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ORIGINAL RESEARCH

Effect of End-Stage Kidney Disease Factor on the Sedative Effects of Ciprofol

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Purpose: To investigate the effect of end-stage kidney disease (ESKD) factor on the sedative effects of ciprofol.

Patients and Methods: Elective kidney transplant recipients aged 18–64 years, with a body mass index (BMI) of 18.5–24.0 kg/m^2, Mallampati class I or II, interincisor distance ≥ 3.5 cm, and undergoing regular preoperative dialysis were enrolled. A matched control group with normal kidney function was included for comparison. The Dixon's up-and-down method was used to determine the median effective dose (ED_{50}) of ciprofol required to suppress the response to I-gel insertion. Secondary outcomes included ciprofol consumption during anesthesia maintenance, recovery time, perioperative hemodynamic changes, and adverse events. The total dosage of ciprofol used for anesthesia maintenance was recorded, and average ciprofol consumption per unit time per body weight was calculated.

Results: No statistically significant difference were observed in the ED_{50} or 95% confidence interval (CI) of ciprofol for suppressing the I-gel insertion response between the ESKD and control groups. Similarly, recovery time and mean ciprofol consumption during anesthesia maintenance were comparable between groups. Hemodynamic parameters remained stable throughout the perioperative period in both groups, with no significant intergroup differences. The incidence of adverse events, including hypotension, bradycardia, and respiratory depression, was also comparable between groups.

Conclusion: ESKD appears to have no significant effect on the sedative efficacy, anesthetic consumption, recovery profile, or safety of ciprofol.

Keywords: end-stage kidney disease, ciprofol, sedative effects

Introduction

End-stage kidney disease (ESKD) is a significant factor driving morbidity and mortality worldwide,[1] and kidney transplantation remains the optimal treatment.[2] This surgical procedure is typically performed under general anesthesia. Clarifying the influence of disease-related factors on pharmacodynamics is of great importance, as it facilitates precise anesthetic medication.

The kidneys are the primary organ for drug elimination. In patients with kidney disease, the half-life of renally excreted drugs is prolonged, predisposing to systemic accumulation. Furthermore, ESKD patients typically present with compromised cardiovascular function, hypoalbuminemia, anemia, and metabolic acidosis - all of which may affect drug distribution, protein binding, tissue perfusion, and pharmacodynamic response. Moreover, uremia-related impairment of hepatic metabolism and transporter activity further contributes to variability in anesthetic drug behavior.[3] Consistent with these pathophysiological changes, previous studies have reported that ESKD may reduce the duration of propofol's clinical effects,[4] and prolong rocuronium-induced neuromuscular blockade.[5] It has been reported that ESKD patients exhibit a 16% decrease in sevoflurane MACawake compared to individuals with normal kidney function.[6]

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Ciprofol is a novel intravenous anesthetic drug belonging to the class of short-acting GABAA receptor agonists, characterized by rapid onset, short duration of action, and favorable hemodynamic stability. Importantly, ciprofol is primarily metabolized in the liver via UGT1A9-mediated glucuronidation, with less than 5% of the parent drug excreted renally.[7] Although its clearance is not predominantly renal, the profound physiological alterations associated with ESKD may still influence its sedative effects by modifying protein binding, drug distribution, and pharmacodynamic sensitivity. Ciprofol has demonstrated efficacy and safety in anesthesia induction and maintenance during kidney transplantation and has been reported to provide improved sedative effects relative to propofol.[8] However, the influence of ESKD on the sedative response to ciprofol remains unclear. Therefore, this study aimed to investigate the effect of ESKD on the sedative efficacy of ciprofol, providing evidence to support its rational and individualized use in patients with renal impairment.

Materials and Methods

This study was approved by the Medical Research Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (2022KY Ethical Review No. 197), and registered in the Chinese Clinical Trial Registry (ChiCTR2200063628). All transplanted kidneys were donated voluntarily with written informed consent, and all transplantation procedures were conducted in accordance with the Declaration of Istanbul, the Declaration of Helsinki, and ethical principles of the above ethics committee.

