

ORIGINAL RESEARCH

Medicine Science 2019;8(1):180-5

The effects of different agents preferred for general anesthesia on lactate and liver enzymes in patients undergoing laparoscopic cholecystectomy

Mehmet Sargin¹, Ahmet Topal², Mehmet Selcuk Uluer³, Eray Yasar², Seref Otelcioglu²

¹ Selcuk University Medical Faculty, Department of Anesthesiology and Reanimation Konya, Turkey

² Necmettin Erbakan University, Meram Medical Faculty, Department of Anesthesiology and Reanimation, Konya, Turkey

³ Konya Training and Research Hospital, Department of Anesthesiology and Reanimation, Konya, Turkey

Received 05 December 2018; Accepted 14 December 2018

Available online 26.12.2018 with doi:10.5455/medscience.2018.07.8949

Copyright © 2019 by authors and Medicine Science Publishing Inc.

Abstract

In this study, we aimed to evaluate the effects of different agents used for anesthesia maintenance on liver enzymes and lactate changes in patients undergoing laparoscopic cholecystectomy using CO₂ pneumoperitoneum with constant pressure. Seventy-five patients planned to undergo laparoscopic cholecystectomy operation have been randomly divided into 3 groups. Liver function tests have been evaluated preoperatively and postoperatively in the 24th hour. Arterial blood samples for lactate level determination were obtained: (T₁) immediately before pneumoperitoneum, (T₂) 10 min after pneumoperitoneum, (T₃) 30 min after pneumoperitoneum, (T₄) 60 min after desufflation of CO₂. Patients scheduled to undergo laparoscopic cholecystectomy operation. The possible effects of different agents used for anesthesia maintenance on liver enzymes and lactate changes in patients undergoing laparoscopic cholecystectomy. In comparison of lactate values, there were no differences between the three groups in T₁, T₂ and T₄ measurements ($P=0.059$, $P=0.108$, $P=0.225$). However, in the T₃ measurements, lactate values are lower in the Group P, compared to Group S and D ($P=0.001$, $P=0.001$). Postoperative AST and ALT values are lower in the Group P, compared to Group S and D ($P<0.001$, $P<0.001$) and postoperative ALP and LDH values are lower in the Group D and Group P, compared to Group S ($P=0.001$, $P<0.001$). There were no differences between the three groups in postoperative GGT values ($P=0.056$). It was concluded that propofol had a positive effect on postoperative AST and ALT values, and preoperative lactate changes in comparison to sevoflurane and desflurane.

Keywords: Sevoflurane, desflurane, propofol, lactate, liver enzymes

Introduction

With introduction of laparoscopy in surgery, laparoscopic cholecystectomy (LC) has been adopted as golden standard in surgical treatment of cholelithiasis and gall bladder diseases [1]. Carbon dioxide (CO₂) pneumoperitoneum (PP) is used in revealing adequate imaging and surgical site in laparoscopy. Laparoscopic cholecystectomy has several advantages such as short durations of hospital stay, minimal postoperative pain, fast-track recovery, and better cosmetic results [2].

However, PP is related to some adverse effects including cardiovascular, respiratory, renal and acid base balance [3-5].

While some of these adverse effects are related to acidemia and hypercapnia following the absorption of CO₂ through peritoneal cavity, others are direct results of increased intraabdominal pressure (IAP) due to continuous gas insufflation [4,5].

One of the important haemodynamic changes is the transient reduction in hepatic blood flow, which is caused by PP [6-9]. Experimental and clinical studies have shown a reduction in gastric, hepatic, peritoneal and splanchnic blood flow due to increased intraabdominal pressure [10,11]. The pressure and duration of the PP have been shown to affect the degree of hepatic ischemia and therefore cause elevation of liver enzymes [7,12,13]. The effect of different PP pressures on liver enzyme changes has been evaluated and there are not enough studies evaluating the effects of agents used in anesthesia maintenance.

In this study, we aimed to evaluate the effects of different agents

*Corresponding Author: Mehmet Sargin, Selcuk University Medical Faculty, Department of Anesthesiology and Reanimation Konya, Turkey,
E-mail: mehmet21sargin@yahoo.com

used for anesthesia maintenance on liver enzymes and lactate changes in patients undergoing LC using CO₂ PP with constant pressure (12 mmHg).

