

A Comparison of the Effect of Isoflurane and Propofol on Liver Enzymes

Abstract

Background: Isoflurane and propofol are routinely used for the maintenance of general anaesthesia. However, recently, they have been implicated in hepatotoxicity resulting in acute liver failure. **Objective:** We compared the effects of isoflurane and propofol on liver enzymes; aspartate transaminases (AST), alanine transaminases (ALT), alkaline phosphatase (ALP) and total bilirubin (Tbil) following general anaesthesia. **Materials and Methods:** This randomized, controlled clinical trial involved 60 ASA I and II patients aged 18–64 years scheduled for elective surgery requiring general anaesthesia. Anaesthesia was induced with intravenous sodium thiopentone 5 mg/kg and atracurium 0.5 mg/kg, and maintained in group I with isoflurane (MAC, 0.8%–1.5%) and in group P with (propofol infusion, 100–200 µg/kg/minute). Blood samples were taken pre-induction, immediate- and 24 hours post-operatively. The serum levels of AST, ALT, ALP, Tbil were analyzed and compared in both groups. Risk factors for post operative hepatotoxicity were determined. **Result:** Propofol caused a significant reduction in ALP ($P = 0.005$) but increase in Tbil ($P = 0.010$) 24 hours postoperatively. Though isoflurane had consistently higher values of AST, ALP and Tbil than propofol, only the mean AST values at 24 hours post-operative was significantly higher ($P = 0.045$). There was a significant increase in the 24 hours post-operative Tbil following massive blood loss; [odds ratio 23.91, 95%, CI (1.685–339.315)], $P = 0.019$. **Conclusion:** Both agents had a varied effect on liver enzymes. Isoflurane resulted in a significantly higher increase in 24 hours post-operative serum AST than propofol. Propofol caused a significant increase in 24 hours post-operative total bilirubin. Caution is therefore recommended in their use in patients with altered liver enzymes.

Keywords: General anaesthesia, isoflurane, liver enzymes, propofol

Introduction

The halogenated inhalational anaesthetics have been linked to idiosyncratic liver injury for more than 50 years with presentation ranging from asymptomatic alanine transaminase (ALT) elevations to fatal hepatic necrosis.^[1,2] This injury is usually recognized when it results in fulminant hepatitis, however authors have reported that milder cases of hepatitis are quite common with transaminases of 5 to 22 times the upper limit in 1% of patients.^[1] The estimated incidence of volatile anaesthetic drug induced liver injury is 3%.^[1] The overall incidence of significant liver injury after halothane was estimated at 1 per 15,000 initial exposures, and probably 1 per 1000 repeated exposures, particularly if the re-exposure was within 28 days.^[2] As a result of this, the Committee on Safety of Medicines recommended that repeated exposure to halothane within a period of

three months should be avoided unless there are overriding clinical circumstances.^[3] Consequent to this, its use has been replaced by other halogenated anaesthetics including enflurane (1972), isoflurane (1981), desflurane (1993) and sevoflurane (1995).^[2]

Total intravenous anaesthesia with propofol is expected to have a lower risk of direct liver damage from anaesthetic metabolites but its use has been associated with rare instances of idiosyncratic acute liver injury.^[2] In addition, prolonged high dose propofol therapy (doses greater than 4 mg/kg/hour for more than 48 hours) can lead to “Propofol infusion syndrome” which is marked by bradyarrhythmias, metabolic acidosis, rhabdomyolysis, hyperlipidemia and an enlarged or fatty liver.^[4]

Several case reports have documented liver failure in patients anaesthetized with isoflurane and propofol.^[5-7] Varying results ranging from no effect to mild derangements on post-operative liver enzymes have been reported in patients

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undergoing surgery under general anaesthesia with either isoflurane or propofol.^[8-10] This study thus examined the changes in concentration of liver enzymes over 24 hours after isoflurane or propofol anaesthesia and identified risk factors for significant change.

