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ORIGINAL RESEARCH

Effect of Remimazolam on Induction and Maintenance of General Anesthesia in Kidney Transplant Patients

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Purpose: This study aims to evaluate the effect of remimazolam on induction and maintenance of general anesthesia in kidney transplant patients.

Methods: 120 patients undergoing kidney transplant were divided into two groups: Propofol group (Group P) and Remimazolam group (Group R). Anesthesia induction: remimazolam had injected IV at a dose of 0.15–0.35 mg/kg in Group R, while propofol had injected IV at a dose of 2.0–2.5 mg/kg in Group P. Anesthesia maintenance: remimazolam was injected IV at a dose of 0.3–1.0 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ and propofol was injected IV at a dose of 1–12 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ in Group R, propofol was injected IV at a dose of 3–12 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ in Group P. All patients have the same remaining anesthesia durgs.

Results: Compared with Group P, in Group R the time of disappearance of the eyelash reflex and the time to drop to 60 in BIS was longer ($P < 0.05$), the time of awakening was shorted ($P < 0.05$), the MAP of T_6 was fluctuated less ($P < 0.05$), the incidence of hypotension and injection pain during induction was reduced ($P < 0.001$), the incidence of intraoperative bradycardia during operation was reduced ($P < 0.05$), the dosages of sedatives drug during maintenance was reduced ($P < 0.05$). There was no statistically significant difference in postoperative renal function between the two groups of patients ($P > 0.05$).

Conclusion: Remimazolam can be safely and effectively used for the induction and maintenance of general anesthesia in kidney transplant patients.

Keywords: remimazolam, propofol, general anesthesia, kidney transplant

Introduction

Propofol, a widely used sedative in clinical anesthesia, has the characteristics of fast sedation, short action time, rapid and complete awakening, etc, however, it has strong inhibitory effect on circulatory function, which can cause a significant decrease in blood pressure by directly inhibiting myocardial contraction and dilating blood vessels.[1] Moreover, it is prone to inducing injection pain during the infusion process.[2] Furthermore, prolonged and high-dose intravenous infusion of propofol can cause propofol infusion syndrome.[3] Remimazolam, as a new benzodiazepine sedative drug, has the characteristics of fast onset, short duration of action, no liver or renal metabolism, minor impact on the cardiovascular system, no injection pain, and can be antagonized by the benzodiazepine receptor antagonist flumazenil.[4] Currently, remimazolam is mainly used for sedation during gastroscopy and colonoscopy, as well as induction and maintenance of general anesthesia.[5,6] But the effect of remimazolam on induction and maintenance of general anesthesia in patients undergoing kidney transplant has yet to be explored. This study aims to evaluate the effect of remimazolam on induction and maintenance of general anesthesia in patients undergoing kidney transplant, providing a basis for clinical application.

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Materials and Methods

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Affiliated Hospital of Guangxi medical University (2022-KY-0150). It was registered at the Chinese Clinical Trials Registry (ChiCTR2200061051).

All donor organizations in this study were sourced from deceased citizens and voluntarily donated with the informed consent of their families, and that this was conducted in accordance with the Declaration of Istanbul. Before the operation, all patients to participate and their families also signed and informed consent form.

Design and Patients

This was a randomized, single-blind, prospective controlled clinical trial. 120 patients undergoing kidney transplant from June 2022 to June 2023 who underwent elective tracheal intubation and general anesthesia, gender unlimited, 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. Patients were excluded according to the following criteria: Non first-time kidney transplant patients, individuals with liver, mental, or neurological disorders, coagulation disorders, heart failure, respiratory failure, long-term use of sedatives or antidepressants, pregnant or breastfeeding women, those unable to communicate and cooperate. Patients were withdrawn from the study according to the following criteria: severe bleeding during operation (bleeding volume >2000 mL), sustained hypoxemia (SpO_2 ≤90%, >5 min), severe cardiovascular events (malignant arrhythmias, acute myocardial ischemia, etc.), anaphylactic shock, etc. A total of 113 patients were selected and included based on the above criteria, they were divided randomly into two groups: Propofol group (Group P, n = 57) and Remimazolam group (Group R, n = 56).

