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Comparison of postoperative liver dysfunction following halothane and sevoflurane anesthesia in women undergoing mastectomy for cancer

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Abstract: The incidence of an abnormal increase in the serum levels of glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) following anesthesia with halothane and 65% nitrous oxide in oxygen (halothane group) or with sevoflurane and 65% nitrous oxide in oxygen (sevoflurane group) was compared in women undergoing surgery for breast cancer. An abnormal increase in GOT and GPT, both defined as higher than 50 IU, occurred postoperatively in 2 of the 150 patients (1.7%) in the sevoflurane group, and in 37 of the 200 (18.5%) in the halothane group ($P < 0.001$). The elevated levels of serum transaminases after sevoflurane ranged from 50 to 65 IU whereas those after halothane ranged from 50 to 1000 IU, except for a value greater than 5000 IU in 1 patient. In the halothane group, there was a significant association between postoperative increases in serum transaminases and previous exposure to inhalation anesthetics, postoperative mitomycin therapy, and radiation therapy (all $P < 0.001$). The results of multivariate analysis, when data from all patients were taken together, showed that the type of anesthetic (halothane) was the highest factor related to postoperative increases in GOT and GPT (odds ratio 35.85; 95% confidence interval 5.92–217.37), followed next by prior exposure to inhalation anesthetics (8.65; 2.96–25.27), postoperative radiation therapy (4.37; 1.70–11.19), and postoperative mitomycin therapy (3.56; 1.23–10.35). These data suggest that sevoflurane is less likely to cause anesthesia-related liver dysfunction than halothane.

Key words: Halothane, Sevoflurane, Liver function, Transaminases

Introduction

Unexplained increases in serum concentration of glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) can occur in surgical patients postoperatively. If halothane is used in such situations, it is often suspected as a possible cause of postoperative increases in serum transaminases. Prospective studies done in the 1970s regarding the effect of halothane on liver function tests showed that mild increases in serum transaminases postoperatively are seen with halothane more often than with the other halogenated anesthetics [1–4]. More recent studies using radioimmunoassay of glutathione-S-transferase (GST), which is more sensitive and specific to the liver damage than GOT and GPT, demonstrated that halothane but not isoflurane anesthesia was frequently associated with abnormal GST levels [5,6].

The actual incidence of halothane hepatitis is uncertain because it is difficult to exclude other possible causes of postoperative liver damage. Most clinical studies have been done on patients undergoing various surgical procedures, irrespective of major or minor surgery, and with the combined use of other anesthetics, such as thiopentone as an induction agent. For induction and maintenance of anesthesia in combination with a volatile anesthetic agent, nitrous oxide and oxygen is preferred for breast surgery at our institution as it is simple and safe. Halothane was used in an earlier period, and we later switched to sevoflurane when it became available. The study was originally done to analyze factors associated with an abnormal increase in GOT and GPT after halothane anesthesia, followed by the same study done in a sevoflurane series. We report here a comparison between these two series of postoperative liver dysfunction in women undergoing breast surgery.

Materials and methods

Three hundred and fifty Japanese women with ASA status I–II undergoing elective breast surgery to remove a malignant tumor were enrolled in the study. The 200

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who underwent breast surgery between October 1988 and May 1991 received halothane in 35% oxygen/65% nitrous oxide (halothane group) and the 150 who underwent breast surgery between June 1991 and March 1993 received sevoflurane in 35% oxygen/65% nitrous oxide (sevoflurane group). No patient had a history of liver disease or preoperative liver dysfunction, and cases when anesthesia was supplemented with either intravenous anesthetics or a muscle relaxant or both were not included in the data analysis. The protocol was approved by the Ethics Committee of Kobe City General Hospital, and informed consent was obtained from each patient. All patients were premedicated with atropine sulfate 0.5 mg, i.m. The induction of anesthesia consisted of nitrous oxide (65%) in oxygen and either halothane (up to 3.0%) or sevoflurane (up to 5.0%) to facilitate tracheal intubation, without the aid of a muscle relaxant. Anesthesia was maintained using halothane (0.4%–1.0%) or sevoflurane (1.0%–2.5%) and nitrous oxide (65%) in oxygen. Lactated Ringer's solution was given at a rate of 5 to 8 ml·kg·h i.v. intraoperatively. None of the patients received a blood transfusion.

