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Effects of sevoflurane anesthesia combined with epidural block on renal function in the elderly: comparison with isoflurane

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Abstract

Purpose. Renal function declines with age, but little is known about the renal effects of the inhaled anesthetic sevoflurane in the elderly. We therefore compared the renal effects of sevoflurane and isoflurane anesthesia in elderly patients.

Methods. Thirteen patients aged ≥70 years undergoing gastrectomy with epidural anesthesia combined with general anesthesia were randomly assigned to receive either sevoflurane ($n = 7$) or isoflurane ($n = 6$). Dopamine (3–5 μg·kg^{-1}·min^{-1}) was administered to all patients. Blood and urine samples were collected before, during, and after anesthesia. Serum and urinary inorganic fluoride was measured, and renal function tests were performed.

Results. Serum inorganic fluoride was significantly elevated in both groups. The production of inorganic fluoride was significantly greater in the sevoflurane group, but the level did not exceed 50 μmol·l^{-1} in any patient. No abnormalities were observed in blood urea nitrogen (BUN), serum creatinine, or urine volume in either group. The albumin excretion index increased during anesthesia and decreased after anesthesia in both groups. Creatinine clearance was unchanged in the sevoflurane group but fluctuated during and after anesthesia in the isoflurane group. α_1-Microglobulin (MG), β_2-MG, and urinary *N*-acetyl-β-D-glucosaminidase (NAG) excretion increased up to 3 h after anesthesia, and α_1-MG and β_2-MG excretion increased on postanesthesia day 3.

Conclusion. In both groups, glomerular and tubular function were transiently affected, but no abnormalities were found in routine laboratory tests, suggesting that neither isoflurane nor sevoflurane in combination with dopamine and epidural anesthesia seriously affects renal function in the elderly.

Key words: Sevoflurane, Isoflurane, Nephrotoxicity, Elderly patients

This study was performed at Tokyo Metropolitan Geriatric Hospital

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Introduction

The inhaled anesthetic sevoflurane, a fluorinated ether derivative, is metabolized to produce inorganic fluoride. In a low-flow closed anesthetic circuit, sevoflurane reacts with the CO_2 absorbent, and two degradation products, $CF_2 = C(CF_3)OCH_2F$ (compound A) and $CH_3OCF_2CH(CF_3)OCH_2F$ (compound B), are detected [1–3]. Inorganic fluoride generated by methoxyflurane metabolism has been reported to cause renal dysfunction [4], and compound A produces nephrotoxicity in rats [5,6], leading to concerns about possible renal impairment following sevoflurane anesthesia. However, in studies of clinical anesthesia reported to date, inorganic fluoride or compound A produced during sevoflurane anesthesia has not been shown to cause nephrotoxicity in adults with normal renal function. Therefore, further studies on nephrotoxicity should be focused on sevoflurane anesthesia in patients with impaired renal function or in the elderly, since renal function declines with increasing age [7]. However, to date few studies have examined the effects of sevoflurane anesthesia on renal function in the elderly. In the present study, we compared the effects of sevoflurane and isoflurane anesthesia on renal function in elderly patients, employing routine anesthetic techniques in our institution.

Materials and methods

The study was approved by the institutional committee on human research, and informed consent was obtained from all patients. The subjects were 13 patients aged ≥70 years (mean, 77.9 years; range, 70 to 87 years) who underwent gastrectomy at our hospital between September 1995 and February 1996 and in whom no abnormalities in renal function were found in routine preoperative examination. The subjects were randomly assigned to receive either sevoflurane anesthesia ($n = 7$)

