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Effect of ciprofol on induction and maintenance of general anesthesia in patients undergoing kidney transplantation

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Abstract. – OBJECTIVE: This study aims at evaluating the effects of ciprofol on the induction and maintenance of general anesthesia in patients undergoing kidney transplantation.

PATIENTS AND METHODS: This prospective, randomized, single-blind study enrolled 120 patients aged 18-65 years who underwent general anesthesia for kidney transplantation. The patients were randomized into a ciprofol group (group C) and a propofol group (group P). Anesthesia induction: group C had injected IV with ciprofol 0.4 mg/kg, group P had injected IV with propofol 2.0 mg/kg, while both groups had injected IV with sufentanil 0.4-0.5 μg/kg and cisatracurium 0.2 mg/kg. Anesthesia maintenance: ciprofol was injected IV with 0.8-2.4 mg·kg^{-1}·h^{-1} in group C, propofol was injected IV with 4-12 mg·kg^{-1}·h^{-1} in group P, while remifentanil was injected IV with 8-15 μg·kg^{-1}·h^{-1} and cisatracurium was injected IV with 0.1-0.2mg·kg^{-1}·h^{-1}, with the bispectral index (BIS) maintained at 40-60 during the operation.

RESULTS: The success rate of sedation in both groups was 100%. Compared with the P group, in group C the time of disappearance of the eyelash reflex and a decline in the BIS to 60 was shorter (p<0.001); the time of awakening was prolonged (p<0.001); the number of sedative drugs administered was reduced (p<0.001); MAP fluctuated less five mins after transplantation (p<0.01); the incidence of injection pain during induction was reduced (p<0.001) and intraoperative hypotension was decreased (p<0.01).

CONCLUSIONS: Ciprofol is safe and effective for anesthesia induction and maintenance in kidney transplantation and its sedative effect is better than that of propofol.

Key Words:
Kidney transplantation; General anesthesia; GABA$_A$ receptor agonist; Ciprofol.

Introduction

Ciprofol is a new drug for IV anesthesia and sedation. It is a 2.6-disubstituted phenol derivative that binds to the gamma-aminobutyric acid-A (GABA$_A$) receptor[1]. By enhancing GABA receptor mediated Cl^- influx, GABAergic neurons are activated and the nerve cell membrane supersized, resulting in central nervous system inhibition to achieve sedative or anesthetic effects[2]. Phase I trials have shown that a single IV injection of ciprofol in healthy volunteers over a dose range of 0.15-0.90 mg/kg was well tolerated, and showed non-linear pharmacokinetic characteristics in the dose range of 0.40-0.90 mg/kg[3,4]. The results of phase II and phase III clinical trials showed that ciprofol had a rapid onset, rapid recovery, a high titer, and less injection pain, characteristics that are suitable mainly for sedation in gastrointestinal endoscopy and induction of general anesthesia in adult patients[5,6].

The effect of general anesthesia induction and maintenance of ciprofol in kidney transplantation patients has not yet been studied. The aim of this study was to evaluate the effect of ciprofol on the induction and maintenance of general anesthesia in patients with kidney transplantation and provide a basis for its clinical application.

Patients and Methods

The study was approved by the Hospital Ethics Committee and registered by the China Clinical Trial Registry (ChiCTR2200058826). Signed, informed consent to participate in the study was obtained from the patients and their families before the operation.