All patients were monitored intraoperatively with ECG, pulse oximetry, and noninvasive blood pressure measurements. Venous blood samples were taken immediately before the operation, on days 1–3, and 1 week after the operation, and then at various intervals for up to 2 months postoperatively. The serum levels of GOT, GPT, and total bilirubin were measured using an automated Hitachi 736 Analyser (Hitachi, Hitachinaka, Japan). Value greater than 50 IU (normal range of both GOT and GPT are 8–40 IU by this method) was taken as an abnormal increase in GOT and GPT.

The following information was obtained on each patient: preoperative factors: age; Broca's index calculated by body weight, height, ideal body weight; co-existing diseases; and prior exposure to inhalational anesthetics. Intraoperative and postoperative factors: duration of surgery, exposure time to anesthetics, intraoperative blood loss, amounts of fluids given intraoperatively, mean blood pressure during anesthesia, and postoperative therapy including antibiotics, mitomycin, and radiation.

Statistical analysis

Differences in discrete variables between the two anesthetic groups, as well as between patients with and without postoperative increases in GOT and GPT, were analyzed using the chi square test and differences in continuous variables were analyzed by Student's t-test. An association between factors examined and postoperative increases in GOT and GPT was analyzed by univariate and multiple logistic regression analysis. The correlation between the time when an abnormal increase in GOT and GPT was noted and serum transaminase levels were analyzed using simple linear regression analysis. All reported P values are two-tailed and were considered significant at $P < 0.05$. Statistical analysis was made using Statistical Analysis Systems for Personal Computer (SAS Institute, Cary, USA).

Results

Patient characteristics

The two groups were well matched for age, Broca's index, duration of surgery, and exposure time to anesthetics. Values related to halothane and sevoflurane did not differ with regard to the incidence of co-existing diseases and prior exposure to general anesthetics, respectively. Intraoperative blood loss was significantly higher in the halothane group, but the amount of fluid infused did not differ between the two groups. Both the maximum and minimum mean blood pressure during anesthesia were significantly lower in the halothane group (both, $P < 0.001$). The antibiotics used most frequently was cefazolin in the halothane group while it was flomoxef in the sevoflurane group. There were no significant differences between the groups regarding the duration and type of antibiotics prescribed postoperatively. The number of patients given mitomycin and/or radiation therapy postoperatively was greater in the halothane group than in the sevoflurane group ($P < 0.02$, $P < 0.001$, respectively) (Table 1).

Incidence of postoperati e increases GOT and GPT

Thirty-seven patients in the halothane group (18.5%) and 2 in the sevoflurane group (1.7%) developed an abnormal increase in GOT and GPT postoperatively, the incidence being significantly higher in the halothane group ($P < 0.001$). The levels of GOT and GPT on the day when an abnormal increase was noted are plotted in Fig. 1. Of the patients in the halothane group, both GOT and GPT levels ranged from 50 to 100 units in 16, from 100 to 500 units in 15, from 500 to 1000 units in 5, and higher than 5000 units in 1. In two patients who received sevoflurane, GOT and GPT levels ranged from 50 to 65 units. The serum bilirubin levels were within normal in all but one patient in the halothane group in whom the serum bilirubin level was 16.6 mg/dl and serum transaminase levels were higher than 5000 units. The interval between breast surgery and the onset of abnormal GOT and GPT levels ranged from 3 to 60 days, with a median of 19 days. There were 4 patients in whom an abnormal increase in serum transaminases manifested after 28 days. There was no correlation

Table 1. Patient characteristics and clinical data

	Halothane	Sevoflurane
	(n = 200)	(n = 150)
Age (years)	52 ± 13	51 ± 11
Height (cm)	153 ± 5.8	153 ± 5.6
Weight (kg)	53 ± 8.0	53 ± 8.4
Broca's index (%)	11 ± 16.5	12 ± 17.0
Co-existing diseases	53 (26.5%)	30 (20%)
Prior exposure to inhalational anesthetics	38 (19%)	34 (22.6%)
Duration of surgery (min)	119 ± 42	118 ± 43
Exposure time to anesthetics (min)	140 ± 40	144 ± 45
Maximum MAP during anesthesia (mmHg)	103 ± 14	113 ± 15***
Minimum MAP during anesthesia (mmHg)	72 ± 11	80 ± 10***
Intraoperative fluid volume (ml)	1801 ± 606	1729 ± 609
Intraoperative blood loss (ml)	319 ± 204	266 ± 193*
Postoperative: Antibiotics	200 (100%)	150 (100%)
Mitomycin	48 (24%)	20 (13.3%)**
Radiation	58 (29%)	13 (8.7%)***
Incidence of postoperative increase in GOT and GPT	37 (18.5%)	2 (1.3%)***