Anesthesia Management

Both groups of patients fasted for 6–8 hours before operation, underwent hemodialysis one day before operation, and did not use preoperative sedatives. Upon patients entering the operating room, venous access was established, preoxygenation was administered using a mask and oxygen flow rate was set at 6 L/min, electrocardiogram (ECG), non-invasive blood pressure (NIBP), peripheral oxygen saturation (SpO_2), heart rate (HR), and temperature (T) were monitored routinely. On the non-arterial fistula side of the forearm, local anesthesia was performed to monitor invasive blood pressure (IBP) through radial artery puncture and catheterization. Ultrasound guided right internal jugular vein puncture and catheterization were performed to establish a rapid intravenous drug delivery pathway and monitor central venous pressure (CVP). The depth of anesthesia was monitored using bispectral index (BIS). Remimazolam (Batch number: H20190034, Jiangsu Hengrui Medicine Co., Ltd.) had injected IV at a dose of 0.15–0.35 mg/kg in Group R, while 1% propofol (Batch number: JX20160026, Beijing Fresenius Kabi Pharmaceutical Co., Ltd.) had injected IV at a dose of 2.0–2.5 mg/kg in Group P. The administration was stopped, when the eyelash reflex disappears and the BIS ≤ 60. Both groups of patients had injected IV with sufentanil 0.4–0.5 μg/kg and cisatracurium 0.15–0.2 mg/kg. Endotracheal intubation was performed when sufentanil and muscle relaxation were fully effective and BIS < 50. Subsequently, a ventilator was connected for mechanical ventilation, with parameters of Tidal Volume (VT) of 6–8 mL/kg, Respiratory Rate (RR) of 12–20 times/min, Inspiration Time/Expiration Time (I:E) of 1:2, oxygen flow rate of 2 L/min, and $P_{ET}CO_2$ maintained at 35–45 mmHg (1mmHg = 0.133 kPa). Anesthesia maintenance: remimazolam was injected IV at a dose of 0.3–1.0 - $mg \cdot kg^{-1} \cdot h^{-1}$ and propofol was injected IV at a dose of 1–12 $mg \cdot kg^{-1} \cdot h^{-1}$ in Group R, propofol was injected IV at a dose of 3–12 $mg \cdot kg^{-1} \cdot h^{-1}$ in Group P, while both groups of patients were injected IV with remifentanil at a dose of 8–15 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and cisatracurium at a dose of 0.1–0.2 $mg \cdot kg^{-1} \cdot h^{-1}$. Both groups of patients were routinely given the same type of diuretics, hormones, and immunosuppressants before the opening of the transplanted renal blood vessels, and dopamine at a dose of 1–10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was pumped through the internal jugular vein adjust blood pressure. Both groups of patients maintained MAP at ±30% of the preoperative baseline value before and after the opening of the transplanted renal blood vessels. Adjust the dosage of the drug based on IBP, HR, and CVP to maintain BIS between 40 and 60. After the surgery, all patients were admitted to the Transplantation intensive care unit (TICU) for specialized care.

Data Collection

Recorded the general data, operation time, anesthesia time, intraoperative infusion volume, and intraoperative bleeding volume of the two groups of patients; Recorded the time of disappearance of the eyelash reflex, the time to drop to 60 in BIS, and the time of awakening (from cessation of medication after operation to Ramsay score ≤2 points) of the two groups of patients; Recorded the MAP and HR before anesthesia induction (T_0), 1 minute after anesthesia induction (T_1), 3 minutes after anesthesia induction (T_2), 5 minutes after anesthesia induction (T_3), 5 minutes before transplant renal vessel opening (T_4), immediately after transplant renal vessel opening (T_5), and 5 minutes after transplant renal vessel opening (T_6) of the two groups of patients; Recorded the dosage of sedative drugs, remifentanil, cisatracurium, and dopamine of the two groups of patients during the anesthesia maintenance period; record the incidence of hypotension, bradycardia and injection pain of the two groups of patients during induction; Recorded the incidence of hypotension, sinus bradycardia, and sinus tachycardia of the two groups of patients during operation; Recorded the incidence of and nausea and vomiting, restlessness, and awakening delayed of the two groups of patients after 24-hours after operation; Recorded the urea, creatinine, cystatin C, and glomerular filtration rate of the two groups of patients on 1 day before operation (T_7), 1 day after operation (T_8), 3 days after operation (T_9), and 7 days after operation (T_{10}); Recorded urine volume of the two groups of patients on 1 day after operation (T_{11}), 3 days after operation (T_{12}), and 7 days after operation (T_{13}).

