hemodynamic alterations, inflammatory mechanisms, apoptosis, and ischemia/reperfusion (I/R) injury.[8] Although advances in immunosuppressive therapy and treatment of hypertension and hyperlipidemia have improved outcomes following kidney transplantation, poor initial graft function occurs in up to 5% of living donor recipients and up to 20% of deceased donor recipients. Infection occurs in up to 30% of renal transplant recipients during the first 3 months post-transplantation.[9,10]

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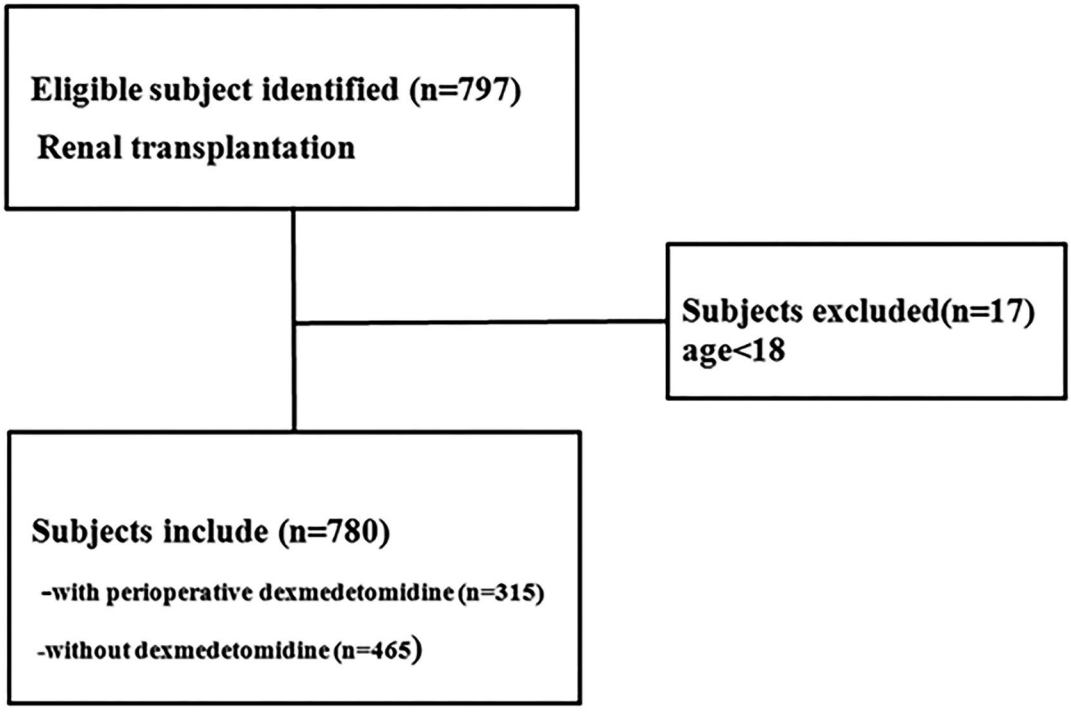

Figure 1 Study population recruitment summary.

The transplant population has expanded to older and sicker patients, and only about 7.3% candidates on the US kidney transplant waiting list received deceased donor kidney transplantations.[11] Approximately 15% of procured kidneys were discarded despite long waiting lists.[11] At the same time, graft rejection episodes occur in about 20% of low-risk transplant recipients within the first 26 weeks post-transplantation.[9] The probability of first-year all-cause graft failure (return to dialysis, repeat transplantation, or death with a functioning transplant) for deceased donor kidney transplant recipients was about 7.7%.[3,12,13] It is important to identify factors responsible for decreased graft function and find appropriate interventions.

It is well known that renal function is closely associated with hemodynamic performance, sympathetic activity, inflammatory responses, and I/R injury. The hemodynamic stabilizing and sympatholytic effects produced by alpha$_2$ agonists have been shown to prevent the deterioration of renal function after cardiac surgery.[12,14,15] The mechanisms could be inhibition of renin release, increased glomerular filtration, and increased excretion of sodium and water via the kidneys.[16] Dexmedetomidine (Dex) is a short-acting selective alpha$_2$ agonist in comparison to clonidine and has an alpha$_2$ to alpha$_1$ selectivity ratio of 1,600:1.[17] Dex has a stabilizing effect on hemodynamics mediated by reducing sympathetic tone, decreasing inflammatory response, alleviating I/R injury, inhibiting renin release, increasing glomerular filtration rate, increasing secretion of sodium and water by the kidneys, and decreasing insulin secretion.[18,19] Although Dex has been shown to alleviate acute kidney injury (AKI) in other surgeries,[14,15] no study has demonstrated the benefit of Dex on graft function in renal transplantation. Thus, this study was designed to determine whether the perioperative use of Dex is associated with improved graft kidney function and decreased incidence of complications after renal transplantation.