Values are mean ± SD.
*$P < 0.05$, **$P < 0.02$, ***$P < 0.001$.
MAP, mean arterial pressure; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

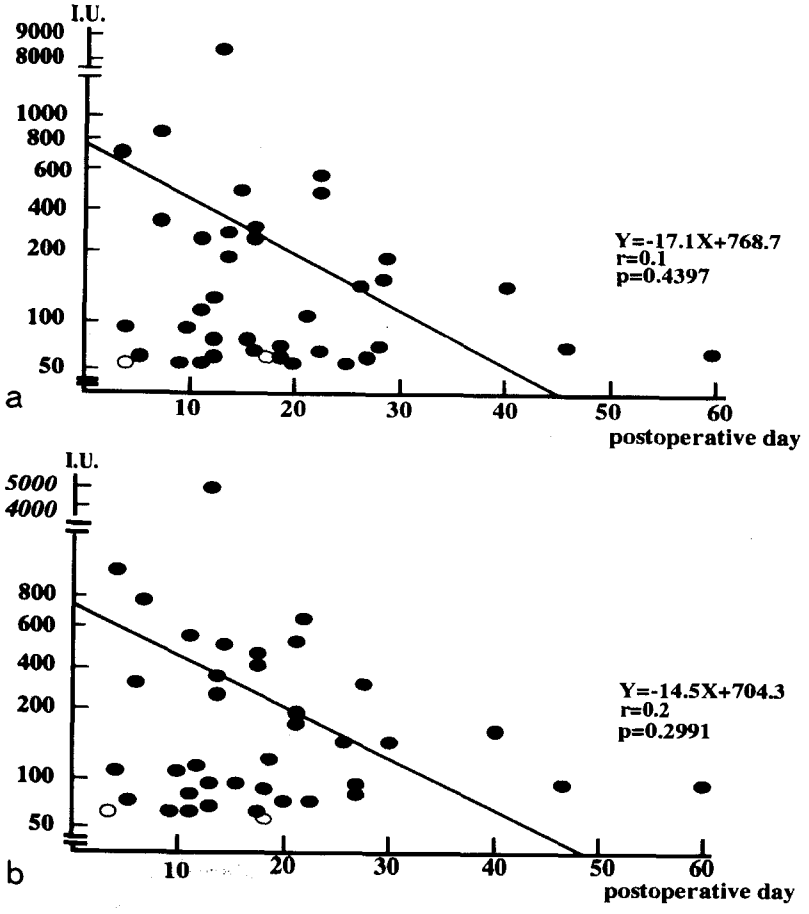

Fig. 1a,b. Values of **a** glutamic oxaloacetic transaminase (GOT) and **b** glutamic pyruvic transaminase (GPT) on the day when an abnormal increase was noted following halothane (*closed circles*) and sevoflurane (*open circles*) anesthesia. There was no correlation between the interval and the levels of GOT and GPT

Table 2. Comparison of data between patients with and without postoperative increases in GOT and GPT in the halothane group

	Postoperative increases in GOT and GPT	
	No (n = 163)	Yes (n = 37)
Age (years)	52 ± 13	51 ± 9
Broca's index (%)	11 ± 16.5	12 ± 17.0
Co-existing diseases	33 (20%)	8 (21%)
Prior exposure to inhalational anesthetics	23 (14%)	15 (41%)*
Duration of surgery (min)	115 ± 40	127 ± 47
Exposure time to anesthetics (min)	137 ± 40	150 ± 47
Maximum MAP during anesthesia (mmHg)	103 ± 13	105 ± 13
Minimum MAP during anesthesia (mmHg)	71 ± 11	72 ± 11
Intraoperative fluid volume (ml)	1745 ± 610	1948 ± 704
Intraoperative blood loss (ml)	310 ± 215	363 ± 142
Postoperative mitomycin therapy	30 (18%)	18 (49%)*
Postoperative radiation therapy	35 (21%)	23 (62%)*

Values are mean SD.
*$P < 0.001$ between groups with and without postoperative increases in GOT and GPT.

between the interval and the abnormal transaminase concentrations.

