

# Ketamine Anesthesia Increases Urine Output

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**Summary.** The effect of ketamine on urine production was studied in 40 patients undergoing major surgery. Urine output both during and after ketamine-nitrous oxide anesthesia was significantly higher than that during ( $p < 0.05$ ) and after ( $p < 0.01$ ) halothane-nitrous oxide anesthesia. Urine output for one hour immediately after halothane-nitrous oxide anesthesia significantly ( $rS = 0.462$  (Spearman's rank correlation),  $p < 0.05$ ) correlated with the total infusion during the anesthesia, whereas that after ketamine-nitrous oxide anesthesia significantly ( $rS = 0.525$ ,  $p < 0.05$ ) correlated with the total dose of ketamine administered during the anesthesia. Moreover, a significant ( $p < 0.05-0.01$ ) increase in urine output was maintained for a few days after ketamine administration, this being dose-dependent. Urine osmolality after ketamine administration showed a significant inverse relationship ( $p < 0.05$ ) with the urine output. Furthermore, significant dose-dependent decreases in the serum levels of sodium ( $p < 0.05-0.01$ ) and chloride ( $p < 0.05$ ) were observed after ketamine administration. These results suggest that ketamine has a mild and long-lasting diuretic effect.

**Key words**—ketamine, urine output, diuretic effect.

## INTRODUCTION

The maintenance of sufficient urine output during and after surgical operation is one of the most important aspects of management for surgical patients. There seem to be many factors that work to reduce urine production during and after surgery and anesthesia. Surgical stress as well as general anesthesia are considered to depress urine production due to a rise in the plasma levels of the antidiuretic hormone (ADH),<sup>1-3</sup> adrenocorticotrophic hormone (ACTH),<sup>4,5</sup> renin<sup>6</sup> and adrenocortical hormones (glucocorticoids)<sup>4,7</sup>

and mineralcorticoids).<sup>5,6</sup> Moreover, volatile anesthetics including halothane have been demonstrated to depress renal function.<sup>8,9</sup> On the other hand, a change in the distribution of extracellular fluid (ECF), so-called sequestration, also causes a decrease in urine output during and after surgery.

Ketamine anesthesia, generally used for minor surgery, has recently also been adopted as one of several agents for total intravenous anesthesia (TIVA).<sup>12</sup> As a result, ketamine has come to be used more often for major surgery, which requires a longer duration of anesthesia and larger doses of anesthetics. However, there have been few studies concerning the effect of ketamine on urine production, although the ketamine administered and its metabolites have been demonstrated to be excreted mostly in urine.<sup>13,14</sup> Therefore, in this study, we measured the effects of ketamine on urine production and compared them with those of halothane in a context of major surgery.

## METHODS

After approval by the Institutional Committee for Human Investigation and obtaining informed consent, 40 patients prepared for elective surgical operations were included in the study. None of the patients had renal, cardiac, hepatic or endocrinological dysfunction; two nephrectomized patient due to a renal tumor had a normal renal function (normal serum values of creatinine, blood urea nitrogen (BUN) and electrolytes). On the day before surgery, a balloon catheter was introduced into the urinary bladder to monitor urine output until the fourth postoperative day. The volume of urine collected for 24 h, from 0600 h to the same time on the next day, was calculated as the daily urine output.

At 0800h, the patients were premedicated with 0.01 mg·kg<sup>-1</sup> of atropine and 0.7 mg·kg<sup>-1</sup> of meperidine intramuscularly. Anesthesia started at 0900 h. Mean

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blood pressure (NIBP) was measured by means of BP-308ET (Colin, Japan).

### Study I. Comparison of urine output between ketamine and halothane anesthesia

The patients were divided into two groups: a ketamine group (10 males, 10 females) and halothane group (8 males, 12 females). The forms of surgery varied within each group, but were similar between the groups (3 subtotal gastrectomy, 2 cholecystectomy, 1 hemicolectomy, 1 strumectomy, 2 removal of mediastinal tumor, 5 pulmonary lobectomy, 1 mastectomy, 4 hysterectomy and 1 nephrectomy, respectively). There were no significant differences in patient age, duration of anesthesia, body weight (BW) (Table 1) or infusion rate (Fig. 1) between the groups.