Material and Methods

Institutional ethics committee approval and written consent from patients were obtained for this prospective, randomized study. Seventy-five patients between the ages of 18-65 yr, ASA (American Society of Anesthesiologists) physical status I and II, scheduled to undergo routine LC under general anesthesia, were studied. Patients with morbid obesity (body mass index > 35 kg/m²), high levels of enzymes before operation, positive serology for hepatitis B or C viruses, cerebrovascular, respiratory, cardiovascular and metabolic disease were excluded from the present study. And also patients with acute cholecystectomy were excluded from the present study.

The patients were randomized, by using a computer-generated block randomisation, into 3 groups: Group S (n:25) = Sevoflurane, Group D (n:25) = Desflurane, Group P (n:25) = Propofol (Fig.1). Routine monitors (consisting of a pulse oximeter, 3-lead ECG and a non-invasive blood pressure cuff) were applied.

Fasting periods were in accordance with ASA guidelines, and no one premedicated. Anesthesia was induced with propofol (2 mg/kg) and remifentanyl (1 µg/kg), and endotracheal intubation was facilitated using atracurium. After induction, volume-controlled mechanical ventilation (tidal volume adjusted to 8 mL/kg with no application of positive end-expiratory pressure (PEEP) and respiratory rates were adjusted to achieve an end-tidal carbon dioxide (ETCO₂) of 30 to 35 mmHg) was initiated. All patients were ventilated with the same anesthetic machine (Dräger Primus - Germany). Anaesthesia was maintained using sevoflurane 1-2% in an oxygen / air mixture and remifentanyl (0.25 µg/kg/min) in Group S, desflurane 3-6% in an oxygen / air mixture and remifentanyl (0.25 µg/kg/min) in Group D and propofol 6-12 mg/kg/h and remifentanyl (0.25 µg/kg/min) in Group P to maintain systolic blood pressure within 80% to 100% of the baseline value.

The CO₂ PP was introduced with a closed Veress needle technique, and the intraabdominal insufflation pressure was limited to 10-12 mmHg. After introduction of the four trocars and insufflation of CO₂, the patient was placed in the reverse Trendelenburg position, using up to 30° of head-up tilt.

Heart rate (HR), mean blood pressure (MBP) and oxygen saturation (SpO₂) values were continuously recorded from awake status to post-anesthesia care unit (PACU) discharge [baseline (t₀), immediately after induction (t₁), 2 min after intubation (t₂), immediately after pneumoperitoneum (t₃), every 10 minutes during pneumoperitoneum (t₄₋₆), immediately after desufflation of CO₂ (t₇), immediately after extubation (t₈), arrival in the PACU (t₉) and PACU discharge (t₁₀)].

No other medication was administered to the patients prior or after the operation except for i.v. antibiotics and tramadol for postoperative pain control. Saline and dextrose solutions were given to all patients for the first 24 hours. Blood samples were taken from a superficial vein in the antecubital region of each patient before the operation as a part of routine preoperative

preparation and 20-24 hours after the operation for comparison of the liver enzyme [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and gamma-glutamyltransferase (GGT)] level alterations.

Arterial blood samples for lactate level determination were obtained from radial artery cannula: (T₁) immediately before pneumoperitoneum, (T₂) 10 min after pneumoperitoneum, (T₃) 30 min after pneumoperitoneum, (T₄) 60 min after desufflation of CO₂.

Statistical analysis

Sample size calculation was based on our prior study with 18 patients (also their data were not included in the study). The primary outcome variable was the value of lactate levels 30 min after pneumoperitoneum. When a mean and standard deviation (SD) of the lactate values (30 min after pneumoperitoneum) between groups lactate values were taken to be 1.15 (0.19), 1.43 (0.21) and 0.88 (0.13) as was determined based on a preliminary study in 18 patients, 18 subjects were required for an α value of 0.05 and a power of 95%. Thus, 25 subjects were included to cope with an expected loss.