In the halothane group, there was a significant association between postoperative increases in serum transaminases and previous exposure to anesthetics, mitomycin therapy, and radiation therapy (all $P < 0.001$) (Table 2).

Multiple logistic regression analysis

When data from all patients in both groups were taken together, factors significantly associated with postoperative increases in GOT and GPT were the type of anesthetics, mitomycin therapy, radiation therapy, prior exposure to inhalational anesthetics, duration of surgery, exposure time to anesthetics, intraoperative fluid volume, and blood loss (Table 3). The multivariate analysis removed the latter four factors, whereas the former four factors remained independently associated with postoperative increases in GOT and GPT (Table 4). The type of anesthetic administered (halothane vs. sevoflurane) was the strongest determinant of postoperative increases in GOT and GPT (odds ratio 35.85; 95% confidence interval 5.92–217.37), followed by prior

Table 3. Univariate analysis of individual factors and their association with postoperative increases in GOT and GPT in the halothane and sevoflurane groups combined

	Postoperative Increases in GOT and GPT	
Factor	NO (n = 311)	Yes (n = 39)
Age (years)	52 ± 12	52 ± 9
Broca's index (%)	11 ± 16.5	14 ± 17.6
Anesthetics: Halothane/Sevoflurane	163/148	37/2***
Co-existing diseases	75 (24%)	8 (20%)
Prior exposure to inhalational anesthetics	56 (18%)	16 (41%)**
Duration of surgery (min)	116 ± 43	136 ± 37**
Exposure time to anesthetics (min)	170 ± 45	190 ± 43**
Maximum MAP during anesthesia (mmHg)	108 ± 15	106 ± 14
Minimum MAP during anesthesia (mmHg)	76 ± 11	72 ± 11
Intraoperative fluid volume (ml)	1737 ± 609	2038 ± 591**
Intraoperative blood loss (ml)	289 ± 206	363 ± 140*
Postoperative mitomycin therapy	49 (16%)	19 (49%)***
Postoperative radiation therapy	47 (15%)	24 (62%)***

Values are mean ± SD.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ between groups with and without postoperative increases in GOT and GPT.

Table 4. Factors predicting postoperative increases in GOT and GPT: logistic regression results

Factor	Regression coefficient (SE)	*P*	Odds Ratio (95% Confidence Intervals)
Anesthetics: halothane vs. sevoflurane	3.579 (0.919)	0.0001	35.85 (5.92–217.37)
Prior exposure to inhalational anesthetics	2.158 (0.547)	0.0001	8.65 (2.96–25.27)
Postoperative radiation therapy	1.474 (0.480)	0.0022	4.37 (1.70–11.19)
Postoperative mitomycin therapy	1.270 (0.544)	0.0196	3.56 (1.23–10.35)

exposure to inhalational anesthetics (8.65; 2.96–25.27), postoperative radiation therapy (4.37; 1.70–11.19), and postoperative mitomycin therapy (3.56; 1.23–10.35). Halothane was 36 times more likely to be associated with a risk of postoperative increases in GOT and GPT, compared with sevoflurane.

Discussion

The present results demonstrated that the incidence and the extent of postoperative increases in GOT and GPT were minimal following sevoflurane, and indicated a strong association between the anesthetic used and postoperative increases in GOT and GPT in women undergoing breast surgery. Since sevoflurane was introduced into clinical practice in 1991, three cases of liver dysfunction but no case of fulminant hepatic failure attributable to sevoflurane have been reported in Japan [7–9]. However, precise data on the actual incidence of liver dysfunction following sevoflurane anesthesia have not appeared. In a multicenter study, the only one for available data, 68 patients receiving sevoflurane were compared with 66 patients receiving enflurane, using total serum bilirubin, GOT, and GPT as indexes of liver dysfunction [10]. They found no significant changes in liver function tests following anesthesia in either group. There is no available evidence that sevoflurane is hepatotoxic in humans, but hepatic injury was induced in enzyme-induced hypoxic rats, albeit to a lesser extent than seen with halothane [11,12]. Sevoflurane is similar to enflurane with respect to biotransformation; they all release fluoride ions [13,14]. However, the metabolic pathway of sevoflurane probably differs from that of enflurane [14]. Despite no significant difference in the number of patients with previous exposure to anesthetics between our halothane and sevoflurane groups, the incidence and the extent of postoperative increases in GOT and GPT were minimal in the latter group. These results support the notion that sevoflurane is unlikely to cross-react with other halogenated anesthetics [15]. It seems that hepatotoxicity associated with sevoflurane may be a rare occurrence and mechanisms other than immunological ones would need to be considered, if any.