Materials and Methods

This prospective randomized clinical trial was conducted in 60 ASA I and II patients, aged 18–64 years, scheduled for elective surgical procedures under general anaesthesia between August 2018 to July 2019. Ethical approval from the Human Research Ethics Committee of our institution and informed consent were obtained. Exclusion criteria included patients with underlying liver pathology, patients scheduled for liver surgery, exposure to general anaesthesia within the last 3 months and alcohol or substance abuse. The patients were allocated into group I (maintenance with isoflurane) or group P (maintenance with propofol infusion) using computer generated random numbers. After induction of anaesthesia with intravenous (IV) sodium thiopentone (5 mg/kg) and IV atracurium (0.5 mg/kg), patients were manually ventilated with 100% oxygen for 4 minutes alongside respective maintenance agent isoflurane (0.8–1.5%) and propofol infusion (100–200µg/kg /min) in group I and P respectively.

After successful tracheal intubation, group P patients were maintained on propofol infusion with a stepwise reduction in dosage at 10 minutes interval from 200µg/kg/min to 166µg/kg/min to 133µg/kg/min stabilizing at 100µg/kg/min which was adjusted based on haemodynamic changes thereafter. Patients in group I were maintained on isoflurane at a minimum alveolar concentration (MAC) of 0.8–1.5%. Muscle relaxation was maintained with atracurium 0.16 mg/kg and the lungs mechanically ventilated with 100% oxygen using a closed circle system with a fresh gas flow of 1-2litres per minute. Intravenous (IV) fentanyl 2µg/kg, intramuscular (IM) diclofenac 1 mg/kg and IV paracetamol 15 mg/kg were given for analgesia.

Standard monitoring was employed and haemodynamic stability maintained by titrating the doses of anaesthetic agents, administration of intravenous fluid, or IV ephedrine as required. The total dose of propofol used for maintenance, duration of anaesthesia and presence of hypotension were recorded. Hypotension was defined as a 25% reduction in baseline systolic blood pressure.^[11] Blood loss was estimated by the visual method and massive blood loss was defined as estimated blood loss greater than 1500ml.

At the end of surgery, the anaesthetic agents were discontinued; residual neuromuscular block was reversed with 0.04 mg/kg neostigmine and 0.02 mg/kg atropine. All patients were extubated in the operating room and transferred to the recovery room on supplemental oxygen for post operative care before transfer to the ward.

Venous blood (5mls) was withdrawn before induction of anaesthesia (H0), immediate post-operative period (H1), and 24 hours post induction, (H2) before the patient commenced oral intake. All blood samples were immediately centrifuged and the serum stored in the Central Research Laboratory at a temperature of -20°C. The serum concentration of ALT, ALP, AST and Tbil were estimated using a colorimetric technique where the substrate is converted by the enzyme into a soluble, coloured reaction product. This allows precise determination of the enzyme activity by optical density. The primary outcome was a difference in concentration of liver enzymes in the two groups in the immediate and 24 hour post operative period.

To achieve a power of 80% and a significance level of $\alpha = 0.05$, a minimum sample size of 30 per group was considered adequate using the mean level of ALT in a previous study.^[8] Data collected was analyzed using the Statistical Product and Service Solution version 23 computer software, (SPSS, Chicago, IL) and presented as mean \pm SD, frequency and percentages. Analyzed using independent T-test, ANOVA, odd ratio, and 95% CI as needed. Factors causing an increase in liver enzymes were identified using binary logistic regression. Variables considered for regression included duration of surgery, duration of anaesthesia, presence of hypotension, and massive blood loss. The variables with $P < 0.20$ were further analyzed using a stepwise, multivariate, logistic regression analysis. This p-value corresponds to the probability of observing the extreme values of the independent variables by chance. A p-value less than 0.05 was considered statistically significant.

Results

The demographic and clinical data were comparable in both groups. Duration of surgery and anaesthesia, as well as incidence and duration of hypotension were significantly greater in group I, [Table 1].

Both isoflurane and Propofol exhibited increases in ALT throughout the study period. Though propofol exhibited higher values these were not significantly different, $P > 0.05$. [Table 2]

The AST levels were comparable within each group despite a progressive rise in the isoflurane group and a progressive decrease in the propofol group. A comparable percentage change (11.48%) was observed in both groups in the immediate post-operative period. A significant difference however existed between groups in the 24 hour post operative period (isoflurane 53.63 (22.72%) vs 36.70 (10.20%) $P = 0.045$)[Table 2].