Statistical analyses were performed with SPSS 15.0 software (SPSS Institute, Chicago, IL, USA). Normal distributions of data were assessed using the Kolmogorov-Smirnov test. Demographic data were compared between the groups by using an One-Way ANOVA test. Lactate and liver enzyme values and hemodynamic changes between time points within the group were compared by using univariate ANOVA with post hoc comparisons using Bonferroni correction. A P-value <0.05 was considered statistically significant.

Results

A total of 75 patients were enrolled in the study and all patients completed the investigation. Figure 1 shows the CONSORT flow chart detailing patient recruitment. Data analysis was performed on the three groups. No patient was withdrawn from the study after induction of anesthesia.

Patients demographic data are summarised in Table 1 and there were no significant differences between the three groups regarding age, gender, weight, height, body mass index (BMI), ASA physical status and operation time (P=0.212, P=0.846, P=0.935, P=0.945, P=0.924, P=0.820, P=0.919, respectively).

Changes in HR and MBP is seen in figure 2. The measurements of hemodynamic parameters (HR and MBP) were statistically similar between three groups in all measurement timepoints [baseline (t₀), immediately after induction (t₁), 2 min after intubation (t₂), immediately after pneumoperitoneum (t₃), every 10 minutes during pneumoperitoneum (t₄₋₆), immediately after desufflation of CO₂ (t₇), immediately after extubation (t₈), arrival in the PACU (t₉) and PACU discharge (t₁₀)] (P=0.150, P=0.474, P=0.465, P=0.616, P=0.482, P=0.881, P=0.929, P=0.528, P=0.165, P=0.612, P=0.883, and P=0.888, P=0.496, P=0.687, P=0.652, P=0.762, P=0.526, P=0.714, P=0.644, P=0.911, P=0.742, P=0.635, respectively).

Comparison of lactate values between the groups are summarised in **Table 2** and there were no significant differences between the three groups in T₁, T₂ and T₄ measurement timepoints (P=0.059, P=0.108, P=0.225, respectively). However, in the T₃

measurement timepoint, lactate values are significantly lower in the Group P, compared to Group S and D (P=0.001, P=0.001, respectively).

Table 1. Comparison of patients' baseline characteristics between the groups

Patients' baseline characteristics	Group S (n=25)	Group D (n=25)	Group P (n=25)	p
Age; years	47.74 (11.15)	43.12 (13.22)	49.56 (14.77)	0.212
Gender (M/F)	10 (40%) / 15 (60%)	11 (44%) / 14 (56%)	9 (36%) / 16 (64%)	0.846
ASA (I / II)	18 (72%) / 7 (28%)	19 (76%) / 6 (24%)	17 (68%) / 8 (32%)	0.820
Height; cm	161.76 (9.26)	160.56 (10.80)	162.60 (6.57)	0.945
Weight; kg	75.08 (9.64)	76.32 (12.37)	75.80 (13.72)	0.935
BMI (kg/m ²)	28.79 (3.94)	28.32 (4.29)	28.68 (4.93)	0.924
Operation time; min	47.64 (4.34)	46.05 (4.62)	47.16 (4.74)	0.814

Values are mean (SD) or number (proportion)

Table 2. Comparison of lactate values between the groups.

Measurement timepoints	Group S (n=25)	Group D (n=25)	Group P (n=25)	p
Lactate; mmol/L				
T ₁	0.87 (0.17)	0.90 (0.25)	1.02 (0.26)	0.059
T ₂	1.17 (0.31)	1.15 (0.31)	1.01 (0.27)	0.108
T ₃	1.30 (0.32)	1.33 (0.26)	1.04 (0.32) * #	0.001
T ₄	1.38 (0.40)	1.06 (0.24)	0.99 (0.28)	0.225

Values are mean (SD).

T₁; immediately before pneumoperitoneum, T₂; 10 min after pneumoperitoneum, T₃; 30 min after pneumoperitoneum, T₄; 60 min after desufflation of CO₂.

