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Liver and renal functions following total intravenous anesthesia using midazolam and fentanyl—comparison with enflurane–nitrous oxide anesthesia

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Abstract: Thirty patients undergoing lower abdominal surgery were studied to compare liver and renal functions in total intravenous anesthesia (TIVA) using midazolam and fentanyl with those in enflurane–nitrous oxide anesthesia (GOE).

Patients were randomly divided into two groups of 15. In the TIVA group, anesthesia was induced with 0.3 mg·kg^{-1} midazolam and maintained with 0.68 mg·kg^{-1}·h^{-1} midazolam for 15 min followed by 0.125 mg·kg^{-1}·h^{-1} midazolam and fentanyl. In the GOE group, anesthesia was induced with 5 mg·kg^{-1} thiamylal and maintained with enflurane–nitrous oxide in oxygen. Plasma levels of aspartate aminotransferase, alanine aminotransferase (ALT), lactate dehydrogenase, total bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase (γ-GTP), blood urea nitrogen (BUN), and creatinine (Cr) were measured before and at 1, 7, and 30 days after surgery. There were transient increases beyond the normal range in ALT and γ-GTP in both groups. BUN and Cr were within the normal range. There were no differences between the two groups regarding these parameters and the numbers with abnormally high levels of each parameter. In conclusion, liver and renal functions following TIVA using midazolam and fentanyl were the same as those following enflurane–nitrous oxide anesthesia.

Key words: Liver function, Renal function, Total intravenous anesthesia, Midazolam, Enflurane

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Introduction

Total intravenous anesthesia (TIVA) has been discussed in many reports because volatile anesthetics produce problems of air pollution, bone marrow suppression, and possible toxicity to the liver and kidneys [1,2]. We also previously studied the hemodynamics, plasma levels of catecholamine, and postoperative analgesia in TIVA using midazolam and fentanyl [3,4]. It is well known that each of these two intravenous anesthetics has little effect on liver and renal functions. However, the elevated serum catecholamine levels during TIVA [5] will increase the metabolism and vascular resistance in the liver and kidney, which might affect liver and renal functions. No reports have appeared regarding postoperative liver and renal functions following TIVA. The aim of this study was to compare liver and renal functions after TIVA using midazolam and fentanyl with those following enflurane–nitrous oxide anesthesia (GOE).

Methods

Following the approval of the Ethics Committee of the hospital and gaining informed consent, we studied 30 patients, aged 40–70 years with ASA class 1 or 2, scheduled for elective lower abdominal surgery. Those who had abnormally high plasma levels of liver enzymes, blood urea nitrogen (BUN), or creatinine (Cr), or were taking any drugs prior to surgery were excluded. They were divided into two groups according to a random-number table: a TIVA group and a GOE group of 15 patients each.

Atropine (0.5 mg) and hydroxyzine (50 mg) were injected intramuscularly as premedication 30 min before the patient entered the operating room. Prior to general anesthesia, an epidural catheter was inserted into a

single interspace from Th10 to L2 for postoperative pain control.

In the TIVA group, anesthesia was induced with 0.3 mg·kg^{-1} midazolam, and tracheal intubation was performed with 1 mg pancuronium followed by 1 mg·kg^{-1} suxamethonium. Midazolam was infused at 0.68 mg·kg^{-1}·h^{-1} for 15 min followed by 0.125 mg·kg^{-1}·h^{-1} according to the method of Persson et al. [6], with its infusion being stopped about 30 min before the end of surgery. Fentanyl and pancuronium were intermittently administered as necessary. Oxygen (6 l·min^{-1}) was inhaled and no volatile anesthetics were used. Atropine (1 mg) and neostigmine (2 mg), naloxone (0.2 mg), and aminophylline (125 mg) were administered at the end of surgery to antagonize muscle relaxant, fentanyl, and midazolam, respectively.

In the GOE group, anesthesia was induced with 5 mg·kg^{-1} thiamylal and tracheal intubation was performed as in the TIVA group. Anesthesia was maintained with 1.0%–2.0% (end-tidal concentration) enflurane and 3 l·min^{-1} nitrous oxide in 2 l·min^{-1} oxygen. Atropine (1 mg) and neostigmine (2 mg) were administered at the end of surgery. An end-tidal concentration of 1.68% enflurane was calculated as 1 minimum alveolar concentration (MAC).

