Comparison Of Glutathione-S-Transferase, Reduced Glutathione And Oxidized Glutathione Levels On Giving General Anesthesia With Halothane Or Isoflurane

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Citation

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Abstract

Subclinical hepatic injuries after anesthesia continue to provoke interest particularly with newer, more sensitive methods of assessment such as measurement of plasma Glutathione–S transferase (GST), reduced glutathione, and oxidized glutathione concentration. GST is rapidly released in circulation after hepatic damage and its short plasma half-life allow early detection of hepatic injury and its resolution. Hepatic blood flow usually decreases during regional and general anesthesia. Multiple factors are probably responsible including both direct and indirect effect of anesthetic agent a (Denno et al, 1995).

Hepatocellular protective functions of anesthetics through activation of antioxidant enzymes in the liver in an ischemic re-perfusion model were also reported [Beck-Schimmer et al, 2008; Schmidt et al, 2007]. Many factors such as antioxidant enzymes, hepatic detox enzymes, heat shock proteins (HSPs), and direct effects of anesthetics may mediate hepatocellular protection from biological stresses [Schmidt et al, 2007; Hoetzel et al, 2006]. Other hepatocellular antioxidant enzymes such as catalase (CAT), glutathione S transferase (GST), superoxide dismutase (SOD), and aldehyde dehydrogenase-7A1 (ALDH7A1) also show liver protective functions by scavenging reactive oxygen species (ROS) or in other ways [Brocker et al,2010]. Intravenous anesthetics such as propofol do not seem to have comparable protective properties [Cope et al, 1997].

Halothane (Röhm et al, 2005; Russell et al, 1982) is oxidized in liver by a particular isozyme of cytochrome p-450 to its metabolite. Halothane causes hepatic blood flow to decrease in proportion to the depression of cardiac output. Hepatic artery vasospasm has been reported during halothane anesthesia. This reduced blood flow is responsible for observed increase in Glutathoine-s-transferase concentration, hepatic cellular dysfunction and transaminase elevation. The probable mechanism is most likely an immune-mediated hepatotoxicity; antibodies are against modified liver microsomal proteins on hepatocyte surfaces (Fallahian, 2009).
In healthy cells and tissues more than 90% of total glutathione pool is in the reduced form (GSH) and less than 10% exist in oxidized form (GSSG). An increased oxidized glutathione (GSSG) to reduced glutathione (GSH) ratio is considered to be indicative of oxidative stress (Evan et al, 2001) . In the present study, we measures GST concentration along with the reduced and oxidized glutathione concentration in patients undergoing general anesthesia with halothane or isoflurane to assess its effect on the hepatocellular integrity.

INTRODUCTION

Subclinical hepatic injuries after anesthesia continue to provoke interest particularly with newer, more sensitive methods of assessment such as measurement of plasma Glutathione–S transferase (GST), reduced glutathione, and oxidized glutathione concentration. GST is rapidly released in circulation after hepatic damage and its short plasma half-life allow early detection of hepatic injury and its resolution. Hepatic blood flow usually decreases during regional and general anesthesia. Multiple factors are probably responsible including both direct and indirect effect of anesthetic agent a (Denno et al, 1995).

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MATERIAL AND METHODS

The study was approved by the Ethical Committee of the Institution, and each patient gave informed and written consent. Sixty patients belonging to age group of 18-60 years of both sexes with ASA Grade 1 and 2 undergoing elective surgery under general anesthesia were included in this study. The patients with obesity (body wt >20% of ideal wt), excessive alcohol intake, previous liver disease, pregnancy, renal failure and any exposure to general anesthesia with inhalation anesthetics with in 3 month were excluded from the study.

The patients were divided into following groups:

Group 1

Thirty patients receiving standard protocol of general anesthesia with halothane.

Group 2

Thirty patients receiving standard protocol of general anesthesia with Isoflurane.

