Original Article

Comparative effect of desflurane and sevoflurane on liver function tests of patients with impaired hepatic function undergoing cholecystectomy: A randomized clinical study

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ABSTRACT

Background and Aim: Desflurane and sevoflurane are the most common volatile anesthetics used during laparoscopic and hepatic surgery. The objective of the study was to evaluate the effect of desflurane and sevoflurane in patients with elevated preoperative liver functions undergoing laparoscopic cholecystectomy. **Methods:** The study was a randomized study and included 162 patients classified randomly into two groups: Desflurane group: The patients received desflurane (end-tidal concentration 4%–6%) as an inhalational agent during the whole procedure. Sevoflurane group: The patients received sevoflurane (end-tidal concentration 2%–4%) as an inhalational agent during the whole procedure. The investigations included serum level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and total bilirubin. The values were serially collected at the following timepoints; T0:at the preoperative period, T1:directly after surgery, T2:1st postoperative day, T3:2nd postoperative day, T4:3rd postoperative day, T5:5th postoperative day, T6:7th postoperative day, and T7:10th postoperative day. The statistics were described in terms of mean ± standard deviation, frequencies, and percentages. **Results:** The preoperative liver enzymes and total bilirubin were higher than the normal range in patients of the two groups. Postoperatively, there was a decrease in the AST and ALT with desflurane more than sevoflurane from T1 to T6($P < 0.05$). The ALP, GGT, and bilirubin decreased in patients of the two groups, but the comparison was insignificant ($P > 0.05$). **Conclusion:** The desflurane is a safe inhalational volatile for maintenance of anesthesia in patients with impaired liver function undergoing laparoscopic cholecystectomy. It was associated with a decrease in the liver enzymes more than the sevoflurane.

Key words: Desflurane, hepatic protection, laparoscopic cholecystectomy, liver enzymes, sevoflurane

INTRODUCTION

Laparoscopic cholecystectomy is considered the gold standard method to treat uncomplicated cholelithiasis. Many studies showed changes in the postoperative liver functions after laparoscopic procedures.[1-3] These changes may be related to hepatocellular damage secondary to the combination of carboxy pneumoperitoneum, liver manipulation, use of diathermy, general anesthesia, and hepatic artery injury.[4-6]

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Desflurane and sevoflurane are the most common volatile anesthetics used during laparoscopic and hepatic surgery,[7-10] and we hypothesized that desflurane and sevoflurane provide equal hepatic protection in patients with acute cholecystitis and impaired preoperative liver functions undergoing laparoscopic cholecystectomy.

This study aimed to evaluate the effect of desflurane and sevoflurane in patients with acute cholecystitis and impaired preoperative liver functions undergoing laparoscopic cholecystectomy.

METHODS

After obtaining informed consent and approval of local ethics and research committee in the hospital (312016, 20/01/2016), a prospective randomized study included 162 patients (through 2016–2019) with ASA (American Society of Anesthesiologists) physical status I and II, acute cholecystitis, and elevated preoperative liver functions [higher than two times of the normal range: AST (5-34 U/L), ALT (7-55U/L), ALP (40-150U/L) GGT (12-64U/L), total bilirubin (3.4–20.5μmol/L), and direct bilirubin (<8.5μmol/L)].

Exclusion criteria of the study included patients with morbid obesity (body mass index > 35kg/m^2), obstructive jaundice, fulminant hepatitis, significant severe cardiovascular, renal, respiratory, and neurological and psychiatric diseases. Preoperative magnetic resonance cholangiopancreatography (MRCP) was done for all patients to exclude obstructive jaundice and to provide detailed images of the hepatobiliary and pancreatic systems, including the liver, gallbladder, bile ducts, pancreas, and pancreatic duct. All the cases were anesthetized by the same anesthetic team and the same surgeon.

The patients were randomly allocated (the concealment of allocation was done by using random numbers generated through excel) into two equal groups (n = 81 each). Desflurane group: The patients received desflurane (end-tidal concentration 4%–6%) as an inhalational agent during the whole procedure. Sevoflurane group: The patients received sevoflurane (end-tidal concentration 2%–4%) as an inhalational agent during the whole procedure.