* compared to Group S, p=0.001

compared to Group D, p=0.001

Table 3. Comparison of liver enzyme values between the groups

IU/L	Group S (n=25)	Group D (n=25)	Group P (n=25)	p
AST; preoperative	24.88 (9.33)	20.60 (5.11)	21.12 (3.53)	0.057
AST; postoperative	49.36 (22.49)	42.96 (13.12)	26.76 (5.25) * #	<0.001
ALT; preoperative	28.12 (15.66)	21.04 (7.60)	23.48 (5.88)	0.063
ALT; postoperative	55.00 (32.12)	41.60 (14.04)	27.28 (6.79) * #	<0.001
ALP; preoperative	80.01 (33.00)	67.40 (34.96)	64.64 (7.15)	0.122
ALP; postoperative	97.40 (52.45)	69.36 (30.39) *	66.32 (6.56) *	0.001
GGT; preoperative	24.76 (17.55)	19.84 (18.99)	20.64 (8.59)	0.498
GGT; postoperative	39.40 (27.87)	30.00 (28.84)	22.96 (9.69)	0.056
LDH; preoperative	113.36 (26.61)	96.36 (50.27)	122.40 (56.65)	0.138
LDH; postoperative	228.68 (62.28)	147.72 (60.55) *	145.52 (61.87) *	<0.001

Values are mean (SD).

