Original Article

A comparison between the effect of halothane and propofol on liver enzymes after general anesthesia

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Abstract

Background: *Halothane is the routine used inhalation anesthetic drug in the world but at present, there is an increasing interest for using intravenous anesthetics like propofol. The purpose of this study was to compare these anesthetic effects on hepatic enzymes.*

Methods: *From 2006 to 2007, this study was performed on fifty eight patients classified in class I of American Society of Anesthetics. These patients had no preliminary symptomatic hepatic, cardiac or renal disease admitted for elective surgery in Yahyahnejiad Hospital, Babol University of Medical Sciences. These patients were divided randomly into two groups. Thirty patients in the study group (Propofol) and twenty eight patients in the control group (Halothane). In both groups, pre-meditation and induction of anesthesia were the same. For the maintenance of anesthesia in the study group there was continuous infusion of propofol and for the control group, 0.5-1% halothane inhalation. From all the patients, we got three blood samples separately prior to the anesthesia, twenty four hours and seven days after the anesthesia. These samples were tested for aspartate aminotransferase (AST), alanine amino transferase (ALT), alkaline phosphates (ALP) and Billirubin (total and direct).*

Results: *Seven days after anesthesia ALP, the total and direct Billirubin levels did not have differences between the two groups. However, AST (p=0.008) and ALT (p=0.003) increased in halothane group in compared with propofol group.*

Conclusion: *The results show that propofol has less effect on liver enzymes as compared to halothane.*

Key words: *Halothane, Propofol, Liver enzymes, General anesthesia.*

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Halothane was first introduced into use as an anesthetic in 1956, and replaced ether as the anesthetic of choice. Within two years, isolated case reports of severe hepatitis were reported (1-3). In 1969, the National Institute of Health organized one of the largest epidemiological studies ever performed in the United States to evaluate halothane toxicity. A review of 250,000 cases of halothane use revealed an incidence of fatal hepatic necrosis of about 1 in 35,000 exposures (4). Furthermore, halothane is possibly the most commonly used inhalational anesthetic in all patients worldwide (5) and reports of hepatotoxicity continue to be published (6-8). Toxicity to halothane may result from its metabolism to reactive intermediates, which occurs by both reductive and oxidative mechanisms in part mediated by cytochrome P450 (CYP450) (9, 10). Of the commonly used volatile anesthetics, halothane is the most extensively metabolized, which may explain its propensity to hepatotoxicity (9). Propofol is a substituted isopropylphenol medication, which promotes GABA activity in the brain. While it may be used as a single agent, it is typically administered along with small bolus doses of a short-acting opiate, such as fentanyl and a benzodiazepine, a combination termed "balanced propofol sedation".

Its benefits include its rapid onset of action (distribution two to four minutes), rapid clearance, and reversibility of effect once the drip is shut off. It has some anti-emetic effect and has a weaker amnestic effect than midazolam, but no analgesic effect (9-11). A survey of gastroenterologists in the United States found that propofol was being used for sedation in approximately 25% of endoscopies (12). The major drawback of propofol is its effect as a respiratory depressant. Reversal is only possible by stopping the medication and maintaining ventilation until the medication effect elapses. The airway must also be protected. For these reasons, the use of propofol has been limited to anesthesiologists in most centers in the United States (13). On the other hand, there is growing experience and literature establishing outstanding safety data for the administration of propofol-based sedation by non-anesthesiologist nurses and physicians highly trained in airway management (14-17). A meta-analysis of 20 randomized controlled trials comparing propofol to other sedation regimens for colonoscopy found that propofol sedation was associated with faster recovery and discharge times, and increased patient satisfaction without increased side-effects (18).

Therefore, this study was conducted to compare halothane & propofol effects on hepatic enzymes in general anesthesia.

Methods

This study was conducted on class1 A.S.A (American Anesthesiologists Association) who had referred to Yahyahnejiad Hospital, Babol University of Medical Sciences from 2006 to 2007. Inclusion criteria include nose, pharynx and ear surgeries (septoplasty, polypectomy, or crack palate remedy), eye (cataract and putting lens) orthopedy (foreleg, and hand fracture, removing the pin) general surgery (herniorrhaphy) and urology (varicoclectomy, removing the vesical stone). The exclusion criteria included children less than 12 years old, emergency surgical operations, surgeries with thoracotomy or laparotomy, major surgeries with the risk of bloodshed and hemodynamic disorder who received blood transfusion and persons with hepatic, renal or heart disease. The cases that were not accomplished every three experiment stages were completely omitted during the study. Finally, thirty persons in halothane group and twenty eight persons in propofol group were considered in the study.