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The study design was a prospective, randomized, single-blind study conducted on 120 patients who had a kidney transplant under general anesthesia with tracheal intubation at the Second Affiliated Hospital of Guangxi Medical University, and was aged 18-65 years, with a body mass index (BMI) of 18-30 kg/m^2 and an American Society of Anesthesiology (ASA) physical status of III-IV. The surgeons who performed the kidney transplants were all from the same group. Patients were excluded according to the following criteria: patients with liver, mental, nervous system diseases, coagulation dysfunctions, heart failure, respiratory failure, long-term use of sedatives or antidepressants, pregnant or lactating women, and unable to communicate or cooperate. Patients were withdrawn from the study according to the following criteria: severe bleeding (bleeding volume > 2,000 mL), persistent hypoxemia ($SpO_2 \leq$ 90%, > 5 min), severe cardiovascular events (malignant arrhythmia, acute myocardial ischemia), and anaphylactic shock. The patients were divided randomly into two groups (n=60), a ciprofol group (group C) and a propofol group (group P). All patients had fasted for 6-8 hours before the operation and hemodialysis was performed one day before the operation, without preoperative sedatives. After the patients had entered the operating room, peripheral venous access was opened, an electrocardiogram (ECG) was performed, and non-invasive blood pressure (NIBP), peripheral oxygen saturation (SpO2), heart rate (HR), and temperature (T) were monitored routinely. Invasive blood pressure (IBP) was monitored by radial artery puncture, while intubation under local anesthesia of the anterior upper limb on the side of non-arterial fistula and the depth of anesthe-sia were monitored by the bispectral index (BIS). Rapid intravenous induction was used in both groups. Group C received an IV injection of ciprofol (batch number: H20200013, Liaoning Haisike Pharmaceutical Co., Ltd.) at a dose of 0.4 mg/kg, and administration time of 10-30 s, while group P received an IV injection of 1% propofol (batch number: JX20160026, Fissenius Carbi Pharmaceutical Co. Ltd., Beijing) at a dose of 2.0 mg/kg. When the eyelash reflex disappeared and the BIS value was ≤60 administration was stopped, followed by an IV injection of sufentanil 0.4-0.5 μg/kg and cisatracurium 0.2 mg/kg. Endotrache-al intubation was performed when sufentanil and the muscle relaxant had worked fully, and the BIS value was <50. A ventilator was then connected for mechanical ventilation using the following parameters: VT 6-8 ml/kg, RR 12-20 times/min, the inspiratory-to-expiratory ratio of 1:2, oxygen flowed 2 L/min, and maintaining $P_{ET}CO_2$ at 35-45 mmHg (1 mmHg=0.133 kPa). Maintenance of anesthesia: group C received an IV infusion of ciprofol 0.8-2.4 mg•kg^{-1}•h^{-1}, group P received an IV infusion of propofol 4-12 mg•kg^{-1}•h^{-1}, while both groups received remifentanil 8-15 μg•kg^{-1}•h^{-1} and cisatracurium 0.1-0.2 mg•kg^{-1}•h^{-1}. Before the blood vessels of the transplanted kidney were opened, diuretics (furosemide and mannitol), hormones, and immunosuppressants were given routinely. Dopamine (1-10 μg•kg^{-1}•min^{-1}) was IV pumped through the internal jugular vein to adjust blood pressure. The mean arterial pressure (MAP) of the patients was maintained at 80-130 mmHg or ± 30% of the preoperative basic blood pressure before and after the vascular opening of the transplanted kidney. The dose of the drugs was adjusted according to IBP, BIS value, HR, and the patient's body movements with the aim of maintaining the BIS value between 40-60.

The success rate of sedation (BIS value 40-60 after administration, and no intraoperative awareness), the time for disappearance of the eyelash reflex, the time BIS dropped to 60, recovery time (drug withdrawal to Ramsay score ≤2), operation time, and anesthesia time were recorded. MAP and HR were recorded before anesthesia induction (T0), 1 min (T1), 3 min (T2), and 5 min (T3) after anesthesia induction, 5 min (T4) before the vascular opening of the transplanted kidney, immediately after (T5) the vascular opening of the transplanted kidney, and 5 min after (T6) the vascular opening of the transplanted kidney. Urea, creatinine, cystatin C levels, and glomerular filtration rate were recorded one day before the operation (T7), one day after the operation (T8), and 7 days after the operation (T9). Urine volume was recorded one day after the operation (T10), 3 days after the operation (T11), and 7 days after the operation (T12). The dosages of the sedatives, remifentanil, cisatracurium, and dopamine were recorded during the maintenance period. The following events were also recorded: the occurrence of hypotension, bradycardia, and injection pain during induction; the occurrence of hypertension, sinus bradycardia, and sinus tachycardia during the operation; the occurrence of postoperative nausea and vomiting, agitation during recovery, and delayed recovery; the 24 hours cognitive situation (MMSE scale assessment, normal 27-30 points, cognitive dysfunction < 27 points) and intraoperative awareness.