Statistical Analysis

Statistical analysis was conducted using SPSS 21.0 statistical software (IBM Corp., Armonk, NY, USA), where measurement data were expressed as mean ± standard deviation ($\bar{x}\pm$ s), independent sample *t*-tests were used for inter group comparisons; count data were represented as numbers and composition ratio *(n, %)*, and tested by chi-square test. $P < 0.05$ was statistically significant.

Results

A total of 120 patients were initially included in the study, but three patients refused to participate, two patients non first-time kidney transplant and two patients had a history of liver failure were excluded. Ultimately, 113 patients (Group P, n = 57 and Group R, n = 56) completed the trial (Figure 1).

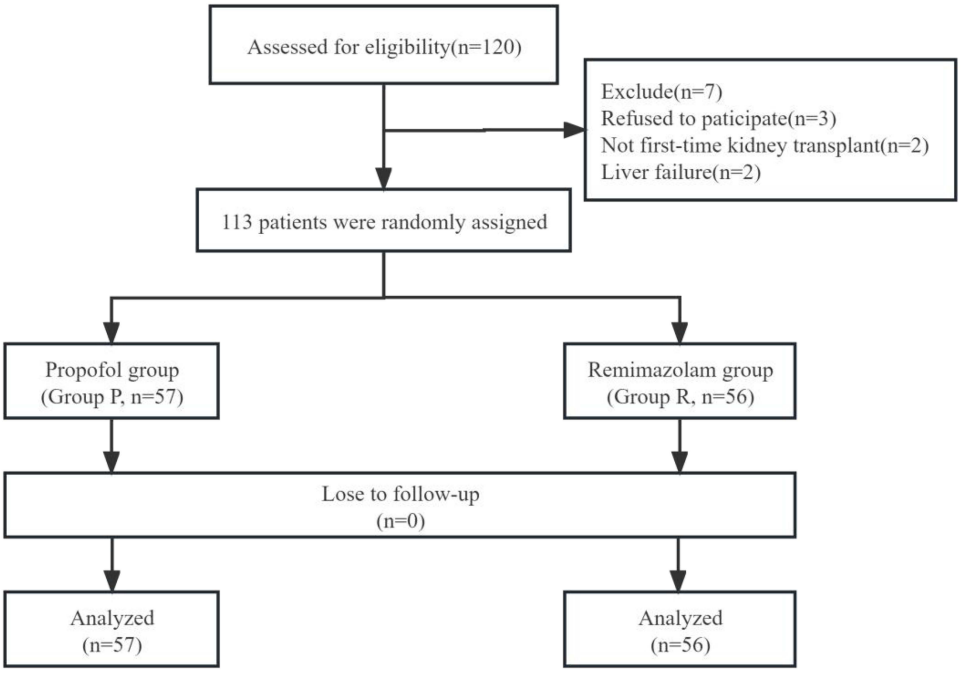

Figure 1 Flow diagram of the study.

As shown in Table 1, there was no statistically significant difference in the general and surgical conditions between the two groups ($P > 0.05$).

As shown in Table 2, compared with Group P, in Group R the time of disappearance of the eyelash reflex, and the time to drop to 60 in BIS was longer ($P < 0.05$), the time of awakening was shorted ($P < 0.05$).

As shown in Figure 2, there was no statistically significant difference in the comparison of HR between the two groups of patients at $T_{0\text{-}6}$ ($P > 0.05$).

