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Effects of propofol versus isoflurane on liver function after open thoracotomy

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Abstract

Background: Anesthetic agents and type of surgery may contribute to postoperative hepatic injury. Inhalational anesthetics have been associated with hepatic dysfunction after surgery, however, propofol is expected to have a lower potential for postoperative liver injury. This prospective double-blind randomized clinical study was planned to determine whether postoperative liver function differs after anesthesia with isoflurane and total intravenous anesthesia with propofol in patients undergoing a posterolateral thoracotomy.

Methods: Eighty-eight patients in American Society of Anesthesiologists physical status 1 or 2, aged 16–60 years, and scheduled for an elective posterolateral thoracotomy, were randomly assigned to an anesthetic protocol: propofol ($n = 44$) or isoflurane ($n = 44$). Induction of anesthesia was similar in both groups. Serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, and γ-glutamyltransferase were measured before induction of anesthesia and on the first and third days after either propofol or isoflurane anesthesia.

Results: Mild changes in postoperative serum levels of liver enzymes were significant within each group but the differences between groups were not significant.

Conclusions: Propofol and isoflurane anesthesia have a comparable minor effect on liver function after an elective posterolateral thoracotomy.

Keywords

Anesthetics, inhalation, isoflurane, liver function tests, postoperative complications, propofol, thoracotomy

Introduction

Surgery and anesthesia may contribute to postoperative liver injury depending on the type of anesthesia, damage from surgery, and preexisting liver disease.[1–3] All volatile anesthetics variably affect hepatic function after surgery. Among them, sevoflurane, desflurane, and isoflurane have been shown to better preserve hepatic blood flow and function than halothane or

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enflurane. The effects of intravenous anesthetics on liver function have been less extensively investigated than those of halogenated agents, and are still a matter of controversy. Propofol is expected to have a less significant impact on postoperative hepatic integrity compared to inhaled agents if hepatic blood flow is maintained.[4] However, to date, a limited number of studies have compared the effects on liver function of volatile anesthetics and total intravenous anesthesia (TIVA). Operations on the pleural cavity may be associated with changes in pulmonary circulation, general changes in hemodynamics, and hypoxic events, and thus have a potential for postoperative liver injury. These changes are influenced by the lateral position of patient's body during surgery, the extent of damage from surgery, and the operation time.[5,6] TIVA with propofol or isoflurane is widely used for thoracic procedures. Propofol is expected to have a lower potential for postoperative liver injury, although previous studies comparing the effect of isoflurane and propofol on liver function had variable results. However, to our knowledge, no study has compared the effect of the two anesthetics on liver function after open thoracotomy. Concerning previous knowledge of hepatic injury with isoflurane, this study was planned to determine whether postoperative liver function differs after anesthesia with isoflurane and TIVA with propofol in patients undergoing a posterolateral thoracotomy.

Patients and methods

The hospital ethics committee approved this study, and the patients gave written informed consent for participation. Ninety-two patients aged 16–60 years who were in American Society of Anesthesiologists physical status I and II and scheduled for an elective posterolateral thoracotomy in the lateral decubitus position, requiring one-lung ventilation, were included in the study. All patients selected for the study had normal values of serum liver enzymes preoperatively. Exclusion criteria were liver or renal disease, alcohol or substance abuse, exposure to general anesthesia within the last 3 months, or a known allergy to any of the drugs used in the study.

According to a computer-generated randomization table, the anesthetic protocol was identified by a number and covered in an envelope until the start of anesthesia. Eligible patients were allocated by lottery to one of two groups of 46 patients each, to receive either isoflurane or propofol for maintenance of anesthesia. In all patients, serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), and lactate dehydrogenase (LDH) were measured before induction of anesthesia (baseline) and on the 1st, 3rd, and 7th days after surgery, using common methods at the laboratory of our hospital.

