Effect of Isoflurane versus Propofol on the Early Outcome of Living Donor Adult Kidney Transplantation

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ABSTRACT

Background: Optimizing anesthetic management for the best possible outcome is essential in kidney transplantation (KT).

Objective: To evaluate the difference in grafted kidney function and early kidney transplant outcome when the pairs of donor-recipient were anesthetized with isoflurane compared to propofol.

Methods: Thirty-eight pairs of kidney transplant donor-recipient were anesthetized with isoflurane, and 22 pairs were anesthetized with propofol. Blood urea nitrogen (BUN), serum creatinine (SCr), estimated glomerular filtration rate (eGFR) were assessed in the preoperative period, on the first postoperative day, before discharge from the hospital, and 6 months after KT. Short-term (6 months) outcomes of KT were assessed by the incidence of delayed graft function, acute rejection episodes, and graft failure.

Results: There was no statistically significant difference between the two groups in the serial measurements of SCr, BUN, eGFR, and the early outcomes (6 months) after surgery. Interestingly, donor warm ischemic time in the propofol group was significantly longer than in the isoflurane group (4.05±1.02, 2.93±0.87 minutes, respectively) (p=0.001). Moreover, postoperative hospital stay in the propofol group were significantly shorter compared to the isoflurane group (9.63±2.96, 11.78±4.91 days, respectively) (p=0.02).

Conclusion: There were no significant differences in transplanted kidney function and the early outcome of kidney transplantation between the two study groups. However, earlier hospital discharge after surgery in the propofol group suggests that propofol may be a more appropriate anesthetic choice in these patients.

KEYWORDS: Kidney; Transplantation; Propofol; Isoflurane

INTRODUCTION

Choice of appropriate anesthetic technique for renal procedures, especially transplantations, is essential. Importantly, careful intraoperative monitoring, optimization of fluid and hemodynamic status, and appropriate anesthetics are crucial for the success of kidney transplantation (KT). Different anesthetics have various hemodynamic effects on overall circulation and/or renal perfusion, and they may have the potential for inducing anti-inflammatory, anti-apoptotic, and anti-necrotic effects [1]. Ischemia-reperfusion injury (IRI) is the tissue damage caused by reperfusion to tissue after an ischemic period. The injury is associated with high morbidity and mortality [2]. Modifying IRI will have important outcomes.

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Anesthetic conditioning (AC) is the ability of anesthetics to induce biochemical changes that may reduce IRI [3]. Definition of the process based on the time of administering the agents included: before ischemia (preconditioning), during ischemia (perconditioning), and directly upon reperfusion (post-conditioning) [4].

Isoflurane - a non-toxic volatile anesthetic - is commonly used in clinical anesthesia. Volatile anesthetics such as isoflurane protect against IRI by reducing inflammation and necrosis [5]. Isoflurane may exert its reno-protective effects by inducing preconditioning [6].

Furthermore, studies have shown the non-anesthetic effects of propofol some of which include immunomodulatory, antioxidative, and neuroprotective [7]. Propofol may reduce hypothermic and ischemic acute kidney injury (AKI) in renal transplantation because of its antioxidant effects [8]. Propofol has also been studied for its reno-protective effect [9].

This study aimed to evaluate the effects of isoflurane versus propofol on transplanted kidney function and early outcomes (6 months) among adult living donor renal transplantation.

MATERIALS AND METHODS

Patients and Study Design

In this study, sixty related donor-recipient pairs who underwent living donor KT were enrolled. Inclusion criteria were: age >18 years, no history of allergy, and stable hemodynamics during the transplant surgery. We defined stable hemodynamics as intra-operative mean blood pressure (MAP) within 30% of baseline preoperative values. Simultaneous renal and non-renal solid organ transplantation and kidney re-transplant surgery (re-KT) were excluded from the study.

At the discretion of the nephrologist, dialysis was performed before surgery. After establishing routine hemodynamic monitoring, general anesthesia was induced for all donors and recipients, with 0.03mg/kg of midazolam, 50-100 µg fentanyl, 3-5 mg/kg thiopental, and 0.5 mg/kg atracurium. Following tracheal intubation, mechanical ventilation with a tidal volume of 8 to 10 mL/kg was delivered using a mixture of medical air and oxygen at a fresh gas flow rate of 2 L/min. The respiratory rate was adjusted as needed to maintain normocapnia. Anesthesia was maintained using isoflurane 0.6% to 1.2% (group I, n=38) or propofol 50 to 100 mcg/kg/minute; titrated to clinical response (group P, n=22), and all patients received bolus doses of atracurium and fentanyl during the surgery. After induction of anesthesia, a central venous pressure catheter and a radial artery catheter were placed for continuous hemodynamic monitoring and blood sampling. During surgery, normothermia was maintained by infusion of warmed fluids and the use of heated blankets.