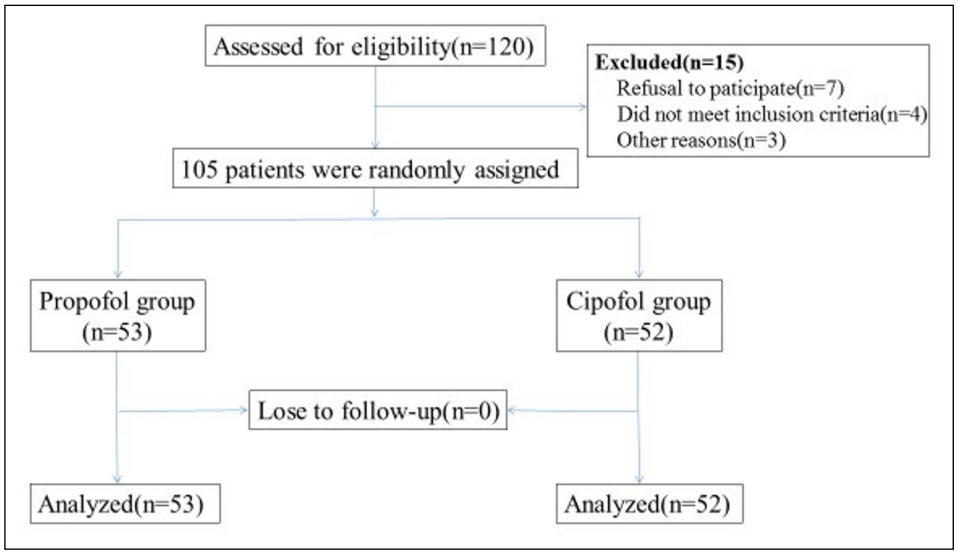

Figure 1. Flow diagram of the study.

Statistical Analysis

SPSS 21.0 was used for the statistical analyses (IBM Corp., Armonk, NY, USA). Categorical data were expressed as percentages and analyzed using the Chi-square test, while continuous data were expressed as mean ± SD. The independent-sample *t*-test was used for comparison between groups and the paired *t*-test was used for comparison within groups. A test level α=0.05 and a *p*-value <0.05 indicated that the differences were statistically significant.

Results

A total of 105 patients completed the study (Figure 1). As shown in Table I, there was no significant difference in the general situation of each index between the two groups (p>0.05).

The success rate of sedation in both groups was 100%. As shown in Figure 2, in group C the time of disappearance of the eyelash reflex and the time taken for the BIS to drop to 60 was shortened (p<0.001), the recovery time prolonged (p<0.001), and the dosages of the sedative drugs reduced during the operation (p<0.001) compared to those observed in group P.

The hemodynamic changes are presented in Figure 3. HR showed no significant difference between the two groups (p>0.05). MAP decreased more significantly in group P at T6 (p<0.05).

There was no significant difference in the dosages of maintenance anesthetic and vasoactive drugs (p>0.05) (Table II).

Table I. Characteristic of patients.

	Group Propofol (n=53)	Group Ciprofol (n=52)	t/χ^2	*p*
Age (years)	41.25±10.63	39.00±10.10	1.109	0.27
Gender, n (%)				
Male	18 (34.0)	18 (34.6)	0.005	0.944
Female	35 (66.0)	34 (65.4)		
BMI (kg/m²)	22.63±2.38	23.38±3.33	-1.314	0.192
ASA PS, n (%)				
III	44 (83.0)	42 (80.8)	0.09	0.765
IV	9 (17.0)	10 (19.2)		
Operation time	165.49±34.27	175.88±42.22	-1.386	0.169
Anesthesia time	234.58±41.16	241.92±55.23	-0.771	0.443

Data are presented as the mean±standard deviation or as numbers with percentages; BMI, body mass index; ASA PS: American Society of Anesthesiologists physical status.