#### Ketamine group

Following the induction of anesthesia with 0.2 mg·kg<sup>-1</sup> of diazepam and 2 mg·kg<sup>-1</sup> of ketamine, 20 patients underwent tracheal intubation after muscle relaxation with 0.16 mg·kg<sup>-1</sup> of pancuronium. Anesthesia was maintained by a constant infusion of a ketamine-pancuronium mixture (1 mg·kg<sup>-1</sup>·h<sup>-1</sup> and 0.08 mg·kg<sup>-1</sup>·h<sup>-1</sup>, respectively) with an electrically driven syringe pump, and inhalation of a nitrous oxide-oxygen gas mixture (3 and 2 l·min<sup>-1</sup> respective-

ly) with a semiclosed system, according to the method of Hatano et al.<sup>15)</sup>

#### Halothane group

Following induction with 5 mg·kg<sup>-1</sup> of thiamylal, the patients were tracheally intubated after muscle relaxation with 0.16 mg·kg<sup>-1</sup> of pancuronium. Anesthesia was maintained by the inhalation of a halothane-nitrous oxide-oxygen gas mixture (1%, 3 l·min<sup>-1</sup> and 2 ml·min<sup>-1</sup>, respectively) with a semiclosed system and intravenous infusion of 0.08 mg·kg<sup>-1</sup> of pancuronium by an electrically driven syringe pump.

Table 1. Age, body weight (BW), duration of anesthesia

	Age (yr)	BW (kg)	Duration of anesthesia (min)
Ketamine group	48.7±10.6	53.7±7.7	199±65
Halothane group	49.1±12.8	52.4±6.5	199±67
sub-group 0	54.6±12.0	55.6±7.2	196±74
sub-group 2	45.4±14.6	53.6±6.0	201±46
sub-group 4	50.6± 7.3	48.6±2.3	199±43
sub-group 8	45.8±12.5	51.8±7.1	201±86

There were no significant differences between the groups and among the sub-groups by Student's *t* test and one-way ANOVA. Values are given as means±SDs.

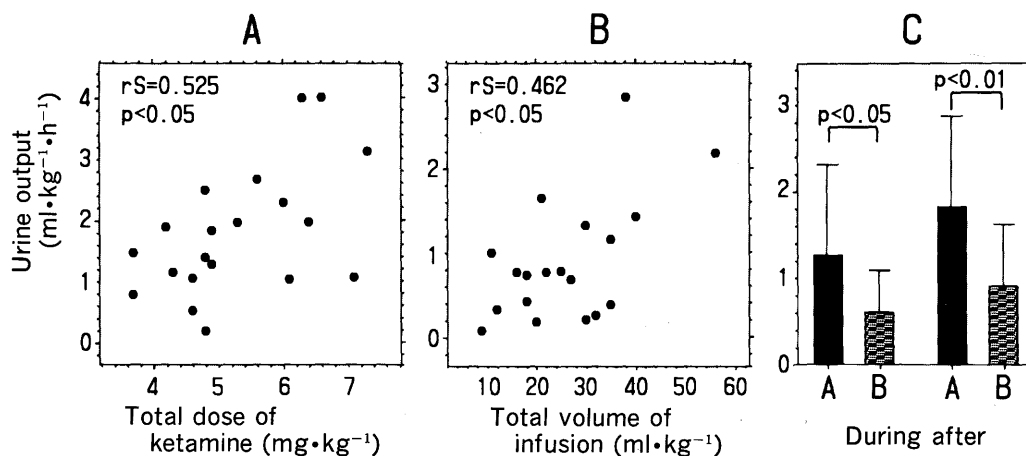


Fig. 1. Urine output during anesthesia and the first hour following anesthesia (Study I). A significant Spearman's rank correlation (*rS*) between total dosage of ketamine administered during anesthesia and urine output during the first hour following anesthesia can be noted in the ketamine group (A), whereas that between total infusion volume during anesthesia and urine output for one hour during the first hour following anesthesia is noted in the halothane group (B). Urine output in the ketamine group during and after anesthesia is significantly higher (Student's *t* test) than that of the halothane group (C). Values are given means±SDs.