Fluid management in the donors included 6 to 8 mL/kg of crystalloids. In addition, isotonic saline (approximately 5 mL/kg/h) was infused in the recipients to maintain central venous pressure at 10 to 15 mmHg and ensure adequate perfusion of the transplanted kidney. Intravenous 20% mannitol (200-250 ml) was routinely used for both donors (after induction of anesthesia until before arterial clamping) and recipients (before reperfusion of graft). The use of inotropes and vasopressors was at the discretion of the anesthetist and in response to the patient's hemodynamic status. Transfusion of packed red blood cells (PRBCs) was used to target hematocrit of 21%. At the end of the surgery, tracheal extubation was performed for all patients.

An immunosuppressed condition was obtained using the following regimen for recipients in both groups: induction of immunosuppression with methylprednisolone and maintenance with methylprednisolone, a calcineurin inhibitor (tacrolimus or cyclosporine), and an antimetabolite (mizoribine or mycophenolic acid).

We analyzed the demographic characteristic of the patients. Also, intraoperative variables including cold and warm ischemia time, crystalloid infused, blood loss, and urine output were assessed. Blood urea nitrogen (BUN),

Table 1: Demographic characteristics and perioperative data of the renal transplant donors.

Variables*	Isoflurane Group (n=38)	Propofol Group (n=22)	*P* value
Age, year	30.43±5.11	30.13±5.38	0.83
Male gender, no.(%)	30 (81.8%)	15 (68.2%)	0.26
Body mass index, kg/m^2	26.5±2.4	26.4±1.8	0.52
Pre-op BUN, mmol/L	9.85±2.61	8.93±2.54	0.19
Pre-op Cr, µmol/L	83.98±12.37	79.56±13.26	0.26
Fluid intake, L	4.99±0.86	4.88±1.04	0.67
Urine output, L	2.52±0.84	2.49±0.80	0.86
Blood loss, L	0.21±0.09	0.23±0.08	0.11

Preoperative serum blood urea nitrogen (Pre-op BUN), Preoperative serum creatinine (Pre-op Cr).

*Values are expressed as mean±standard deviation (SD) or the number (%)

serum creatinine (SCr), estimated glomerular filtration rate (eGFR) results were evaluated during the preoperative period, on the first postoperative day, and before discharge from the hospital. Postoperative variables included the length of postoperative hospital stay, the occurrence of delayed graft function, acute rejection episodes, and graft failure within the 6 months following transplantation.

Ethical Considerations

This study was approved by Mashhad University of Medical Sciences Ethics Committee (No.IR.MUMS.REC.1393.138). All patients provided written informed consent.

Statistical Analysis

Results were expressed as frequency and percentage for categorical variables and mean ± SD or median (range) for continuous variables. The chi-square test or the Fisher exact test was used for comparison of qualitative variables, and the Mann-Whitney test was used for comparison of continuous variables. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software, version 16. The sample size was determined using the serum creatinine variable in the study by Sahin SH et al. [10] with the following assumptions: test power of 80%, α=0.10, and β=0.19.

RESULTS

Sixty donor-recipient couples who underwent kidney transplantation were included in the present study.

Clinical and demographic characteristics of the renal transplant donors are shown in (Table 1). There were no significant differences in the variables between the two groups (p>0.05).

Baseline demographic and perioperative parameters of the recipients in the propofol and isoflurane groups are detailed in Table 2. The results showed that "donor warm ischemic time" in the propofol group was significantly longer than the isoflurane group (p=0.001). In addition, patients anesthetized with propofol were discharged significantly earlier after kidney transplantation than those anesthetized with isoflurane (9.63±2.96 versus 11.78±4.91 days, respectively; p=0.02).

Transplanted kidney function and outcomes up to 6 months after surgery are shown in Table 3. Accordingly, there were no significant differences in the occurrence of delayed graft function (DGF) or acute rejection episode (ARE) 6 months after transplantation (p>0.99, p=0.37, respectively). Furthermore, there was no graft loss within 6 months of transplantation.

DISCUSSION

Based on the results of our study, both methods of anesthesia may be considered safe in living donor kidney transplant patients. However, fewer days of hospitalization after surgery in the propofol group suggests that propofol may be a more appropriate anesthetic choice in these patients. Also, the results showed that the donor warm ischemic time in the propofol

Table 2: Demographic and perioperative data of the renal transplant recipients.