or isoflurane anesthesia ($n = 6$), and the effects of these inhaled anesthetics on renal function were prospectively investigated. Premedication was not administered in either group. After the patient entered the operating room, an epidural catheter was placed at an intervertebral space (T7–T10), and fentanyl (3–5 μg·kg^{-1}) was administered in divided doses until the induction of anesthesia. Anesthesia was induced with sevoflurane or isoflurane and oxygen, and a laryngeal mask was applied to patients showing spontaneous ventilation. Anesthesia was maintained with oxygen (3 l·min^{-1}), air (2 l·min^{-1}), and either sevoflurane or isoflurane. After administration of vecuronium (0.08 mg·kg^{-1}), controlled mechanical ventilation was employed to maintain an end-tidal CO_2 partial pressure of approximately 35 mmHg. An appropriate amount of 1% or 2% mepivacaine was injected though the epidural catheter, followed by administration of 1 ml of 0.5% bupivacaine as required. The anesthetic system was a semi-closed circuit with soda lime as CO_2 absorbent. Dopamine (3–5 μg·kg^{-1}·min^{-1}) was administered to prevent the systolic blood pressure from falling below 80% of the preanesthesia level and to maintain urine production above 2 ml·kg^{-1}·h^{-1}. Body temperature was maintained between 36° and 37°C.

The parameters monitored in this study were serum and urinary inorganic fluoride, blood urea nitrogen (BUN), serum creatinine, urinary α_1-microglobulin (MG), urinary β_2-MG, urinary *N*-acetyl-β-D-glucosaminidase (NAG), and urinary albumin. Blood and urine samples were collected when the patient was transferred to the operating room (before the start of anesthesia), immediately before surgery, 2 h after the start and at the end of surgery, and 3 h and 1, 3, and 7 days after anesthesia. Immediately after collection of blood samples, the serum was separated and frozen until analysis. When the patient entered the operating room, a urine sample was collected via a catheter that was inserted preoperatively as part of the routine procedure. Cumulative urine samples were collected for the period from entry into the operating room until the end of anesthesia, and then up to 3 h after anesthesia, and for 24-h periods on days 1, 3, and 7 after anesthesia. Urine samples were also frozen until analysis. Inorganic fluoride concentrations were measured with a Fluoride Electrode Model 96–09 (Orion Research, Boston, MA, USA) and an Ionanalyzer Model 901 (Orion Research). Albumin, α_1- and β_2-MG, and NAG activities were determined by turbidimetric immunoassay (TIA), radioimmunoassay (RIA), and the synthetic substrate m-cresol purple (MCP) method, respectively. Urine volume during anesthesia and up to 3 days after anesthesia and creatinine clearance before and after anesthesia were also determined. Measured values for α_1-MG, β_2-MG, NAG, and albumin were corrected for urinary creatinine levels and expressed as excretion indices. Minimum alveolar concentration (MAC) values used to calculate MAC·h were 1.0% for isoflurane and 1.3% for sevoflurane, based on data obtained by Stevens et al. [8] and at our hospital [9], respectively.

Statistical analysis was carried out as follows. Repeated-measures ANOVA was used for intra- and inter-comparisons of changes in measurement points over time. The Wilcoxon signed-ranks test was used to test the differences between the values at entry into the operating room and those at measurement points in each group. For comparisons of patient characteristics between the two groups, the Mann-Whitney U-test was used. The ratio of patients was compared between the two groups by Fisher's exact test. Values of $P < 0.05$ were considered statistically significant.

Results

There were no significant differences between the two groups in patient characteristics, including age, sex ratio, body weight, urine production, and infusion volume (Table 1). Since the anesthesia time in the sevoflurane group tended to be longer (524 min), blood loss volume

Table 1. Patient characteristics[a]

Characteristic	Sevoflurane group ($n = 7$)	Isoflurane group ($n = 6$)
Male : female	3 : 4	3 : 3
Age (yr)	77.6 ± 1.7	78.5 ± 2.8
Body weight (kg)	46.9 ± 2.5	50.5 ± 4.5
Anesthesia time (min)	524.0 ± 57.1	434.2 ± 26.0
Blood loss (ml)	902.9 ± 289.0	513.3 ± 126.5
Urine production (ml·kg^{-1}·h^{-1})	3.4 ± 0.7	3.7 ± 0.7
Infusion volume (ml·kg^{-1}·h^{-1})	8.1 ± 0.7	8.1 ± 0.4
MAC·h	5.1 ± 0.7	3.7 ± 0.4