All the patients were properly evaluated with preoperative assessment. Proper reassurance was established with patients, night before operation. Tab alprazolam 0.25mg were given to facilitate sleep and relieve anxiety. Next morning the patients were taken inside the operation theatre and intravenous cannula were applied. All other monitors like pulse oximeter, blood pressure monitor (NIBP), ECG monitor, were applied. After this all patients were premedicated with midazolam 1 mg, glycopyrolate 0.2 mg, ondensetron 4 mg, fentanyl 2 g/kg. All these patients induced with propofol 2 to 3 mg/kg, and succinyl choline 2 mg/kg. Patients were intubated.

Group 1: Anaesthesia was maintained with 60% nitrous oxide, 40% oxygen, intermittent dose of vecuronium with 1 MAC of halothane. Halothane was switched off 30 minutes before the end of surgery.

Group 2: Anesthesia was maintained similarly but with 1 Mac of isoflurane. Isoflurane were switched off 30 minutes before the end of surgery. Total dose of inhalational agent were calculated in MAC hours in each patient.

The patients were reversed with 0.04 to 0.08 mg/kg neostigmine + Atropine 0.02 mg/kg.

• Intraoperatively, these patients were monitored for pulse rate, blood pressure, spO¬2, ECG every 15 minutes for first hour of surgery then every 20 hour till the end of surgery.

• Halothane and isoflurane were maintained at 1 MAC fluids were infused during anesthesia according to blood loss and hemodynamics.

• Hydroxyethyl starch was infused to make up blood loss when blood loss exceeded 400 ml. relative hypotension was defined as a mean arterial pressure of less than 68% of base line for more than 15 minutes and absolute hypotension as a mean arterial pressure of less than 60 mm Hg for more than 15 min.

• Decrease of arterial pressure due to hypotension and volatile anaesthetics was treated with intravenous fluid and temporary decrease of volatile anesthetics to 0.8 MAC.

• Heart rate was classified as bradycardia (less than 50 beat/minute), normal (60 to 90 beat/minute) or trachycardia (more than 100 beat/minute).

All these patients were measured for plasma levels of glutathione-s- transferase, oxidized glutathione and reduced and glutathione, preoperatively (base line) and at 1, 6, and 24 hour after induction of anaesthesia along with SGOT/SGPT, albumin, globulin preoperative and postoperative (after 24 hours). The blood was taken and protein [albumin, globulin], Glutathione-s-transferase,

reduced Glutathione, Oxidized Glutathione and SGOT /SGPT were measured.

Data analysis

The data obtained from the study was analyzed using Statistical Package for Social Sciences (SPSS) Version 17.0. Categorical data was compared using Chi-square test for proportions. Parametric data was compared using independent sample's "t" test for intergroup comparisons and paired "t" test for within group comparison. The confidence level of the study was kept at 95%, hence a "p" value less than 0.05 indicated a statistically significant difference.

RESULTS

Table-1 shows the baseline characteristics of Group A and Group B. The mean age, weight and duration of surgery were similar in both the groups ($p>0.05$). Similarly, the levels of biochemical parameters were also similar in both the groups preoperatively (baseline).

At 1 hr the mean GST value in Group A (halothane) was 5.0±0.3 while in Group B (isoflurane) group, it was 3.8±0.3 ($p<0.001$). At 6 hours, mean GST values in Group A and Group B were 5.4+0.3 and 3.9+0.4 and the difference was statistically significant ($p<0.001$). Similarly, at 24 hours intervals too, Group A group showed significantly higher mean GST values (4.8+0.4) as compared to that in Group B (3.6+0.3) ($p<0.001$). The GSH levels at 1 hour in Group A (Halothane group) and Group B (Isoflurane group) were 5.52+0.40 and 4.65+0.40 respectively. The difference between the groups was highly significant ($p<0.0001$). At 6 hours duration mean GSH level in Group A was 6.21+0.20 and in Group B 4.70+0.54, the difference between the GSH levels of both groups was statistically highly significant. Similarly, at 24 hours duration mean GSH value in Group A (5.78+0.22) was found to be significantly higher ($p<0.001$) as compared to that in Group B (4.68+0.50). At 1 hour, mean GSSG value for Group A (Halothane) was 2.49+0.31 and for Group B (Isoflurane) 1.79+0.19, the difference in GSSG values of both the groups was found to be significantly higher ($p<0.001$). At 6 hours interval too the GSSG values in Group A (2.77+0.31) were significantly higher as compared to that in Group B (1.81+0.17) ($p<0.001$). Similar trend in GSSG values in Group A (2.46+0.26) were observed as compared to that in Group B (1.74+0.14) ($p<0.001$). At 1 hour interval, GSH/GSSG ratio in Group A was observed to be 2.25+0.27 and in Group B as 2.64+0.39. The difference between the values in both groups was statistically highly significant ($p<0.001$). At 6 hours mean GSH/GSSG ratio was 2.64+0.39 in Group A and 2.60+0.32 in Group B. This difference was statistically higher ($p<0.001$). Similar trends in values of ratio of GSH/GSSG at 24 h were observed. In Group A this ratio was 2.37+0.25 as compared to that in Group B (2.72+0.38) with a statistically higher difference between the groups ($p<0.001$) (Fig.1).