The patients were not premedicated before arrival in the operating room. Prior to induction of anesthesia, a 20-gauge intravascular catheter was inserted into the radial artery of the dependent arm to obtain continuous blood pressure measurements and intermittent arterial blood gas values. The electrocardiogram and arterial oxygenation (SpO_2) using pulse oximetry were also monitored throughout the procedure. Intermittent arterial blood gas analysis was performed before induction of anesthesia (baseline), during two-lung ventilation in the lateral decubitus position, 60 min after initiation of one-lung ventilation, and at the end of surgery. At the same intervals, mean arterial blood pressure, heart rate, and SpO_2 values were also recorded. Significant changes in hemodynamic parameters and oxygenation during the entire surgical procedure were also registered. Anesthesia was induced in both groups with thiopental $5\,mg\,kg^{-1}$, midazolam 2–3 mg, and fentanyl $2–4\,\mu g\,kg^{-1}$, and tracheal intubation was facilitated with atracurium $0.6\,mg\,kg^{-1}$. A properly sized Robertshaw double-lumen endotracheal tube was placed, and the correct position was confirmed fiberoptically. Patients in the isoflurane group received isoflurane at an inspired concentration of 0.6%–1.5% in 100% oxygen. Those in the propofol group were given continuous infusions of propofol $100–200\,\mu g\,kg^{-1}\,min^{-1}$. In both groups, a continuous infusion of remifentanil $0.5–1.0\,\mu g\,kg^{-1}\,min^{-1}$ was administered throughout the operation. A bolus of atracurium was given at regular intervals to maintain muscle relaxation. The lungs were mechanically ventilated with 100% oxygen using a semiclosed circle system with a fresh gas flow of $4\,L\,min^{-1}$ during anesthesia. All patients were placed in the lateral decubitus position for surgery. Ventilation was adjusted to keep SpO_2 greater than 90% ($PaO_2 > 60\,mm\,Hg$) and to achieve a partial pressure of carbon dioxide and pH in the physiological range. Hemodynamic stability was maintained by changing doses of anesthetics, altering the rate of intravenous fluid infusion, or giving ephedrine or epinephrine as necessary. Packed red blood cells were transfused according to blood loss and hematocrit measurements. At the end of anesthesia, neuromuscular block was reversed with neostigmine and atropine. All patients were extubated in the operating room and transferred to the intensive care unit. Postoperative analgesia was provided by epidural analgesia with bupivacaine plus morphine, and intravenous increments of morphine, if necessary. The anesthesiologists were aware of which anesthetic regimen each subject was receiving, but the patients, surgeons,

nurses, and medical laboratory staff were blinded to the study groups.

Data analyses was performed using Statistical Package for Social Sciences version 16.0. The number of study patients required to detect a $5\,IU\,L^{-1}$ difference in serum GGT level after surgery with a power of 80% and a significance level of 5% was calculated to be a minimum of 34 in each group. Student's *t* test and the Mann-Whitney *U* test were used to compare normally distributed and non-normally distributed continuous variables, respectively, between the two groups. Intragroup comparisons of normally distributed and non-normally distributed measurements were performed using two-way repeated measures analysis of variance and the Friedman test, respectively. Comparisons of abnormal liver enzyme values and differences in the number of patients with abnormal liver function between the groups were evaluated by Fisher's exact test. The chi-square test or Fisher's exact test was utilized for comparisons of categorical variables between groups. Data are presented as mean ± standard deviation and numbers. A *p* value of less than 0.05 was considered statistically significant.

Results

Of the 92 patients studied, 4 were excluded from the analysis because of missing blood samples. In addition, liver function data analysis on the 7th postoperative day was not included because 80 of the participating patients were not available on postoperative day 7. Statistical analysis was therefore conducted with 88 patients. Patient characteristics and operative data were similar in both groups (Table 1). Mean arterial blood pressure, heart rate, SpO_2, and arterial blood gas values were within the acceptable ranges and comparable between the two groups during anesthesia (Table 2). The total propofol dose was 2059 ± 1040 mg (range 200–5000 mg), and the dose of isoflurane was 0.85% ± 0.17% (range 0.5%–1%). Time to tracheal extubation was significantly shorter in the propofol group (14.25 ± 15.39 min) than in the isoflurane group (16.68 ± 10.45 min; $p = 0.036$), which could not have a clinically important effect. Significant changes in hemodynamic parameters and oxygenation were not detected during the entire surgical procedure. There were no serious intra- or postoperative complications throughout the study period. The entire postoperative course of the

Table 1. Characteristics and operative data of 88 patients undergoing a posterolateral thoracotomy with isoflurane or propofol.