As shown in Figure 3, compared with the MAP of T_4, both groups showed a decrease in the MAP of T_6, but compared with Group P, the MAP of T_6 in Group R was fluctuated less ($P < 0.01$).

Table 1 Comparison of General and Surgical Data Between the Two Groups

Item	Group P (n=57)	Group R (n=56)	t/x^2 value	*P* value
Gender (Male/Female, n)	40/17	41/15	0.075	0.844
Age (years)	43.45±12.33	42.30±12.10	1.003	0.474
BMI (kg/m^2)	24.40±2.38	23.18±2.33	−1.214	0.392
ASA (III/IV, n)	44/13	42/14	0.061	0.565
operation time(min)	170.58±31.65	169.88±32.22	−1.386	0.169
Anesthesia time(min)	240.16±42.56	238.92±45.23	−0.631	0.443

Notes: Data are presented as n or the mean±standard deviation.
Abbreviations: Group P, propofol group; Group R, remimazolam group; BMI, body mass index; ASA: American Society of Anesthesiologists.

Table 2 Comparison of Sedative Effect Between the Two Groups

Item	Group P (n=57)	Group R (n=56)	*t* value	*P* value
Time of disappearance of the eyelash reflex (s)	42.51±2.35	53.65±2.61	6.421	< 0.001**
Time to drop to 60 in BIS(s)	80.91±22.19	111.02±20.90	3.201	< 0.001**
Time of awakening(min)	18.11±6.26	16.85±5.32	1.624	0.03*

Note: *P versus Group P, $P < 0.05$; **P versus Group P, $P < 0.001$. Data are presented as the mean±standard deviation.
Abbreviations: Group P, propofol group; Group R, remimazolam group.

As shown in Table 3, postoperative 24-hour follow-up, there was no awakening delay or intraoperative awareness in both groups of patients. Compared with Group P, in Group R the incidence of hypotension and injection pain during induction was reduced ($P < 0.001$), the incidence of intraoperative bradycardia during operation was reduced ($P < 0.05$).

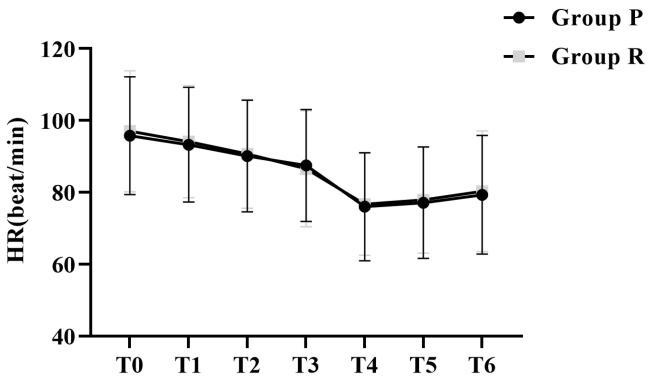

Figure 2 Comparison of HR between two groups of patients at different moments.
Notes: Data were expressed as the mean ± standard deviation.
Abbreviations: HR, Heat rate. Group P, propofol group; Group R, remimazolam group.

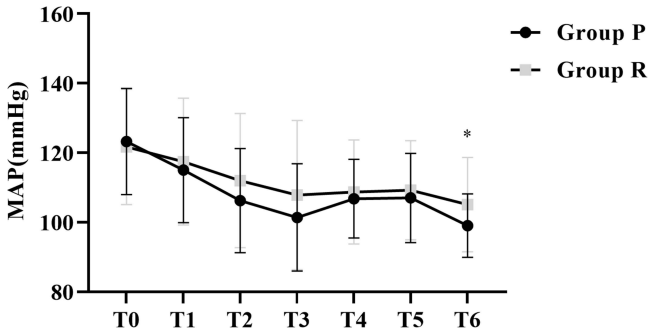

Figure 3 Comparison of MAP between two groups of patients at different moments.
Note: *P versus Group P, $P < 0.05$; Data were expressed as the mean ± standard deviation.
Abbreviations: MAP, mean arterial pressure. Group P, propofol group; Group R, remimazolam group.

