

Comparison of effects of anaesthesia with desflurane and enflurane on liver function

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ABSTRACT

Introduction: Although most general anaesthesia procedures are performed without any complications, volatile agents may have adverse effects on various living systems. This study aimed to compare the effects of desflurane and enflurane on liver function.

Methods: 40 patients, who were in the ASA I-III risk groups and were planned to undergo head and neck surgery of at least three hours' duration, were randomly divided into two groups: the desflurane (Group D) and enflurane groups (Group E). Venous blood samples (5 ml) of the patients were obtained before anaesthesia induction, in the postoperative first hour and on the first and seventh days. The samples were centrifuged and then stored at -80°C until the determination of glutathione S-transferase (GST) levels. For maintenance of anaesthesia in Group D, desflurane (6 percent) was used, while in Group E, enflurane (1.2 percent) was used.

Results: GST levels were significantly higher in Group E in the postoperative first hour (p-value is 0.002), and on the first day (p-value is 0.025) and seventh day (p-value is 0.035), although there were no differences preoperatively (p-value is more than 0.05). When postoperative levels were compared with preoperative levels, the postoperative GST levels of Group E were significantly higher (first hour [p-value is 0.008], first day [p-value is 0.010], seventh day [p-value is 0.038]).

Conclusion: Subclinical hepatic injury after anaesthesia continues to be an issue of interest, particularly with the development of new, more sensitive methods of measuring GST levels. The increase in GST concentration after anaesthesia is thought to be a result of reduced hepatic blood

flow. This study has shown that desflurane has fewer effects than enflurane on liver function tests in lengthy operations of up to 330 minutes.

Keywords: alanine aminotransferase, aspartate aminotransferase, desflurane, enflurane, glutathione S-transferase

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INTRODUCTION

Volatile agents are frequently used in general anaesthesia practice without complications. However, they continue to have adverse affects on various body systems. Although most of these effects are minimal and reversible, fatal complications such as fulminant hepatitis may occasionally occur. Hepatitis is most frequently caused by halothane, a volatile anaesthetic. Desflurane has been reported to be more innocent than other agents. Nevertheless, there are few reported cases of hepatitis in the literature.⁽¹⁻⁵⁾ The main difference with new inhalation anaesthetics is their resistance against *in vivo* metabolism. Desflurane is almost neutral to biological degradation with a 0.02% calculated metabolism ratio, while enflurane is metabolised at a ratio of 5%–11%.^(6,7) Prolonged administration of volatile anaesthetics may be a risk factor for hepatic damage, which often remains undetected by standard liver function tests such as aminotransferase activity due to their lack of specificity and sensitivity.⁽⁸⁾

Volatile agents are known to have an adverse effect on the hepatic antioxidant defence mechanism as well as accelerating peroxidation.⁽⁹⁾ As a result, volatile agents are assumed to cause some structural changes in hepatic tissues.⁽¹⁰⁾ These changes in hepatic tissues cause the release of many enzymes into circulation. Although it has not been definitively shown to be the case, determination of glutathione S-transferase (GST) levels seems to be a more specific indicator of liver injury.⁽¹¹⁾ An increase in GST concentrations may be detected before changes occur in routine liver function tests (aminotransferase activity, bilirubin concentrations). It has been reported that with hepatocellular injury, there is a rapid release of

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Table I. Demographical features, ASA distribution, surgery duration and anaesthesia duration of the two groups.

Characteristics	Group D	Group E
	(n = 20) Mean \pm SD (range)	(n = 20) Mean \pm SD (range)
Age (years)	55.9 \pm 13.9 (24–80)	59.5 \pm 12.8 (34–95)
Weight (kg)	77.8 \pm 8.3 (59–90)	83.5 \pm 9.8 (58–106)
Height (cm)	165.5 \pm 8.3 (153–187)	168.4 \pm 7.8 (158–190)
ASA status (I/II/III)	5/10/5	6/9/5
Gender (M/F)	10/10	12/8
Duration of anaesthesia (min)	330.8 \pm 127.6 (185–654)	340.6 \pm 106.5 (180–545)
Duration of surgery (min)	307.9 \pm 120.6 (160–630)	316.2 \pm 102.4 (160–515)