Another important finding is that we identified factors other than anesthetics that contribute to postoperative increases in GOT and GPT. Although the levels of serum GOT and GPT do not always reflect the extent of liver dysfunction, these levels are commonly used to assess liver dysfunction after general anesthesia. According to the definition of halothane hepatitis by Neuberger and Williams, the mild type of halothane hepatitis is characterized by a moderate increase in the concentration of liver transaminases, which is generally more than twice the normal and appears within 28 days of halothane exposure [16,17]. More recently, GST has become accepted as a more sensitive index than serum transaminases [5,6], but the measurement of GST by radioimmunoassay is not always popular for clinical use. There are many causes of postoperative increases in liver transaminases, including surgery, hypoxia, hypotension, sepsis, and drugs used perioperatively. We chose to study the effects of anesthetics on postoperative liver function in women undergoing mastectomy for cancer for the following reasons: (1) feasibility of anesthetic management with inhalation anesthetics alone, (2) little effect of surgical procedures on liver blood flow, (3) no requirement of blood transfusion, (4) most patients undergoing this type of surgery in Japan are middle-aged and obese, these being risk factors for halothane hepatitis, and (5) perioperative drug therapy is not complicated. In such patients, factors including previous exposure to inhalation anesthetics, radiation therapy, and mitomycin therapy were found to be significantly associated with an abnormal increase in GOT and GPT following halothane anesthesia.

The incidence of mild-type halothane hepatitis may be as high as 20%, but the actual incidence is uncertain because of ambiguous definitions [17]. The overall incidence of postoperative increases in GOT and GPT following halothane anesthesia was 18.5% in our series. However, the incidence of mild increases in GOT and GPT was 8.5% if we excluded data on 21 patients: 1 with severe liver dysfunction, 16 in whom the levels in serum transaminases were less than twice normal, and 4 in whom abnormalities were manifested after 28 days. Thus, the actual incidence of mild increases in GOT and GPT attributable to halothane would have been

markedly lower compared to the reported incidence of 20%.

The study period differed between the two groups, as reflected by surgical techniques and postoperative treatment variables. Resection of a breast for breast cancer was minimized during the period of the sevoflurane study, as compared with extensive surgery in the earlier period when halothane was used; significant difference of intraoperative blood loss was noted between the groups. Similarly, adjuvant therapy for breast cancer was modified; there was a significant decrease in the number of women prescribed mitomycin and radiation in the sevoflurane group. The increased incidence of postoperative abnormality in GOT and GPT in the halothane group can be explained in part by a bias in relation to mitomycin and radiation therapy. We examined the association between perioperative factors and postoperative increases in serum transaminases by univariate and multivariate analysis in the halothane and the sevoflurane groups combined. As a result, the type of anesthetic (halothane versus sevoflurane) was the strongest determinant of postoperative increases in serum transaminases. It was also confirmed that previous exposure to anesthetics is one of the risk factors for postoperative liver dysfunction [1,3,4,18]. However, the effect of previous exposure to anesthetics on postoperative increases in GOT and GPT was quite different between the sevoflurane and halothane groups, suggesting that immune-mediated liver dysfunction may be rare in cases of sevoflurane usage. A link among radiation therapy, mitomycin therapy, and an abnormal increase in serum transaminases was identified, and there was no association with antibiotic therapy.

In summary, we compared halothane versus sevoflurane with respect to the incidence of postoperative increases in GOT and GPT in women undergoing mastectomy for cancer. The patients anesthetized with halothane were 36 times more likely to have an abnormal increase in serum transaminases than those anesthetized with sevoflurane.

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