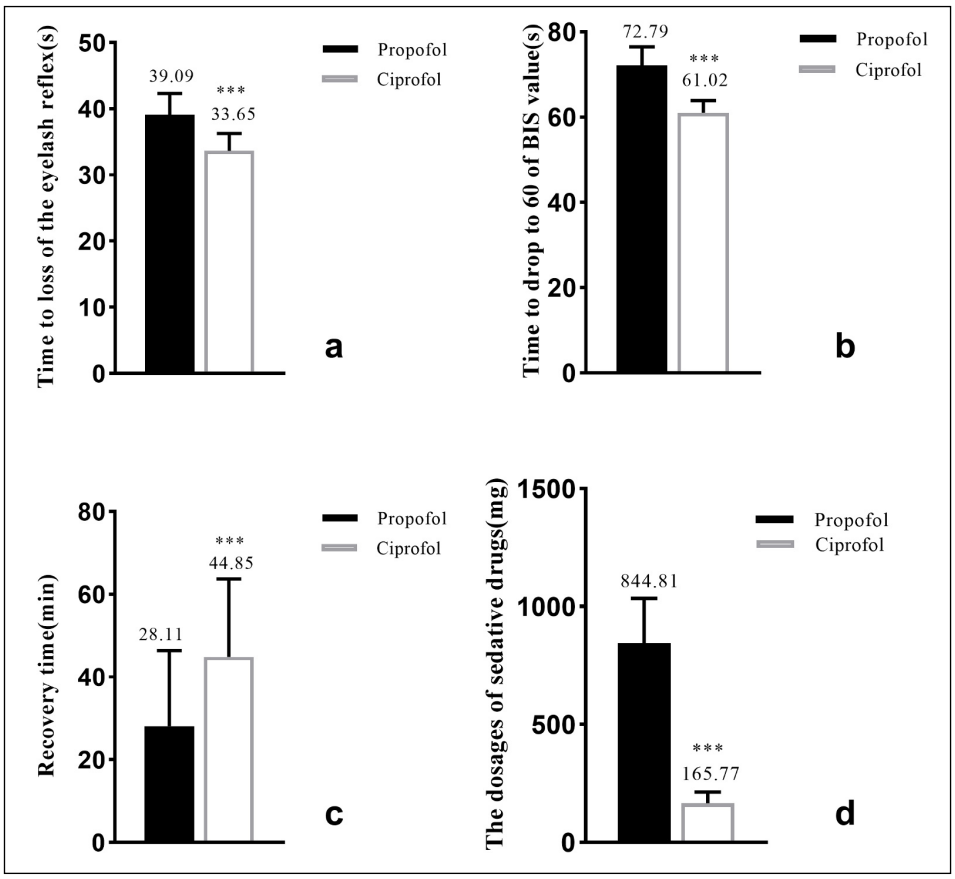

Figure 2. Comparison of the sedative effect in introduction and the dosages of sedative drug during operation. Data is presented as mean; BIS, bispectral index. ***p<0.001 between the two groups.