Patients in group P demonstrated a significant reduction in ALP throughout the study period. ($P = 0.005$). In Group I, ALP values remained similar throughout the study period ($P = 0.485$) [Table 2]. Though isoflurane had consistently

Table 1: Demographic and clinical characteristics

Variable	Isoflurane (n=30) (mean ±SD)	Propofol (n=30) (mean ±SD)	p value
Age (years)	39.7 ± 11.69	40.77 ± 11.75	0.718
BMI (kg/m ²)	26.20 ± 4.45	24.63 ± 4.67	0.190
Gender ratio (M:F)	1:3.3	1:1.5	0.165
ASA classification ratio ASA 1:11	1:1.1	1:2.3	0.114
Duration of surgery (mins)	184.17 ± 64.74	119.83 ± 64.27	0.001*
Duration of Anaesthesia (mins)	210.17 ± 70.83	141.00 ± 64.88	0.001*
Blood loss (mls)	823.33 ± 784.96	515.67 ± 750.70	0.126
Incidence of hypotension (n/%)	17 (56.67%)	9 (30%)	0.037*
Duration of hypotension (mins)	7.17 ± 7.39	2.63 ± 5.17	0.008*

*indicates significant difference p < 0.05

Table 2: Comparison of the effect of isoflurane and Propofol on Liver Enzymes

Liver Enzymes	Baseline (H0)	Immediate post op (H1)	24hrs post op (H2)	p-value
ALT				
Iso	18.07 ± 13.66	18.13 ± 15.85	18.57 ± 7.42	0.949
Pro	15.57 ± 8.89	20.97 ± 28.51	21.03 ± 19.05	0.287
P value	0.404	0.684	0.582	
AST				
Iso	39.20 ± 21.12	43.70 ± 29.70	53.63 ± 38.60	0.131
Pro	46.17 ± 21.56	40.87 ± 19.93	36.70 ± 23.8	0.176
P value	0.211	0.666	0.045 ^y	
ALP				
Iso	89.97 ± 74.53	82.57 ± 65.80	82.30 ± 56.81	0.485
Pro	73.37 ± 24.46	66.90 ± 25.45	63.97 ± 21.29	0.005*
P value	0.251	0.229	0.103	
Tbil				
Iso	3.94 ± 3.08	3.75 ± 2.80	3.19 ± 2.10	0.287
Pro	2.53 ± 2.5	4.02 ± 2.81	2.91 ± 2.38	0.010*
P value	0.056	0.710	0.631	

*Indicates significant difference within group p < 0.05^y Indicate significant difference between groups

higher values of ALP, this did not differ significantly from the propofol group at any time during the study.

Group I patients had comparable total bilirubin throughout the study period. In group P, there was a 58.89% increase in the immediate post operative period, followed by a 27.61% reduction in the 24-hours post operative period to values approaching baseline. The differences observed in the mean values in group P were significant (*P* = 0.010) [Table 2]. Though isoflurane had consistently higher values of total bilirubin, it was comparable to the propofol group at all times during the study.

Hypotension was observed in 17 patients (56.67%) in the isoflurane group and 9 patients (30%) in the propofol group (*P* = 0.037). The duration of hypotension also differed significantly; 7.17 ± 7.39 minutes in isoflurane group, and 2.63 ± 5.17 minutes in the propofol group (*P* = 0.008). Hypotension however had no significant effect on post operative liver enzyme changes [Table 3]

The degree of blood loss was comparable between groups, only 5 patients had blood loss in excess of 1500ml;

(3 (10%) in group I and 2 in group P (6.7%)). Binomial predictors of post operative changes in liver enzyme showed that the degree of blood loss only affected total bilirubin with an odds ratio of 12.923 (*P* = 0.007) [Table 3]. Further analysis revealed that massive blood loss was the singular independent risk factor (OR 23.911, *P* = 0.019) for developing hyperbilirubinemia [Table 4].

Discussion

Our study supports the knowledge that anaesthetic agents cause changes in liver enzymes but to a varying degree. Propofol caused a significant decrease in ALP 24 hours post-surgery while total bilirubin rose significantly at the immediate post-operative period but declined after 24 hours though, it did not return to baseline. Isoflurane on the other hand, produced non-significant changes in all the liver enzymes analysed. Though we demonstrated a significant fall in ALP levels in the propofol group at the end of the study, none of our patients' exhibited values outside the normal range. Other researchers have also noted this.^[8,10] The reduction in ALP may be related

Table 3: Binomial Predictors of Factors affecting Liver Enzymes after General Anaesthesia