[a] Values are means ± SE

and MAC·h also tended to be greater in the sevoflurane group; however, these differences were not statistically significant. Overall, there were no significant differences in patient characteristics between the two groups. The antibiotics administered during and after surgery were either cefazolin sodium (CEZ) or piperacillin sodium (PIPC). In the sevoflurane group, three patients received CEZ and 4 received PIPC; in the isoflurane group, three received CEZ and three received PIPC. There was no significant difference between the two groups in antibiotic use. The volumes of local anesthetics used for epidural anesthesia and dopamine administered during anesthesia also did not differ between the two groups.

Both serum and urinary fluoride levels were increased during anesthesia in the two groups, and changes in the levels over time within each group and between the two groups were statistically significant (Fig. 1). In the sevoflurane group, serum inorganic fluoride (Fig. 1, upper panel) was significantly elevated immediately before surgery compared with the preanesthesia value, reaching a maximum of 17.7 ± 1.7 μmol·l^{-1} 3 h after anesthesia and remaining elevated until postanesthesia day 1. However, the serum inorganic fluoride level did not exceed 50 μmol·l^{-1} in any patient, was substantially decreased on day 3 after anesthesia but was significantly greater than the preanesthesia value, and had almost returned to the preanesthesia value on day 7 after anesthesia. In the isoflurane group, a small but significant elevation in inorganic fluoride levels was observed from the end of anesthesia to postanesthesia day 1, as compared with the preanesthesia value. Changes in urinary inorganic fluoride levels over time (Fig. 1, lower panel) were similar to those seen in serum inorganic fluoride levels in both groups.

There were no significant changes in BUN levels, serum creatinine levels, urine volume (Table 2), and creatinine clearance (Fig. 2, lower panel) over time within the sevoflurane or the isoflurane group, and there were no differences in these measurements between the two groups. BUN and serum creatinine levels were shifted within the normal range over time.

In the sevoflurane group, no marked change in creatinine clearance was observed. In the isoflurane group, creatinine clearance showed a tendency to increase during anesthesia but was transitorily decreased 3 h after anesthesia (statistically significant compared with the preanesthesia value) and thereafter almost returned to the preanesthesia level.

Changes in the albumin excretion index (Fig. 2, upper panel), α_1-MG excretion index (Fig. 3), β_2-MG excretion index (Fig. 4), and NAG excretion index (Fig. 5) over time were significantly different within each group but not between the two groups. The albumin excretion index was increased during and up to 3 h after anesthesia, and almost returned to the preanesthesia level after postanesthesia day 1 in both groups.

Both the α_1-MG excretion index and the β_2-MG excretion index showed similar changes over time in the