PATIENTS AND METHODS

Study design

This study was approved by University of California Davis Institutional Review Board (IRB 521455). This was a single-center, retrospective cohort study of 797 consecutive patients undergoing renal transplantation at a university medical center from January 1, 2012, to July 22, 2014. Due to the nature of the study, written consent was waived. Patients younger than 18 years old were excluded from this study (**Figure 1**). Patients were categorized into two groups, those who received Dex (Dex group; n = 315; 40.38%) and those who did not receive Dex (No-Dex group; n = 465; 59.62%) during the perioperative period for kidney transplantation and included kidney-alone and kidney plus pancreas transplants. Of kidney transplants, 123 kidneys were from living donors, 511 from deceased donors, 135 from pediatric en-block donors, and 11 kidney + pancreas donors (**Table 1**). Patients received standard immunosuppression therapy used in this institute (see **Supplemental Material S1**).

Data collection

Patient data were collected from the institutional renal transplantation database and hospital medical records and included demographics, patient history, medical record information, and pretransplantation risk factors: etiology of ESRD, comorbidity, presence, length and mode of dialysis therapy prior to transplantation, number of human leukocyte antigen (HLA) mismatches, ABO blood type of

Table 1 Demographic and clinical characteristics

Characteristics	Dexmedetomidine Yes (*N* = 315)	Dexmedetomidine No (*N* = 465)	*P* value
Recipient factors			
Age, mean (SD)	51.9 (13.6)	52.5 (13.3)	0.548
Sex, *n* (%) female	121 (38.4)	147 (31.6)	0.050
BMI, mean (SD)	27.6 (4.6)	27.4 (4.7)	0.523
Race *n* (%)			
White	107 (34.0)	167 (35.9)	0.516
Black	40 (12.7)	37 (8.0)	0.021
Other	168 (53.3)	261 (56.1)	0.477
Primary cause of ESRD *n* (%)			
Diabetes	86 (27.30)	136 (29.3)	0.555
GMN	59 (18.7)	107 (23.0)	0.152
HTN	26 (8.3)	29 (6.24)	0.280
PKD	34 (10.8)	49 (10.5)	0.978
Other	111 (35.2)	142 (30.5)	0.169
Comorbid disease *n* (%)			
CAD	44 (14.0)	69 (14.8)	0.735
HTN	305 (96.8)	455 (97.9)	0.375
PVD	3 (1.0)	10 (2.2)	0.200
CVD	9 (2.9)	18 (3.9)	0.365
Diabetes	118 (37.5)	169 (36.3)	0.751
Malignancy	20 (6.4)	41 (8.8)	0.208
Prior kidney transplant *n* (%)	22 (7.0)	37 (8.0)	0.614
Dialysis prior to transplants *n* (%)	226 (71.8)	345 (74.2)	0.449
Hemodialysis prior to transplant *n* (%)	185 (58.7)	289 (62.2)	0.337
Type of dialysis prior to transplant *n* (%)			
No	40 (12.7)	58 (12.5)	0.970
Hemodialysis	185 (58.7)	291 (62.6)	0.521
Peritoneal dialysis	90 (28.6)	116 (25.0)	0.232
ABO blood of recipient *n* (%)			
A	115 (36.5)	164 (35.1)	0.677
B	34 (10.2)	70 (15.5)	0.032
AB	15 (4.8)	22 (4.7)	0.873
O	151 (48.6)	209 (45.2)	0.349
CMV *n* (%)	233 (74.0)	340 (73.1)	0.792
HCV *n* (%)	9 (2.9)	14 (3.0)	0.901
Length of dialysis prior to transplants (month), mean (SD)	34.7 (28.1)	35.3 (28.3)	0.785
PRA > 10% *n* (%)	112 (35.6)	133 (28.6)	0.040
Most recent PRA value, mean (SD)	19.9 (32.2)	15.5 (28.0)	0.048
HLA mismatches, mean (SD)	4.2 (1.5)	4.1 (1.6)	0.733
CIT, hour, mean (SD)	25.9 (14.6)	25.0 (15.4)	0.394
WIT, minute, mean (SD)	46.9 (11.6)	46.1 (11.1)	0.355
Pulsatile pump preservation *n* (%)	238 (75.6)	339 (72.9)	0.408
Prednisone on discharge *n* (%)	69 (22.0)	85 (18.3)	0.212
Donor factors			
Age, years, mean (SD)	32.3 (20.1)	31.7 (19.6)	0.655
Sex *n* (%) female	139 (44.1)	207 (44.5)	0.915
Race *n* (%)			
White	201 (63.8)	298 (64.1)	0.937
Black	34 (10.8)	44 (9.5)	0.543
Other	80 (25.4)	124 (26.7)	0.692
Modality of transplant *n* (%)			
DCD	213 (67.6)	306 (65.8)	0.599
Pediatric en bloc	54 (17.1)	80 (17.2)	0.982
Living	46 (14.6)	77 (16.6)	0.462
Kidney-pancreas	6 (1.3)	4 (1.3)	0.980
CMV status *n* (%)	190 (60.3)	279 (60.0)	0.929
HCV status *n* (%)	3 (1.0)	5 (1.1)	0.867
HBsAg status *n* (%)	18 (5.7)	22 (4.7)	0.541
Terminal SCr, mg, mean (SD)	1.30 (1.3)	1.31 (1.3)	0.733
Propensity score	0.411 (0.059)	0.398 (0.053)	0.002