Risk Factors	Liver Enzymes	Odds ratio	Confidence interval (95%)	p-value
Degree of blood loss	ALT1	0.964	0.915-1.014	0.665
	ALT2	0.982	0.947-1.018	0.761
	AST1	0.927	0.861-0.999	0.533
	AST2	0.800	0.701-0.913	0.268
	TBil1	12.923	1.325-126.079	0.007*
	TBil2	4.846	0.729-32.215	0.078*
Presence of hypotension	ALT1	0.758	0.045-12.711	0.847
	ALT2	1.030	0.972-1.092	0.378
	AST1	2.419	0.237-24.710	0.444
	AST2	1.426	0.369-5.508	0.606
	TBil1	1.594	0.499-5.092	0.429
	TBil2	0.692	0.219-2.186	0.530

* indicate statistical significance p<0.2

NB: Alkaline phosphatase value was less than 3 times the upper limit of normal throughout the study period in both groups.

Table 4: Independent Predictors of risk factors for post operative hyperbilirubinemia

Variables	Odds ratio	Confidence interval	p-value
TbilH1			
Presence of hypotension	1.838	0.454-7.445	0.394
Degree of blood loss	23.911	1.685-339.315	0.019*
TbilH2			
Presence of hypotension	1.106	0.291-4.207	0.882
Degree of blood loss	1.890	0.240-14.867	0.545

*Indicates statistical significance p<0.05

to the dose of propofol employed as, Kim^[12] and Song^[13] who employed a lower concentration than ours (2–4µg/ml via target controlled infusion), found no change in ALP. Another contributory factor to reduction in ALP after anaesthesia could be the type of opioid used. While we used fentanyl, which is considered to be cardiostable, Dabir *et al.*,^[8] employed remifentanyl and reported significant reduction in ALP in their isoflurane group. Remifentanyl causes a 20% reduction in mean arterial pressure which could in turn further reduce the hepatic perfusion,^[14]

Anaesthetic agents and types of surgery may contribute to post-operative hepatic injury by various mechanisms. Majority of anaesthetics cause a decrease in portal blood flow associated with a decrease in cardiac output while hepatic arterial circulation may be preserved, increased or decreased. If the hepatic arterial flow increases but is not sufficient to compensate for the reduction in portal blood flow, then total hepatic blood flow is reduced.^[15] This may result in reduction in clearance of endogenous and exogenous metabolites with high blood extraction ratio like propofol, thus the possibility of accumulation occurs.

We observed that mean ALP levels in our isoflurane patients remained relatively stable throughout the period of study though five patients had values greater than the upper limit of the normal range of 40-150U/L. Despite the decrease in the level of ALP observed in the two groups, the observed differences were comparable between the two groups.

Alkaline phosphatase usually increases in cholestatic diseases and values of 1.5 to 3.0 times the upper limit of normal (ULN) are consistent with hepatocellular causes e.g., viral infection, drug toxicity and alcohol, whereas values more than 3 times the ULN are usually associated with biliary involvement.^[16,17] Low levels of ALP can be found post cardiac surgery, in patients with heart failure and zinc deficiency. Propofol has been documented to cause a reduction in serum zinc in the post operative period as well as a reduction in ALP which may thus be interrelated.^[18-20]

In our study, propofol caused a significant increase in the serum total bilirubin level immediately post-surgery but this returned to near baseline after 24 hours. Bilirubin level is elevated in liver parenchymal dysfunction and cholestasis which is the basic pattern in drug induced liver injury. Propofol increases hepatic and portal blood flow, thus hepatic ischaemia from reduced blood flow found in other anaesthetic agents is not expected with the use of propofol. On the other hand, propofol has a mean clearance of 2.2L/min which is greater than total hepatic blood flow, it is therefore possible that it accumulates after prolonged infusion. Similarly, Dabir *et al.*,^[21] recorded a significant increase in total bilirubin even at 24 hours post operatively. This suggests that the duration of propofol infusion is a risk factor for development of significant changes in total bilirubin. This was demonstrated by Kashifard and colleagues^[10] where a significant reduction was observed in total bilirubin after 90mins of surgery. They however

excluded surgeries associated with significant blood loss. Significant blood loss associated with haemodynamic changes is a known risk factor for post-operative hepatotoxicity.