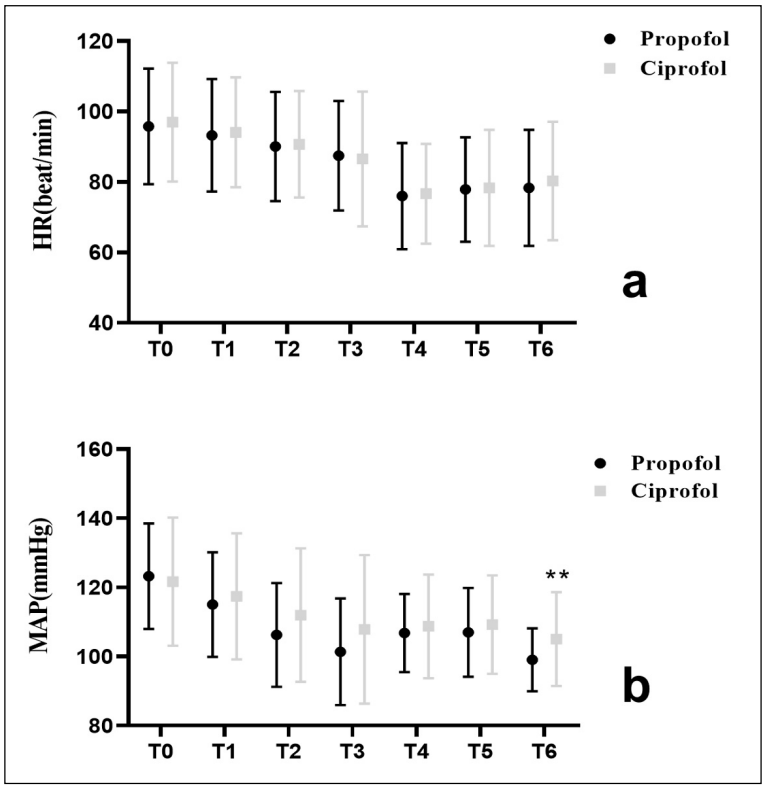

Figure 3. Heart rate and mean arterial pressure variations. Values are expressed as means. **p<0.01 between the two groups at the same time point. HR, heart rate; MAP, mean arterial pressure.

Table II. Comparison of the dosages of intraoperative drugs.

	Group Propofol (n=53)	Group Ciprofol (n=52)	t	p
Remifentanil (mg)	1.62±0.40	1.67±0.60	-0.471	0.639
Citracurium (mg)	19.49±8.61	20.94±8.01	-0.894	0.374
Dopamine (mg)	37.60±24.69	35.42±27.79	0.425	0.672

Data are presented as mean±standard deviation or as numbers.

After 24 hours of follow-up, no cognitive dysfunction and intraoperative awareness occurred in the two groups. Compared to group P, the incidence of injection pain during induction was reduced ($p<0.001$) and intraoperative hypotension was decreased in group C ($p<0.01$). As shown in Table III, there was no significant difference between the two groups in the incidence of sinus tachycardia, sinus bradycardia, post-operative nausea and vomiting, restlessness during recovery, and delayed recovery ($p>0.05$).

There was no significant difference in the postoperative kidney function recovery index between the two groups at T7-9 and T10-12 (all $p>0.05$) (Figure 4).

Discussion

With the extension of maintenance hemodialysis time, the survival rate of hemodialysis patients with end-stage renal disease (ESRD) has decreased year by year[7], with allogeneic kidney transplantation being the most effective treatment for ESRD[8]. With the progress of surgical techniques, the hemodynamics of patients fluctuates greatly, and how to maintain stable hemodynamics is now a key issue in kidney transplantation anesthesia[9]. This requires strict control of anesthetic drugs used during the perioperative period. Appropriate sedative drugs combined with an appropriate depth of anesthesia not only avoid intraoperative knowledge but also prevent excessive accumulation of anesthetic drugs conducive to the early awakening of patients, reduce medical costs and decrease the occurrence of complications.

Propofol and etomidate are commonly used as intravenous sedatives in clinical anesthesia. Studies[10] have shown that when propofol is administered IV in uremic patients, the plasma clearance rate hardly changes. However, it should be noted that the dosage will cause hemodynamic fluctuations, as it can cause hemodynamic inhibition and peripheral vascular dilation, resulting in hypotension, injection pain, and the propofol infusion syndrome[11-13]. Injection pain affects the comfort experience of patients with anesthesia induction, while intraoperative and early post-operative hypotension, as risk factors for delayed recovery of transplanted renal function, may lead to delayed or even non-recovery of transplanted renal function[14]. Etomidate causes relatively stable hemodynamics during anesthesia induction, whereas long-term and high-dose IV infusion of this sedative can inhibit kidney cortex function, resulting in the disappearance of the perioperative stress response,

Table III. Summary of drug-related adverse events.