In Group A, mean SBP preoperatively was 116.3±8.9 mm Hg while in Group B it was 115.7±9.0 mm Hg, thus showing no statistically significant difference between the two groups. However, at 15 min after induction, the mean value of Group A was found to be significantly higher as compared to Group B but from 30 min onwards till 140 minutes there was no statistically significant difference between the two groups and this situation prevailed till 180 minutes post induction. At 200 min time interval once again the differences between the two groups were not significant statistically but at 220 minutes interval once again the mean value of Group A was significantly lower as compared to that of Group B but from 240 minutes onwards till 300 minutes there was no statistically significant difference between the two groups. At 300 minutes time interval, the mean SBP value of Group A was significantly higher as compared to that in Group B. But from 320 minutes onwards no statistically significant difference between the two groups could be seen though the mean value of Group A was higher as compared to that in Group B (Table-2).

For DBP, statistically, no significant difference between two groups was seen till 80 minutes post-induction. At 80 minutes post-induction, the mean DBP value of Group A was significantly lower as compared to that in Group B and this situation prevailed till 220 minutes post-induction. However, from 240 minutes post-induction onwards the mean DBP value of Group A picked up and from this time onwards there was no statistically significant difference between the two groups ($p>0.05$) (Table-2).

Statistically no significant difference in mean heart rate of two groups was seen preoperatively and 15 minutes post induction. However, from 30 minutes till 120 minutes post-induction intervals, a statistically significant difference between two groups was seen with Group A showing significantly lower mean heart rate at all time intervals. 160 minutes post induction till 220 minutes post-induction, the mean heart rate of Group A was found to be significantly higher as compared to that in Group B. At 260 min and 340 minutes once again statistically significant differences between two groups were seen with Group B showing significantly higher mean values as compared to Group A

(Table-2).

Statistically no significant difference between the two groups was seen in mean oxygen saturation at pre-op. and 15 minutes post-induction interval, however, from 30 minutes onwards statistically significant differences between the two groups were seen at 30, 45, 60 and 80 minutes, the mean oxygen saturation in Group B being significantly lower as compared to that in Group A. Though qualitatively only at 60 minutes, the mean oxygen saturation in Group A was found to be significantly lower with mean value reaching at 91.1±10.8%. Although statistically significant difference between the two groups was seen at 120, 140, 200 and 240 minutes post-induction but at all these time intervals the qualitative difference was not significant (Fig.2).
Table-3 shows that post-operatively, Group A had significantly higher mean SGOT (59.7+5.0) and SGPT (59.3+4.6) values as compared to Group B (SGOT – 24.0+4.3 and SGPT – 24.7+5.9) (p=0.000) while the mean Globulin values of Group B (2.3+0.4) were found to be significantly higher (p=0.010) as compared to that of Group A (2.1+0.2). For albumin, no statistically significant difference between Group A (3.5+0.3) and Group B (3.5+0.2) was seen.