Postoperative pain control was performed with intermittent epidural injection of 0.25% bupivacaine and buprenorphine. Cefazolin was used as an antibiotic for 7 days after surgery in every case. Those who had apparent infection were excluded from this study.

Plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total bilirubin (T.Bil), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), BUN, and Cr were measured before surgery and at 1, 7, and 30 days after surgery. All parameters were measured at the hospital's central laboratory according to standard procedures.

Data are given as mean ± standard error. Statistical analysis consisted of an analysis of variance (ANOVA) with repeated measures for each parameter before and after anesthesia, a χ^2 test for sex, and the Mann–Whitney *U*-test for other parameters between groups. A *P* value less than 0.05 was considered statistically significant.

Results

There were no significant differences between the two groups for age, sex, body weight, duration of surgery, and anesthesia (Table 1), and blood pressure and heart rate (Table 2) during surgery. In the TIVA group, 48.5 ± 4.1 mg (range 41.0–61.4 mg) midazolam and 717 ± 60 μg (range 600–900 μg) fentanyl were administered. In the GOE group, 4.1 ± 0.2 MAC·h (range 3.1–4.7 MAC·h) enflurane was used.

Table 1. Demographic data

	TIVA group	GOE group
Number of cases	15	15
Sex (male/female)	9/6	8/7
Age (years)	56 ± 5	55 ± 3
Body weight (kg)	52.9 ± 3.1	53.4 ± 4.8
Duration of		
Surgery (min)	223 ± 37	218 ± 32
Anesthesia (min)	295 ± 27	288 ± 35

TIVA, total intravenous anesthesia; GOE, enflurane–nitrous oxide anesthesia.
Mean ± SEM.
There is no significant difference between the two groups.

Table 2. Blood pressure and heart rate

	TIVA group	GOE group
Blood pressure		
Systolic/diastolic (mmHg)		
Before induction	135 ± 7/72 ± 6	130 ± 9/66 ± 7
Start of surgery	142 ± 9/79 ± 8	139 ± 7/72 ± 9
1 h after the start of surgery	140 ± 6/80 ± 5	131 ± 7/75 ± 9
End of surgery	130 ± 8/71 ± 6	128 ± 9/70 ± 6
After extubation	128 ± 8/71 ± 6	130 ± 7/71 ± 5
Heart rate (beats·min^{-1})		
Before induction	65 ± 4	68 ± 5
Start of surgery	76 ± 6	77 ± 4
1 h after the start of surgery	69 ± 3	70 ± 5
End of surgery	68 ± 3	68 ± 4
After extubation	71 ± 3	72 ± 3

Mean ± SEM.
There is no significant difference between the two groups.

AST and ALT on the 7th day after surgery and T. Bil on the 1st day after surgery in the TIVA group, and LDH on the 1st and 7th days after surgery in both groups increased significantly compared to the presurgical values. However, they returned to the presurgical values on the 30th day after surgery. BUN and Cr were within the normal range in both groups. There were no significant differences in these parameters between the two groups. The numbers who had abnormally high levels in each parameter did not significantly differ between the two groups (Fig. 1).

Discussion

Halothane [7] and enflurane [8] are known to cause liver dysfunction. Nitrous oxide is reported to depress bone marrow function [9]. Therefore, extended exposure to volatile anesthetics is dangerous not only to the