GST, and this could be used as an indicator of changes in hepatocellular integrity.⁽¹²⁾ Compared to enflurane, sevoflurane and isoflurane, desflurane is less soluble in plasma and in tissues. Thus, it has almost absolutely no risk of hepatotoxicity. It may preserve the majority of vital tissues, but human studies are required to identify if it is in any way different from other anaesthetic agents in tissue protection.⁽¹⁰⁾

Subclinical hepatic injury after anaesthesia remains an interesting subject, particularly with the development of new, more sensitive methods of measuring GST levels. Following hepatic injury, GST quickly enters circulation. Its brief half-life (<90 minutes) provides early detection of both hepatic injury and recovery. Minor changes in hepatocellular integrity after halothane, enflurane, sevoflurane and desflurane anaesthesia have been reported by several researchers.^(13,14) Propofol-remifentanyl anaesthesia has been shown to have no effect on hepatic integrity during and after surgery, whereas the administration of desflurane, fentanyl and thiopental has been associated with a mild, but statistically significant, increase in α -GST concentrations.⁽⁸⁾ Although it is still being evaluated, it has been reported that isoflurane anaesthesia has no effect on plasma GST concentration. Hepatic blood flow reduction is thought to be responsible for the increase in GST concentration after anaesthesia.⁽¹⁵⁾ This study aimed to compare the effects of desflurane and enflurane on liver function.

METHODS

This prospective, randomised and phase IV clinical study was performed between February and November 2004, in the operation room of the Ear, Nose and Throat Department of the Faculty of Medicine, Gazi University, Turkey. Upon obtaining approval from the National and Faculty Committees for Ethics, 40 adult patients from the American Society of Anesthesiologist (ASA) I–III risk groups and who were planned for a head and neck surgery of at least three hours' duration under general anaesthesia were studied. The patients were assigned into two groups: desflurane group (Group D) and enflurane group (Group E).

Exclusion criteria were the presence of severe hepatic, renal or cardiovascular disease, elevated aminotransaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), drug allergies, bronchial asthma, chronic obstructive pulmonary disease, haematological disorders, pregnancy, alcohol or drug addiction, a history of convulsion, unstable angina pectoris, myocardial infarction within the last six months and general anaesthesia within the last three months. The anaesthesiologists were not blinded to the study groups, but the statisticians and the laboratory specialist who analysed the samples were.

The patients in both groups were taken to the operating room and monitored for systolic, diastolic and mean blood pressures (SBP, DBP, MBP) using a noninvasive method; for heart rate (HR) with an electrocardiography and for peripheral oxygen saturation (SpO₂) with a pulse oximeter (Odam Physiogard SM 786, 1995, France). The patients had provided their informed consent preoperatively for blood sampling in the postoperative first hour and on the first and seventh days. The blood samples were obtained to determine preoperative GST, AST and ALT levels. First, an intravenous (IV) 18 G cannula was placed on the dorsal side of the hand and 5 ml of blood was obtained before induction in the first hour, first day and seventh day after the operation. The samples were kept under room temperature for almost one hour, and then serum was separated by centrifugation for five minutes at 3,000 U/min and 1 ml aliquots were frozen at -80°C until the analysis.

Serum GST activities were measured using the spectrophotometer, as described by Habig et al.⁽¹⁶⁾ Activities of aminotransferases (AST, ALT) were measured in routine hospital laboratory tests.