Table 1

Baseline Characteristics

	Group A Halothane (n=30)	Group B Isoflurane (n=30)	p-value
Age in years, mean±sd	38.2±3.6	38.2±3.7	1.00
Weight in kg, mean±sd	55.1±5.2	57.1±5.7	0.176
Duration of surgery in minutes, mean±sd	252.3±48.5	246.7±42.2	0.631
Male sex, no. (%)	12 (40.0)	12 (40.0)	1.00
Bio-chemical assessment			
SGOT	26.7±5.1	26.1±4.9	0.644
SGPT	27.2±4.0	26.8±5.7	0.776
Globulin	2.9±0.3	2.8±0.4	0.497
Albumin	4.1±0.2	4.3±0.3	0.054
Glutathione-s-transferase	3.9±0.6	3.7±0.5	0.090
Reduced glutathione	4.5±0.4	4.5±0.2	0.733
Oxidised glutathione	1.9±0.3	1.9±0.3	0.834
GSH/GSSG	2.4±0.39	2.5±0.48	0.514

Figure 1

Comparison of biochemical parameters at different time intervals

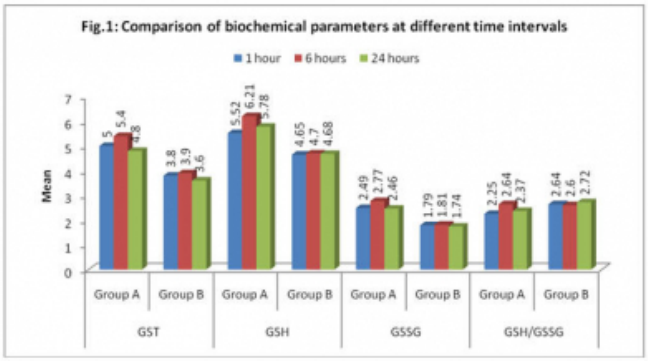

Table 2

Comparison of blood pressure and heart rate

Time	SBP		DBP		Heart rate	
	Group A Halothane (n=30)	Group B Isoflurane (n=30)	Group A Halothane (n=30)	Group B Isoflurane (n=30)	Group A Halothane (n=30)	Group B Isoflurane (n=30)
Pre-op.	116.3±8.9	115.7±9.0	77.3±6.9	76.0±6.2	78.8±10.5	80.3±5.9
15 min	119.7±7.6[1]	112.0±11.0[1]	76.5±6.9	76.1±8.0	80.8±10.8	79.1±4.7
30 min	126.7±8.1	108.3±14.2	77.0±7.1	73.7±7.6	70.2±10.1[2]	78.0±5.4[2]
45 min	112.3±9.0	112.8±12.8	77.4±8.7	76.6±6.7	72.8±6.2[3]	76.7±5.4[3]
60 min	111.0±10.3	109.3±9.1	74.0±7.6	74.1±8.7	67.7±6.4[2]	73.9±5.4[2]
80 min	107.7±9.0	107.3±9.1	67.5±4.0[2]	75.1±7.7[2]	68.7±7.4[2]	75.9±6.1[2]
100 min	102.4±20.7	110.3±9.6	70.1±9.2[3]	74.7±7.1[3]	70.8±6.8[1]	75.7±5.2[1]
120 min	107.3±9.8	111.7±9.5	65.8±5.2[2]	74.9±7.3[2]	70.8±7.1[1]	76.1±5.8[1]
140 min	96.3±15.4[2]	113.7±10.3[2]	65.7±4.0[2]	77.3±6.5[2]	79.3±8.0	75.9±6.8
160 min	101.7±10.2[2]	113.0±8.8[2]	66.2±5.5[2]	76.5±6.8[2]	80.4±7.2[3]	76.5±6.3[3]
180 min	103.7±13.5[2]	116.0±8.6[2]	69.3±9.4[1]	76.6±7.7[1]	84.2±7.4[2]	77.1±6.2[2]
200 min	110.4±13.0	115.0±9.5	70.4±7.5[1]	76.2±7.5[1]	84.7±4.9[2]	77.4±4.5[2]
220 min	111.7±13.4[3]	119.2±9.1[3]	72.2±9.3[3]	76.9±7.1[3]	80.6±2.7[3]	77.1±5.5[3]
240 min	122.5±15.7	121.7±9.6	80.9±10.1	82.9±6.0	82.5±4.6	80.4±6.4
260 min	122.1±10.5	122.1±11.2	79.9±9.8	83.7±9.4	77.0±8.5[3]	83.8±4.9[3]
280 min	122.5±4.6	125.0±10.7	81.3±9.9	80.0±7.6	82.0±8.9	75.7±7.9
300 min	131.7±7.5[3]	117.5±5.0[3]	83.3±8.2	85.0±5.5	86.0±5.5	78.3±7.5
320 min	126.7±5.8	116.7±5.8	80.0±7.8	84.7±5.0	84.7±8.1	83.3±5.8
340 min	126.7±11.5	120.0±14.1	90.0±6.9	85.0±7.1	80.0±12.6[3]	89.0±1.4[3]
360 min	130.0±10.5	130.0±16.7	95.0±10.7	90.0±7.9	85.0±8.7	88.0±4.8

