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ORIGINAL ARTICLE

Ketamine pharmacokinetics in recipients and donors of ABO blood type-compatible and -incompatible living kidney transplantation

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Abstract In kidney transplantation, stable hemodynamics is essential to preserve graft function. We used ketamine as an anesthetic because of its sympathomimetic properties. On the other hand, ketamine has several adverse effects, such as prolonged emergence from anesthesia or psychological reactions. Altered ketamine pharmacokinetics was previously reported in rabbits with renal insufficiency, but no study has examined human living kidney transplantation, which has the potential to cause renal insufficiency in the donor and recipient. Therefore, we evaluated ketamine pharmacokinetics in the donor and recipient of living kidney transplantation in various situation including ABO blood type-compatible and -incompatible transplantation.

Materials and Methods: We examined the ketamine pharmacokinetics in donors (n=8), and ABO blood type -compatible (n=8) and -incompatible (n=8) recipients of living kidney transplantation. We also measured the estimated glomerular filtration ratio (eGFR), blood urea nitrogen (BUN), and serum creatinine in these patients.

Results: The time course of changes in the ketamine level after stopping ketamine administration did not differ between the donors and recipients. We also found that the eGFR in recipients gradually improved 48 h after the kidney transplantation. No patient developed ketamine-related adverse effects or allograft rejection.

Conclusion: We conclude that ketamine can be safely applied as an adjuvant with intravenous anesthesia during ABO blood type-compatible and -incompatible living kidney transplantation.

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Key words: Ketamine; Living kidney transplantation; ABO blood type-compatible and -incompatible kidney transplantation; Pharmacokinetics; Graft function.

Introduction

The primary consideration in anesthetic management for organ transplantation is to maintain graft function. In kidney transplantation, maintaining hemodynamics is essential to preserve function of the transplanted kidney[1)]. Clinically available anesthetics, such as inhalational anesthetics, morphine and fentanyl, often reduce renal blood flow (RBF) and the glomerular filtration rate (GFR)[2, 3)]; therefore, they may be harmful for both the donor and recipient of kidney transplantation. On the other hand, previous reports suggested that total intravenous anesthesia (TIVA) with propofol has similar effects on hemodynamics as balanced anesthesia with thiopental, fentanyl and isoflurane, but greater analgesic effects[4)]. Ketamine may be available as an adjuvant to TIVA because it preserves renal blood flow via sympathomimetic effects on the heart, thereby preserving cardiac output[5)]. Moreover, it prevents acute tolerance to opioids[6)]. Previously, we reported that ketamine in TIVA had no significant adverse effects on hepatic or renal function, or anesthesia in healthy patients[7, 8)]. Therefore, TIVA with ketamine may be available for kidney transplantation; however, no detailed study, except one case report, has been carried out[9)].

A previous study reported altered ketamine

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pharmacokinetics under renal impairment, ketamine metabolism was prolonged in rabbits with uremia[10]. Taking into account this finding, the ketamine kinetics may decrease in patients after renal transplantation. As a result, they may develop ketamine-related adverse events such as prolonged recovery from anesthesia or hallucinations induced by residual ketamine. Therefore, impaired renal function may influence ketamine plasma levels[11], although one report stated that ketamine may be used under such renal impairment conditions[12]. In other reports, ketamine had no adverse effects on renal function compared with other anesthetic agents used in major surgery[13]. Currently in Japan, both ABO blood type-compatible and -incompatible living kidney transplantation are performed[14-16]. ABO blood type incompatibility was once believed to be a contraindication to renal transplantation due to the increased risk for antibody-mediated rejection and early graft loss. Recent advance of pretransplant desensitization strategies, such as removal of isoagglutinins and antibody-producing cells, have achieved successful outcomes[14]. As the recipient has reduced renal function immediately after transplantation[17], the ketamine pharmacokinetics may be altered. Therefore, adverse effects of ketamine could be more serious in recipient. However, no study has examined the ketamine pharmacokinetics in recipient of living kidney transplantation. Moreover, no evidence shows whether ketamine pharmacokinetics would be differ in the recipient of ABO blood type -compatible and -incompatible living kidney transplantation. The ketamine pharmacokinetics should be elucidated from the view of patient safety. In addition, the donor would have transient impaired renal function immediately after kidney harvest; thus, the donor might also suffer from the adverse effects of ketamine.