BMI, body mass index; CAD, coronary artery disease; CIT, cold ischemic time; CMV, cytomegalovirus; CVD, cerebral vascular disease; DCD, deceased donor; ESRD, endstage renal disease; GMN, glomerulonephritis; HBsAg, hepatitis B virus; HCV, hepatitis C virus; HLA, human leukocyte antigen; HTN, hypertension; PKD, polycystic kidney disease; PRA, panel reactive antibodies; PVD, peripheral vascular disease; SCr, serum creatinine; WIT, warm ischemia time.

recipient, cold ischemia time (CIT), warm ischemia time (WIT), panel reactive antibodies (PRAs) > 10%, most recent PRA (prior to transplantation), presence of anti-hepatitis C virus (HCV), and anti-cytomegalovirus (CMV) antibodies in recipient/donor plasma, terminal serum creatinine (SCr) of donor, type of transplant, post-transplantation SCr, and estimated glomerular filtration rate (eGFR) data. Data on each patient was entered during the course of the hospitalization and follow-up.

All patients received standard acetylsalicylic acid monitoring: electrocardiogram, pulse oximeter, noninvasive blood pressure, and temperature. General anesthesia was induced with propofol or etomidate and maintained with sevoflurane. Ventilation was maintained to an end-tidal CO_2 of 35–45 mmHg by adjustment of tidal volume and respiratory rate. As standard practice at this institution, all patients received 2,000–3,000 mL of crystalloid solution during surgery. Dex is a frequently administered anesthesia adjuvant at this institution. Attending anesthesiologists assigned to the cases were responsible for making decisions regarding use of Dex during anesthesia care according to his/her judgment. Perioperative Dex use was defined as an intravenous infusion (0.24–0.6 μg/kg/hour) initiated after induction of anesthesia and discontinued at the end of surgery. The infusion rate of Dex was adjusted according to the patients' hemodynamic status within this range. Some patients received small doses of phenylephrine or ephedrine to maintain the mean blood pressure between 70 and 90 mmHg.

Primary and secondary outcomes

The primary outcomes of this study were the incidence of delayed graft function (DGF), and acute rejection in the

early post-transplantation. DGF was defined as the need for dialysis in the 7 days after transplantation.[7] Secondary outcomes included length of hospital stay (LOS), infection, overall complications (including graft thrombosis, peri-graft hematoma, bleeding, primary no function (PNF), renal artery stenosis, and urinary complications, including stenosis, obstruction, and leak), post-transplantation 7-day, 30-day, and 90-day SCr and eGFR calculated according to the modification of diet in renal disease formula eGFR = $175*(SCr)^{-1.154}*(age)^{-0.203}*0.742$ (if female recipient) *1.212 (if African American) (mL/minute *1.73 m^2),[20] and 90 days post-transplantation graft functional status.

Complications were extracted from the transplant data base with diagnoses reached following accepted guidelines and definitions.[21] Rejection was strongly suspected in a post-transplant patient with fever, graft tenderness, or reduced urine output after ruling out other potential causes of graft dysfunction, such as ureteral obstruction or graft thrombosis. According to the Banff criteria, the gold standard to diagnose rejection is transplant kidney biopsy.[22] An infectious episode was defined as the association of compatible clinical signs, symptoms such as fever (> 38.0°C), laboratory tests, and a microbiological pathogen recovered from a normally sterile body site, and the introduction of an antimicrobial regimen directed against the incriminated microorganism. The diagnosis of urinary tract, blood stream, pneumonia, or surgical site infections were made according the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) surveillance definitions.[23] Graft thrombosis was diagnosed by Doppler or technetium scan and confirmed by computed tomography scan. Perigraft hematoma was diagnosed by abdominal ultrasound.[21] Graft functional status 90 days after transplant was defined as patients who did not require dialysis 90 days post-transplantation.