* compared to Group S, p<0.001

compared to Group D, p=0.001

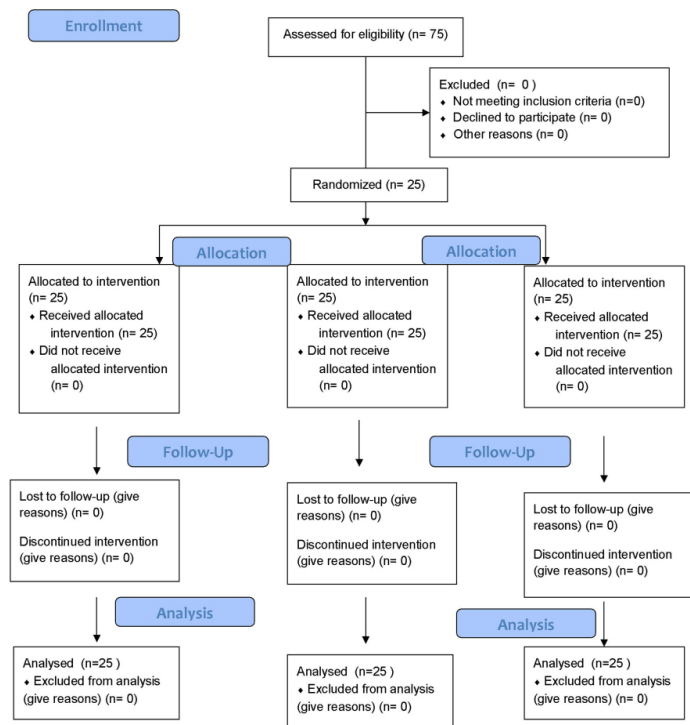


Figure 1. CONSORT flowchart detailing patient recruitment

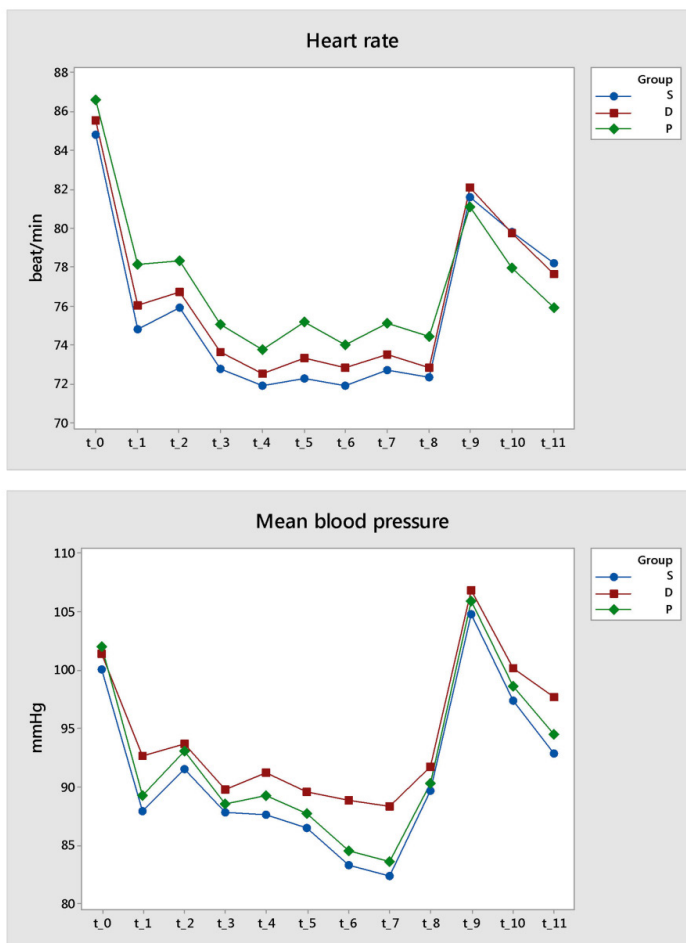


Figure 2. Changes in heart rate and mean blood pressure

Comparison of liver enzyme (AST, ALT, ALP, GGT and LDH) values between the groups are summarised in Table 3 and there were

no significant differences between the three groups in preoperative measurements ($P=0.057$, $P=0.063$, $P=0.122$, $P=0.498$, $P=0.138$ respectively). However, postoperative AST and ALT values are significant lower in the Group P, compared to Group S and D ($P<0.001$, $P<0.001$, respectively) and postoperative ALP and LDH values are significant lower in the Group D and Group P, compared to Group S ($P=0.001$, $P<0.001$, respectively). There were no significant differences between the three groups in postoperative GGT values ($P=0.056$).

Discussion

The results of this study have shown that propofol maintained anesthesia provides lower lactate and liver enzyme values than sevoflurane and desflurane maintained anesthesia in patients undergoing LC.

Laparoscopy is a well-established method, used in several surgical procedures, and often performed in the Trendelenburg position. To facilitate laparoscopic surgical manipulation, a PP is usually induced through carbon dioxide insufflation. Today, the increase in liver enzymes such as AST, ALT after non-complicated LC has become a well-known finding [14]. Factors such as; increased intraperitoneal pressure, cauterization used to provide hemostasis during LC, manipulation of external bile ducts and general anesthesia have been shown as possible causes of the increase in liver enzymes [15]. However, the most widely accepted reason among these causes is transient hepatic ischemia, which is caused by increased intraperitoneal pressure. Various studies have reported that, portal venous pressure, which provides about half of the hepatic blood flow, is between 7-10 mmHg and PP at 14 mmHg pressure is the main cause of transient hepatic ischemia during LC [6,12,16-17]. In addition, PP pressures below 12-15 mmHg have been shown to reduce normal hepatic blood flow and induce hepatic ischemia at different degrees [18].

However, whichever of these reasons is valid, the effect of the preferred anesthetic agents in the maintenance of general anesthesia to liver enzyme changes after LC has not been evaluated before.

In a study in which sevoflurane was preferred in anesthesia maintenance and the change in AST, ALT, ALP, GGT and LDH values at 24 h after LC was assessed, higher rates of AST, ALT changes are shown, compared to Group S in our study [14]. The change in GGT values of this study is similar to the values in our study, but the ALP results are not consistent with our results.

Hasukic et al evaluated the changes in liver enzymes after LC and 14 mmHg PP pressure was used in their studies and they preferred propofol in anesthesia maintenance [9]. Similar to present study, they have evaluated AST, ALT, ALP, GGT and LDH values preoperatively and postoperatively at 24 hours. However, in this study, increases of AST and ALT by more than twice were shown, compared to Group P in our study. In addition, the operation times in this study are quite long from the operation times of our study.

Studies of Tan et al., evaluating AST and ALT changes on postoperative 1st day after LC, showed an increase in AST and ALT values, similar to the results in Group S and D in our study [16]. In addition, similar PP pressures were used in this study. However, no information was provided about the induction and maintenance of

anesthesia in this study.

In another study that did not mention the preferred agents for anesthesia induction and maintenance, it was shown that the increase in AST and ALT 24 hours after LC, was higher than the increase in Group S and D in our study. But there was no increase in the ALP values different from our study [19]. Pneumoperitoneum pressures were preferred in this study, similar to our study. However, unlike our study, longer surgery durations were noted.