	Group Propofol (n=53)	Group Ciprofol (n=52)	χ^2	p
Study drug-related adverse events n (%)				
Induced hypotension	5 (9.4)	4 (7.7)	0.0001	1.000
Induced bradycardia	5 (9.4)	2 (3.8)	0.572	0.449
Induced injection pain	32 (60.4)	1 (1.9)	41.615	0.0001***
Intraoperative hypotension	11 (20.8)	2 (3.8)	6.918	0.009**
Intraoperative bradycardia	14 (26.4)	7 (13.5)	2.753	0.097
Intraoperative tachycardia	18 (34.0)	11 (21.2)	2.154	0.142
Postoperative nausea and vomiting	3 (5.7)	2 (3.8)	0.0001	1.000
Restlessness during awakening	2 (3.8)	3 (5.8)	0.0001	0.983
Awakening delay	0 (0)	0 (0)		

Data are presented as numbers with percentages; ***$p < 0.001$ and **$p < 0.01$ between the two groups.

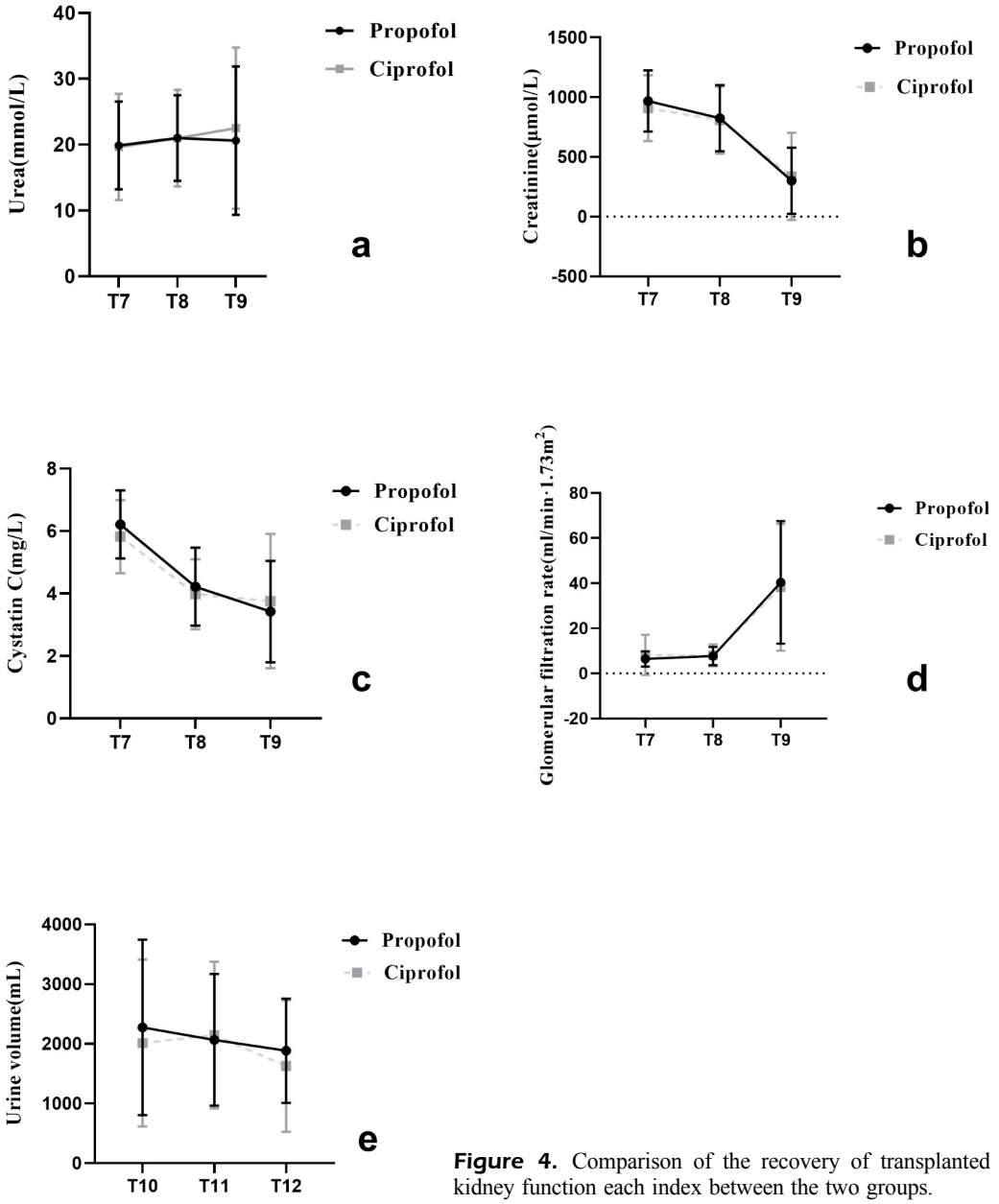

Figure 4. Comparison of the recovery of transplanted kidney function each index between the two groups.

thereby reducing the body's tolerance to emergency stimuli, changes which are not beneficial or patients with kidney failure[15]. As a new short-acting $GABA_A$ receptor agonist, ciprofol induces sedation or anesthesia by enhancing GABA-mediated Cl^- influx. According to the completed clinical trials of sedation or anesthesia and general anesthesia induction of gastrointestinal endoscopy, the sedative effect of ciprofol was accurate, with lower doses producing a satisfactory general anesthetic effect. The incidence of injection pain was significantly lower than that of propofol. The incidence of common adverse reactions, such as hypotension and bradycardia, within 30 minutes after induction was no different from that of propofol, although the awaking time was similar to or slightly longer than that associated with propofol[6]. The results of phase II clinical trials[16] have shown that the recommended initial maintenance dose of ciprofol is 0.8 $mg•kg^{-1}•h^{-1}$.

Previous studies[17] have shown that a high concentration of propofol in the aqueous phase of emulsion will lead to injection pain. In the current study, the incidence of injection pain with

ciprofol was significantly lower than that caused by propofol. The mechanism for this reduction in pain may be that ciprofol is insoluble and is formulated as water in an oil emulsion[11]. In addition, compared with propofol, the higher hydrophobicity and lower plasma concentration of ciprofol may lead to a reduction in injection pain[18]. A reduction in injection pain is conducive to alleviating a patient's emotional tension and fear, reducing hemodynamic fluctuations, and improving the stability of anesthesia induction.