Statistical analysis

We compared patient baseline characteristics between Dex use and control (no Dex use) groups. Continuous and categorical variables were reported as mean ± SD or percentages and compared with a two-sample *t* tests or a χ^2 test (two-tailed), respectively, for univariate and multivariate clinical outcome variables. To mitigate selection bias in Dex use, we used the propensity score, that is, the conditional probability of each patient receiving Dex with a multivariable logistic regression model that includes patient demographic and clinical risk factors (**Table 1**). The parsimonious multivariable propensity model for Dex use included age, sex, race, body mass index, etiology of ESRD, number of HLA mismatches, recipient ABO blood type, CIT, WIT, PRA > 10%, dialysis prior to transplantation, length of dialysis therapy before transplantation, and presence of anti-HCV antibodies and anti-CMV antibodies in recipient plasma. To achieve model parsimony and stability, the backward selection procedure was applied with a dropout criterion of $P > 0.05$ (**Figure 2**). A propensity

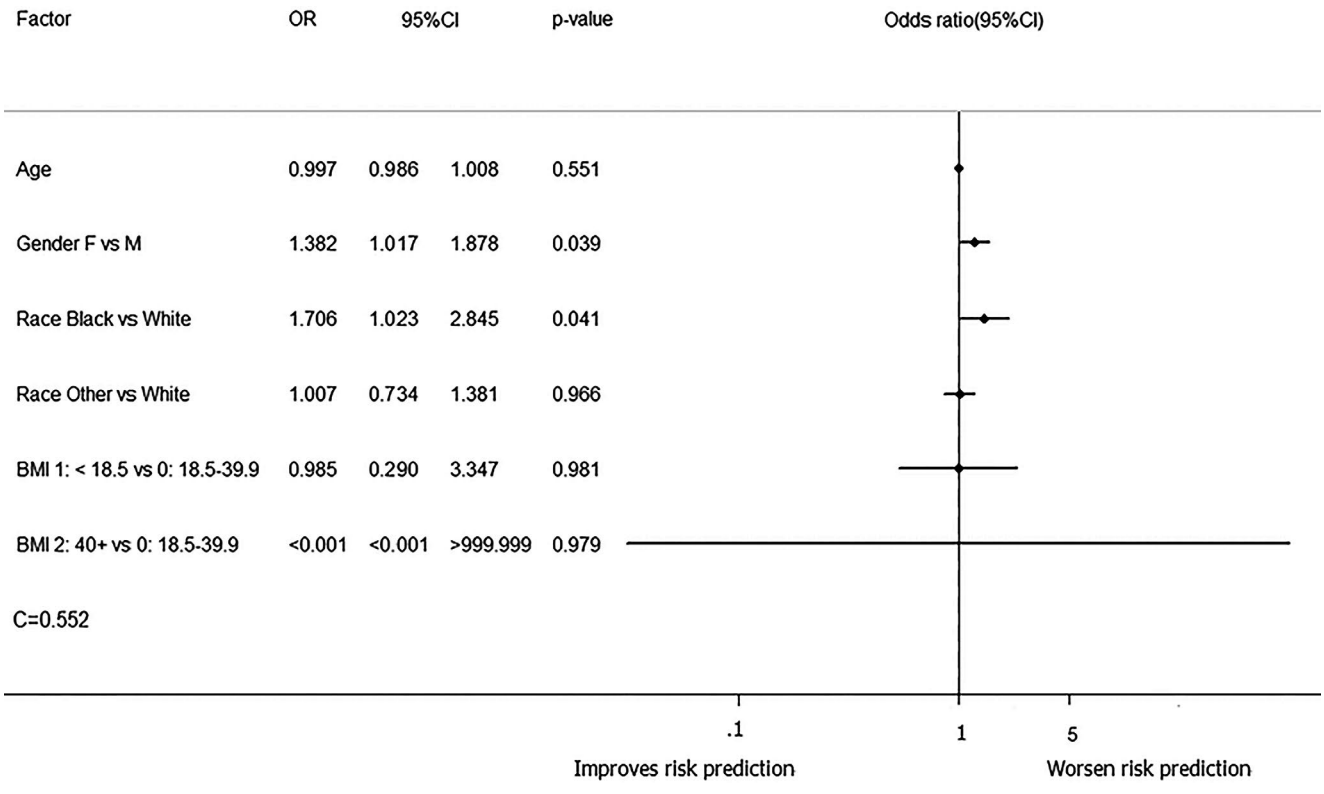

Figure 2 Parsimonious multivariable propensity model for dexmedetomidine use. BMI, body mass index; CI, confidence interval; OR, odds ratio.

weighted multivariable logistic regression model was used for risk adjustment for post-transplantation complications using inverse (estimated) propensity score weights for patients with Dex and the inverse of 1 minus the propensity score for patients without Dex. The model included patient preoperative risk factors and use of Dex as an independent factor. All models that fit analysis were evaluated with the Hosmer–Lemeshow goodness-of-fit statistic. The C statistic was reported as a measure of predictive power. For continuous outcome measures (LOS and SCr/eGFR values at different follow-up periods), we developed parsimonious multivariable general linear models and compared risk-adjusted outcomes between Dex use and no Dex use group with the *t*-test. The results are reported as percentages and odds ratios (ORs) and with 95% confidence intervals (CIs). All reported *P* values were two-sided, and values of $P < 0.05$ were considered statistically significant. Statistical analysis was performed with SAS version 9.4 for Windows (SAS, Cary, NC).