By evaluating the ketamine pharmacokinetics in both the donor and recipient of ABO-compatible or -incompatible living kidney transplantation, and assessing ketamine-related adverse effects, such as prolonged anesthesia emergence or psychological reactions, this study will provide evidence for the use of ketamine in TIVA for various situation of living kidney transplantation.

This study aimed to evaluate the safety and efficacy of ketamine in TIVA for anesthetic practice during renal transplantation.

Methods

Study design

This study protocol was approved by the local institutional review board and was registered in a publicly accessible database, the UMIN Clinical Trial Registry (UMIN Clinical Trial Registry; UMIN000005855). Written informed consent was received from all patients. Their data were collected between Jun. 28, 2011 and Dec. 31, 2016 at Hirosaki University Hospital. Underlying medical conditions of ABO blood-compatible recipients are IgA nephropathy (n=3), interstitial nephritis (n=1), polycystic kidney (n=2), diabetic nephropathy (n=1), focal glomerular sclerosis (n=1). On the other hand, underlying medical conditions of ABO blood-incompatible recipients are IgA nephropathy (n=3), interstitial nephritis (n=1), diabetic nephropathy (n=2), purpura nephritis (n=1), and nephrosclerosis (n=1). Fourteen cases received hemodialysis (n=7 in ABO blood-compatible; n=7 in ABO blood-incompatible respectively). Each one case of ABO blood-compatible and -incompatible had no hemodialysis (n=2). All recipient had chronic kidney disease (CKD) grade 5 (n=16).

Research subjects were allocated into two groups, donors (n=8) and recipients of the transplanted kidney (n=16). Then, the recipient group was subdivided into two groups, ABO blood type-compatible and -incompatible (n=8 each).

Anesthesia

Anesthesia was induced with propofol (1–1.5 mg/kg), remifentanil (0.1-0.2 μg/kg/min), ketamine (0.5 mg/kg) and rocuronium (0.6–1.0 mg/kg), and was maintained by the continuous infusion of propofol (4–7 mg/kg/h), ketamine (0.5 mg/kg/h) and remifentanil (0.1-0.2 μg/kg/min). Rocuronium was intermittently administrated intravenously. Anesthesia was maintained to hold BIS values between 40 and 60. BIS value is an indicator of anesthesia depth that is calculated from EEG obtained. Adequate depth of anesthesia would suppose to have BIS value between 40 and 60. Ketamine administration was discontinued after the onset of transplanted kidney reperfusion in the recipient and at renal artery clamp period in the donor. As the surgeon required a central venous pressure above 10 cmH_2O and systolic blood pressure above 140 mmHg after establishing reperfusion, fluids and vasopressors were administered to maintain these values.

Blood withdrawal procedure

Blood samples were obtained at the following time-points: 0, 15, 30, 45, 60, 120, 180 minutes and 18 hours after discontinuing ketamine administration. The sample at time 0 was defined as an internal control. The samples were collected in heparinized tubes. Plasma was obtained by centrifugation (3000 rpm) of the blood samples and was stored at −20° C prior to measurement. Levels of ketamine and norketamine were quantified by liquid chromatography as previously reported[18]. The variation coefficients of the technique were 2.8 and 7.9% for ketamine and norketamine, respectively. The sensitivity limit for both ketamine and norketamine was 10 ng/ml.