[1]p<0.01, [2]p<0.0001, [3]p<0.05

Figure 2

Comparison of SpO2 in two groups at different time intervals

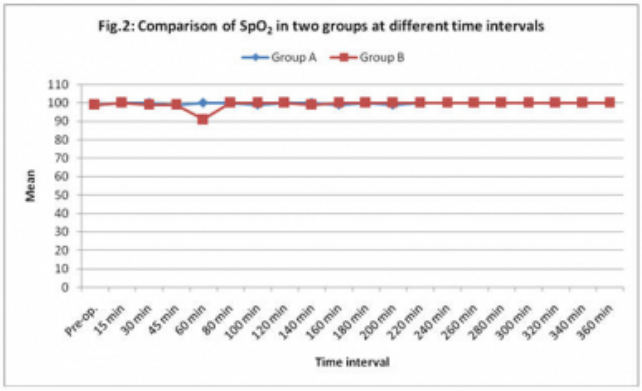

Table 3

Postoperative Biochemical Assessment

	Group A Halothane (n=30)	Group B Isoflurane (n=30)	p-value
SGOT	59.7±5.0	24.0±4.3	0.0001*
SGPT	59.3±4.6	24.7±5.9	0.0001*
Globulin	2.1±0.2	2.3±0.4	0.01*
Albumin	3.5±0.3	3.5±0.2	0.795

*Significant

DISCUSSION

Volatile anaesthetics especially halothane can produced hepatic damage (Brown BR et al., 1987) although the mechanism by which this rare but severe cause of fulminant hepatic failure occurs is unknown yet prolonged administration of anaesthetics is a risk factor. Our study suggests that administration of halothane has detrimental effect on hepatocellular intergrity. In our study data suggests that halothane produced an increase in plasma Glutathione-s-transferase, Reduced glutathione and oxidised glutathione concentration from first hour to 24 hour after induction of anaesthesia, although increase in all enzymes was more at 1 and 6 hours after induction than base line. At 24 hour we found the level of all three enzymes to be decreased as compared to that at 1 and 6 hour time intervals, but it failed to reach near baseline. Thus, the findings in our study are very much similar to that of Allen et al. (1987) who reported that anaesthesia with halothane causes hepatocellular damage whereas, in present study, no such increase in any of the three enzyme measured could be demonstrated at any time after administration of anaesthesia with isoflurane. This shows hepatocellular intergrity is well maintained with isoflurane.

PC Hayes et al. (1991) studied Halothane anaesthesia may be followed by unexplained hepatitis that may be mild or severe. The more severe form (type 2) has a 20-50% mortality but the nature of the mechanism and predisposing factors that relate to type 2 halothane hepatitis remain unclear, although hypersensitivity and familial constitutional susceptibility have been implicated.