Elective kidney transplant recipients aged 18–64 years, with a body mass index (BMI) of 18.5–24.0 kg/m^2, Mallampati class I or II, interincisor distance $\geq$ 3.5 cm, and receiving regular preoperative dialysis were included. All ESKD patients underwent protocol-directed dialysis within 24 hours prior to surgery to achieve target dry weight. A matched control group with normal kidney function was established for comparison. Patients were excluded if they had one of the following criteria: History of allergy to propofol, ciprofol, or soy products; gastroesophageal reflux disease; long-term use of sedatives or analgesics; severe dysfunction of major organs (except for kidney dysfunction in the ESKD group). Patients were divided into two groups based on whether they had ESKD or not: the non-ESKD group (Group NE) and the ESKD group (Group E).

Anesthesia Management

All patients followed standard preoperative fasting protocols without premedication. Upon entering the operating room, patients received supplemental oxygen via nasal cannula and peripheral intravenous access was established. Standard monitoring included continuous electrocardiogram (ECG), non-invasive blood pressure (BP) measurements at 5-min intervals, pulse oximetry (SpO_2), and invasive arterial pressure monitoring through radial artery cannulation performed under local anesthesia.

Anesthesia was induced with intravenous ciprofol (Batch No: 20230743, Haisco Pharmaceutical Co., Ltd, Liaoning, China), with an initial dose of 0.4 mg/kg.[9] The I-gel (Intersurgical Ltd, UK) was inserted using the rotational technique[10] following loss of eyelash reflex and when the bispectral index (BIS) value decreased below 60. In accordance with the manufacturer's guidelines, the selection of the I-gel size was determined by the patients' body weight. Specifically, size 3 was chosen for patients weighing between 30 kg and 60 kg, size 4 for those weighing more than 60 kg but not exceeding 90 kg, and size 5 for patients with a body weight greater than 90 kg. The Dixon's up-and-down method[11] was employed to determine the median effective dose (ED_{50}) of ciprofol required to suppress I-gel insertion responses. Based on the occurrence or no occurrence of the responses of the previous patient to I-gel placement, the dose of ciprofol increased or decreased by 10% in the next patient (Figure 1). The trial was terminated once six consecutive crossover points (alternations between negative and positive responses) were observed in each group (Figure 2).

Each I-gel placement procedure was carried out by an anesthesiologist with substantial experience. A three-point, six-category scale (labeled a-f)[12] was employed to assess the insertion conditions of the I-gel. The scale details are as follows: a. Resistance to mouth opening grading: no, significant, or undue force required; b. Resistance to insertion grading: no, significant, or undue force required; c. Swallowing grading: nil, slight, or gross; d. Coughing and gagging grading: nil, slight, or gross; e. Head or body movement grading: nil, slight, or gross; f. Laryngospasm grading: nil, partial, or total. Laryngospasm was defined as prolonged obstruction with a correctly placed I-gel. A total score for

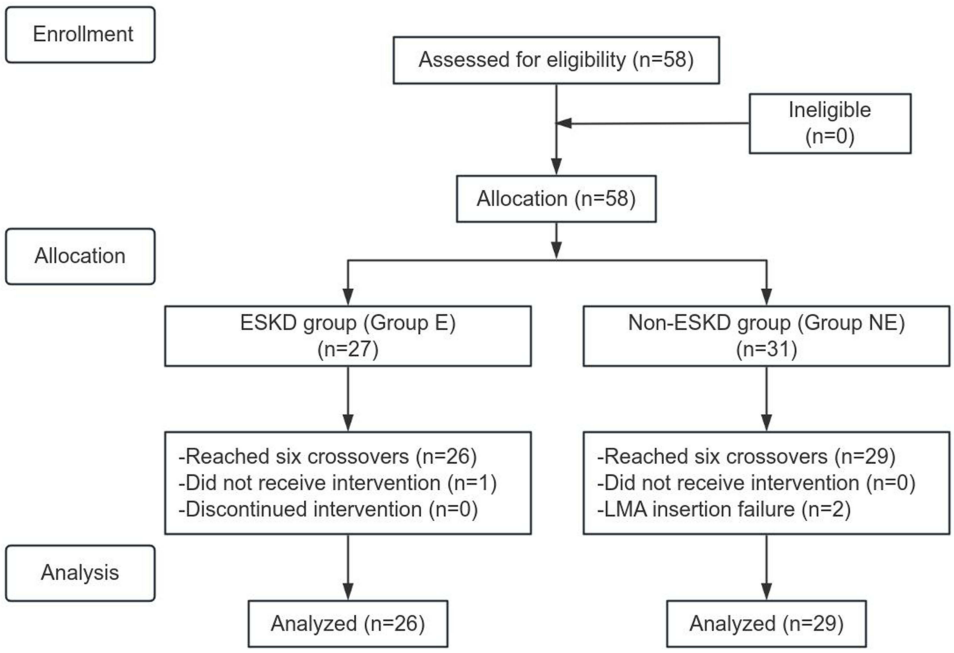

Figure 1 Flow chart for the Dixon's up-and-down method.