Variable	Isoflurane ($n = 44$)	Propofol ($n = 44$)	*p* value
Age (years)	38.20 ± 12.87	40.40 ± 14.73	0.45
Sex (M/F)	28/16	26/18	0.66
Weight (kg)	65.75 ± 13.58	70.38 ± 19.24	0.19
Height (cm)	167.31 ± 10.44	165.04 ± 9.67	0.29
ASA status 1/2	21/23	27/17	0.19
Anesthetic time (min)	365.93 ± 126.77	347.20 ± 118.58	0.47
Remifentanil (mg)	2.44 ± 1.21	2.03 ± 0.99	0.17
Fentanyl (μg)	194.88 ± 65.27	202.84 ± 53.16	0.33
Crystalloids (mL)	3390.90 ± 1381.53	3306.81 ± 1319.33	0.81
Blood transfusion (*n*)	7	5	0.53
Packed RBC (units)	1.85 ± 0.89	2 ± 0.70	0.75
Right/left thoracotomy	24/20	24/20	0.1
Operative time (min)	287.84 ± 116.09	275.34 ± 109.08	0.55
Surgical procedures (*n*)			
Cyst excision	9	9	
Limited lung resection	4	5	0.65
Lobectomy	13	18	
Pneumonectomy	5	4	
Bilobectomy	5	1	
Decortication	4	2	
Miscellaneous	4	5	

ASA: American Society of Anesthesiologists; RBC: red blood cells.

Table 2. Hemodynamic and arterial blood gas values during anesthesia.

Variable	Group	Baseline	During 2-lung ventilation in lateral position	During one-lung ventilation	At end of anesthesia
MAP (mm Hg)	Iso	128.9 ± 18	115.2 ± 16.2	103..9 ± 24.6	125.8 ± 2
	Pro	128.5 ± 20	118.6 ± 18.8	114.3 ± 18.5	123 ± 2.6
HR (beats min^{-1})	Iso	92 ± 17	79.6 ± 14.2	82.6 ± 12	102.5 ± 20.5
	Pro	90 ± 16.6	85 ± 16	81 ± 14	94.6 ± 23
SaO_2	Iso	94% ± 5%	98% ± 2.1%	97.5% ± 4%	99% ± 2.6%
	Pro	95.8% ± 3%	99% ± 1.5%	97.7% ± 3%	99% ± 1.4%
$PaCO_2$ (mm Hg)	Iso	38.3 ± 6	38.4 ± 9.7	40.7 ± 10	45 ± 11
	Pro	38 ± 4.6	36.7 ± 10	41.4 ± 12	41.5 ± 8
PaO_2 (mm Hg)	Iso	84.4 ± 27	260 ± 129.5	157 ± 100	263 ± 118.4
	Pro	83.5 ± 26	288 ± 126.4	131 ± 68	287 ± 103.4
pH	Iso	7.45 ± 0.05	7.37 ± 0.07	7.34 ± 0.06	7.27 ± 0.06
	Pro	7.41 ± 0.05	7.36 ± 0.07	7.33 ± 0.09	7.23 ± 0.4
HCO_3	Iso	24 ± 5	23 ± 5.2	22.1 ± 4.17	21 ± 3.97
	Pro	24 ± 3.5	21.4 ± 3.8	21.5 ± 3.37	20 ± 3.22

There was no difference in hemodynamic and arterial blood gas values between the two anesthetic groups at the selected times. HR: heart rate; Iso: isoflurane group, MAP: mean arterial blood pressure; Pro: propofol group.

Table 3. Serum levels of liver enzymes during study period.