RESULTS

Baseline and intraoperative parameters

Preoperative demographic and clinical data of the patients who did and did not receive intraoperative Dex in kidney transplant surgery are presented in **Table 1**. Most characteristics, including age and sex, were similar between the

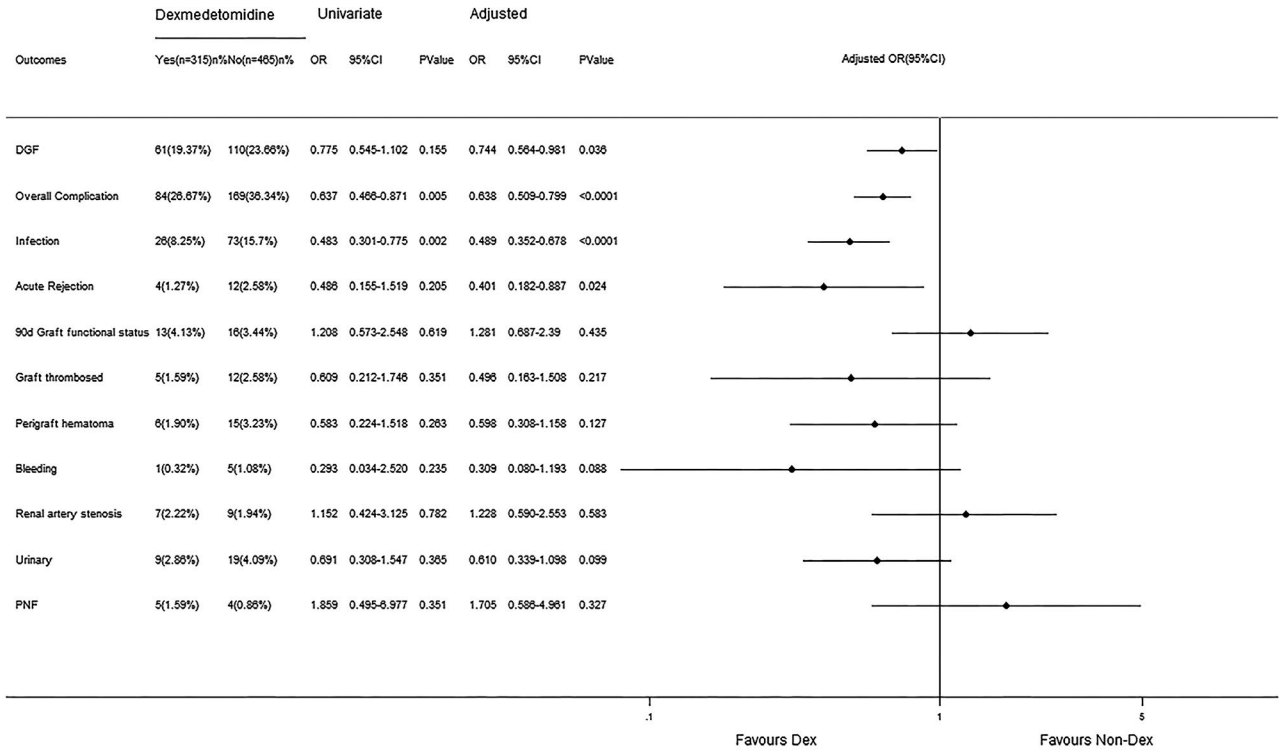

Figure 3 Effects of dexmedetomidine on post-transplantation complications. Values are numbers (%) for categorical variables. CI, confidence interval; DEX, dexmedetomidine; DGF, delayed graft function; OR, odds ratio; PNF, primary no function. ※Adjusted for propensity score, recipient age, sex, race, anti-Hepatitis C Virus status, hypertension, peripheral vascular disease (PVD), hemodialysis prior to transplant, PRA > 10%, donors' terminal SCr, sex, body mass index, cold ischemic time (CIT), warm ischemic time (WIT), and prednisone on discharge. $Adjusted for propensity score, recipient age, sex, race, ABO blood group, primary cause of ESRD, modality of transplant, donor's age, sex, hepatitis B virus (HBsAg) status, and CIT. §Adjusted for propensity score, recipient sex, race, ABO blood group, donor's sex, and HBsAg statute. #Adjusted for propensity score recipient age, sex, race, dialysis prior to transplant, and prednisone on discharge. ★Adjusted for propensity score, recipient age, sex, race, primary cause of endstage renal disease (ESRD), diabetes, coronary artery disease, malignancy disease, prior kidney transplant, dialysis, length and type of dialysis prior to transplant, PRA > 10%, numbers of HLA mismatches, modality of transplant, donor's age, sex, WIT, and prednisone on discharge. ▲Adjusted for propensity score, recipient age, sex, race, anti-CMV status, primary cause of ESRD, coronary artery disease, hypertension, PVD, malignancy, prior kidney transplant, length of dialysis, and hemodialysis prior to transplant, most recent PRA value, PRA > 10%, numbers of HLA mismatches, modality of transplant, donor's age, sex, race, anti-CMV status and terminal SCr, CIT, pulsatile-pump preservation, and prednisone on discharge.◆Adjusted for propensity score, recipient age, race, most recent PRA value, PRA > 10%, CIT, cardiovascular disease, and donor's anti-HCV statute. △Adjusted for propensity score, recipient sex, and race. ◇Adjusted for propensity score, recipient age, sex, race, ABO blood group, HCV status, cardiovascular disease, diabetes, malignancy, prior kidney transplant, length of dialysis prior to transplant, PRA > 10%, numbers of HLA