During the procedure, the dial concentration of desflurane and sevoflurane vaporizers was adjusted every 5 min to maintain the concentration around one MAC (minimum alveolar concentration) and to control the changes in the heart rate and blood pressure. The MAC of desflurane and sevoflurane were measured using Dräger infinity C700 (Dräger, Lübeck Germany). The age was not considered during adjustment of the MAC.

The carboxy pneumoperitoneum during laparoscopic cholecystectomy was maintained at a pressure of 10–15 mmHg.

For all patients, a peripheral venous line G18was inserted and intravenous administration of 500 mL of crystalloids was administered before surgery. Premedication of two mg of midazolam was given intravenously 30 min before induction. After attaching the monitors (ECG, pulse oximeter, noninvasive arterial blood pressure), the induction of anesthesia was done for all patients by pre-oxygenation, intravenous propofol (1–2mg/kg) followed by fentanyl (1-2μg/kg) and atracurium 0.5mg/kg as a bolus dose over 30 s. After tracheal intubation, anesthesia was maintained with oxygen: air (concentration 50:50%, flow 2L: 2L constant with all patients) and desflurane or sevoflurane according to the study medication protocol. An additional dose of intravenous atracurium (0.08–0.1mg/kg) was given and guided by the peripheral nerve stimulator to provide a train-of-four count zero. The ventilation was adjusted to maintain the end-tidal $PaCO_2$ within 30–35 mmHg (CO_2 absorber was the same type for all patients and it was CLIC absorber 800+ Drägerwerk AG and Co. Lübeck Germany). Volatile anesthetic concentration adjusted to maintain the mean arterial blood pressure and heart rate within ± 20% of the preinduction baseline values. Intraoperative tachycardia (heart rate >100 bpm), and systemic hypertension (systolic arterial blood pressure >20% above baseline) was managed by increasing the concentration of desflurane or sevoflurane by increments of 1% and bolus doses of fentanyl (0.5–1μg/kg). Intraoperative hypotension (systolic arterial blood pressure <20% below baseline) was managed by bolus doses of ephedrine 5–10mg and fluid administrations. Bradycardia (heart rate <60 bpm) was managed by a bolus dose of atropine (0.02mg/kg). At the end of the surgery, the volatile agent was discontinued, and controlled ventilation with 100% oxygen was maintained until end-tidal volatile anesthetic concentration was less than 0.1%. Intravenous lidocaine 1mg/kg was given for all patients 2 min before removal of the endotracheal tube to provide smooth extubation. The residual neuromuscular blockade was reversed

with a combination of neostigmine 0.05mg/kg mg and atropine 0.02mg/kg intravenously. Postoperative nausea and vomiting were managed by intravenous administration of ondansetron (0.1–0.15mg/kg).

At the end of anesthesia and after extubation, the patients were shifted to the post-anesthesia care unit and later to the ward. After discharge from the hospital, the patients were informed to repeat the liver function test as the scheduled plan in the study until postoperative day 10.

The variables used during the study included serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and total bilirubin. The blood samples were withdrawn in the main hospital laboratory either the preoperative or postoperative investigations which were done by using the resources of the hospital and not funded from any company. The values were serially collected at the following timepoints; T0:at the preoperative period, T1:directly after surgery, T2:1st postoperative day, T3:2nd postoperative day, T4:3rd postoperative day, T5:5th postoperative day, T6:7th postoperative day, T7:10th postoperative day. Also, the monitors included the heart rate, mean arterial blood pressure, arterial oxygen saturation, end-tidal $PaCO_{2,}$ end-tidal concentration of desflurane and sevoflurane, emergence and extubation time, the total dose of fentanyl, atracurium, ephedrine and atropine, duration of surgery and anesthesia, intraoperative fluids, blood loss, postoperative hematocrit values, and the renal functions tests.

The primary outcome was the hepatic protective effect as assessed by the decreased postoperative level of liver enzymes. Secondary outcomes were the safety of the study medications, as assessed by the incidence of adverse events such as arrhythmia, hypotension, hypertension, emergence cough, emergence agitation, postoperative nausea and vomiting.

Power analysis was performed using the Chi-square test for independent samples on the frequency of patients associated with decreased postoperative liver enzymes because it was the main outcome variable in this study. A pilot study was done before starting this study because there is no available data in the literature for the comparison of the hepatic protective effect in patients with impaired liver functions undergoing laparoscopic cholecystectomy. The results of the pilot study showed that the postoperative liver enzymes level decreased in 40% with desflurane and 20% with sevoflurane. Taking power 0.8, α error 0.05, β 0.2, and power 0.8, a minimum sample size of 81 patients was calculated for each group.