Unlike the results of many studies evaluating the alteration of liver enzymes after LC, Bickel et al. have shown that there is no significant change in AST, ALT, ALP, GGT and LDH after LC [20]. However, in this study, there is no information about which agents are preferred in the induction and maintenance of anesthesia.

Ibraheim et al. evaluated the change in lactate levels during LC and sevoflurane was preferred for anesthesia maintenance [21]. In this study, lactate values were evaluated similar to the measurement times in our study. The increase in lactate levels in the patient groups in which used the PP pressures similar to our study, was higher than in Group S in our study. However, the low number of patient populations in this study and differences in baseline values may be considered probable causes for this difference.

In another study evaluating the change in lactate levels during and after LC, a 12 mmHg PP press was preferred, similar to our study [22]. Intraoperative lactate measurement times were similar to the measurement times in our study, and unlike our study results, there was no increase in lactate levels during LC. In this study, preferred anesthetic agents for induction and maintenance of anesthesia were not mentioned.

Despite all these studies, it is clear that the role of anesthetic agents in assessing liver enzyme changes and intraoperative lactate levels after LC has not been adequately assessed. Given the fact that the most important cause of transient ischemia of liver during LC is a decrease in hepatic blood flow, the use of agents used in anesthesia maintenance is more evident. Because, in various clinical and experimental studies, propofol was clearly shown to increase hepatic blood flow [23,24]. Meierhenrich et al evaluated the effect of propofol and desflurane anesthesia on human hepatic blood flow [23]. In this study it has been shown that propofol was associated with significantly greater blood flow index in the right hepatic vein and middle hepatic vein compared with desflurane and propofol anesthesia was associated with significantly greater hepatic blood flow than desflurane anesthesia.

In an experimental study of Zhu et al, has been shown that propofol increases total hepatic blood flow, primarily by increasing hepatic portal venous flow [24].

In our study, we evaluated the effects of sevoflurane, desflurane and propofol on the liver enzymes after LC and intraoperative lactate levels. In patients who prefer propofol in anesthesia maintenance, lower increases in liver enzymes and lactate changes are shown relative to the patient in whom sevoflurane and desflurane are preferred. This is because we believe that the increase in the hepatic blood flow caused by propofol.

The present study included some limitations. Bispectral index

(BIS) monitoring was not performed, and this is one of the limitations. Other parameters used to evaluate liver function such as bilirubin were not evaluated.

Conclusion

In conclusion, propofol, compared with sevoflurane and desflurane, was found to cause less change in liver enzymes and lactate levels in LC operation. These changes under sevoflurane and desflurane anesthesia do not affect the perioperative and postoperative morbidity and mortality in the patient population in which there is a low clinical significance and no serious comorbid pathologies, but we believe that these changes can cause significant consequences in critical patients.

In conclusion, our study results suggest no relationship between the NLR and PLR and PDPH in the preoperative and early postoperative period in patients who undergoing cesarean section. However, further large-scale studies are required to establish a definite conclusion.

Competing interests

The authors declare that they have no competing interest

Financial Disclosure

The financial support for this study was provided by the investigators themselves.

Ethical approval

Institutional ethics committee approval was obtained (Necmettin Erbakan University, Meram Medical Faculty Ethics Committee , 2013/82).