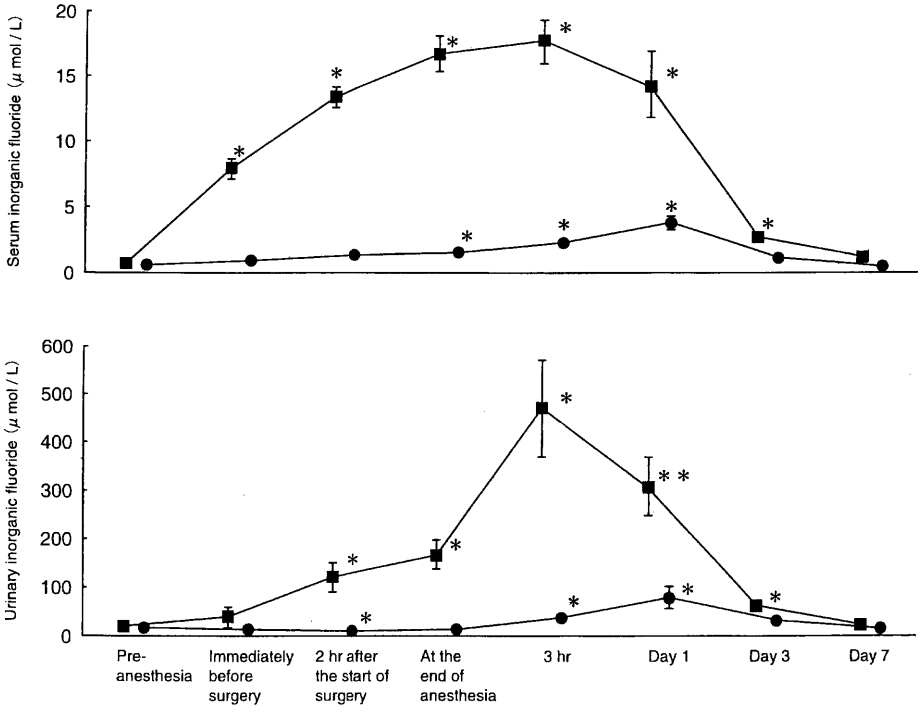

Fig. 1. Upper panel: Serum inorganic fluoride levels in the sevoflurane and isoflurane groups. **Lower panel**: Urinary inorganic fluoride levels in the sevoflurane and isoflurane groups. Values are means ± SE. *Closed squares*: sevoflurane group; *closed circles*: isoflurane group. *$P < 0.05$ compared with preanesthesia value

Table 2. Changes in blood urea nitrogen (BUN) levels, serum creatinine levels, and urine volume in the sevoflurane and isoflurane groups[a]

Parameter	Group	Preanesthesia	Immediately before surgery	2h after the start of surgery	At the end of anesthesia	Postanesthesia			
						3h	Day 1	Day 3	Day 7
BUN ($mg \cdot dl^{-1}$)	Isoflurane	14.0 ± 1.9	13.5 ± 2.0	13.3 ± 1.9	12.7 ± 1.6	12.3 ± 1.5	14.3 ± 2.3	12.5 ± 1.9	13.8 ± 1.7
	Sevoflurane	11.4 ± 1.2	10.9 ± 1.3	10.4 ± 1.1	10.2 ± 1.1	11.6 ± 0.9	14.1 ± 1.3	10.9 ± 2.1	15.4 ± 4.5
Serum creatinine ($mg \cdot dl^{-1}$)	Isoflurane	0.90 ± 0.10	0.87 ± 0.09	0.83 ± 0.08	0.85 ± 0.06	0.85 ± 0.07	0.97 ± 0.14	0.73 ± 0.10	0.85 ± 0.06
	Sevoflurane	0.81 ± 0.06	0.79 ± 0.06	0.77 ± 0.04	0.74 ± 0.06	0.79 ± 0.07	0.84 ± 0.08	0.80 ± 0.09	0.90 ± 0.14
Urine volume ($ml \cdot kg^{-1} \cdot h^{-1}$)	Isoflurane				3.7 ± 0.7[b]	1.9 ± 0.3	1.7 ± 0.6	1.8 ± 0.4	
	Sevoflurane				3.4 ± 0.4[b]	2.9 ± 1.0	1.5 ± 0.2	1.5 ± 0.2	

[a] Values are means ± SE
[b] Urine volume during anesthesia

two groups. Both indices were increased from 2h after the start of anesthesia to 3h after anesthesia, and although the value on postanesthesia day 1 tended to show a decrease, higher values were maintained up to postanesthesia day 3, and values decreased on postanesthesia day 7.

The NAG excretion index was increased from 2h after the start of anesthesia to 3h after anesthesia, and then decreased to almost the preanesthesia value.