Variables*	Isoflurane Group (n=38)	Propofol Group (n=22)	*P* value
Age, year	34.81±11.31	34.77±12.75	0.99
Male gender, no.(%)	24 (64.9)	12 (54.5)	0.58
Body mass index, kg/m²	24.5±3.6	24.6±4.1	0.65
Cause of ESRD			
Hypertension	10 (27%)	8 (36.4%)	
Diabetes mellitus	3 (8.1%)	2 (9.1%)	
Glomerulonephritis	5 (13.5%)	1 (4.5%)	0.86
Polycystic kidney disease	2 (5.4%)	2 (9.1%)	
Unkown	12 (32.4%)	6 (27.3)	
Others	5 (13.5%)	3 (13.6%)	
Pre-op BUN, mmol/L	35.63±13.14	30.35±12.54	0.19
Pre-op Cr, µmol/L	724.89±318.24	751.41±291.72	0.58
Preop eGFR, ml/s	0.14±0.05	0.14±0.06	0.38
CIT, min	40.94±12.25	39.77±17.67	0.76
WIT, min	2.93±0.87	4.05±1.02	0.001
Intra-op Fluid intake, L	3.89±0.73	4.0±0.96	0.63
Intra-op Urine output, L	0.98±0.65	1.03±0.73	0.75
Intra-op Blood loss, L	0.34±0.17	0.40±0.10	0.15
Duration of surgery, min	276±38.9	282±39.1	0.21
Post-op type of calcineurin inhibitor Tacrolimus, Cyclosporine	36, 2	19, 3	0.54

Preoperative serum blood urea nitrogen (Pre-op BUN), Preoperative serum creatinine (Pre-op Cr), Preoperative estimated glomerular filtration rate (Pre-op eGFR), Cold ischemia time (CIT), Warm ischemic time (WIT), Intra-operative (Intra-op).

*Values are expressed as mean±standard deviation (SD) or the frequency (%)

group was significantly longer.

The study, by Lee and colleagues [11] concluded that there were no differences between anesthesia with desflurane versus propofol on grafted kidney function when the same anesthetic was used in the recipient and the matching live donor (preconditioning). However, in our study, early postoperative hospital discharge in the propofol group could be related to differences in characteristics between the two anesthetic agents.

First, propofol has anxiolytic effects through the GABAA receptor [12]. Previous studies have shown that propofol has analgesic and antinociceptive effects [13]. Propofol also acts on other receptors involved in pain signaling, which may be important in the central sensitization of pain [14]. In addition, Cheng et al. [15] reported that general anesthesia with propofol was associated with less postoperative pain and analgesic use than general anesthesia with isoflurane.

Second, propofol is known to have an antiemetic effect, which is associated with inhibition of the 5-hydroxytryptamine- 3 (5-HT) receptors in the serotonergic system, dopaminergic (D2) receptors in the chemoreceptor trigger zone, and the limbic system [13]. Postoperative nausea and vomiting (PONV) can lead to prolonged hospitalization and hospital readmission. Based on the randomized controlled trial performed by Apfel and colleagues [16], total intravenous anesthesia has become part of multimodal strategies to reduce a patient's risk of PONV. A recent meta-analysis demonstrated that total intravenous anesthesia (TIVA) reduces the relative risk of PONV compared with inhalational anesthetics [17].

Finally, the clinical effects of anesthetics on

Table 3: Grafted kidney function and outcomes in 6 months after transplantation.

Variables*	Isoflurane Group (n=38)	Propofol Group (n=22)	*P* value
Hospitalization days after surgery	11.78±4.91	9.63±2.96	0.02
Creatinine, µmol/L			
On the day of discharge	112.29±29.18	114. 95±39.79	0.38
In 6 months after surgery	114.06±30.95	119.37±48.63	0.40
Patients with DGF, no.(%)	1 (2.7%)	0 (0%)	>0.99
AREs within 6 months, no.(%)	3 (7.9%)	1 (4.5%)	0.37

Delayed graft function (DGF), Estimated glomerular filtration rate (eGFR), Acute rejection episode (ARE).
*Values are expressed as mean±standard deviation (SD) or the frequency (%)

intraoperative hemostasis showed an interesting trend in which intraoperative bleeding was less with using intravenous propofol than the volatile anesthetics isoflurane and sevoflurane. As in endoscopic sinus surgery, volatile agents impaired platelet aggregation and clot stability more than propofol [18]. However, the dose and duration of exposure to the anesthetic drugs have not been reported.

Donor warm ischemia is also known as extraction time, which is the time interval from clamping the vascular pedicle of the donor's kidney to placing the retrieval kidney in cold storage [19]. Literature on the effect of kidney-donor warm ischemic time on the early graft function has been scarce. Interestingly, our study showed a significantly longer "donor warm-ischemia time" in the propofol group. However, there were no adverse effects on renal graft function or the short-term outcome of renal transplantation.

The main limitation of this study is the small sample size. Despite this limitation, our study provides some guidance for future studies on the effects of anesthetics in kidney transplants.

We evaluated the effect of isoflurane against total intravenous anesthesia with propofol on renal graft function by practical and available laboratory tests. We conclude that both methods of anesthesia have no superiority in terms of kidney graft function and early outcome of surgery. Nevertheless, kidney recipients receiving intravenous propofol were discharged from the hospital earlier than those receiving isoflurane. Therefore, intravenous propofol should be considered as the anesthetic method of choice in living-donor kidney transplantation to facilitate early postoperative hospital discharge.

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