Data analysis

We performed a power analysis in G Power3 to calculate the required number of samples for comparison of ketamine and norketamine among the three groups. When running a power analysis on a repeated measures ANOVA with 3 groups, 8 measurements, a power of 0.95, an alpha level of 0.05, and a medium effect size (f = 0.25), the required a total sample size was 144. We included 192 samples obtained from 24 patients. All data are presented as the mean ± SD. A p-value <0.05 was accepted as significant. The statistical analysis was performed using GraphPad Prism ver. 6.0 (GraphPad Software, La Jolla, CA, USA). Patient characteristics were analyzed by one-way ANOVA following Tukey's multiple comparisons test. Two-way ANOVA for repeated measurements was used to analyze the level of ketamine and norketamine among the three groups, changes in eGFR, BUN and creatinine. For further analysis, Tukey's multiple comparisons test was used to detect differences within groups across time points. On the other hand, Sidak's multiple comparisons test was used to detect differences among groups at the same time point.

Results

The physical and medical backgrounds of the patients are shown in table 1. The mean age of donors was 20 years older than that of ABO blood type-compatible recipients and 12 years older than that of ABO blood type-incompatible recipients. The duration of surgery and anesthesia was longer in both recipients than donors, but there was no difference between the recipients. There was no difference in administered fluid volume (3650.0 ± 864.5 ml in donors; 3556.0 ± 622.0 ml in ABO blood type-compatible recipients; 3119.0+/−618.0 ml ABO blood type-incompatible recipients) or total administered dose of ketamine (2.2 ± 0.2 ng/ml in donors; 2.2 ± 0.3 ng/ml in ABO blood type-compatible recipients: 2.3 ± 0.3 ng/ml in ABO blood type-incompatible recipients). Plasma ketamine concentrations at

Table 1 Patient profile

	Donor (n=8)	ABO blood type-compatible recipient (n=8)	ABO blood type-incompatible recipient (n=8)
Age (year)	58.9 ± 11.4	38.4 ± 12.0**	46.9 ± 11.6
BMI	23.7 ± 2.7	24.3 ± 3.0	22.6 ± 1.8
Duration of surgery (min.)	196.1 ± 19.2	258.1 ± 31.0**	259.8 ± 43.0**
Duration of anesthesia (min.)	283.6 ± 27.3	326.3 ± 53.4	329.5 ± 53.4
Toal ketamine dose (mg/kg)	2.2 ± 0.2	2.2 ± 0.3	2.3 ± 0.3
Toal fluid dose (ml)	3650.0 ± 864.5	3556.0 ± 622.0	3119.0 ± 618.0
Ketamine at time 0 (ng/ml)	173.5 ± 56.1	191.8 ± 90.0	193.9 ± 111.3
Norketamine at time 0 (ng/ml)	148.5 ± 148.1	272.0 ± 145.0	215.8 ± 183.1

**p<0.01 vs Donor

the time of ketamine discontinuation (time 0) were 173.5 ± 56.1 ng/ml in donors, 191.8 ± 90.0 ng/ml in ABO blood type-compatible recipients and 193.9 ± 111.3 ng/ml ABO blood type-incompatible recipients. There was no significance among the groups. The concentration rapidly decreased after discontinuing ketamine. Time courses of changes in the concentration were similar, and there was no significant difference among donors and recipients at each sampling time point (Figure 1A).

The plasma norketamine concentration at the time of ketamine discontinuation (time 0) was 148.5 ± 148.1 ng/ml in donors, 272.0 ± 145.0 ng/ml in ABO blood type-compatible recipients and 215.8 ± 183.1 ng/ml in ABO blood type-incompatible recipients. The concentration in recipients was slightly higher than that in donors, but not significantly. The concentration rapidly decreased after ketamine was discontinued. Time courses of changes in the concentration were similar, and there was no significant difference between recipients and donors at each sampling time point (Figure 1B).

On laboratory data analysis, the eGFR before kidney transplantation was significantly lower in both recipient groups than the time-matched value in the donor group. It improved significantly after kidney transplantation in both recip-