In our isoflurane group, total bilirubin levels remained comparatively unchanged over the study period. This was also demonstrated by Yang *et al.*,^[9] even though they employed a higher MAC of 1.2%.

Anaesthesia techniques may also influence the changes in bilirubin. Nishiyama *et al.*^[22] observed a significant increase after isoflurane anaesthesia. They however employed 67% nitrous oxide which reduces hepatic blood flow and has been identified as being responsible for the development of hepatic ischaemia.^[23] Their use of anticonvulsants, which are metabolized and eliminated in the liver may also have contributed to the hepatic injury they observed. In addition, others have reported elevated bilirubin in isolated cases ranging from 2 to 8.5 times the upper limit of normal. The diagnosis was made by exclusion in patients who survived or a post mortem report of centrilobular necrosis of the liver which is in keeping with drug induced hepatotoxicity.^[7,24,25]

Isoflurane caused a progressive increase in the serum level of AST (11.48%-22.42%) during the study period. This increase was more than the upper limit of normal in the immediate post operative period (43.70 ± 29.70 mmol/l) and 24hours post operative period (53.63 ± 38.60 mmol/l). The difference in the mean values was however not significant ($P = 0.131$). AST is elevated in liver parenchymal dysfunction and could be normal or reduced in advanced stage liver disease.^[4] It begins to rise after 8 hours and reaches its peak at 24–36 hours after liver damage.^[8] The normal value is 5–34mmol/l, our maximum increase of 22.4% was much less than 89% noted by Kim *et al.*,^[12] and 168% by Dabir *et al.*,^[8] both of whom documented longer duration of surgery than we did. Decline in AST levels varied in both studies, while Kim^[12] had a return to normal values by 72 hours, Dabir^[8] still documented high values at 72 hours. We are unable to verify this as our study period was restricted to 24 hours post operatively. The higher increase in AST found by Dabir^[8] might also be due to rhabdomyolysis as a result of prolonged lateral decubitus position, however all surgeries in our own study were done in supine position.

Though the serum level of AST decreased progressively throughout the study period in the propofol group the difference within the group was not significant ($P = 0.582$). This is similar to results of other researchers.^[8,10,12] Our results may not be applicable in patients with pre-existing liver disease as demonstrated by Yang *et al.*,^[9] who observed a dramatic increase in AST of 6.5 times the upper limit of normal following propofol infusion via a target controlled infusion at 3–6µg/ml in patients with liver cirrhosis. Our study revealed that it was only at the 24 hour sample that AST levels differed significantly between the isoflurane and propofol groups.

We demonstrated insignificant changes in ALT in both study groups which suggests that hepatocellular damage did not occur in our patients. Other researchers have recorded differing results which may be a consequence of dosage or concentration, duration of anaesthesia, study population and surgical procedure.^[8,9] Where manipulation of the liver occurred with hepatectomy, Yang^[9] documented an 18 fold increase in ALT. Alanine transaminase is the traditional biomarker of hepatocellular damage. Values greater than 500U/L are observed primarily in diseases that affect the hepatocytes such as viral hepatitis, toxin induced liver damage and ischaemic liver injury.^[26]

This study found that prolonged duration of surgery and blood loss greater than 1500mls, were risk factors for developing hyperbilirubinemia, which is a pointer of cholestatic disease, a pattern found in drug induced liver injury. These factors had no significant effect on other liver enzymes. Several studies have implicated massive blood loss and its resultant hypovolemia as risk factors for post operative hepatocellular injury.^[1,2,16] Volatile anaesthetic agents may reduce hepatic blood flow by 30–50% following induction.^[1] If this is not corrected intra operatively, the blood loss from surgery will further reduce the hepatic blood flow thus resulting in ischaemic changes in the hepatocytes. Massive blood loss will cause hepatic injury probably secondary to reduction in hepatic blood flow

Conclusion

It was concluded that isoflurane and propofol had mild effects on the liver enzymes in patients with no documented evidence of liver disease. Alanine transaminases (a traditional biomarker of liver disease), and total bilirubin (a pointer to hepatocellular damage and a pattern observed in drug-induced liver injury) were significantly increased in the propofol group. The major risk factor for developing post operative hepatotoxicity is massive blood loss. Caution is therefore recommended in their use in patients with altered liver enzymes.

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Conflicts of interest

There are no conflicts of interest.

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