Enzyme (normal range)	Group	Baseline	Day 1	Day 3
GGT				
Men ($\leqslant$ 49 IU L^{-1})	Iso ($n = 28$)	23.68 ± 9.4	19.60 ± 7.97*	29.35 ± 16.46†
	Pro ($n = 26$)	27.11 ± 10.52	25.07 ± 9.91*	31.20 ± 15.14†
Women ($\leqslant$ 32 IU L^{-1})	Iso ($n = 16$)	19.25 ± 11.82	17.12 ± 12.84*	23.31 ± 14.49†
	Pro ($n = 18$)	17.94 ± 5.80	18.27 ± 11.80	24.05 ± 12.18*†
LDH (225–500 IU L^{-1})	Iso	328.40 ± 85.50	476.00 ± 127.92*	459.04 ± 175.88*
	Pro	358.25 ± 78.11	443.72 ± 124.38*	435.00 ± 104.96*
AST (5–40 IU L^{-1})	Iso	17.36 ± 6.82	46.59 ± 36.85*	40.56 ± 43.04*†
	Pro	18.25 ± 6.09	38.31 ± 24.77*	32.68 ± 22.50*†
ALT (5–40 IU L^{-1})	Iso	16.75 ± 10.78	22.27 ± 14.20*	26.63 ± 25.99*
	Pro	17.63 ± 8.81	20.72 ± 13.93	20.81 ± 13.48
ALP (64–306 IU L^{-1})	Iso	198.09 ± 61.11	173.47 ± 52.89*	184.45 ± 44.57*†
	Pro	204.15 ± 52.78	185.86 ± 48.77*	201.20 ± 63.31
TBil (0.1–1.2 mg dL^{-1})	Iso	0.46 ± 0.27	0.91 ± 1.03*	0.58 ± 0.78†
	Pro	0.38 ± 0.21	0.70 ± 0.60*	0.41 ± 0.34†

*$p < 0.05$ vs. baseline.

†$p < 0.05$ vs. first postoperative day. There was no difference between the two anesthetic groups in liver enzymes levels at the selected times after thoracotomy. ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Baseline: before induction of anesthesia; GGT: γ-glutamyltransferase; Iso: isoflurane group; LDH: lactate dehydrogenase; Pro: propofol group; TBil: total bilirubin.

patients was uneventful. Hemodynamic parameters on the first postoperative day were acceptable and in the same range in the propofol group (blood pressure 110 ± 12/68 ± 7 mm Hg, heart rate 87 ± 10 beats min^{-1}) and the isoflurane group (blood pressure 111 ± 11/69 ± 7 mm Hg, heart rate 87 ± 9 beats min^{-1}; $p > 0.05$). The changes in serum liver enzyme levels were significant within each group but the difference between groups was not significant (Table 3). The level of serum ALT was increased significantly at 24 and 72 h

Table 4. The number of patients with abnormal serum levels of liver enzymes in the propofol and isoflurane groups on the first and third day after thoracotomy.

	Isoflurane ($n = 44$)		Propofol ($n = 44$)	
Enzyme (normal range)	Abnormal values	No. of patients	Abnormal values	No. of patients
LDH (225–500 IU L^{-1})				
3rd day	1079	1		0
AST (5–40 IU L^{-1})				
1st day	85, 97, 127, 157, 197	5	111, 148	2
3rd day	85, 88, 291	3	151	1
ALT (5–40 IU L^{-1})				
3rd day	117, 136	2		0
TBiL (0.1–1.2 mg dL^{-1})				
1st day	2.5, 2.5, 6.8	3	3.6	1
3rd day	5.3	1		0

ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; TBil: total bilirubin. The numbers of patients with abnormal LDH, AST, ALT and TBil levels were not different in the isoflurane and propofol groups.

after the operation in the isoflurane group but the changes were within the normal range. There were no significant changes in ALT over time in the propofol group. AST was significantly increased at 24 and 72 h after surgery in both groups. These changes were within the normal limit in propofol group, however, there was a minor elevation of AST in the isoflurane group on postoperative day 1, which returned to normal on postoperative day 3. The changes in TBiL, LDH, GGT, and ALP levels in both groups did not exceeded the normal range. In a small number of patients in both groups, elevated serum levels of LDH, AST, ALT, and TBil to greater than twice the upper reference values were noted; the number of patients was greater in the isoflurane group, but it was not statistically significant ($p > 0.05$; Table 4). No clinical signs of hepatitis were seen.