After entering the patients to the surgery room and connecting the necessary monitors to them, 0.1mg/kg morphine and 0.1 mg/kg diazepam as pre-medications was injected to all of them. Anesthesia induction was started with 5mg/kg sodium thiopental and 0.6 mg/kg atracurium associated with 1.5 mg/kg lidocaine. Keeping anesthesia was done in study group with propofol 100-120 mg/kg/min associated with O_2 and N_2O (50%) and in control group with halothane 0.5-1% associated with O_2 and N_2O (50%). In order to determine the amount of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) and total and direct bilirubin, blood samples were taken from all the patients before starting anesthesia twenty four hours and seven days later.

Likewise, the patient specifications and information about other factors that may interfere with study results were collected and recorded. This information included: age, sex, weight, alcohol, and cigarette consumption, diabetes, complete blood count, blood lipids consist of triglyceride (TG) and cholesterol, surgery history during the last six months and kinds of anesthetic drug. Also, the other information included anesthesia type and the time after operation. The informed consent was obtained from all the participants prior to enrollment. The Research Center of Babol University of Medical Sciences financially supported this study.

The study was approved by the Ethics Committee of Babol University of Medical Sciences. The data were analyzed by SPSS. Student t test, X^2 and fisher's exact tests were used when appropriate.

Results

Fifteen out of the 30 patients on propofol group were men and fifteen were women. The halothane group consists of twenty men and eight women. The mean age of the patients in halothane group was 14.95±30.75 (ranged 14 to 64 years) and for propofol group was 10.74±34.9 (ranged 18 to 66 years) (p=0.228). About the underlying diseases such as diabetes two subjects come from the propofol group and one subject from the halothane group. While three persons in the propofol group and two in halothane group had hyperlipidemia.

The anesthesia duration time in propofol group for three patients was one hour, twenty three persons were in 90 minute operation time and four persons were in a 120 minute duration time. In halothane group, the anesthesia duration

time, three patients had 60 minutes, nineteen patients had 90 minutes and six patients had 120 minutes. The blood chemistry profiles are shown in table 1.

Table 1: Blood markers of persons under study in two halothane and propofol group before anesthesia

Marker	Mean±SD	p- value
Hemoglobin (g/dl)		
Halothane	14.39±1.2	0.607
Propofol	14.2±1.5	
Leukocyte(μl^{-1})		
Halothane	6142.86±1315.27	0.073
Propofol	6091±1401.48	
FBS (mg/dl)		
Halothane	86.14±14.58	0.446
Propofol	92.27±39.73	
Triglyceride(mg/dl)		
Halothane	100.68±27.26	0.023
Propofol	129.1±59.39	
Cholesterol (mg/dl)		
Halothane	168.61±28.48	0.213
Propofol	179.9±38.57	

Table 2 shows mean AST, ALT, ALP, bilirubin total and direct bilirubin in persons under study at the different times. The mean AST (p=0.295) and ALT (p=0577) before the operation and one day after the anesthesia between halothane and propofol groups were not statistically significant. The mean AST (p=0.008) and ALT (p=0.003) before operation and seven days after anesthesia between the two groups was statistically significant (table 2). The mean alkaline phosphtase levels before operation and one day after anesthesia (p=0.572), and before operation and seven days anesthesia (p=0.514), between halothane and propofol groups were not statistically meaningful.

The mean total bilirubin before operation and one day after anesthesia between the two groups was not statistically significant (p=0.08). The difference of total bilirubin levels before operation and seven days after anesthesia was (p=0.722), and the mean difference of direct bilirubin before operation and one day after operation was (p=0.357), and the mean difference of direct bilirubin before operation and seven days after anesthesia (p=0123) was not significant between halothane and propofol groups.