### Anesthetic care

All patients were ventilated artificially at  $0.09 \text{ l}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , and the means  $\pm$  standard deviations (SDs) of arterial pH,  $\text{PCO}_2$ , and  $\text{PO}_2$  were  $7.41 \pm 0.04$ ,  $4.97 \pm 0.51$  kPa and  $18.09 \pm 0.93$  kPa, respectively. At the end of anesthesia, adequate doses of atropine (0.5 mg) and neostigmine (1.5–2.0 mg) were administered to reverse the muscle relaxation. Throughout anesthesia, lactate-Ringer solution was infused in every patient.

### Study II. Relationship between dosage of ketamine and urine output

After surgery, the halothane group was re-divided into four sub-groups, 0, 2, 4 and 8, each of which consisted of five patients. There were no significant differences in age, BW or duration of anesthesia (Table 1), although the types of surgery varied among the sub-groups. After observation of urine output for the first hour following anesthesia, each sub-group 0, 2, 4 or 8 received an intravenous infusion of ketamine at a dose of 0, 2, 4 or  $8 \text{ mg}\cdot\text{kg}^{-1}$  for postoperative pain relief.<sup>16)</sup> The effects of ketamine at the respective doses on urine output, urine osmolality and mean blood pressure were examined until the fourth postoperative day.

### Perioperative care

Before, during and after anesthesia and surgery, none of the patients were treated with agents considered to affect urine production, such as diuretics or digitalis. All aspects of perioperative care, such as infusion, administration of antibiotics, vitamins, antipyretics or analgesics and physical treatment were made to correspond as closely as possible among the respective patients. In both groups, oral food and water were not given on the day of surgery or the first postoperative day, and varied on the second, third and fourth postoperative days according to the surgery performed. Lactate-Ringer solution ( $500\text{--}1000 \text{ ml}\cdot\text{day}^{-1}$ ), amino acid solution (12%,  $200 \text{ ml}\cdot\text{day}^{-1}$ ), fat emulsion (10%,  $250 \text{ ml}\cdot\text{day}^{-1}$ ) and glucose solution (5%,  $500\text{--}100 \text{ ml}\cdot\text{day}^{-1}$ ) were infused intravenously from the day of surgery to the fourth postoperative day.

Serum electrolytes (sodium (Na), potassium (K) and chloride (Cl)), blood urea nitrogen (BUN), creatinine, glutamate oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) were measured on the day before surgery and on the third postoperative day.

### Statistical analysis

The data obtained were represented as means  $\pm$  SDs, and analyzed statistically using Student's *t* test, three-way analysis of variance (ANOVA), Turkey's multiple comparisons test (when values were significant by three-way ANOVA) and Spearman's rank correlation (*r*S). Differences at  $p < 0.05$  were considered significant.

## RESULTS

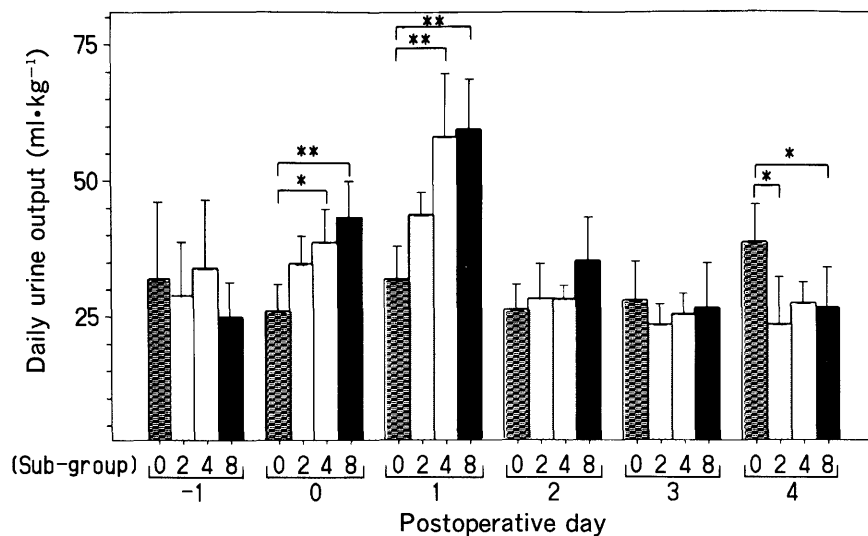
### Study I. Urine output during and immediately after ketamine and halothane anesthesia