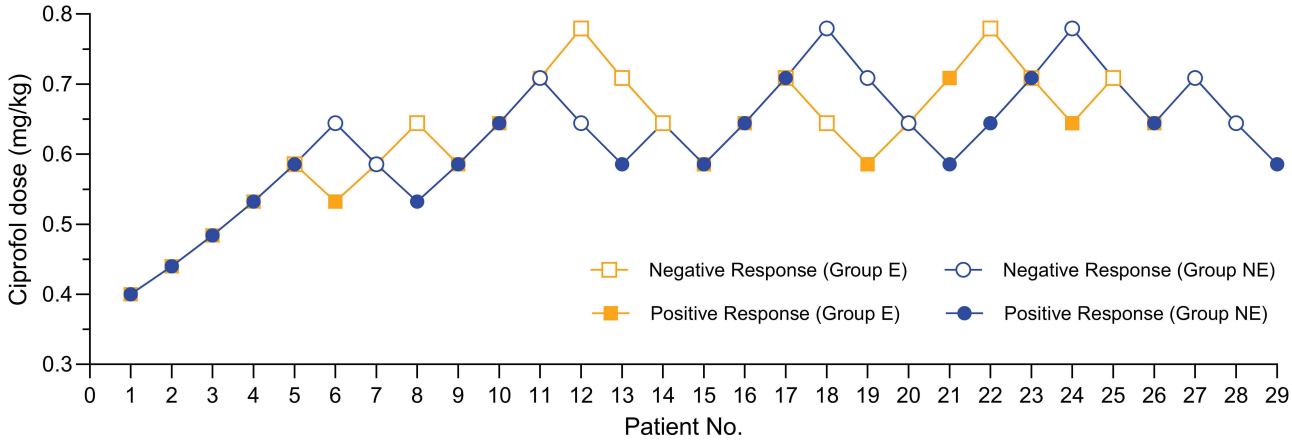

Figure 2 Response of the patients to different doses of ciprofol in the two groups.

insertion conditions was calculated by adding up the swallowing, gagging, movement, and laryngospasm grades (1, 2, or 3). A score of 4 was considered as an optimal condition for I-gel placement.[12] In the event that the patient exhibited an excessively strong response, resulting in the failure of I-gel placement, an additional intravenous dose of ciprofol at 0.2 mg/kg was administered prior to making another attempt at placement. In cases of respiratory depression, immediate ventilatory support was provided via either facemask or through the established I-gel airway. Patients who require conversion to endotracheal intubation due to poor ventilation after I-gel placement will be excluded.

Following I-gel insertion, sequential intravenous administration of sufentanil 0.2 μg/kg and cis-atracurium 0.15 mg/kg was performed. Mechanical ventilation was initiated, with tidal volume set at 6–8 mL/kg, ventilation frequency of 12–14 breaths/min, and I:E ratio of 1:2, adjusted to maintain end-tidal CO_2 ($ETCO_2$) at 35–45 mmHg. For ciprofol continuous intravenous infusion, the initial dosage is set at 0.8 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$,with a range of 0.4–2.4 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$.[13] Target-controlled infusion (TCI) of remifentanil (plasma target concentration: 1.0–5.0 ng/mL), and 1% inhaled sevoflurane, titrated to maintain BIS values between 40 and 60. Additional boluses of cis-atracurium (0.05 mg/kg) were

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Table 1 Comparison of Demographic and Baseline Characteristics Between the Two Groups

Group	Age (y)	Gender (M/F)	BMI (kg/m^2)	Mallampati (I/II)	Interincisor Distance (cm)	Serum Albumin (g/L)
NE (n=29)	36±8	15/14	21.4±1.7	9/20	4.43±0.32	43.07±3.08
E (n=26)	34±7	19/7	21.5±2.1	13/13	4.34±0.29	41.99±5.21
P value	0.202	0.104	0.945	0.152	0.268	0.360

Notes: Data are presented as mean ± SD or n.
Abbreviation: BMI, body mass index.

administered if required. Discontinuation of anesthetics at the end of surgery. Intravenous atropine (10 μg/kg) was administered for bradycardia (HR < 50 beats/min), and phenylephrine (1–2 μg/kg IV) for hypotension (MAP < 60 mmHg or > 30% decrease from baseline).