There was no statistically significant difference in the incidence of bradycardia during induction, intraoperative hypotension, intraoperative tachycardia, postoperative nausea and vomiting, and restlessness during recovery between the two groups of patients ($P > 0.05$).

As shown in Table 4, compared with Group P, in Group R the dosage of sedative drugs during anesthesia maintenance decreased ($P < 0.001$). There was no statistically significant difference in the dosage of remifentanil, cisatracurium, and dopamine between the two groups of patients during the anesthesia maintenance period ($P > 0.05$).

As shown in Figure 4, there was no statistically significant difference in urea, creatinine, cystatin C, and glomerular filtration rate between the two groups on T_7-T_{10} ($P > 0.05$); There was no statistically significant difference in urine volume between the two groups on T_{11}-T_{13} ($P > 0.05$).

Discussion

The extension of maintenance hemodialysis duration in end-stage renal disease hemodialysis patients leads to a decrease in their survival rate year by year.[7] Kidney transplant is the most effective treatment for end-stage renal disease.[8] As the surgical procedure progresses, there are significant fluctuations in hemodynamics during kidney transplant operation, and how to maintain stable hemodynamics is one of the key contents of kidney transplant anesthesia.[9] This requires the use of anesthetic drugs during surgery to be safe and effective for kidney transplant patients. On the one hand, hemodynamics should be stable on the other hand, it should be conducive to the recovery of postoperative renal function in patients.

During anesthesia induction in this study, the sedation onset time of the remimazolam group was slightly longer than that of the propofol group. On the one hand, remimazolam is effective against γ-aminobutyric acid type A receptor ($GABA_A$) α1-subunit has a high affinity, while the affinity for the β-subunit is similar to that of propofol, its distribution

Table 3 Comparison of Adverse Events Between the Two Groups

Periods	Adverse Events	Group P (n=57)	Group R (n=56)	x^2 value	*P* value
Induction	Hypotension	17 (29.82)	3 (5.36)	11.609	< 0.001**
	Bradycardia	6 (10.53)	2 (3.57)	2.077	0.150
	Injection pain	35 (61.40)	0 (0)	49.816	< 0.001**
Intraoperative	Hypotension	11 (19.30)	8 (14.29)	0.507	0.476
	Bradycardia	14 (24.56)	4 (7.14)	6.400	0.011*
	Tachycardia	5 (8.77)	1 (1.79)	2.742	0.098
	Awareness	0 (0)	0 (0)	0.000	1.000
Postoperative	Nausea and vomiting	12 (21.05)	15 (26.79)	0.511	0.475
	Restlessness	4 (7.02)	3 (5.36)	0.134	0.714
	Awakening delay	0 (0)	0 (0)	0.000	1.000

Note: *P versus Group P, $P < 0.05$; **P versus Group P, $P < 0.001$. Data are presented as n (%).
Abbreviations: Group P, propofol group; Group R, remimazolam group.

Table 4 Comparison of the Dosage of Drugs During Operation Between the Two Groups

Drugs		Group P (n=57)	Group R (n=56)	*t* value	*P* value
Sedative drugs (mg)	Propofol	844.81±189.59	565.77±27.80	5.421	< 0.001**
	Remimazolam	0	28.43±5.23	1.035	< 0.001**
Remimazolam (mg)		1.61±0.44	1.57±0.54	−0.471	0.436
Cisatracurium (mg)		21.06±5.61	20.34±5.01	−0.894	0.324
Dopamine (mg)		47.60±9.69	45.42±10.79	0.325	0.672

Note: **P versus Group P, $P < 0.001$. Data were expressed as the mean±standard deviation.
Abbreviations: Group P, propofol group; Group R, remimazolam group.