There were no significant differences in the infusion rate between the ketamine and halothane groups during (ketamine group;  $19.1 \pm 8.6 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ , halothane group;  $20.6 \pm 11.4 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) and for one hour immediately after (ketamine group;  $3.7 \pm 2.2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ , halothane group;  $4.5 \pm 1.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) anesthesia. Blood loss during surgery was below  $10 \text{ ml}\cdot\text{kg}^{-1}$  in all patients (ketamine group;  $5.2 \pm 2.7 \text{ ml}\cdot\text{kg}^{-1}$ , halothane group;  $5.6 \pm 2.9 \text{ ml}\cdot\text{kg}^{-1}$ ) and did not differ significantly between the groups; no blood transfusion was given in any case.

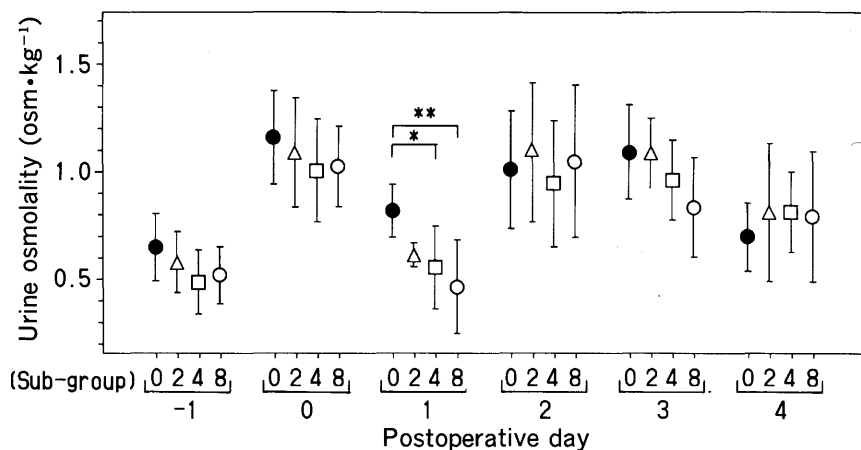
In the ketamine group, a total of  $5.3 \pm 1.1 \text{ mg}\cdot\text{kg}^{-1}$  ketamine was administered. Urine output both during anesthesia ( $p < 0.01$  by Student's *t* test) and the first hour following anesthesia ( $p < 0.01$  by Student's *t* test) in the ketamine group was significantly higher than in the halothane group. In the ketamine group, a significant correlation ( $rS = 0.525$ ,  $p < 0.05$ ) between the total dose of ketamine administered during anesthesia and urine output during the first hour following anesthesia was demonstrated. At the end of anesthesia, no significant difference in blood pressure between the two groups was noted (Table 2). In the halothane group, however, a significant correlation ( $rS = 0.462$ ,  $p = 0.05$ ) was found between the total volume of infusion during anesthesia and urine output during the first hour following anesthesia, whereas in the ketamine group no significant correlation between these parameters was noted (Fig. 1).

### Study II. Effects of ketamine dosage on urine production

Ketamine, administered at doses of 0, 2, 4 and  $8 \text{ mg}\cdot\text{kg}^{-1}$  to the respective sub-groups, significantly ( $p < 0.01$  by three-way ANOVA) increased urine output in a dose-dependent manner. Urine output in both sub-groups 4 and 8 significantly ( $p < 0.01$  by Turkey's test) increased as compared with sub-group 0. This increase was observed significantly on the day of sur-