Discussion

A number of studies have evaluated the effects of sevoflurane anesthesia on renal function. Most of these studies were performed in healthy adults. With regard to serum inorganic fluoride in these studies, no abnormalities were observed when prolonged sevoflurane anesthesia was employed [10,11], and no renal impairment was reported when serum inorganic fluoride concentrations exceeded $50\,\mu mol \cdot l^{-1}$ [12], which is considered the threshold for nephrotoxicity in methoxyflurane anesthesia. Therefore, inorganic fluoride produced during sevoflurane anesthesia appears to cause no renal impairment in healthy adults. With regard to compound A, anesthesia using 3% sevoflurane with a flow rate of 2l for 8h in healthy volunteers resulted in abnormal increases in urinary albumin, urinary glucose, and urinary excretion of glutathione *S*-transferase, although BUN and creatinine levels remained unchanged [13]. However, this data was not confirmed by the subsequent study [14]. In the studies on low-flow sevoflurane anesthesia in adult patients [15,16], renal impairment was not found in either study. Moreover, the editorial [17] commented that there is no difference between the safety of low-flow sevoflurane and of low-flow isoflurane. Therefore, compound A is also likely not to cause renal impairment in healthy adults in low-flow sevoflurane anesthesia.

Unlike methoxyflurane anesthesia, sevoflurane causes no nephrotoxicity, which may be due to the facts that (1) the serum inorganic fluoride concentration continues to increase for an extended period after methoxyflurane anesthesia, whereas in sevoflurane anesthesia, even when the maximum serum inorganic fluoride concentration exceeds $50\,\mu mol \cdot l^{-1}$, the concentration falls rapidly after anesthesia; and (2) sevoflurane and methoxyflurane are metabolized differently in the kidney, with methoxyflurane metabolized to a greater extent than sevoflurane [18]. With increasing age, not only is there a reduction in glomerular filtration rate (GFR), which at 80 years of age is approximately 50% of that at 30 years of age, but also there is a decline in tubular function [7]. Therefore, some concern has been expressed regarding the effects of sevoflurane administra-

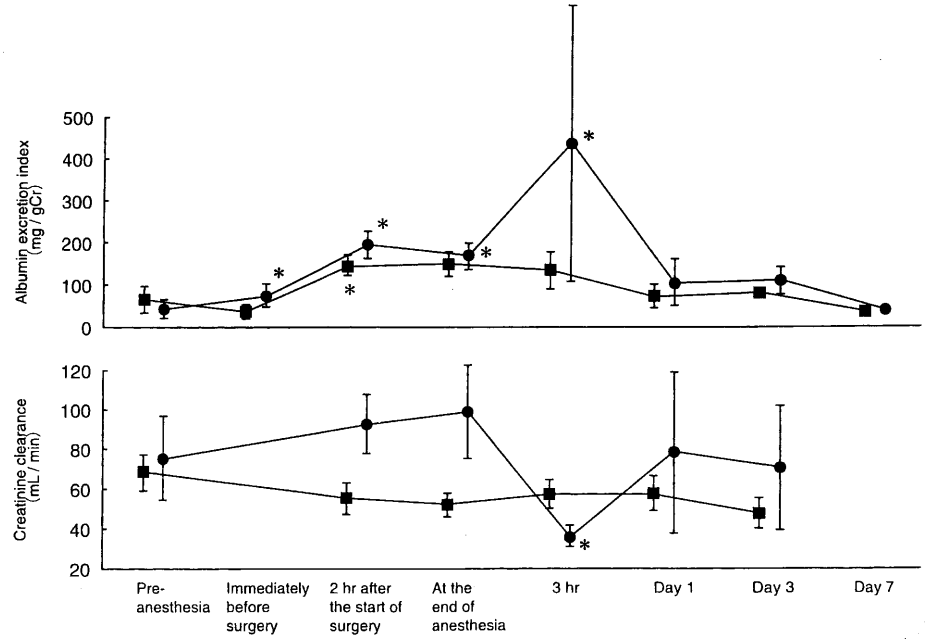

Fig. 2. Upper panel: Albumin excretion index in the sevoflurane and isoflurane groups. **Lower panel**: Creatinine clearance. Values are means ± SE. *Closed squares*: sevoflurane group; *closed circles*: isoflurane group. $*P < 0.05$ compared with preanesthesia value