Table 2: Mean of hepatic aminotransferase in persons under study at different times

Time	Before anesthesia	1 day after anesthesia	p value	7days after anesthesia	p value
Amino transferase	**Mean±SD**	**Mean±SD**		**Mean±SD**	
AST*					
Halothane	19.04±7.55	20.54±10.16	0.467	24.61±9.83	0.008
Propofol	22.3±8.12	21.53±9.32	0.232	22.2±9.18	0.863
ALT**					
Halothane	19.75±17.35	17.96±13.87	0.152	24.21±18.07	0.012
Propofol	17.5±7.63	16.57±7.18	0.061	16.5±7.34	0.02
ALP					
Halothane	217.5±233.7	207.5±224.6	0.088	206±203	0.168
Propofol	186.8±44	180±41	0.013	181±42	0.005
Total					
Halothane	0.7±0.37	0.7±0.37	0.882	0.62±0.19	0.208
Propofol	0.73±0.22	0.69±0.2	0.006	0.68±0.18	0.003
Direct					
Halothane	0.22±0.18	0.19±0.16	0.058	016±0.1	0.035
Propofol	0.19±0.09	0.18±0.08	0.476	0.18±0.09	0.293

*Aspartate Aminotransferase **Alanine Aminotransferase

Discussion

In this study, halothane caused increasing levels of AST and ALT, but the difference between one day after anesthesia and before operation was not significant, but the difference between seven days after anesthesia and before operation was significant. While the AST alterations in propofol group was not significant but ALT in propofol group was. ALT alterations were significant between the halothane and propofol groups after seven days lapsed. Similar results were obtained by Robinson et al. in hepatic effect of propofol as major anesthesia drug on thirty women (19). Lorsomradee et al. showed that propofol caused postoperative transient elevation of serum AST, ALT and lactate dehydrogenase in patients undergoing coronary artery surgery but renal biochemical marker remains unchanged (20). Other reports showed that halothane is commonly associated with asymptomatic elevation in serum aminotransferases (21). The aminotransferases remains elevated for one to two weeks following exposure, and resolved without treatment. A much more unpredictable and rare occurrence is an acute hepatitis, which is often fatal (acute liver failure) (22).

In our study, the mean ALP level in one and seven days after anesthesia between the two groups was not significant. Robinson's et al. obtained similar results like our findings (19). In a study that was accomplished by Topal showed that halothane with respect to isoflurane had caused increase in hepatic enzymes such as hepatic aminotransferases and alkaline phosphatase until the 14^{th} day after anesthesia (23). Therefore, much time for considering ALP level is needed as we did in our study.

Regarding total bilirubin levels, our findings also were similar to that found by Chen et al. and they showed that propofol with mooring activity related to dose had caused deduction of conjugation enzymes activity in hepatic tissue but did not have such effect on extra hepatic tissue (24). By considering the above subjects, we can conclude that the effect of halothane and propofol on ALT and AST enzymes one day after anesthesia was insignificant but seven days after the anesthesia in both of these enzymes in halothane group meaningfully increased but decreased in propofol group and these results were similar with the reports of the other researchers (19, 23, 25-28). Amoros et al. used propofol in the sedation of patients with cirrhosis during endoscope procedures and showed that propofol did not precipitate minimal or overt hepatic encephalopathy (29). Weston et al. used propofol for upper endoscopy in patients with chronic liver disease. It was efficacious and well tolerated in these patients (30). In summary, the results show that propofol has fewer effects on liver enzymes as compared to halothane.

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References

1. Virtue RW, Payne KW. Postoperative death after Fluothane. Anesthesiology 1958; 19:562.
2. Lindenbaum J, Leifer E. Hepatic necrosis associated with halothane anesthesia. N Engl J Med 1963; 268: 525-30.
3. Brody GL, Sweet RB. Halothane anesthesia as a possible cause of massive hepatic necrosis. Anesthesiology 1963; 24: 29-37.
4. Bunker JP, Forrest WH, Mosteller, F et al (Eds). National Halothane Study. A sudy of the possible association between halothane anesthesia and postoperative hepatic necrosis. U.S. Government Printing Office, Washington, DC 1969.
5. Wiklund RA, Rosenbaum SH. Anesthesiology. First of two parts. N Engl J Med 1997; 337:1132-41.
6. Qureshi MA, Saeed F, Hussain T. Halothane induced fulminant hepatic failure. J Coll Physicians Surg Pak 2007; 17:103-4.
7. Kumar GP, Bhat VJ, Sowdi V. Fulminant hepatic failure following halothane anaesthesia. J Clin Forensic Med 2005; 12: 271-3.
8. Otedo AE. Halothane induced hepatitis: case report. East Afr Med J 2004; 81: 538-9.
9. Gut J. Molecular basis of halothane hepatitis. Arch Toxicol Suppl 1998; 20: 3-17.
10. Masubuchi Y, Horie T. Toxicological significance of mechanism-based inactivation of cytochrome p450 enzymes by drugs. Crit Rev Toxicol 2007; 37: 389-412.
11. Graber, RG. Propofol in the endoscopy suite: an anesthesiologist's perspective. Gastrointest Endosc 1999; 49: 803-6.
12. Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a nationwide survey. Am J Gastroenterol 2006; 101: 967-74.