Hussey et al. (1988) studied the plasma concentration of hepatic glutathione S-transferase (GST) measured in matched groups of patients who received halothane, enflurane or isoflurane anaesthesia for elective minor surgery. The GST concentrations increased significantly at 3 hour after anaesthesia in patients who received halothane or enflurane, but not in patients who were given isoflurane. The small but significant increase in GST concentrations in patients receiving halothane or enflurane suggests an impairment of hepatocellular integrity following the administration of these anaesthetics. In contrast, isoflurane anaesthesia did not appear to be associated with this effect. In our study, significant differences as compared to baseline were recorded between two groups at all time intervals for GST measured upto 24hr after induction. At 1 hr the mean GST value in halothane (5.0±0.3) while in isoflurane group it was (3.8±0.3), thus showing a statistically difference between the two group ($p<0.001$). Similarly at 6hr and 24hr interval too, halothane group showed significant higher mean GST values as compared to that in isoflurane group ($p<0.001$). For reduced glutathione and oxidised glutathione too mean value in halothane group was found to be significantly higher ($p<0.001$) as compared to that in isoflurane group at all time intervals ($p<0.001$).
Murray et al. (1994) have studied the effects of isoflurane or propofol anaesthesia on hepatic giutathione-S-transferase (GST) concentrations in 20 patients during and after prolonged plastic and reconstructive surgery (approximately 10 h). Mean plasma concentrations of GST did not exceed the normal range in any sample from any patient. Our study suggests that administration of isoflurane for general anaesthesia has no detrimental effect on hepatocellular integrity. We were unable to demonstrate any significant increase in any of the three enzymes measured at any time from baseline to 24 hr after intubation but small increase in GST from the baseline was observed at the 1 and 6 hr interval, at 24hr interval level of GST activities started decreasing but not reached to baseline value. This also shows that the centrilobular cell can rapidly recover from an acute insult as illustrated by the rapid decrease in plasma

GST concentration in the 24 after admission.

Allan et al. (1987) studied that patient receiving halothane showed more hepatocellular damage than the patients receiving isoflurane. There were in significant changes in glutathione-s-transferase activity in patients receiving isoflurane.

J.R. Darling et al. (2000) studied the effect of halothane or isoflurane anaesthesia on hepatic function in 30 patients undergoing lumbar discectomy. Hepatic function was assessed before anaesthesia, at the end of surgery, and at 3, 6, 24 and 48 h after surgery using routine enzyme tests of hepatic function and mitochondrial aspartate transaminase (mAST) activity. Although serum mAST activities increased after surgery in both groups of patients, these increases were statistically significantly greater in the group that received halothane.

Ray et al. (1995) studied the biological variation and the effect of fasting and halothane anaesthesia on plasma glutathione S-transferase concentrations and found that increases in GST concentration after anaesthesia do not result from incidental factors. The concentration was significantly lower at 3 and 6 h after than in the fasting sample ($P = 0.0019$ and $P = 0.015$, respectively).

In our study, we found that significant change in GST and plasma albumin concentration in 30 patients each after halothane anaesthesia. GST concentration was increased in all samples (at 1, 6, 24 hour) it was maximum at 6 hour and started declining after that, at 24 h value of GST was decreased but not reached to baseline value. In isoflurane group no significant difference was observed from base line, but plasma albumin and globulin concentrations were lower at post operative interval than that at baseline. This suggests that increase in plasma GST concentration seen 3 to 6 hr after halothane does not result from hemoconcentration or from diminished clearance of GST, for, if this had been the case, then albumin and globulin activity would have been increased, the parallel decrease in albumin and globulin concentration in post operative sample after halothane anaesthesia. Our findings suggest that incidental factors do not result in change in plasma GST concentration after anaesthesia because change in GST concentration may occur in healthy individuals within the day or after overnight fasting.

Our data support the use of isoflurane rather than halothane for prolonged anaesthesia. As in our study, Glutathiones-transeferase activity was increased significantly in halothane group throughout the period of study compared with those received isoflurane. Denno et al. (1995) reported that the ratio of reduced glutathione/oxidized glutathione is maintained in the liver during short-term hepatic hypoxia. In our study on comparing the ratio GSH/GSSG at different time intervals i.e. 1, 6 and 24 hour in the two study groups, statistically significant differences were seen between the two group at all time intervals ($p<0.001$) with isoflurane showing significant higher mean value as compared to halothane. So our data suggest that GSH/GSSG ratio will have no significant difference from baseline was seen in both groups but it was significantly higher in Group B.

CONCLUSION

In clinically identical situations, anaesthesia with halothane but not isoflurane lead to demonstrable impairment of hepatocellular integrity. hemodynamic stability is also better maintained with isoflurane as compared to halothane. So, isoflurane can be used as volatile anaesthetic without risk of producing hepatic damage in most patients.

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