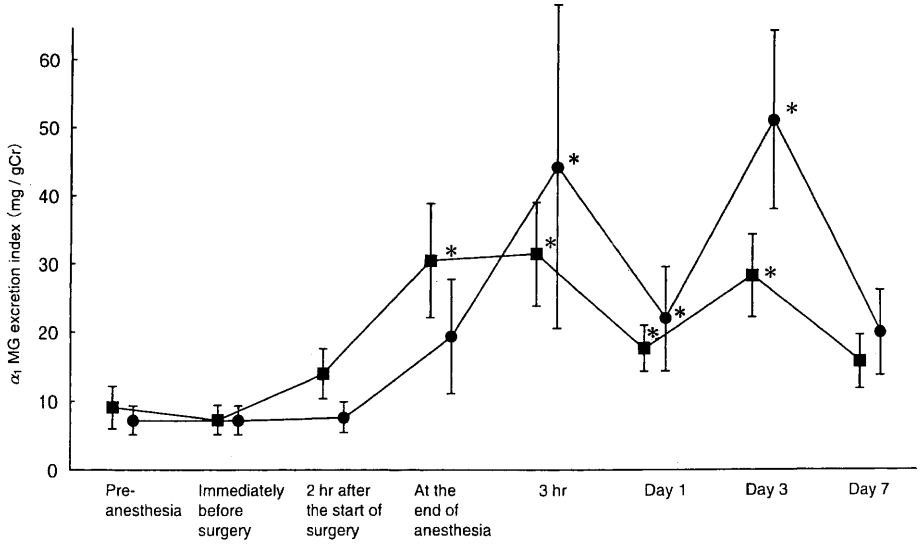

Fig. 3. α_1-Microglobulin (MG) excretion index in the sevoflurane and isoflurane groups. Values are means ± SE. *Closed squares*: sevoflurane group; *closed circles*: isoflurane group. $*P < 0.05$ compared with preanesthesia value

tion on renal function in the elderly or in patients with impaired renal function.

The present study was carried out using the anesthetic technique that we routinely perform in our institution. We used soda lime, which produces less compound A in the reaction with sevoflurane [1,3], and a semi-closed circuit system with a high total flow rate of $5 l \cdot mm^{-1}$ was employed. Therefore, the concentrations of compound A formed in the circuit were considered to be negligible. It should also be noted that our results may have been influenced not only by the low concentration of the inhalational anesthetics applied due to the combined use of epidural anesthesia, but also by the effect of epidural anesthesia and dopamine infusion on renal function.

With regard to the routine renal function tests (BUN and creatinine) performed in the present study, the changes in these values remained within the normal range throughout the study period in both the sevoflurane and the isoflurane groups. These results are in agreement with those reported for the elderly [19] and for patients with impaired renal function [20]. In the present study, measures of glomerular function and tubular function were also examined.

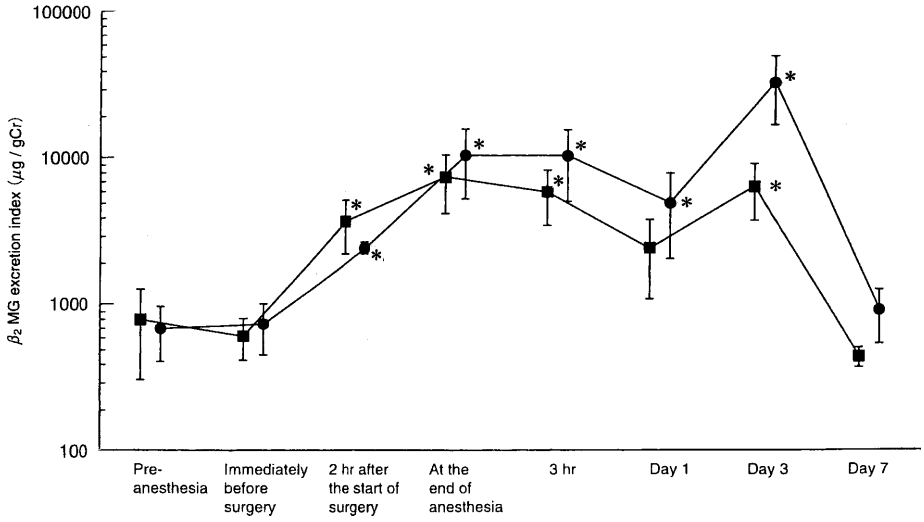

Fig. 4. β_2-Microglobulin (MG) excretion index in the sevoflurane and isoflurane groups. Values are means ± SE. *Closed squares*: sevoflurane group; *closed circles*: isoflurane group. $^*P < 0.05$ compared with preanesthesia value