Data were statistically described in terms of mean ± standard deviation, frequencies, and percentages when appropriate. A comparison of numerical variables between the study groups was done using the Student's *t* test for independent samples. Repeated measure analysis of variance (ANOVA) was used to compare the liver function tests at different follow-up intervals. For comparing categorical data, Chi-square test was performed. An exact test was used instead when the expected frequency is less than 5. A value of $P < 0.05$ was considered statistically significant. All statistical calculations were done using Statistical Package for the Social Sciences (SPSS) software program, version 15.0 for Microsoft Windows (SPSS, Chicago, Illinois).

RESULTS

Figure 1 shows the CONSORT diagram for the flow of participants through each stage of this study. All patients in each group have been completed the study and included in the analysis of this study.

Table 1 shows no significant difference regarding the demographic data, comorbidities, preoperative

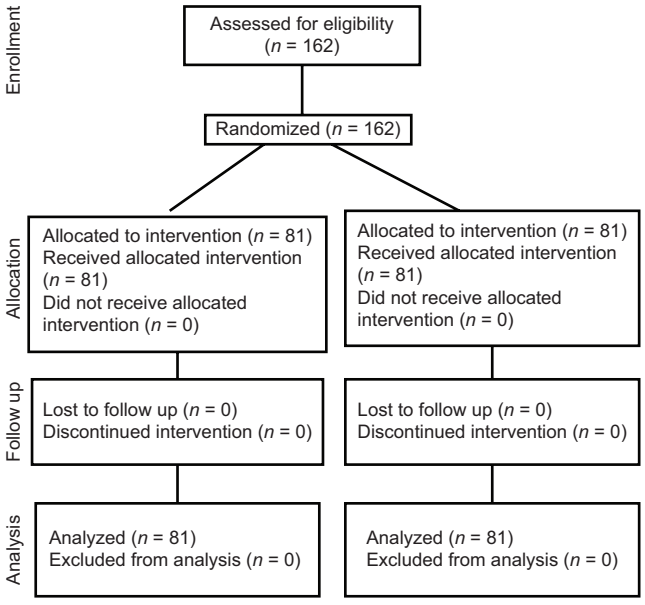

Figure 1: CONSORT diagram for the flow of participants through each stage of this study

Table 1: Preoperative data of patients

Variable	Desflurane group (*n*=81)	Sevoflurane group (*n*=81)	*P*
Age (year)	44.15±15.24	43.66±13.90	0.831
Weight (kg)	88.30±18.65	86.47±19.10	0.538
Gender			
Male:female	38:43	36:45	0.8747
Diabetes mellitus	31 (38.27%)	26 (32.09%)	0.510
Hypertension	24 (29.62%)	28 (34.56%)	0.613
ASA grade			
Grade I:II	55: 26	57: 24	0.865
Anti-diabetic medications			
Oral hypoglycemic drugs	25	19	0.377
Insulin	6	7	0.953
Antihypertensive drugs			
Calcium channel blockers	15	19	0.563
blockers	5	3	0.7196
ACEI	4	6	0.746
Hematocrit (%)	39.40±2.57	38.90±2.49	0.210

ASA – American Society of Anesthesiologists Physical Status Score, ACEI – Angiotensin-converting-enzyme inhibitor. Data are presented as mean±SD, number, %

medications, ASA physical status score, and the hematocrit values ($P > 0.05$).

Table 2 shows the changes in the liver function tests of patients. The preoperative levels of liver enzymes and bilirubin were higher than the normal range in the patients of the two groups, but the difference was insignificant between the two groups ($P > 0.05$). Postoperatively, there were changes in the liver enzymes and bilirubin in the two groups. There was a decrease in the AST and ALT from day 1 to day 7 in patients of the two groups, but it decreased significantly in desflurane group more than sevoflurane group ($P < 0.05$) and the levels become within the normal range at day 10 with insignificant difference between the two groups ($P > 0.05$). There was a decrease in the ALP and GGT from day 1 to day 3 in patients of the two groups, and the decrease was more in the desflurane group than the sevoflurane group, but the difference between the two groups was insignificant ($P > 0.05$). The levels become within the normal range on day 4, and the difference between the two groups was insignificant ($P > 0.05$). There was a decrease in the total bilirubin level from day 1 to day 7 in patients of the two groups, and the decrease was more in the desflurane group than the sevoflurane group, but the difference between the two groups was insignificant ($P > 0.05$). The levels become within the normal range on day 10.