mismatches, donor's sex, race, anti-CMV, pulsatile-pump preservation, and CIT. ☆Adjusted for propensity score, recipient age, sex, race, ABO blood group, anti-CMV status, primary cause of ESRD, PVD, malignancy, type of dialysis prior to transplant, numbers of HLA mismatches, donor's race, and CIT. ⊙Adjusted for propensity score, recipient, sex, race, ABO blood group, anti-CMV status, primary cause of ESRD, prior kidney transplant, length and type of dialysis prior to transplant, most recent PRA value, PRA > 10%, numbers of HLA mismatches, donor's age, SEX, race, anti-CMV status, terminal SCr, WIT, pulsatile-pump preservation, and prednisone on discharge.

Table 2 Post-transplantation LOS, SCr, and eGFR

	Unadjusted			Risk adjusted		
Outcomes	**Dex (*N*)**	**No-Dex (*N*)**	***P* value**	**Dex (*N*)**	**No-Dex (*N*)**	***P* value**
LOS, days	6.3 ± 2.7 (315)	7.1 ± 7.1 (465)	0.038	6.4 (315)	7.1 (465)	<0.0001
7-day SCr, mg	4.1 ± 3.4 (314)	4.3 ± 3.6 (464)	0.552	4.18 (314)	4.29 (464)	0.433
30-day SCr, mg	2.2 ± 1.4 (311)	2.3 ± 1.6 (462)	0.476	2.18 (311)	2.24 (462)	0.210
90-day SCr, mg	1.7 ± 1.2 (310)	1.7 ± 0.9 (456)	0.451	1.73 (310)	1.67 (456)	0.041
7-day eGFR, mL/min/1.73 m^2	38.0 ± 30.8 (314)	39.0 ± 32.9 (464)	0.652	37.7 (314)	39.1 (464)	0.393
30-day eGFR, mL/min/1.73 m^2	53.1 ± 26.5 (311)	51.8 ± 26.3 (462)	0.488	52.9 (311)	51.9 (462)	0.366
90-day eGFR, mL/min/1.73 m^2	63.8 ± 24.7 (310)	64.2 ± 26.4 (456)	0.826	63.6 (310)	64.1 (456)	0.628

Dex, dexmedetomidine; eGFR, estimation of glomerular filtration fate; LOS, length of stay hospital; SCr, serum creatinine.

groups. However, patients who received Dex presented with higher most recent PRA (19.9 ± 32.2 vs. 15.5 ± 28.0; $P = 0.048$) prior to transplantation, a greater incidence of PRA > 10% (35.6% vs. 28.6; $P = 0.040$), African American recipients (12.7% vs. 8.0%; $P = 0.021$), and B blood type recipients (10.2% vs. 15.5%; $P = 0.032$).

Post-transplantation complications

Univariate analysis showed that Dex use was associated with reduced post-transplant risks of infection (8.3% vs.15.7%; OR, 0.483; 95% CI, 0.301–0.775; $P = 0.002$), overall complications (26.67% vs. 36.34%; OR, 0.637; 95% CI, 0.466–0.871; $P = 0.005$), and LOS (6.3 ± 2.7 vs. 7.1 ± 7.1; $P = 0.038$). No differences were seen in DGF, the risk of acute rejection, graft thrombosis, perigraft hematoma, bleeding, PNF, renal artery stenosis, urinary complications, 90-day graft functional status, 7-day, 30-day, and 90-day Scr, and eGFR (**Figure 3** and **Table 2**).