Following a three-minute preoxygenation with a mask, induction of anaesthesia was started with IV 5 mg/kg sodium thiopental (pental sodium, İE Ulagay), 2 $\mu\text{g}/\text{kg}$ fentanyl (fentanyl citrate, Janssen pharmaceutica) and 0.1 mg/kg pancuronium (pavulon, Organon). After orotracheal intubation, anaesthesia was performed on Group D with desflurane in 6% concentration (1.0 ± 0.2 [MAC]) and on Group E with enflurane in 1.2% concentration (1.0 ± 0.2

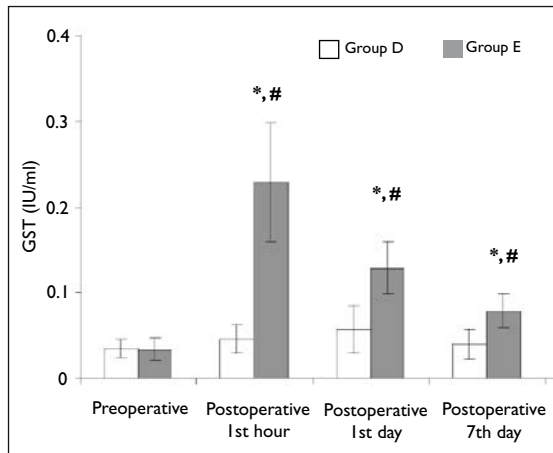


Fig. 1 Bar chart shows the glutathione S-transferase (GST) levels (mean ± SD).

* $p < 0.05$ when compared to the Group E level

$p < 0.05$ when compared to the preoperative level

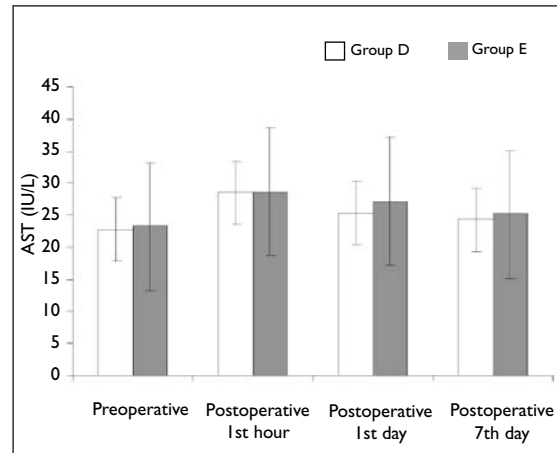


Fig. 2 Bar chart shows the AST levels (mean ± SD).

[MAC]). In both groups, 50/50% O₂ and N₂O 4 L/min were also administered by inhalation. The tubes were secured after endotracheal intubation, and mechanical ventilation was begun in both groups. A muscle relaxant was administered continuously at regular intervals. Crystalloid or colloid solutions (e.g. normal saline, lactated ringer and gelatin) were used when MBP became < 70 mmHg. If this was attributed to vasodilatation, vasopressors (e.g. ephedrine) were administered. HR, MBP and SpO₂ values were recorded before and after induction, every five minutes during the first 30 minutes of operation, then every 30 minutes, and after the 120th minute, every 60 minutes. After the last suture, volatile anaesthetics were stopped; the duration of surgery and cessation time of anaesthetic agents was recorded. Muscle relaxation was antagonised by the administration of IV atropine at 0.015 mg/kg and neostigmine at 0.04 mg/kg. At the end of the operation, the total doses of fentanyl, pancuronium and sodium thiopental were recorded for both groups. After extubation, the patients were followed into the recovery room, where they were monitored for 60 minutes. 10 mg IV methoclopramide was used for nausea when required.

Statistical evaluation was performed using the Statistical Package for Social Sciences version 11.0 (SPSS Inc, Chicago, IL, USA). Patients' *t*-tests were used for intergroup comparisons of age, weight, height, surgery, anaesthesia, surgery times, GST, AST and ALT levels. Paired *t*-test were used in the preoperative level comparison of GST, AST and ALT levels of the groups. Repeated measures of variance analysis evaluated MBP and HR. Bonferroni adjustment was used in the comparisons of intragroup mean MBP and HR values, in which the time factor was considered important through repeated measures of variance analysis. Chi-square and Fisher's exact test were

used to compare the gender and ASA of the groups. $p < 0.05$ was considered to be statistically significant. The results were expressed as mean ± SD, (range), no.