There were minimal and insignificant changes in the perioperative heart rate and mean arterial blood pressure and the difference between the two groups was insignificant ($P > 0.05$) [Table 3].

Table 4 shows the intraoperative data and the outcomes of patients of the two groups. There were no significant differences regarding the duration of surgery and anesthesia, intraoperative fluids and blood loss, temperature, end-tidal $PaCO_2$, the total dose of fentanyl and atracurium, postoperative hematocrit values and the renal functions tests ($P > 0.05$). The comparison of the end-tidal concentration of desflurane and sevoflurane was significant ($P = 0.001$). The required dose of ephedrine and atropine was lower with desflurane than the sevoflurane, but the difference was insignificant ($P = 0.531$ and 0.317, respectively). The incidence of hypotension and bradycardia was lower with desflurane than the sevoflurane, but the difference was insignificant ($P = 0.054$ and 0.077, respectively). The incidence of hypertension and tachycardia was higher in desflurane group than the sevoflurane group, but the difference was insignificant ($P = 0.191$ and 0.368, respectively). The emergence time (time from end of anesthesia to the time of opening the eyes spontaneously or the response to verbal commands) was shorter in the desflurane group than the sevoflurane group ($P = 0.019$). The extubation time (duration from the end of anesthesia until the patients become fully awake and removal of the endotracheal tube) was shorter with desflurane than the sevoflurane ($P = 0.023$). The incidence of emergence cough (coughing during emergence) was insignificant between the two groups ($P = 0.587$). The incidence of nausea and vomiting was significantly lower with desflurane than the sevoflurane ($P = 0.015$). The length of hospital stay was shorter with desflurane than the sevoflurane ($P = 0.011$). There was no incidence of emergence agitation, morbidity, or mortality in patients of the two groups.

DISCUSSION

This study showed that the desflurane has a hepatic protective effect in patients with elevated preoperative liver functions and undergoing laparoscopic cholecystectomy as assessed by the changes in levels of the liver enzymes, especially the AST and ALT that decreased significantly through the first three postoperative days, whereas in patients of sevoflurane group, there were minimal changes in liver enzymes that also increased significantly in some patients. This means that the sevoflurane has no hepatic protective effect in patients undergoing laparoscopic

Table 2: Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and total bilirubin

Variable	Desflurane group (*n*=81)	Sevoflurane group (*n*=81)	*P*
Aspartate aminotransferase (U/L)			
T0	257.43±89.14	248.12±85.37	0.498
T1	164.15±30.70	201.92±41.37	0.001*
T2	103.54±19.40	159.11±29.80	0.001*
T3	72.34±10.25	111.56±17.59	0.001*
T4	55.20±8.04	79.40±11.38	0.001*
T5	32.70±7.25	45.20±9.34	0.001*
T6	25.70±5.40	29.38±7.50	0.001*
T7	23.90±4.51	25.11±5.50	0.127
Alanine aminotransferase (U/L)			
T0	235.22±66.45	227.63±58.70	0.442
T1	180.35±44.80	198.56±56.68	0.024*
T2	157.43±33.72	170.18±42.08	0.034*
T3	129.10±22.60	140.32±37.70	0.020*
T4	98.99±10.43	107.39±21.30	0.002*
T5	67.15±9.90	80.25±13.40	0.006*
T6	44.52±7.18	52.76±10.03	0.001*
T7	26.26±6.30	28.10±8.70	0.125
Alkaline phosphatase (U/L)			
T0	182.65±16.73	179.15±15.36	0.167
T1	172.90±10.43	175.27±12.50	0.192
T2	162.80±8.50	164.45±9.30	0.082
T3	152.40±7.10	153.28±7.34	0.439
T4	143.50±6.28	145.10±5.05	0.075
T5	134.95±4.85	136.40±5.90	0.089
T6	124.70±4.14	125.86±±4.60	0.093
T7	121.80±4.90	122.63±5.60	0.317
Gamma-glutamyltransferase (U/L)			
T0	82.54±7.13	81.59±6.80	0.386
T1	75.30±6.50	75.40±6.13	0.919
T2	68.90±5.20	70.12±5.70	0.156
T3	63.96±4.90	65.19±5.10	0.119
T4	58.80±4.47	60.13±5.23	0.083
T5	52.40±4.52	53.25±4.75	0.245
T6	50.21±5.47	51.29±5.63	0.217
T7	47.80±4.60	48.11±5.52	0.698
Bilirubin (μmol/L)			
T0	42.18±6.40	43.46±7.30	0.237
T1	38.24±6.38	40.04±6.55	0.078
T2	35.77±5.90	37.20±6.10	0.131
T3	31.20±7.50	33.04±6.36	0.094
T4	28.80±7.41	30.14±7.11	0.155
T5	23.96±6.30	26.01±7.92	0.069
T6	21.60±6.19	23.20±7.16	0.130
T7	16.84±5.33	18.53±6.40	0.165