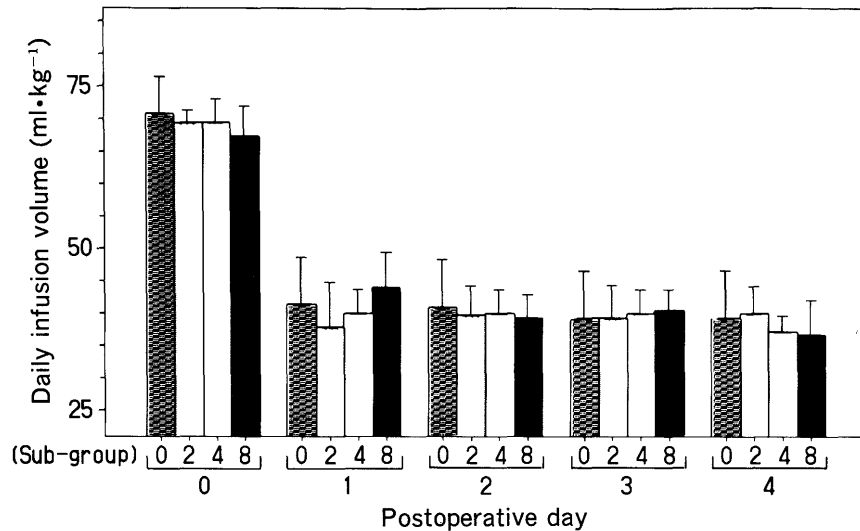
**Fig. 2.** Daily urine output following ketamine administration at various doses (Study II). Ketamine at a dose of 0, 2, 4 or 8 mg·kg<sup>-1</sup> was administered to sub-groups 0, 2, 4 or 8, respectively. A significant dose-dependent increase in urine output by ketamine can be observed on the day of surgery, and the first and second postoperative days ( $p < 0.01$  by three-way ANOVA, respectively). On the other hand, in sub-group 0 (without ketamine), significant ( $p < 0.01$  by three-way ANOVA) diuresis is apparent on the fourth postoperative day (postoperative diuresis in the Phase II of Moore<sup>11</sup>). \* $p < 0.05$  and \*\* $p < 0.01$  as compared with sub-group 0 by Turkey's test. Values are given as means  $\pm$  SDs.



**Fig. 3.** Urine Osmolality (Study II). A significant ( $p < 0.01$  by three-way ANOVA) dose-dependent decrease in urine osmolality can be noted on the first postoperative day. \* $p < 0.05$  and \*\* $p < 0.01$  by Turkey's test. Values are given as means  $\pm$  SDs.

gery and the first postoperative day. On the fourth postoperative day, however, urine output in sub-group 0 (without ketamine) was significantly ( $p < 0.01$  by three-way ANOVA and  $p < 0.05$  by Turkey's test) higher than that in groups 2 and 8 (with ketamine) (Fig. 2).

On the first postoperative day, urine osmolality showed a significant ( $p < 0.01$  by three-way ANOVA) inverse relationship with urine output, and the respective values for sub-groups 4 and 8 were significantly ( $p < 0.05$  and  $p < 0.01$ , respectively by Turkey's test) lower than that of sub-group 0 (Fig. 3).



**Fig. 4.** Daily infusion volume (Study II). There are no significant differences in daily infusion volume among the respective sub-groups from the day of surgery to the fourth postoperative day, where uptake of water was controlled by intravenous infusion. Values are given as means  $\pm$  SDs.

Daily infusion volume did not differ significantly among sub-groups (Fig. 4), and there were no significant differences in blood loss among sub-groups 0 ( $6.1 \pm 3.4 \text{ ml} \cdot \text{kg}^{-1}$ ), 2 ( $5.8 \pm 2.7 \text{ ml} \cdot \text{kg}^{-1}$ ), 4 ( $6.0 \pm 2.8 \text{ ml} \cdot \text{kg}^{-1}$ ) and 8 ( $4.6 \pm 2.0 \text{ ml} \cdot \text{kg}^{-1}$ ).

In sub-groups 4 and 8, a significant elevation of mean blood pressure at the end of ketamine infusion was noted ( $p < 0.05$  and  $p < 0.01$ , respectively by Turkey's test, and  $p < 0.01$  by three-way ANOVA). However, this elevation was only temporary, and subsided within 30 min (Table 2).

The serum levels of Na and Cl in sub-groups 4 and 8 significantly fell in a dose-dependent manner ( $p < 0.01$  by three-way ANOVA and  $p < 0.05$  by Tukey's test, respectively) following ketamine administration. However, all the levels of electrolytes (Na, K and Cl) were within normal limits. No significant changes in serum K, GOT, GPT, BUN or creatinine were found before and after anesthesia (Table 3).