Propensity and multivariate analysis

The final multivariate model assessing DGF status included the propensity score, recipient age, sex, race, anti-HCV status, hypertension (HTN), peripheral vascular disease (PVD), hemodialysis prior to transplant, PRA > 10%, donor's terminal SCr, sex, body mass index, CIT, WIT, and prednisone on discharge. The multivariate model assessing overall complications included the propensity score, recipient age, sex, race, ABO blood type, primary cause of ESRD, modality of transplant, donor's age, sex, HBsAg status, and CIT. The multivariate model for assessing infection included the propensity score, recipient sex, race, ABO blood type, donor's sex, and HBsAg status. The multivariate model for assessing acute rejection included the propensity score, recipient age, sex, race, dialysis prior to transplant, and prednisone on discharge. The multivariate model for assessing graft functional status 90 days after transplant included the propensity score, recipient age, sex, race, primary cause of ESRD, diabetes, coronary artery disease, malignancy disease, prior kidney transplant, dialysis, length and type of dialysis prior to transplant, PRA > 10%, numbers of HLA mismatches, modality of transplant, donor's sex, WIT, and prednisone on discharge. The multivariate model for assessing graft thrombosis included the propensity score, recipient age, sex, race, anti-CMV status, primary cause of ESRD, coronary artery disease, HTN, PVD, malignancy, prior kidney transplant, length of dialysis and hemodialysis prior to transplant, most recent PRA value, PRA > 10%, numbers of HLA mismatches, modality of transplant, donor's sex, race, anti-CMV status, terminal SCr, CIT, pulsatile-pump preservation, and prednisone on discharge. The multivariate model for assessing perigraft hematoma included the propensity score, recipient age, race, most recent PRA value, PRA > 10%, CIT, CVD, and donor's anti-HCV statute. The multivariate model for assessing bleeding included the propensity score, recipient sex, and race. The multivariate model assessing renal artery stenosis included the propensity score, recipient age, sex, race, ABO blood type, HCV status, CVD, diabetes, malignancy, prior kidney transplant, length of dialysis prior to transplant, PRA > 10%, numbers of HLA mismatches, donor's sex, race, anti-CMV, pulsatile-pump preservation, and CIT. The multivariate model for assessing urinary complications included the propensity score, recipient age, sex, race, ABO blood type, anti-CMV status, primary cause of ESRD, PVD, malignancy, type of dialysis prior to transplant, numbers of HLA mismatches, donor's race, and CIT. The multivariate model assessing PNF included the propensity score, recipient age, sex, race, ABO blood group, anti-CMV status, primary cause of ESRD, prior kidney transplant, length and type of dialysis prior to transplant, most recent PRA value, PRA > 10%, numbers of HLA mismatches, donor's age, sex, race, anti-CMV status, terminal SCr, WIT, pulsatile-pump preservation, and prednisone on discharge. The model was calibrated among deciles of observed Dex use (Hosmer–Lemeshow χ^2: 8.7997; $c = 0.552$; $P = 0.3595$). Results of the multivariate analysis are summarized in **Figure 3** and **Table 2**. The observed reduction in infection (adjusted OR, 0.489; 95% CI; 0.352–0.678; $P < 0.0001$) overall complications (adjusted OR, 0.638; 95% CI, 0.509–0.799; $P < 0.0001$), and LOS (6.4 vs. 7.1; $P < 0.0001$) in patients receiving perioperative Dex persisted after propensity adjustment. Differences in DGF status (adjusted OR, 0.744; 95% CI, 0.564–0.981; $P = 0.036$) and acute rejection (adjusted OR, 0.401; 95% CI, 0.182–0.887; $P = 0.024$) were also statistically significant between the Dex and No-Dex groups after propensity adjustment. However, there were no statistical differences in 90-day graft functional status (adjusted OR, 1.281; 95% CI, 0.687–2.390; $P = 0.435$),

7-day, and 30-day SCr, and eGFR and 90-day eGFR between groups after adjustment between groups (**Figure 3** and **Table 2**).

DISCUSSION

This study demonstrates that Dex administration was associated with reduced post-transplantation risk of infection, overall complications, and LOS. This improvement persisted after propensity weighting and risk-adjustment. Our study also suggests that perioperative Dex use is associated with decreased DGF and the risk of acute rejection.