Discussion

Based on our results, propofol and isoflurane anesthesia regimens had comparable minor effects on liver function after an elective posterolateral thoracotomy, with no apparent clinical importance. Hemodynamics and arterial blood gas values were acceptable and in the same range in both groups, and there were no significant instances of hypotension, desaturation, or bleeding. However, the mean arterial blood pressure analysis at only 4 selected time intervals was a limitation of this study because of the possibility of missed periods of hemodynamic differences between the two groups. The number of patients with abnormal AST levels may be attributed to trauma to muscles or lung tissue because AST is also present in skeletal muscle, kidneys, heart, lungs, and pancreas.[7] In addition, the presence of metabolic acidosis in both groups at the end of anesthesia (Table 2) might be a sign of tissue hypoperfusion and could be a factor in the development of abnormalities in liver function tests after surgery. Tissue hypoperfusion may have resulted from the combined effects of lengthy surgery, prolonged lateral positioning, and general anesthesia.[6,8] Individual biological variations and perioperative medications (e.g. antibiotics) might also be involved in postoperative impairment of liver function. The antibiotic use in our patients was cephalosporin solely or in combination with clindamycin or vancomycin. Administration of these antibiotics can also be associated with minor transient elevations in hepatic transaminase levels.

Our results are in agreement with a study by Ono and colleagues[9] who found prevention of abnormal hemodynamic changes, hypoxemia, and excessive bleeding during thoracotomy were the main factors related to postoperative liver damage. In general, regardless of the type of anesthesia or surgery, asymptomatic mild transient elevations (less than two-times normal values) of serum liver enzymes, specially aminotransferase, alkaline phosphatase, or bilirubin concentrations, are common following surgical procedures, may have no clinical significance, and may not even be considered abnormal.[7] On the other hand, intraabdominal operations that are associated with impairment of hepatic blood flow, and procedures associated with a large amount of blood loss, markedly increase the risk of postoperative injury to the liver.[1,4] In addition to surgical trauma, a variety of perioperative factors such as hypotension, hypovolemia, prolonged anesthesia, ventilation mode, operative

position, infection, or perioperative medications may be involved in injury to the liver after surgery.[3,8] Postoperative liver function may be affected by anesthetics and their metabolites. Volatile anesthetic metabolites can produce a variable extent of liver injury by either immune- or nonimmune-mediated mechanisms.[2] Lower metabolism of isoflurane and better preservation of hepatic blood flow may explain the lower incidence of hepatic damage after isoflurane than after halothane or enflurane anesthesia.[2,10] Compared to volatile agents, TIVA with propofol is expected to have a less significant impact on hepatic function and hepatic blood flow when arterial blood pressure is adequately preserved. Propofol may also increase total hepatic blood flow through a significant splanchnic vasodilator effect.[4] Furthermore, TIVA with propofol may carry a lower risk of direct damage from anesthetic metabolites.[11] However, administration of propofol may be associated with various degrees of hepatocellular impairment in surgical patients. The potential reasons are an immunologic mechanism, disturbance of the mitochondrial respiratory chain within the hepatocytes, and reduced cytochrome C oxidase activity.[12]

Previous studies reporting the effect of isoflurane anesthesia and TIVA with propofol on liver function have found variable outcomes. The results of the present study are consistent with studies that found a low potential for hepatocellular injury with both anesthetic agents. In agreement with our results, Kim and colleagues[13] found no significant difference in postoperative hepatic function with enflurane, isoflurane, and propofol after tympanomastoidectomy; they showed a mild temporary increase in AST in all groups, while ALT and ALP were not changed. In a study by Murray and colleagues,[14] prolonged propofol or isoflurane anesthesia had no significant effect on hepatic function after lengthy plastic surgery. Similarly, propofol had little effect on liver enzyme levels after laparoscopic cholecystectomy.[15] Likewise, the changes in hepatic function after TIVA with propofol and remifentanil for thyroidectomy were similar to sevoflurane and within normal limits.[11] Nishiyama and colleagues[16] also found a mild elevation of liver enzymes after isoflurane anesthesia in neurosurgical patients. Furthermore, Tiainen and colleagues[17] detected a mild subclinical disturbance in hepatocellular integrity after either desflurane or isoflurane anesthesia for breast surgery.

Contrary to our findings, significant increases in AST and ALT occurred after propofol anesthesia in patients who had laparoscopic cholecystectomy.[18] Also, the increases in postoperative serum levels of SGPT, SGOT, and LDH were significantly higher in a propofol-based anesthetic regimen compared to sevoflurane anesthesia for coronary artery surgery.[19] Moreover, cases of severe liver dysfunction have been reported following exposure to isoflurane and after short-term propofol anesthesia.[12,20] We concluded that propofol and isoflurane anesthesia had comparable minor effects on liver function after an elective posterolateral thoracotomy.

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Conflict of interest statement

None declared.

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