## DISCUSSION

In Study I, urine output both during anesthesia and during the first hour following anesthesia was significantly higher in the ketamine group than in the halothane group. The urine output during the first hour following anesthesia in the ketamine group was significantly correlated with the total dose of ketamine administered during anesthesia, whereas in the

halothane group it was significantly correlated with the total infusion volume during anesthesia (Fig. 1). These phenomena suggest that ketamine disrupts the relationship between water intake and urine production, i.e. produces diuretic effect. Moreover, in Study II, ketamine significantly increased urine output in a dose-dependent manner (Fig. 2), and urine osmolality on the first postoperative day showed a significant inverse relationship with urine output (Fig. 3). However, no significant differences in infusion volume were evident (Fig. 4). Therefore, ketamine appeared to have a diuretic effect.

Most volatile anesthetics—including halothane—as well as surgical stress raise the levels of plasma ADH,<sup>3)</sup> ACTH,<sup>4)</sup> aldosterone<sup>4-6)</sup> and corticosteroids,<sup>7)</sup> and cause a reduction in urine output. Sequestration of extracellular fluid (ECF) is considered to decrease postoperative urine production.<sup>10,11)</sup> A reduction of urine production is usually observed for 3-4 days after major surgery (Phase I), and postoperative diuresis for a few days (Phase II) follows thereafter due to the large accumulation of ECF.<sup>11)</sup> In sub-group 0 (without ketamine), a significant increase in urine output (postoperative diuresis) was evident on the fourth postoperative day, though a reduction in urine output in Phase I was not so apparent (Fig. 2). These findings might be attributable to the fact that infused water volume on the day of surgery was sufficient (Fig. 4).

In sub-groups 2, 4 and 8 (with ketamine), however,

**Table 2.** Mean blood pressure (Study II)

Sub-group	Postoperative day								
	-1		0		1	2	3	4	
	0900	0900	0900	At the end of anesthesia	At the end of ketamine infusion	0900	0900	0900	0900
	(mmHg)								
0	88.2±4.5	91.6±9.0	86.0±3.4	83.4±8.7	88.8±10.5	87.2±10.3	87.4±7.4	84.0±6.9	85.8±5.4
2	86.2±5.3	92.6±11.8	84.6±7.8	88.2±10.2	86.0±7.8	90.4±8.0	88.6±7.7	87.0±9.3	86.8±3.6
4	87.2±8.1	91.6±7.3	86.0±3.9	89.8±5.8	94.2±4.1*	85.2±7.0	86.6±7.1	87.2±6.8	87.4±5.6
8	87.4±9.4	88.8±11.2	84.6±8.0	84.8±6.6	94.8±5.3**†	85.6±11.2	86.2±9.5	88.4±9.8	84.0±7.2

In sub-groups 4 and 8, a significant elevation in mean blood pressure after ketamine infusion can be noted. However, the elevation was only temporary, and subsided within 30 min. Mean blood pressures at every 0900 h, at the end of anesthesia and after 30 min of ketamine infusion were compared. Values are given as means±SDs. \* $p < 0.05$  and \*\* $p < 0.01$  as compared with the values before ketamine infusion, and † $p < 0.05$  as compared with sub-group 0, by Turkey's test and three-way ANOVA ( $p < 0.01$ ).

**Table 3.** Serum levels of GOT, GPT, BUN, creatinine and electrolytes before and after ketamine administration (Study II)

	Sub-group (dose of ketamine, mg·kg <sup>-1</sup> )							
	0		2		4		8	
	before	after	before	after	before	after	before	after
GOT (IU · I <sup>-1</sup> )	15±4	13±4	19±7	19±8	22±4	24±2	18±3	14±7
GPT (IU · I <sup>-1</sup> )	15±6	13±8	11±8	14±3	10±3	12±7	15±7	15±7
BUN (mmol · I <sup>-1</sup> )	10±3	10±4	9±1	9±3	9±2	9±2	12±3	12±5
Creatinine (μmol · I <sup>-1</sup> )	50±8	53±9	60±7	63±7	58±8	58±10	60±10	64±10
Na (mmol · I <sup>-1</sup> )	139±5	139±3	138±4	137±1	139±2	136±1*†	139±4	133±4**†
K (mmol · I <sup>-1</sup> )	3.9±0.4	4.2±0.4	4.1±0.3	4.3±0.5	4.4±0.4	4.6±0.3	4.3±0.1	4.3±0.2
Cl (mmol · I <sup>-1</sup> )	105±5	104±4	102±9	100±5	107±2	102±4*	104±4	98±6*