13. Yimcharoen P, Fogel EL, McHenry L, et al. Use of Droperidol at ERCP and QTc Prolongation: Do We Need to Follow the Black Box Warning? Gastrointest Endosc 2005; 61:AB125.
14. Dikman AE, Sanyal S, Aisenberg J, et al. Gastroenterologist-Directed, Balanced Propofol Sedation for EGD and Colonoscopy: An Analysis of Safety in 15, 286 Patients. Gastrointest Endosc 2008; 67: AB84.
15. Rex DK, Deenadayalu V, Eid E. Gastroenterologist-directed propofol: an update. Gastrointest Endosc Clin N Am 2008; 18: 717-75, ix.
16. Külling D, Orlandi M, Inauen W. Propofol sedation during endoscopic procedures: how much staff and monitoring are necessary?. Gastrointest Endosc 2007; 66: 443-9.
17. Cohen LB, DeLegge MH, Aisenberg J, et al. AGA Institute Review of Endoscopic Sedation. Gastroenterology 2007; 133: 675-701.
18. Singh H, Poluha W, Cheung M, et al. Propofol for sedation during colonoscopy. Cochrane Database Syst Rev 2008; CD006268.
19. Robinson F.P, Patterson CC, Changes in liver function tests after propofol ('Diprivan'). Postgrad Med J 1985; 61: 160-1.
20. Lorsomradee S,Cromheecke S , Lorsomradee S, De hert SG.Effects of sevoflurane on biomechanical markers of hepatic and renal dysfunction after coronary artery surgery. J cardiothorac vasc Anesth 2006; 20: 684-90.
21. Liu ZX, Kaplowitz N. Immune-mediated drug-induced liver disease. Clin Liver Dis 2002; 6: 755-74.
22. Lo SK, Wendon J, Mieli-Vergani G, Williams R. Halothane-induced acute liver failure: continuing occurrence and use of liver transplantation. Eur J Gastroenterol Hepatol 1998; 10: 635-9.
23. Hepatic effects of halothane, isoflurane or sevoflurane anaesthesia in dogs. J Vet Med A Physiol Pathol Clin Med 2003; 50: 530-3.
24. Chen TL, Wu CH, Chen TG, et al. Effects of propofol on functional activities of hepatic and extrahepatic conjugation enzyme systems. Br J Anaesth 2000; 84: 771-6.
25. Tsao CM, Ho ST, Chen A, et al., Propofol ameliorates liver dysfunction and inhibits aortic superoxide level in conscious rats with endotoxic shock. Eur J Pharmacol 2003; 477: 183-93.
26. Tiainen P, Rosenberg PH. Hepatocellular integrity during and after isoflurane and halothane anaesthesia in surgical patients. Br J Anaesth 1996; 77: 744-7.
27. Murray JM, Rowlands BJ, Trinick TR. Indocyanine green clearance and hepatic function during and after prolonged anaesthesia: comparison of halothane with isoflurane. Br J Anaesth 1992; 68:168-71.
28. Sear JW, Prys-Roberts C, Dye A. Hepatic function after anaesthesia for major vascular reconstructive surgery. Br J Anaesth 1983; 55: 603-9.
29.Amoros A, Aparicio JR, Garmendia M, et al. Deep sedation with propofol does not precipitate hepatic encephalopathy during elective upper endoscopy. Gastrointest Endosc 2009; 70: 262-8.
30. Weston BR, Chadalawada V, Chalasani N, et al. Nurse-administered propofol versus midazolam and meperidine for upper endoscopy in cirrhotic patients. Am j Gastroenterol. 2003; 98: 2440-7.