RESULTS

The age, weight, gender, ASA distribution, surgery duration and anaesthesia duration of the two groups were similar (Table 1). The mean GST levels according to the duration of time are provided in Fig. 1. When changes in the mean GST levels were compared with respect to the change in time, there were no differences preoperatively ($p > 0.05$). GST levels were significantly higher in Group E in the postoperative first hour ($p = 0.002$) and on the first ($p = 0.025$) and seventh days ($p = 0.035$). In both groups, postoperative mean GST levels tended to be higher than control mean GST levels, but they were significantly higher only in Group E when the postoperative levels were compared to the preoperative levels [first hour ($p = 0.008$), first day ($p = 0.010$), seventh day ($p = 0.038$)]. However, there was no significant increase in Group D.

The change in the mean AST levels with the duration of time is shown in Fig. 2. There was no difference between the groups when the mean AST levels were compared. Similarly, the intragroup comparisons showed that there were no significant differences between the mean AST levels of each group in the postoperative first hour and on the first and seventh days. The change in the mean ALT levels according to the duration of time is provided in Fig. 3. There was no difference between the groups when the mean ALT levels were compared. In the intragroup comparisons, there were no significant differences between the mean ALT levels of each group in the postoperative first hour and on the first and seventh days. The change in MBP and HR findings with time is shown in Figs. 4 and 5. The comparisons of the

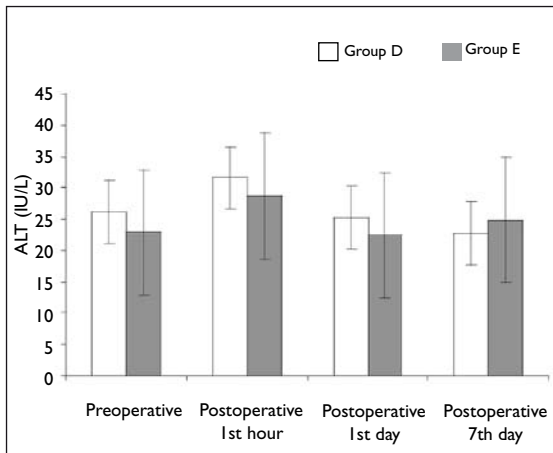


Fig. 3 Bar chart shows the ALT levels (mean ± SD).

results showed that there were no significant differences between the groups and within each group.

DISCUSSION

The results of this study for plasma GST concentrations after anaesthesia are in accordance with previous reports. The increase in GST concentration after anaesthesia was significantly higher in the enflurane group than in the desflurane group. GST concentrations after enflurane anaesthesia were elevated in the postoperative first hour and on the first and seventh days; however, there were no such changes in GST concentrations after desflurane anaesthesia. Halothane, enflurane, isoflurane and desflurane are metabolised to acetylated products by hepatic cytochrome P450 2E1 which induces an immune response, causing hepatic injury. It should be stated that experience with desflurane is more limited than with other fluorinated anaesthetic agents. Hepatotoxicity with enflurane anaesthesia has been discussed in nearly 50 reported cases.^(17,18) On the contrary, there are only four reported cases of injury with desflurane, which has been used on millions of people.⁽¹⁻⁴⁾ Ray et al showed that sevoflurane produced the same GST rise as enflurane, which was attributed to reduced hepatic blood flow, as with enflurane.⁽¹⁴⁾ Hussey et al similarly showed a GST rise in 18% of halothane, 10% of enflurane and interestingly, 10% of desflurane applied patients, which is inconsistent with our results.⁽¹⁹⁾ Similarly, Suttner et al showed that there was a rise in GST after desflurane use,⁽²⁰⁾ which is not in agreement with our results. This difference might be due to the limited sample size.