Assessment of Primary and Secondary Outcomes

The ED_{50} and 95% confidence interval (CI) of ciprofol for suppressing I-gel insertion responses were calculated using Dixon-Massey and Probit analysis. The mean arterial pressure (MAP) and heart rate (HR) were recorded at 10 min after entering the operating room (T_0), immediately after I-gel insertion (T_1), and at the time of skin incision (T_2). The differences in MAP (ΔMAP) and HR (ΔHR) were calculated by subtracting the baseline values (T_0) from the respective time points (T_1 and T_2). Sedation status was assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S)[14] at the end of surgery, with evaluations conducted every 3 min. The time to recovery was recorded, defined as the duration from the end of surgery until the patient achieved three consecutive MOAA/S scores of 5. The total dosage of ciprofol used for anesthesia maintenance was recorded in both groups, and the average ciprofol consumption per unit time per body weight was calculated. The incidence of adverse events in both groups was also recorded.

Statistical Analysis

Statistical analyses were performed using SPSS software version 22.0. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), and intergroup comparisons were conducted using the two-sample *t*-test. Non-normally distributed continuous variables were presented as median (interquartile range) [M(Q)], with intergroup comparisons performed using the Mann–Whitney *U*-test. Categorical data were expressed as number (%) and compared using χ^2 test or Fisher's exact test as appropriate. According to the Dixon's up-and-down method, the trial was terminated after each group achieved six crossover points (Figure 2). The ED_{50} (95% CI) were calculated using the Dixon-Massey method and Probit regression analysis. Intergroup comparisons of ED_{50} values were performed using the Mann–Whitney *U*-test. A P-value of less than 0.05 was considered statistically significant.

Results

Comparison of Baseline Characteristics

This study initially enrolled 58 patients, with 27 patients allocated to the group E and 31 to the group NE. One patient in the group E did not receive the allocated intervention, and two patients in the group NE were excluded because of poor I-gel ventilation. Ultimately, the group E comprised 26 patients, while the group NE comprised 29 patients distributed as follows: gynecology (n = 12, 41.4%), general surgery (n = 8, 27.6%), orthopedics (n = 6, 20.7%), and cerebrovascular intervention (n = 3, 10.3%). Baseline demographic and biochemical characteristics showed no statistically significant differences between the two groups, including serum albumin levels (Table 1).

Comparison of Sedative Effects

Regardless of the calculation method used (Dixon-Massey or Probit regression), there was no statistically significant difference in the ED_{50} (95% CI) of ciprofol for inhibiting I-gel insertion response between the two groups (Table 2). The dose-response curves of ciprofol in the two groups are shown in Figure 3. Similarly, no significant differences were observed in recovery time or mean ciprofol dosage between groups (Table 3).

Table 2 Comparison of Different Methods for Calculating the ED_{50} (95% CI) of Ciprofol in Suppressing Responses to I-Gel Insertion (mg/Kg)

Group	Dixon-Massey	Probit Regression
NE (n=29)	0.617 (0.592–0.642)	0.654 (0.604–0.722)
E (n=26)	0.619 (0.591–0.647)	0.666 (0.611–0.762)
P value	0.917	0.862

Comparison of Vital Signs and Adverse Reactions

The two groups showed comparable ΔHR and ΔMAP values at each time point (Table 4), with no significant differences in the incidence rates of adverse reactions, including bradycardia, hypotension, injection pain, multilingualism, and muscle tremor (Table 5). All adverse events were mild and resolved without sequelae.