*P<0.05 significant comparison between the two groups. T0 – at the preoperative period, T1 – Directly after surgery, T2 – 1st postoperative day, T3 – 2nd postoperative day, T4 – 3rd postoperative day, T5 – 5th postoperative day, T6 – 7th postoperative day, T7 – 10th postoperative day

cholecystectomy. The findings in this study show that desflurane minimized the damage of the liver during laparoscopic cholecystectomy and also provided hepatic protection for the patients with preoperative elevated liver functions better than sevoflurane.

Desflurane showed better hepatic protection than sevoflurane and this may be supported by many factors: (1) the ability of desflurane to preserve the hepatic blood flow and cardiac output better than the sevoflurane[8,11]; (2) the desflurane has a lower degree of metabolism (0.02%) than sevoflurane (1%–5%), this means the sevoflurane metabolism is approximately 100 times greater than desflurane metabolism in humans[12]; (3) sevoflurane metabolism produces an extra metabolite, compound A through a chemical

Table 3: Heart rate and mean arterial blood pressure

Variable	Desflurane group (*n*=81)	Sevoflurane group (*n*=81)	*P*
Heart rate (bpm)			
T0	79.53±12.15	77.34±10.28	0.217
T1	77.93±11.11	76.65±10.31	0.448
T2	78.63±9.82	76.46±9.35	0.151
T3	79.10±10.38	78.55±11.05	0.744
T4	76.38±11.86	75.32±9.53	0.531
T5	78.02±8.80	76.89±10.35	0.455
T6	77.27±9.18	79.46±10.65	0.162
T7	76.42±10.33	77.74±12.09	0.456
Mean arterial blood pressure (mmHg)			
T0	103.17±15.87	104.75±16.35	0.533
T1	105.06±13.79	106.15±14.63	0.6263
T2	104.61±14.84	107.04±15.33	0.306
T3	107.36±13.44	105.61±14.09	0.419
T4	103.80±12.75	106.00±13.23	0.282
T5	105.58±11.66	104.11±10.99	0.410
T6	106.00±12.54	105.20±11.43	0.671
T7	104.65±10.37	106.35±12.73	0.352

T0 – At the preoperative period, T1 – Directly after surgery, T2 – 1st postoperative day, T3 – 2nd postoperative day, T4 – 3rd postoperative day, T5 – 5th postoperative day, T6 – 7th postoperative day, T7 – 10th postoperative day. Data are presented as mean±SD

reaction with CO2 absorbents[13] and several studies have suggested that compound A has a hepatotoxic effect as shown by a transient increase in postoperative liver function tests[14,15]; (4) the desflurane is stable and resists degradation by standard carbon dioxide absorbents more than sevoflurane[16] and undergo minimal metabolism by the liver[17]; (5) many studies showed that hemodynamic stability during anesthesia was significantly better with desflurane than sevoflurane[18-20]; (6) the desflurane is rapidly excreted from the body.[8] These unique properties of desflurane lead to a better postoperative hepatic function.