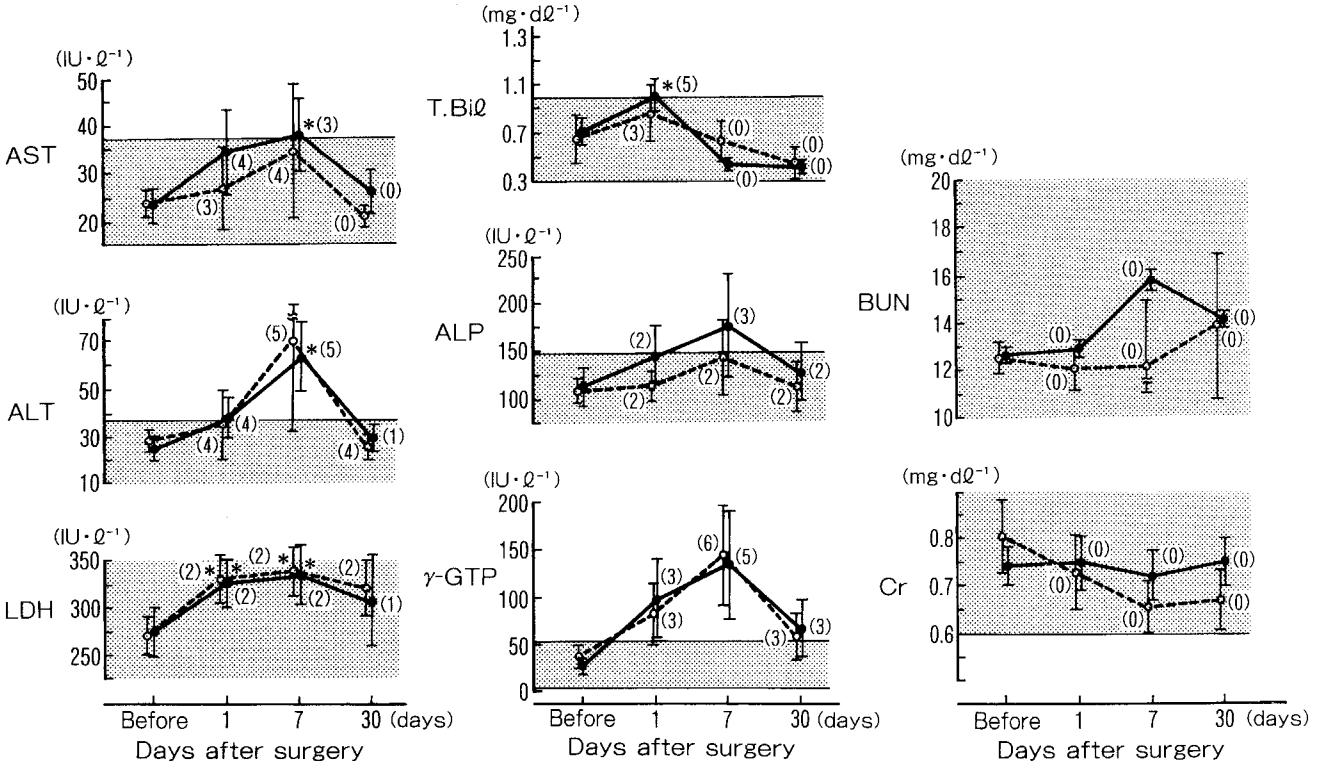

Fig. 1. Liver and renal functions. *Closed circle*, total intravenous anesthesia (TIVA) group (15 patients); *open circle*, enflurane-nitrous oxide (GOE) group (15 patients); *bar*, SEM; *shaded area*, normal range. The number who had an abnormally high value is shown in *parentheses*. *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *LDH*, lactate dehydrogenase; *T.Bil*, total bilirubin; *ALP*, alkaline phosphatase; *γ-GTP*, γ-glutamyl transpeptidase; *BUN*, blood urea nitrogen; *Cr*, creatinine. $*P < 0.05$ *vs* the value before surgery. There are no significant differences in any parameters between the two groups

patients, but also to the operating-room personnel [10]. The newly developed volatile anesthetics isoflurane [11] and sevoflurane [12] are also reported to cause liver dysfunction. However, no reports have indicated that midazolam or fentanyl alone cause liver or other organ dysfunction. In addition, intravenous anesthetics do not result in air pollution.

The TIVA method employed in the present study generated stable hemodynamics and postanesthetic analgesia [3], although it produced higher serum catecholamine levels than did enflurane–nitrous oxide anesthesia during surgery in our previous study [5]. In the present study, the TIVA group presented a transient but significant elevation in AST, ALT, LDH, and T.Bil following surgery, which might be due to increased metabolism or vascular resistance by catecholamine [13,14] in the liver during TIVA. However, these elevations did not differ significantly from those in the GOE group. The increases in liver enzymes were in part due to the abdominal surgical procedure employed, which unquestionably influenced liver blood flow and function.

Regarding the effect on renal function of anesthetics, methoxyflurane is well known to cause renal damage [15] and no other anesthetics are reported to cause renal dysfunction. The normal values of BUN and Cr in the present study indicate that renal function was not clinically affected by either TIVA or enflurane–nitrous oxide anesthesia.

In conclusion, the results of this study suggest that liver and renal functions following TIVA using midazolam and fentanyl are the same as those after enflurane–nitrous oxide anesthesia. To clarify this problem, further studies are necessary in much larger populations.

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