Some studies[19,20] have shown that the injection of sufentanil and midazolam before sedative drugs reduces injection pain, but may also affect judgment concerning the effect of sedative drugs. In order to reduce the interference of analgesics and muscle relaxants on the onset time of sedative drugs and injection pain, the order of anesthesia induction is achieved by the administration of the sedative drugs, sufentanil, and cisatracurium. The results of this study show that the BIS value of the two groups can be reached and maintained at 40-60 at the induction and maintenance doses of the sedatives, with a success rate of sedation of 100%. Compared with the propofol group, the onset time of sedation in the ciprofol group was slightly shorter, and vital signs were more stable. These results confirm that ciprofol can be used effectively for general anesthesia.

There was no significant difference in the incidence of sinus bradycardia and tachycardia during the maintenance of anesthesia between the two study groups. This finding was possibly related to the blood drug concentrations and anesthesia time. However, the incidence of intraoperative hypotension with ciprofol was lower than that of propofol. The reason for this difference is that propofol can cause hemodynamic inhibition and peripheral vasodilation. In order to provide sufficient filtration pressure for the transplanted kidney during transplantation, vasoactive drugs are often used to control intraoperative blood pressure. This is especially relevant after the renal artery is opened when it is necessary to maintain the recipient's arterial blood pressure at a high level to ensure the perfusion of the transplanted kidney. In theory, when dopamine is used in small doses it has a renal protective effect. A dose of 1-3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ activates the dopamine receptor, resulting in renal vasodilation and increased blood flow in the renal vasculature, while a dose of 4-10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ can activate the β_1 adrenergic receptor, thereby accelerating heart rate, enhancing myocardial contractility and increasing cardiac output and renal blood flow[21]. The current study showed no significant difference in the dose of dopamine used during the operations between the two groups. Compared with the propofol group, the hemodynamics of the ciprofol group were more stable, which was more conducive to reducing the stress of the operation, maintaining blood perfusion of the transplanted kidney, and promoting the recovery of the transplanted kidney. Experiments in mice have shown that the therapeutic index (TI) of ciprofol was 6.6, about 2.4-fold higher than that of propofol and that its safety range was also wider[11]. The results also showed that the average dose of propofol used in anesthesia maintenance was about 4-5 times higher than that of ciprofol, which suggests that ciprofol may have stronger $GABA_A$ receptor binding activity. These findings are consistent with those reported in literature.