Values are given as means±SDs. \* $p < 0.05$  and \*\* $p < 0.01$  compared with the values before anesthesia, and † $p < 0.05$  compared with sub-group 0 by Turkey's test and three-way ANOVA ( $p < 0.01$ ).

no postoperative diuresis was apparent on the fourth postoperative day (Fig. 2), while urine osmolality on the first postoperative day showed a significant inverse relationship with urine output (Fig. 3). These phenomena suggest that the accumulation of ECF in Phase I did not occur in sub-groups 2, 4 and 8 treated with ketamine, since a higher level of urine excretion concurrently occurred. Therefore, the subsequent postoperative diuresis observed in Phase II might not have been apparent in sub-groups 2, 4 and 8 (Fig. 2). These results indicate a possible diuretic effect of ketamine, and suggest that the effect is mild and long-lasting. On the other hand, oral intake of water was possible for most patients on the fourth postoperative day. In sub-group 0, therefore, there is a probability that oral water intake resulted in an increase in urine output. However, all patients received a sufficient amount of postoperative infusion

(Fig. 4), while the amount of oral water intake for each patient was very small compared with that of infusion. From all this, oral water intake is considered to have had minimal effect on the urine output.

Moore<sup>11)</sup> has also indicated that not only a large accumulation of ECF but also over-retention of Na and loss of K occurs in Phase I, when the serum level of Na does not fall because the accumulation of ECF is larger than the retention of Na. In the present study, no rise of serum Na or fall of K occurred after ketamine administration, whereas significant drops in Na and Cl were observed with ketamine in a dose-dependent manner (Table 2). These phenomena suggest that an increase in urine output is attributable to a saline diuresis, and support the idea that ketamine reduces the accumulation of ECF and over-retention of Na in Phase I, due to its mild and long-lasting diuretic effect.

Ketamine has been demonstrated to raise the level of serum catecholamine (sympathomimetic action). Since this causes increases in cardiac output and blood pressure,<sup>17-24)</sup> it is also likely to mediate the increase in urine output. However, the sympathomimetic action of ketamine has also been demonstrated to be only temporary.<sup>17-24)</sup> In fact, the elevation of blood pressure by ketamine was also only temporary in the present study (Table 2), while the drug increased urine output for a few days (Fig. 2). Furthermore, ketamine has been demonstrated to decrease renal blood flow during the same period,<sup>22-25)</sup> although the drug is suggested to have no effect on renal blood flow within the dose range used in clinical practice.<sup>25)</sup> Therefore, renal vasoconstriction rather than vasodilatation appears to increase with a rise in the serum catecholamine level following ketamine administration. Therefore, the rise in catecholamine is considered not to contribute to the long-lasting diuretic effect.

On the other hand, ketamine is suggested to stimulate the adrenocortical function<sup>26)</sup> and elevate plasma renin activity<sup>27-29)</sup> via its sympathomimetic effect, whereas the plasma angiotensin level did not rise following ketamine administration.<sup>30)</sup> Therefore, the anesthetic itself dose not appear to affect directly the adrenocortical function and the renin-angiotensin system. Even if the hyperadrenocortical function and hyperactivity of the renin-angiotensin system are associated with a change in urine production, these mechanisms should have decreased rather than increase the production of urine.<sup>3-7)</sup>

Nevertheless, an increase in urine production was maintained for a few days in the present study (Fig. 2). Since biotransformation and the excretion of ketamine is demonstrated to be rapid (the half-life after intravenous administration, 186 min;<sup>33)</sup> elimination half-life, 130 min<sup>34)</sup>), a long-lasting increase in urine production cannot be attributed only to a direct effect of the anesthetic. However, its metabolite (metabolite II) has been demonstrated to remain in plasma for more than 72 h,<sup>13)</sup> and to be excreted mainly in urine.<sup>15)</sup> Therefore, the long-lasting increase in urine production seen in the present study might be attributable to ketamine itself and its metabolite, which act directly on the kidney or indirectly via other humoral mechanisms, such as augmentation of the atrial natriuretic peptide (ANP).<sup>32)</sup>

Before and after anesthesia, there were no significant alterations in the serum levels of BUN, creatinine, GOT and GPT, with slight decreases in Na and Cl noticed, although all of these were within normal limits (Table 3). These findings suggest that ketamine anesthesia might be beneficial for major surgery, making postoperative care easier.

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