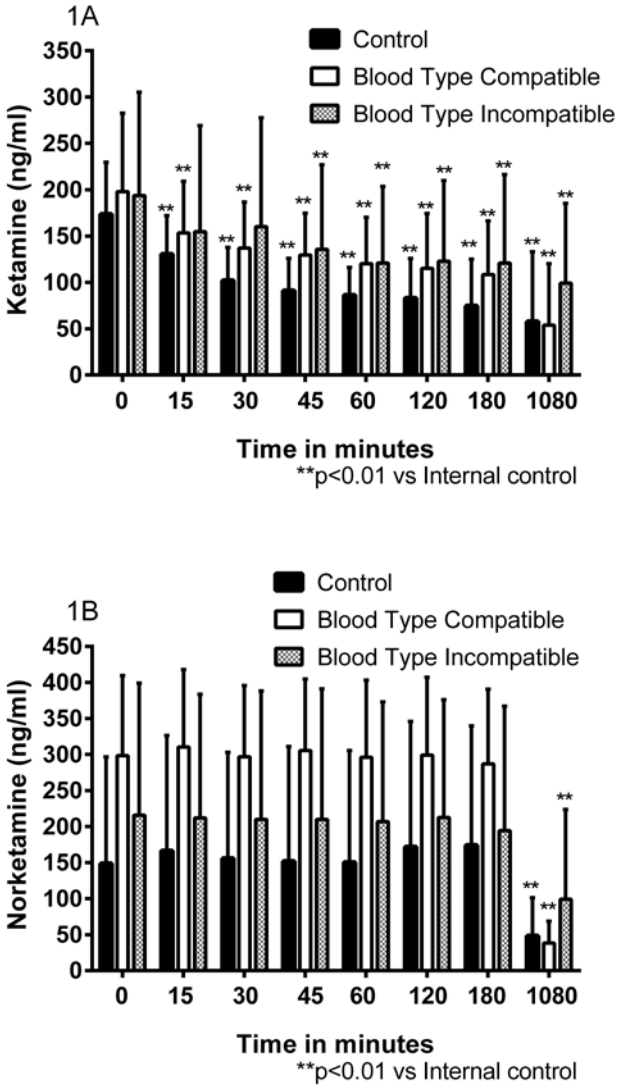

Figure 1

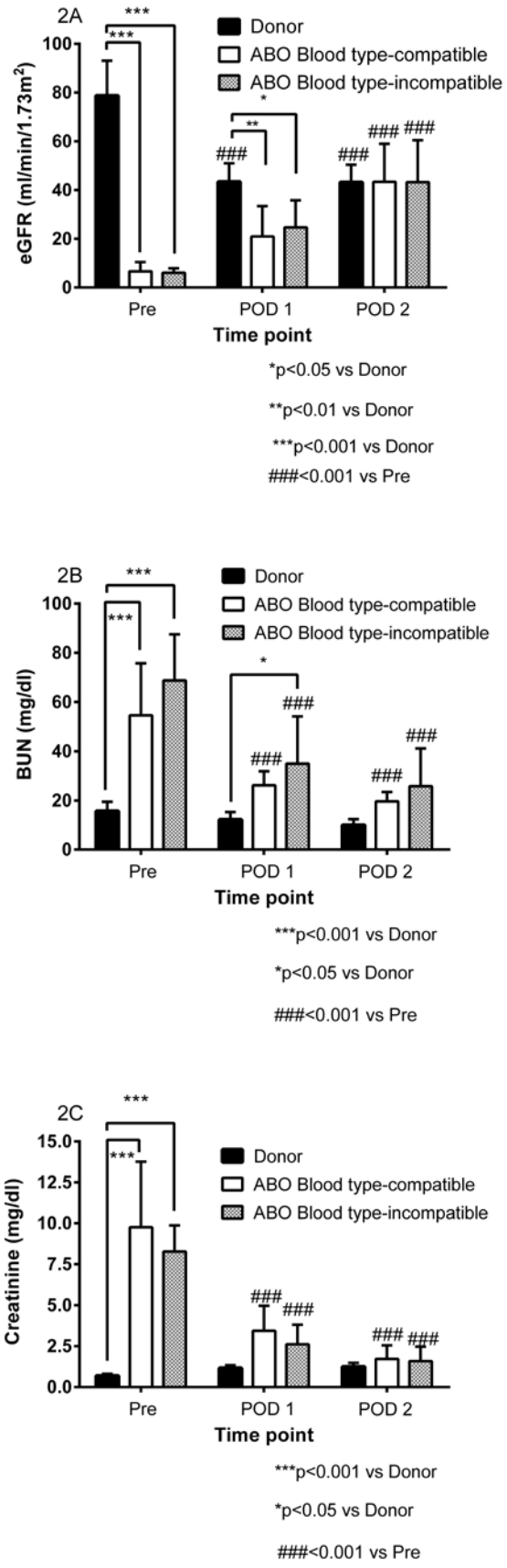

Figure 2

ient groups, but latter decreased at 1 and 2 days after the transplantation (Figure 2A). The BUN in both recipient groups decreased at 1 and 2 days after the transplantation, whereas that in the donors remained within the normal range, less than 20 mg /dl, throughout the study period (Figure 2B). Changes in serum creatinine were similar to the changes in BUN (Figure 2C). No recipient developed allograft rejection.

Discussion

The biotransformation routes of ketamine were previously described by Chang and Glazko[19]. The drug first undergoes N-dealkylation, producing the metabolite norketamine. In rabbits, renal insufficiency prolonged the decrease in the ketamine blood concentration[10]; therefore, changes in ketamine may be prolonged during human kidney transplantation. As the transplantation donor will also have a single kidney, they may also exhibit a prolonged decrease in ketamine concentration. We measured the ketamine blood concentration in recipients and donors of living kidney transplantation. Ketamine was administered at 0.5 mg/kg initially, then continuously at 0.5 mg/kg/hr until kidney harvest from the donor or kidney transplantation to the recipient. Measurements were performed before kidney transplantation and until 180 minutes after stopping ketamine administration. We found that the time course of changes in the ketamine level after stopping ketamine administration did not differ between the recipients and donors. Furthermore, the eGFR in recipients gradually improved for 48 h after the kidney transplantation. To our best knowledge, this was the first study to examine the ketamine blood concentration in both recipients and donors of living kidney transplantation.

Previous studies of ketamine kinetics in humans of varying ages reported that the serum levels of ketamine after discontinuation were

40% at 30 minutes, 30% at 60 minutes, 14% at 120 minutes compared with the level upon discontinuation[8]. The reduction rates in our study were higher at all time points examined, but the level of ketamine was always lower than 500 ng/ml, at which wakefulness is expected[20]. The lower ketamine level may result in emergence from general anesthesia without ketamine-related psychological reactions, such as vivid dreaming, extracorporeal experiences (sense of floating out of body) and illusions.