There were no differences in cognitive impairment and intraoperative awareness during the recovery period and within 24 hours after the operation between the two study groups. There was also no significant difference in the incidence of agitation during awakening and postoperative nausea and vomiting between the two groups. Recovery time in the ciprofol group was slightly longer than that in the propofol group. The reason for this difference is that propofol has a very high metabolic rate in the liver and only a small amount is metabolized in the urine[22], whereas metabolic clearance of ciprofol is mainly through the kidney (84.6%)[23]. The combined effects of the patient's original kidney failure and the transplanted kidney function not having fully recovered, results in slow excretion and accumulation of drugs, causing waking time to be prolonged.

Previous studies[6] have shown that there is generally no need to adjust the dose of sedative drugs in patients with mild/moderate kidney insufficiency (eGFR: 30-89 $ml \cdot min^{-1} \cdot 1.73m^{-2}$). However, relevant clinical data have not been obtained in patients with severe kidney insufficiency. Delayed recovery of transplanted renal function is an early, high-incident complication after renal transplantation. Clinically, this is manifested mainly as oliguria or even anuria, with a slow or absent decrease in serum creatinine levels[24]. Studies have shown that the serum concentrations of urea and creatinine, glomerular filtration rate, and urine volume are classic indicators for clinical evaluation of kidney function and can act as a rough and rapid evaluation of creatinine clearance. Cystatin C levels provide an early marker of small changes in glomerular filtration rate and

have higher specificity and sensitivity to kidney function impairment[25-28]. In the current study, the early postoperative urine volume in the two groups increased significantly, and there was no significant difference between the two groups during this period. Meanwhile, compared with levels measured one day before the operation, the serum concentrations of urea, creatinine, and cystatin C decreased significantly, the glomerular filtration rate increased, and graft function improved significantly in both groups. There was also no significant difference in serum urea, creatinine, and cystatin C levels and glomerular filtration rate between the two groups. Based on these findings, the early postoperative renal transplantation function of the two groups appears to have improved significantly, suggesting that the sedative drugs used in the study had no significant effect on early postoperative renal transplantation function. In addition, no adverse effects on kidney transplant function were observed in the propofol and ciprofol groups, indicating that both these sedative drugs can be safely used in kidney transplantation.

Limitations

Monitoring and comparison of the plasma concentrations of ciprofol and propofol were not carried out during the experiments in the current study. Maintaining a relatively stable plasma concentration with plasma target-controlled infusion of the sedative drugs under BIS guidance during the operation effectively inhibits stress reactions, such as endotracheal intubation, operation, and extubation, beneficial changes which are conducive to rapid rehabilitation of patients[29,30]. In addition, the study did not compare indices of pre-operative and post-operative cellular immune function. Although the two groups of sedatives had no significant effect on the improvement in early post-operative kidney transplant function, their effect on post-operative cellular immune function requires further study. Finally, this study was a small sample, single-center, clinical study, which needs to be confirmed by a large sample, multicenter clinical study.

Conclusions

Ciprofol has similar safety and tolerability to propofol and can be used safely and effectively for induction and maintenance of general anesthesia in patients undergoing kidney transplantation.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Informed Consent

Signed, informed consent to participate in the study was obtained from the patients and their families before the operation.

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