may be an important factor affecting the induction time of anesthesia.[10] On the other hand, which may be related to the high liposolubility and faster distribution of propofol.[11] At the same time, no injection pain occurred in the remimazolam group, while the incidence of injection pain in the propofol group was high, which may be related to the high concentration of free propofol in the aqueous phase of the emulsion.[12] A recent study has shown that remimazolam alleviates neuropathic pain via regulating bradykinin receptor B1 and autophagy. Therefore, remimazolam may also alleviate injection pain by blocking bradykinin signaling.[13,14] The reduction of injection pain occurrence is beneficial for alleviating patients' emotional tension and fear, reducing hemodynamic fluctuations, and improving the stability of anesthesia induction. Moreover, compared to the propofol group, the incidence of induced hypotension in the remimazolam group was lower. Intraoperative and early postoperative hypotension, as one of the risk factors for delayed recovery of transplanted kidney function, can lead to delayed or even non recovery of transplanted kidney function.[15] On the one hand, propofol was used in patients with end-stage renal disease, and the plasma clearance rate was comparable to that of healthy subjects; however, it is important to pay attention to the use of dosage, as it may cause fluctuations in hemodynamics.[16] On the other hand, propofol has the effect of inhibiting myocardial contractility and dilating peripheral blood vessels, which significantly inhibits the circulatory system.[17] But no such mechanism has been found in remimazolam yet. And a study has found that when used for induction in patients undergoing cardiac surgery, remimazolam is more effective in reducing hemodynamic fluctuations and surgical stress reactions caused by surgery compared to propofol and has no significant myocardial inhibitory effect.[18] The above characteristics of remimazolam during induction indicate that remimazolam can be safely used for anesthesia induction in kidney transplant patients.

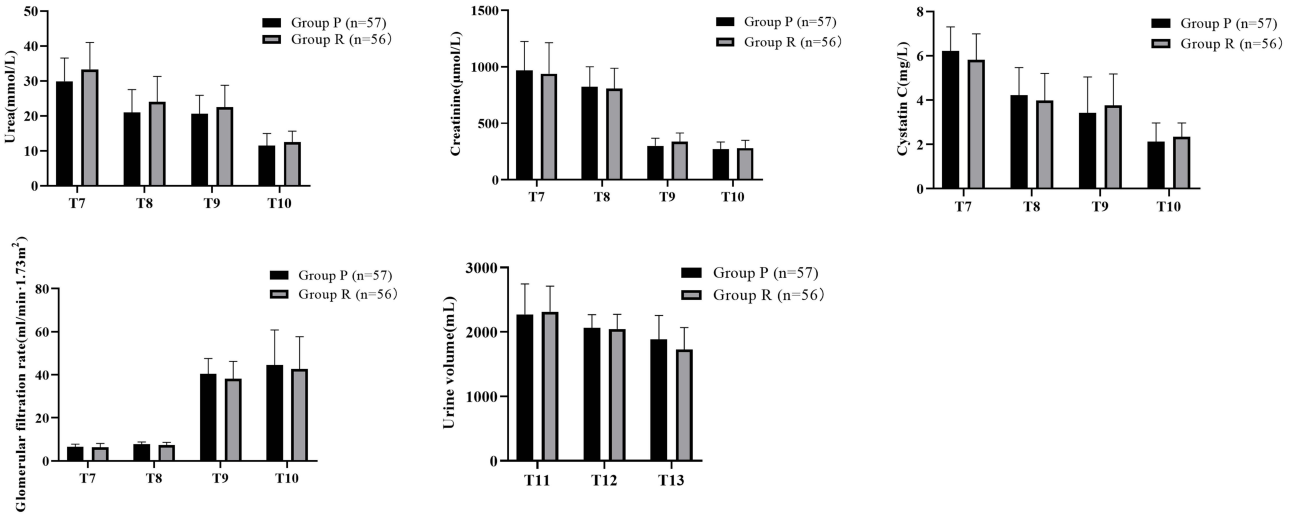

Figure 4 Comparison of postoperative renal function between the two groups.
Note: Data were expressed as the mean ± standard deviation.
Abbreviations: Group P, propofol group; Group R, remimazolam group.