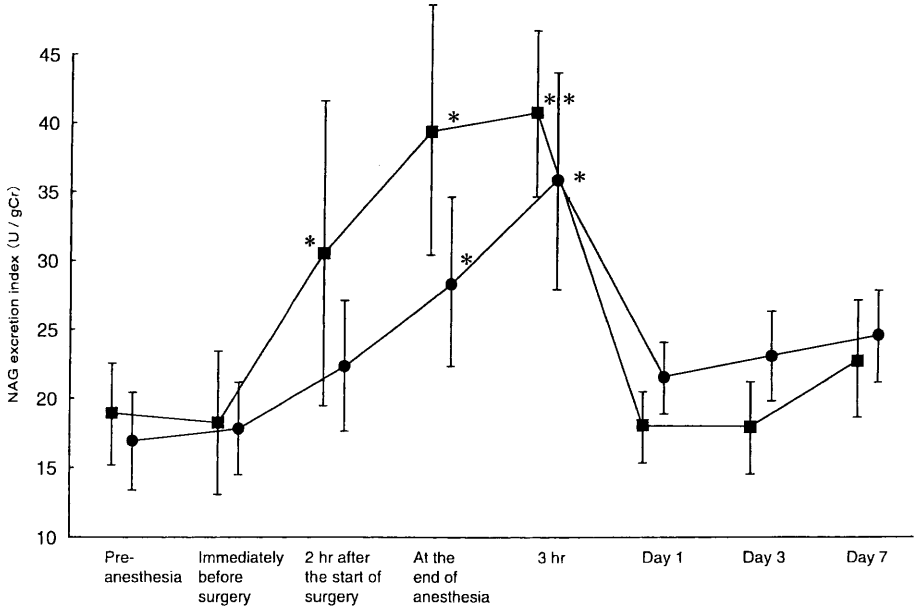

Fig. 5. Urinary *N*-acetyl-β-D-glucosaminidase (NAG) excretion index in the sevoflurane and isoflurane groups. Values are means ± SE. *Closed squares*: sevoflurane group; *closed circles*: isoflurane group. $^*P < 0.05$ compared with preanesthesia value

Effects on glomerular function were assessed by the albumin index and creatinine clearance. Albumin permeability was increased during and up to 3 h after anesthesia in both groups, but returned to the preanesthesia level on postanesthesia day 1. In the isoflurane group, an abnormal increase in albumin excretion was observed in one patient 3 h after anesthesia. However, the course of this patient was uneventful during and after surgery, and no specific reason for the abnormally high level of albumin excretion was identified. If the value measured in this patient is excluded from the analysis, the level of albumin excretion 3 h after anesthesia is similar in the two groups. Therefore, we considered that albumin excretion showed a temporal and equivalent increase during both sevoflurane and isoflurane anesthesia. With regard to creatinine clearance, although no decrease was shown during anesthesia in the isoflurane group, the level dropped 3 h after anesthesia. Isoflurane anesthesia is known to be associated with decreases in renal plasma flow (RPF), GFR, and urine volume [21,22]. The mechanism can be explained as follows. Systemic vascular resistance (SVR) decreases and renal vascular resistance (RVR) increases with isoflurane anesthesia, resulting in redistribution of blood flow, leading to reduced renal blood flow [22]. In the present study, dopamine (3–5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was administered concomitantly, and it appears that in some patients RVR decreased due to interaction with isoflurane and

that renal blood flow was not decreased. However, the renal vessels were not exposed to the effects of isoflurane and dopamine after the end of anesthesia as the administration of these agents was discontinued, possibly resulting in a transitory decrease in creatinine clearance 3 h after anesthesia. On the other hand, in sevoflurane anesthesia, creatinine clearance was not increased and changes were minimal. This difference between sevoflurane and isoflurane anesthesia may reflect differences between the two anesthetics with regard to the vascular system, including the renal blood vessels. In any case, albumin excretion increased during both sevoflurane and isoflurane anesthesia, possibly resulting in transitory impairment of glomerular function.