Delayed graft function is a major complication occurring in the early post-transplantation phase and is a manifestation of AKI that attributes uniquely to the transplant process.[8] Poor kidney function in the first week following transplant is detrimental to allograft longevity. AKI originates from donor ischemic injury, inflammation, recipient reperfusion injury, the innate immune response, and the adaptive immune response.[24] A meta-analysis of 34 studies indicated that acute rejection episodes occurred in 49% of patients with DGF compared with 35% in patients with no DGF.[25] AKI is also a risk factor for kidney transplant graft failure.[26] Although new therapies primarily seek to suppress inflammatory kidney damage resulting from adaptive immune cells, limit cell death, and/or interrupt adverse signaling of necrosis, prevention of organ injury is more important than treatment.[27] Alpha$_2$ adrenoceptors are widely present in renal peritubular vasculature as well as proximal and distal tubules.[28] Dex is an alpha$_2$ adrenoceptor agonist that inhibits inflammatory mediator production, decreasing cell death, apoptosis, and necroptosis. Alpha$_2$ receptor agonists intensify urine flow rate and perioperative renal function.[29] The underlying mechanisms remain unknown. Studies have demonstrated that Dex decreased renal dysfunction by decreasing mRNA expression of IL-6, ICAM-1, and iNOs following renal I/R.[30] Additionally, in renal cells, Dex can also decrease apoptosis and downregulate monocyte chemo-attractant protein-1 through suppressing injury-induced activation of the Janus kinase/signal transducer and activator of transcription signaling pathways during renal I/R injury.[31] These immune modulatory effects may underlie an organ protective effect of Dex from I/R injury. Considering the importance of inflammation and apoptosis, as well as potential anti-inflammation and apoptosis effects,[32,33] Dex has emerged as an effective organ protective agent. Gu and colleagues suggested that Dex activated Akt signaling via α_2 adrenoceptor-dependent and independent-PI3K coupling to improve kidney cell survival. Apart from its cytoprotection, Dex might inhibit HMGB1 release and suppress subsequently toll-like receptor 4-mediated inflammatory actions in the setting of renal ischemia.[34] Studies *in vivo* have reported that the reno-protective property of Dex could be related to modulating vasoreactivity, presented as improved renal blood flow, preserved glomerular filtration, elevated secretion of water and sodium, as well as suppression of renin release.[35–37] Moreover, Dex could induce urination through the inhibition of arginine vasopressin in the collecting duct and aquaporin expression.

Infection occurs in up to 30% of renal transplant recipients during the first 3 months post-transplantation.[9,10] It also worsens AKI, which negatively affects the outcomes.[26] Because of the immunocompromised hosts, a wide spectrum of pathogens has been identified in patients who undergo transplantation. Many are infrequent pathogens in normal individuals.[38] Normal clinical signs and symptoms, such as fever and erythema are diminished; infection may be signaled by more subtle laboratory or radiographic abnormalities. The prevention and management of infection can potentially improve outcomes in kidney transplantation. This study demonstrated reduced risks of infections associated with Dex administration. The mechanism has been suggested as Dex reducing the release of inflammatory cytokines, such as TNF and IL-6, by inhibiting the activation of ERK1/2 and NF-κB and modulating inflammatory mediators.[39–41] Subsequently, Dex could also suppress toll-like receptor 4 signaling, activate the cholinergic anti-inflammatory pathway, and intensify macrophage phagocytosis for bacterial clearance, thus stabilizing hemodynamics.[42–44]

Acute kidney allograft rejection occurs as a consequence of interactions between recipient immune cells within the transplanted organ as is the cause of 64% of renal transplantation failures.[45] The immune system and inflammation play vital roles in the development of this disorder.[46,47] Our study demonstrated that Dex administration was associated with a reduced risk of acute rejection. This can be explained by the immunomodulation and anti-inflammatory properties of Dex.[48,49] Postoperative complications have been associated with prolonged LOS. By decreasing DGF, infection, graft rejection, and overall complications, the LOS was significantly decreased.[50]

There are several limitations in this study. First, this is a single-center, observational, retrospective cohort study. We used the propensity score method because it is the frequently used statistical method for retrospective studies. Multivariate regression, in combination with propensity score adjustments, was applied to this study population to reduce biases, however, the potential confounding biases associated with a nonrandomized study remain. Second, the study showed Dex infusion is associated with improved prognosis of renal transplantation patients, but not in 90-day graft functional status or 7-day, 30-day, and 90-day eGFR. These results do not establish a cause and effect relationship as could a prospective study. Third, we do not have dose response curve in this patient population and the optimal dose could be outside the approved dose range. Fourth, it would be ideal if we could do Dex pretransplant treatment. However, the majority of our transplant surgeries were urgent and we have very limited time before surgery to pretreat the kidneys. Fifth, because the noninvasive hemodynamic monitoring is the standard care for this patient population and the blood pressures were maintained between 70 and 90 mmHg, we are unable to establish the association with the primary and key secondary end points. Finally, the sample size is relatively small. Whether Dex administration could be of benefit if widely applied to clinical donor kidney grafts and the detailed underlying mechanism warrant further studies.

In conclusion, this study demonstrates that perioperative use of Dex was associated with a reduced incidence of DGF, infection, graft rejection, overall complications, and LOS in patients who undergo renal transplantation.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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