Discussion

The findings of this study indicate that the sedative effect of ciprofol appears unaffected by ESKD factor. Patients with ESKD exhibit significant alterations in pharmacodynamics and pharmacokinetics, primarily manifested in the following aspects: First, the expression and activity of various cytochrome P450 enzymes are reduced in ESKD patients,[15–18] leading to decreased clearance of drugs metabolized by this enzyme system (eg, fentanyl and midazolam), resulting in elevated drug concentrations and increased risk of adverse effects. Second, hypoalbuminemia commonly associated with ESKD alters drug plasma protein binding rates, increasing free drug concentrations, which modifies volume of distribution while elevating toxicity risks.[19] Third, ESKD-related factors modify target organ sensitivity to drugs - the accumulation of uremic toxins increases blood-brain barrier permeability, potentiating the central depressant effects of sedatives.[19] Additionally, electrolyte imbalances (eg, hyperkalemia) exacerbate drug-induced cardiotoxicity and circulatory depression.

Ciprofol is a novel non-barbiturate intravenous anesthetic, belonging to the γ-aminobutyric acid (GABA) receptor agonist class. It is characterized by rapid onset, fast metabolism, and a wide safety margin. Compared with propofol, ciprofol demonstrates significant clinical advantages including reduced respiratory depression, less pronounced hemodynamic effects, and lower incidence of injection pain,[20,21] making it widely applicable in clinical anesthesia practice.

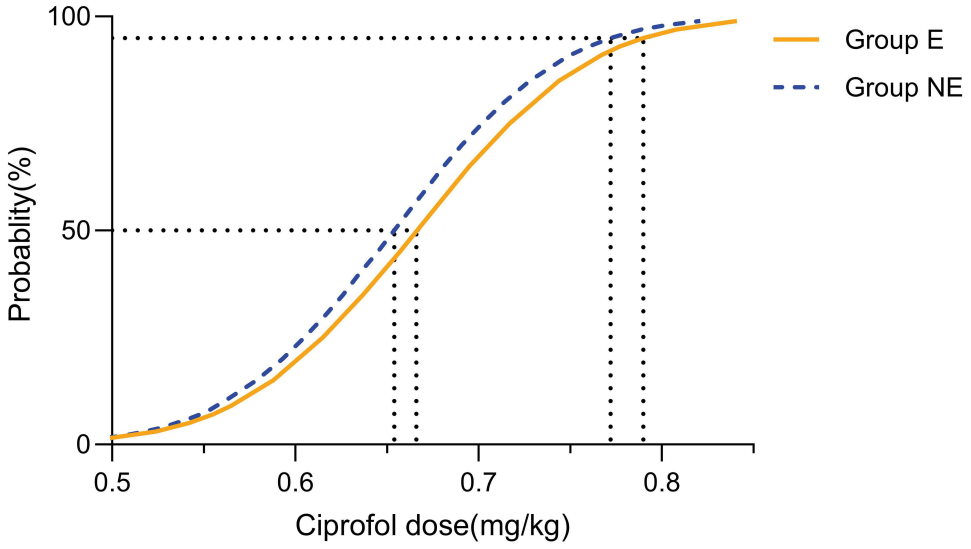

Figure 3 Dose-response curves of ciprofol for I-gel placement in the two groups.

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Table 3 Comparison of Recovery Time and Average Dosage of Ciprofol Between the Two Groups

Group	Recovery Time (min)	Average Ciprofol Dosage (mg·kg^{-1}·h^{-1})
NE (n=29)	25 (16–36)	0.90±0.09
E (n=26)	25 (20–30)	0.87±0.06
P value	0.779	0.181

Notes: Data are presented as mean ± SD or median (interquartile range).

Table 4 Comparison of Vital Signs at Various Time Points Between the Two Groups

Group	ΔHR (beats/min)		ΔMAP (mmHg)	
	T0-1	T0-2	T0-1	T0-2
NE (n=29)	4 (2–10)	10 (5–14)	5 (3–11)	7 (4–12)
E (n=26)	2 (1–6)	14 (9–20)	5 (1–6)	14 (5–22)
P value	0.251	0.107	0.061	0.112

Notes: Data are presented as median (interquartile range).
Abbreviations: HR, heart rates; MAP, mean arterial pressure; T0-1, the difference between the time points T_1 and T_0; T0-2, the difference between the time points T_2 and T_0.