Mehmet Sargin ORCID:0000-0002-6574-273X

Ahmet Topal ORCID:0000-0001-9832-9741

Mehmet Selcuk Uluer ORCID:0000-0002-5699-8688

Eray Yasar ORCID:0000-0003-1466-8194

Seref Otelcioglu ORCID:0000-0002-4352-5064

References

1. Himal HS. Minimally invasive (laparoscopic) surgery. Surg Endosc. 2002;8:265-70.
2. Lal P, Agarwal PN, Malik VK, et al. A difficult laparoscopic cholecystectomy that requires conversion to open procedure can be predicted by preoperative ultrasonography. JSLS. 2002;6:59-63.
3. Meftahuzzaman SM, Islam MM, Chowdhury KK, et al. Haemodynamic and end tidal CO2 changes during laparoscopic cholecystectomy under general anaesthesia. Mymensingh Med J. 2013; 22:473-477.
4. Alijani A, Hanna GB, Cuschieri A. Abdominal wall lift versus positive-pressure capnoperitoneum for laparoscopic cholecystectomy - Randomized controlled trial. Ann Surg. 2004;239:388-94.
5. Henny CP, Hofland J. Laparoscopic surgery: pitfalls due to anesthesia, positioning, and pneumoperitoneum. Surg. Endosc. 2005;19:1163-71.
6. Saber AA, Laraja RD, Nalbandian HI, et al. Changes in liver function tests after laparoscopic cholecystectomy: not so rare, not always ominous. Am Surg. 2000;66:699-702.
7. Morino M, Giraudo G, Festa V. Alterations in hepatic function during laparoscopic surgery. An experimental clinical study. Surg Endosc. 1998;12:968-72.
8. Sakorafas G, Anagnostopoulos G, Stafyla V, et al. Elevation of serum liver enzymes after laparoscopic cholecystectomy. N Z Med J. 2005;118:U1317.
9. Hasukic S, Kosuta D, Muminhodzic K. Comparison of postoperative hepatic function between laparoscopic and open cholecystectomy. Med Princ Pract. 2005;14:147-50.

10. Schilling MK, Redaelli C, Krähenbühl L, et al. Splanchnic microcirculatory changes during CO₂ laparoscopy. *J Am Coll Surg*. 1997;184:378-82.
11. Diebel L, Wilson R, Dulchavsky S, et al. Effect of increased intra-abdominal pressure on hepatic arterial, portal venous and hepatic microcirculatory blood flow. *J Trauma*. 1992;33:279-82.
12. Hasukic S. Postoperative changes in liver function tests: randomized comparison of low and high-pressure laparoscopic cholecystectomy. *Surg Endosc*. 2005;19:1451-5.
13. Giraudo G, Brachet Contul R, Caccetta M, et al. Gasless laparoscopy could avoid alterations in hepatic function. *Surg Endosc*. 2001;15:741-6.
14. Guven HE, Oral S. Liver enzyme alterations after laparoscopic cholecystectomy. *J Gastrointestin Liver Dis*. 2007;16:391-4.
15. Halevy A, Gold-Deutch R, Negri M, et al. Are elevated liver enzymes and bilirubin levels significant after laparoscopic cholecystectomy in the absence of bile duct injury? *Ann Surg*. 1994;219:362-4.
16. Tan M, Xu FF, Peng JS, et al. Changes in the level of serum liver enzymes after laparoscopic surgery. *World J Gastroenterol*. 2003;9:364-7.
17. Jakimowicz J, Stultiens G, Smulders F. Laparoscopic insufflation of the abdomen reduces portal venous flow. *Surg Endosc*. 1998;12:129-32.
18. Neudecker J, Sauerland S, Neugebauer E, et al. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. *Surg Endosc*. 2002;16:1121-243.
19. Singal R, Singal RP, Sandhu K, et al. Evaluation and comparison of postoperative levels of serum bilirubin, serum transaminases and alkaline phosphatase in laparoscopic cholecystectomy versus open cholecystectomy. *J Gastrointest Oncol*. 2015;6:479-86.
20. Bickel A, Weiar A, Eitan A. Evaluation of liver enzymes following elective laparoscopic cholecystectomy: are they really elevated? *J Gastrointest Surg*. 2008;12:1418-21.
21. Ibraheim OA, Samarkandi AH, Alshehry H, et al. Lactate and acid base changes during laparoscopic cholecystectomy. *Middle East J Anaesthesiol*. 2006;18:757-68.
22. Ortiz-Oshiro E, Mayol J, Aparicio Medrano JC, et al. Lactate metabolism during laparoscopic cholecystectomy: comparison between CO₂ pneumoperitoneum and abdominal wall retraction. *World J Surg*. 2001;25:980-4.
23. Meierhenrich R, Gauss A, Mühling B, et al. The effect of propofol and desflurane anaesthesia on human hepatic blood flow: a pilot study. *Anaesthesia*. 2010;65:1085-93.
24. Zhu T, Pang Q, McCluskey SA, et al. Effect of propofol on hepatic blood flow and oxygen balance in rabbits. *Can J Anaesth*. 2008;55:364-70.