During the anesthesia maintenance in this study, the remimazolam group was sedated with both remimazolam and propofol, which can reduce the dosage of propofol and facilitate hemodynamic stability. At the same time, in kidney transplant, dopamine is commonly used to increase arterial blood pressure and maintain a high level to maintain renal perfusion in order to provide sufficient filtration pressure for the transplanted renal. When dopamine is used in small doses, it theoretically has a renal protective effect, 1–3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ can activate dopamine receptors, produce renal vasodilation, and increase renal blood flow; 4–10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ can be activated β-1 adrenergic receptor, which accelerates heart rate, enhances myocardial contractility, and increases cardiac output, thereby increasing renal blood flow.[19] In this study, there was no significant difference in the dosage of dopamine used during surgery between the two groups of patients; however, compared with the MAP of T_4, both groups showed a decrease in the MAP of T_6, but compared to the propofol group, the MAP of T_6 in the remimazolam group was fluctuated less, and the incidence of intraoperative bradycardia was lower. This may be due to the small impact of benzodiazepines on myocardial contractility and a slight increase in HR.[20] In addition, remimazolam can reduce autonomic nervous system activity during general anesthesia induction and maintain a balance of sympathetic and parasympathetic nervous system activity.[21] This indicates that the hemodynamics of remimazolam are more stable, which is more conducive to reducing surgical stress, maintaining perfusion of transplanted renal blood flow and promoting the recovery of transplanted kidney function.

During the postoperative 24-hour follow-up of this study, there was no occurrence of delayed awakening or intraoperative awareness in both groups of patients and there was also no significant difference in the incidence of postoperative nausea, vomiting, and restlessness during awakening between the two groups of patients. Compared to the propofol group, the remimazolam group had a slightly shorter awakening time. On the one hand, the time-dependent half-life and final half-life of remimazolam are shorter than those of propofol.[22] On the other hand, in terms of metabolism, remimazolam can be rapidly hydrolyzed by non-specific esterases to the inactive metabolite CNS7054 (zolam propionic acid), independent of liver and renal metabolism.[23] Therefore, compared to propofol, remimazolam has lower residual levels and shorter accumulation time in the body. Long term and high-dose intravenous administration will not accumulate in the body, and it has lower metabolite activity, which helps patients recover after surgery.[24,25]

Previous studies have shown that urea, creatinine, glomerular filtration rate, and urine volume are classic indicators for clinical evaluation of renal function, which can roughly evaluate a rapid creatinine clearance ability.[26–29] Cystatin C can quickly reflect small changes in glomerular filtration rate and has higher specificity and sensitivity for early renal function damage.[30] In this study, there was a significant increase in urine volume in the early postoperative period between the two groups of patients, and there was no statistically significant difference compared to the same period; Compared with the 1 day before operation, the concentrations of urea, creatinine, and cystatin C in the serum of both groups of patients significantly decreased 7 days after operation, and the glomerular filtration rate increased. Judging from the above indicators, there was a significant improvement in early postoperative kidney transplant function in both groups of patients, indicating that the two groups of sedative drugs did not have a significant impact on the improvement of early postoperative kidney transplant function in kidney transplant patients. Moreover, there was no statistically significant difference in serum urea, creatinine, cystatin C, and glomerular filtration rate between the two groups during the same period. No adverse effects of the two groups of sedative drugs on early postoperative kidney transplant function were found, it is suggested that both groups of sedative drugs can be safely used for kidney transplant.

Limitations

The study had some limitations, including the lack of monitoring of blood concentration of remimazolam and propofol. In addition, this study did not monitor the long-term recovery of transplanted renal function after kidney transplant using two sets of sedative drugs. Finally, this study is a small sample, single center clinical study that needs further confirmation from large sample, multi-center clinical studies.

Conclusion

Remimazolam can be safely and effectively used for the induction and maintenance of general anesthesia in kidney transplant patients.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangxi medical University (2022-KY-0150). The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2200061051). The study was conducted following the declaration of Helsinki, and informed consent was retrieved from patients. All kidneys were donated voluntarily with written informed consent, and that this was conducted in accordance with the Declaration of Istanbul.

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Disclosure

The authors declare no competing financial or personal relationships regarding the publication of this manuscript.

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