Table 5 Comparison of Adverse Events in the Two Groups [n (%)]

Group	Bradycardia	Hypotension	Injection Pain	Multilingualism	Muscle Tremor
NE (n=29)	2 (6.90)	3 (10.34)	1 (3.45)	2 (6.90)	1 (3.45)
E (n=26)	3 (11.54)	2 (7.69)	2 (7.69)	2 (7.69)	1 (3.85)
P value	0.659	> 0.990	0.598	> 0.990	> 0.990

Notes: Data are presented as n (%).

Therefore, elucidating the impact of ESKD on the sedative effects of ciprofol is of importance for its precise clinical application.

The Dixon's up-and-down method offers a practical and efficient approach for estimating the ED_{50} of a drug. Its key advantages include optimal data utilization, a significant reduction in experimental subjects by over 30% compared to traditional methods, and high accuracy in the results.[22] In this study, two methods were employed to calculate the ED_{50} (95% CI) to ensure the accuracy and the reliability of the results. Evidence indicates superior anesthetic efficacy of ciprofol over propofol in kidney transplantation surgery.[8] In the present study, both the initial induction dose and maintenance dose of ciprofol were determined based on the findings from previous research.[13] The observation indicators selected in this study, including the ED_{50} of ciprofol for inhibiting I-gel insertion, recovery time, average ciprofol dosage, adverse reactions, ΔHR, and ΔMAP, are all sensitive indicators reflecting the effects of ciprofol. In this study, rotational technique was adopted for I-gel placement. This method demonstrates the advantages of a higher success rate of insertion, shorter insertion time, and reduced incidence of complications.[10]

The mechanisms underlying the apparently unchanged sedative effect of ciprofol in patients with ESKD remain unclear. Although ESKD is associated with alterations in drug metabolism, protein binding, and blood-brain barrier permeability, the ED_{50} of ciprofol for suppressing I-gel insertion responses was comparable between the two groups in the present study. Ciprofol is primarily metabolized through hepatic pathways involving UGT1A9 and, to a lesser extent, CYP2B6, while renal elimination plays a limited role in its clearance.[7,23] Therefore, it is possible that preserved non-renal metabolic pathways may contribute to the relatively stable anesthetic requirement observed in patients with ESKD.

However, this interpretation remains speculative because pharmacokinetic measurements and plasma metabolite concentrations, including glucuronide-M4, were not evaluated in this study.

This study has several limitations. Sample size was determined per Dixon up-and-down sequential design to estimate the median ED_{50} for successful I-gel insertion, instead of conventional prospective power analysis. The trial halted once six crossover points were acquired in each group, leaving insufficient power to compare secondary outcomes and adverse events, and these findings should therefore be interpreted cautiously. In addition, baseline serum albumin levels were similar between groups, lowering confounding effects of protein binding changes. Nevertheless, free ciprofol concentrations were not tested, lacking direct evidence for drug distribution. Furthermore, full blinding of airway assessors was unachievable as dose adjustment in the Dixon sequential design depended on the response of the preceding patient. Despite standardized evaluation and experienced operators, subjective judgment may cause observer bias. Finally, the study population was limited to non-obese patients with no severe comorbidities except ESKD, restricting result generalizability. Therefore, larger prospective studies incorporating pharmacokinetic-pharmacodynamic analyses are warranted to further validate these findings.

Conclusion

In patients undergoing regular dialysis, the clinical sedative requirements of ciprofol for successful I-gel insertion appeared comparable to those in patients without ESKD. However, equivalent pharmacodynamic responses do not necessarily indicate unchanged pharmacokinetics in this physiologically compromised population. Given the absence of pharmacokinetic measurements and the non-blinded assessment of airway responses, the present findings should be interpreted cautiously. Larger blinded prospective studies incorporating pharmacokinetic-pharmacodynamic analyses are warranted to further clarify the disposition and anesthetic effects of ciprofol in patients with ESKD.

Data Sharing Statement

The datasets used in the current study are available from the corresponding author (Juan Li) upon reasonable request.

Ethical Approval

This study was approved by the Medical Research Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (2022KY Ethical Review No. 197), and registered in the Chinese Clinical Trial Registry (ChiCTR2200063628). All transplanted kidneys were donated voluntarily with written informed consent, and all transplantation procedures were conducted in accordance with the Declaration of Istanbul, the Declaration of Helsinki, and ethical principles of the above ethics committee.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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