Urinary α_1-MG, β_2-MG, and NAG were measured as indices of tubular function in the present study. Large amounts of NAG are found in superficial cells of the proximal tubule, and an increase in urinary NAG level indicates impairment of the renal tubule. Both α_1-MG and β_2-MG readily pass through the glomerular basement membrane but are reabsorbed and catabolized in the proximal tubule, so they are rarely excreted into the urine under normal conditions. Elevated blood levels of α_1-MG and β_2-MG and impairment of tubular function are two factors associated with increases in urinary excretion of α_1-MG and β_2-MG. The changes in α_1-MG index and β_2-MG index showed similar patterns in both groups, i.e., the values started to increase after the start of anesthesia, reached a peak at the end of anesthesia or 3 h after anesthesia, and decreased on postanesthesia day 1, but increased again on day 3 and decreased again on day 7; the changes over time showed a two-peak pattern. Similarly, the NAG index increased after the start of anesthesia, reached a peak 3 h after anesthesia, and thereafter decreased almost to the preanesthesia value in both groups. Therefore, all three indices (α_1-MG, β_2-MG, and NAG) increased during the period from the start of anesthesia to 3 h after anesthesia in both groups, suggesting renal tubular impairment. Moreover, it was unclear why the α_1-MG index and the β_2-MG index increased again on postanesthesia day 3; this might indicate excessive production of these substances due to an unknown mechanism. Furthermore, it has been reported that urinary excretion of substances such as NAG that are found in renal tubular cells increases about 2 days after renal tubular impairment associated with inorganic fluoride [12]. However, in the present study, no such trend was seen, but the level increased only during anesthesia, suggesting that the mechanism of renal tubular impairment in the present study may differ from that previously reported. The mean β_2-MG index in the present study was extremely high compared with values reported in other studies [19,23], and it has been reported that the value is higher when surgical invasion (surgery time and blood loss) is greater [24]. In the present study, not only the prolonged surgical time (8.7 h in the sevoflurane group and 7.2 h in the isoflurane group) and the considerable blood loss (902 ml in the sevoflurane group and 513 ml in the isoflurane group), but also the advanced age of the patients may have contributed to the high β_2-MG index value.

Inorganic fluoride is produced in significantly greater amounts during sevoflurane anesthesia than during isoflurane anesthesia, and in sevoflurane anesthesia compound A is produced when sevoflurane reacts with the CO2 absorbent. However, as previously stated, inorganic fluoride or compound A has not been shown to cause nephrotoxicity in adults with normal renal function. In the present study of elderly patients, a similar transient renal impairment was observed in both sevoflurane and isoflurane anesthesia, indicating that the renal effects that we observed may not have been caused by compound A and inorganic fluoride. Therefore, we should consider other factors attributable to renal impairment, such as the influence of drugs other than the anesthetics used or surgical invasion. Although we did not perform the vasopressin test, the results of serum inorganic fluoride measurements in the sevoflurane group (the level did not exceed 50 $\mu mol \cdot l^{-1}$ in any patient) and the renal tubular function tests in both groups indicate that there was no difference between the two anesthetics in influence on renal concentrating ability, and thus this factor can be neglected.

In conclusion, we found that sevoflurane and isoflurane anesthesia in combination with dopamine and epidural anesthesia resulted in similar degrees of mild, transient glomerular and tubular functional impairment in elderly surgical patients undergoing gastrectomy. The mechanism of these changes remains unknown. The number of patients studied was too small to warrant any definitive statements about the safety of these anesthetics in this patient population. However, no abnormalities were found in routine laboratory tests, suggesting that neither isoflurane nor sevoflurane, when used in our routine anesthetic technique, seriously affects renal function, even in the elderly.

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