Hepatotoxicity with desflurane is theoretically possible because of cross-sensitivity with other inhalation anaesthetics. Nevertheless, since levels of serum trifluoroacetate (TFA), which is a potentially hepatotoxic

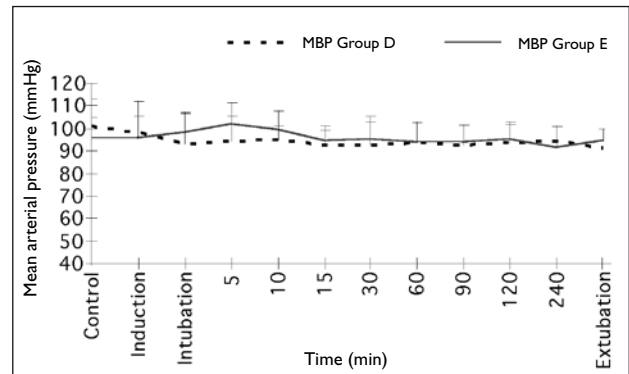


Fig. 4 Graph shows the blood pressure (MBP) (mean ± SD) of both groups.

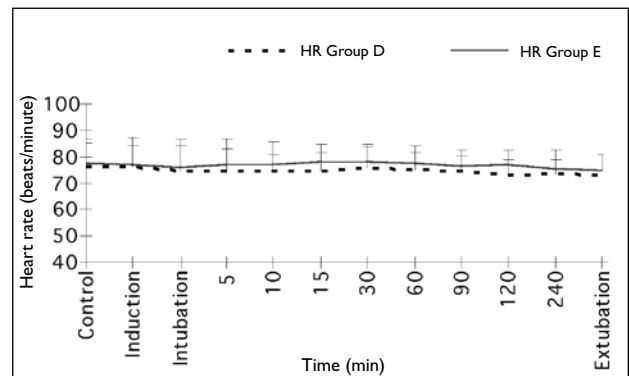


Fig. 5 Graph shows the heart rates (HR) (mean ± SD) of both groups.

metabolite, for desflurane is 1,000 times less than those of halothane, this seems a very unlikely possibility.⁽²¹⁾ This feature could be explained by great variability in oxidative biodegradation of these anaesthetics. The level of metabolism is directly related to hepatic injury potential. When administered, 20% of halothane, 2.4% of enflurane and less than 0.2% of isoflurane are metabolised. Desflurane is resistant to biotransformation and only 0.01% can be metabolised. Yet, if a patient is sensitised to trifluoroacetated proteins, minor amounts of conversion to immunogenic metabolites may produce massive hepatotoxicity. The patient may be sensitised to previously-used anaesthetics and repeated exposure to desflurane may have produced hepatotoxicity. The basic relationship between exposure and injury is similar to that reported with halothane anaesthesia.

Some degree of disruption in hepatocellular integrity is reported after general anaesthesia with all modern inhalation anaesthetics.^(14,22) In these studies, GST levels are used to determine hepatocellular injury, which is more sensitive than the determination of conventional liver enzymes. Advantages of using GST in the detection of hepatocellular injury include its low molecular weight (51 kDa), high cytosolic concentration (4%–5% of all hepatocellular protein) and brief half-life in circulation (< 90 min). Since

GST is rapidly released into circulation after hepatocellular injury, it can be used as a rapid indicator of changes in hepatocellular integrity.⁽¹²⁾ The time course of the changes in GST concentrations implies a minor derangement of hepatocellular integrity that is most likely explained by inadequate hepatocyte oxygenation, rather than an immune response to metabolite-modified hepatic proteins.⁽²³⁾ In this study, no significant increase was detected in routine liver function tests, while GST concentrations had increased in the enflurane group. In the desflurane group, both GST concentrations and liver function tests were not significantly elevated.

There were some limitations to the study. Since measurements of splanchnic blood flow could not be conducted, it was difficult to predict the actual cause of the changes observed in liver function tests. Moreover, the limited number of patients in each group makes it difficult to generalise the results. In order to ensure accuracy of the results, the statisticians and laboratory specialist who analysed the samples were blinded. The anaesthesiologists were not blinded but this did not impact our results. In conclusion, a clinician should keep in mind that hepatitis could occur after anaesthesia with any fluorinated agent. A rise in serum GST level indicates a decrease in splanchnic circulation, which causes a transient reduction in the oxygenation of hepatocytes. Our results showed that during anaesthesia with desflurane, liver functions were well preserved. This study showed that desflurane has less effect compared to enflurane on liver function tests in lengthy operations of up to 330 minutes.

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