Yontem *et al*.[17] reported that desflurane is less metabolized than sevoflurane, and desflurane is preferred for the patients with liver disorders and the same results were shown by other studies.[8,21,22] Chudasama *et al*.[18] concluded that desflurane provided better hemodynamic stability during the postoperative period compared to sevoflurane. Ko *et al*.[23] found that postoperative hepatic function tests were better with desflurane than the sevoflurane in living donors

Table 4: Intraoperative data and outcome of patients

Variable	Desflurane group (*n*=81)	Sevoflurane group (*n*=81)	*P*
Duration of procedure (min)	49.27±5.75	47.94±4.80	0.112
Duration of anesthesia (min)	60.30±13.40	66.59±17.84	0.012*
Temperature (°C)	36.30±0.50	36.20±0.48	0.196
End-tidal CO_2 (mmHg)	35.86±2.28	36.17±2.40	0.400
Total fentanyl dose (μg)	136.25±27.80	130.90±23.63	0.188
Total atracurium dose (mg)	57.35±12.80	54.79±10.75	0.170
End-tidal concentration (%)	5.32±0.31	2.42±0.24	0.001*
Ephedrine			
Number of patients	9 (11.11%)	17 (20.98%)	0.054
Dose (mg)	6.85±2.57	7.15±3.45	0.531
Atropine			
Number of patients	5 (6.7%)	13 (16.04%)	0.077
Dose (mg)	0.58±0.18	0.61±0.20	0.317
Hypotension (SAP ≤20% below baseline)	9 (11.11%)	17 (20.98%)	0.054
Hypertension (SAP ≥20% above baseline)	16 (19.95%)	9 (11.11%)	0.191
Bradycardia (HR <60 bpm)	5 (6.7%)	13 (16.04%)	0.077
Tachycardia (HR >100 bpm)	14 (17.28%)	9 (11.11%)	0.368
Emergence cough	9 (11.11%)	6 (7.40%)	0.587
Emergence time (min)	10.53±4.62	12.48±5.84	0.019*
Extubation time (min)	7.87±3.37	9.18±3.90	0.023*
Emergence agitation	-	-	
Incidence of nausea and vomiting	23 (28.39%)	39 (48.14%)	0.015*
Intraoperative fluids [only crystalloids] (mL)	1873.30±314.80	1840.90±324.10	0.519
Intraoperative blood loss (mL)	73.15±10.54	70.75±9.71	0.133
Hematocrit (%)	35.54±2.15	36.00±2.23	0.183
Renal functions tests			
Serum creatinine (mg/dL)	1.12±0.3	1.17±0.21	0.220
Blood urea nitrogen (mg/dL)	7.98±2.43	8.10±2.31	0.747
Hospital length of stay (days)	4.60±1.15	5.05±±1.10	0.011*
Postoperative morbidity or mortality	-	-	

*P<0.05 significant comparison between the two groups. SAP – Systolic arterial blood pressure, HR – Heart rate. Data are presented as mean±SD, number, %

undergoing right hepatectomy at an equivalent dose of one MAC and there was a higher degree of liver damage after anesthesia in patients with sevoflurane than with desflurane. Abou Hussein *et al*.[7] reported that the hemodynamics was better with desflurane than sevoflurane in cirrhotic patients undergoing major liver resections. Kumari *et al*.[20] showed that desflurane is safe for the maintenance of hemodynamics in normotensive and hypertensive patients undergoing laparoscopic cholecystectomy.

Lin *et al*.[24] reported that sevoflurane was associated with a severe degree of liver damage than desflurane in prolonged surgery as shown by the elevated postoperative AST and ALT with sevoflurane than desflurane.

Contrary to the findings of this study, some studies showed that sevoflurane provided better hepatic protection than desflurane, as the sevoflurane increases significantly the blood levels of antioxidants (superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase) than desflurane,[25] in addition to the increased levels of free oxygen radicals with desflurane more than sevoflurane, especially the release of free oxygen radicals increases during laparoscopic surgery,[26,27] and other studies reported that sevoflurane is superior to other inhalational agents in patients with liver disease.[28,29] Some studies showed no difference between desflurane and sevoflurane regarding their effect on live enzymes.[30-32]

There are some limitations to this study, such as the study was not a blinded, small number of patients and there were no studies assessed the hepatic protective effect of desflurane and sevoflurane in patients with impaired liver functions undergoing laparoscopic cholecystectomy to compare the results of this study.

CONCLUSION

The desflurane is a safe inhalational volatile for maintenance of anesthesia in patients with impaired liver function undergoing laparoscopic cholecystectomy. It was associated with a decrease in the liver enzymes more than the sevoflurane.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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