Some limitations exist in this study. First, there was a difference in age between the donors and ABO blood type-compatible and -incompatible recipients. We cannot exclude the possibility of age-dependent effects on the ketamine kinetics. For example, although not significant, recipients had higher level of norketamine throughout the study. The recipients were younger than the donors; therefore, the metabolism of ketamine may have been affected by this age difference.

We found no difference in ketamine or norketamine kinetics among donors and recipients of living kidney transplantation. The essential issue in anesthetic management for organ transplantation is to maintain graft function, and the safety of the donor and ABO blood type-compatible and -incompatible recipients. Ketamine preserves cardiovascular function, which is beneficial for graft function, and reduces acute tolerance to opioids, which is advantageous for postoperative analgesia. On the other hand, it has several adverse effects, including prolonged recovery and undesirable psychological reactions. If ketamine kinetics in the donor and ABO blood type-compatible and -incompatible recipients are abnormal, ketamine may be harmful in living kidney transplantation. However, no patient developed ketamine-related adverse effects or allograft rejection. Taking the above results into account, we conclude that ketamine can be applied as an adjuvant with intravenous anesthesia to anesthetic practice for organ transplantation.

Conclusion

The changes in the plasma concentration of both ketamine and norketamine were not different among ABO blood type-compatible recipients, -incompatible recipients and donors. Furthermore, no adverse events related to ketamine were observed. Taking the above results into account, we conclude that ketamine can be safely applied as an adjuvant to TIVA in anesthetic practice for ABO blood type-compatible and -incompatible recipients, and donors in living kidney transplantation.

Conflicts of interest to be declared

We have no such conflicts.

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