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Comparison of the Effect of Anesthesia with Isoflurane and TIVA on Liver Enzymes and Coagulation Tests in Patients Undergoing Cholecystectomy

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ABSTRACT

Background and Objective: Anesthetic agents and type of surgery may lead to liver damage after surgery. Inhaled agents are associated with liver dysfunction after surgery. Propofol is expected to have a lower potential for postoperative liver damage. The present study was conducted to compare liver enzyme function after anesthesia with isoflurane and total intravenous anesthesia (TIVA).

Methods: This clinical trial was conducted on 70 patients referred to Imam Ali Hospital in Bojnord. Patients were selected using convenience sampling and then divided into TIVA and Isoflurane groups using block randomization method. During surgery, anesthesia was maintained in the isoflurane group with isoflurane gas (1.2 MAC) and in the TIVA group with infusion of propofol (100 micrograms/kg/minute) and remifentanil (0.1 micrograms/kg/minute). The levels of ALT, AST, ALP, PTT, and INR factors of the patients were examined and compared using laboratory devices before the operation, immediately, 24 and 48 hours after the operation.

Findings: There is no significant difference between the two groups in terms of demographic and interventional variables. ALT enzyme level in TIVA group increased from 17.6±10.7 to 21.2±14.2 and in isoflurane group from 16.7±9.4 to 28.4±16.1 ($p<0.05$). In other enzymes, this difference was not significant.

Conclusion: The results of the study showed that the use of both TIVA and Isoflurane methods has an effect on the level of liver enzymes in patients undergoing laparoscopic cholecystectomy surgery.

Keywords: *Inhalation Anesthetic, Isoflurane, Anesthesia, Propofol, Liver Enzyme*.

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Introduction

Liver function is affected by the type of anesthesia and their metabolites, as well as by surgical injury, sympathetic stimulation, reduced blood perfusion, underlying diseases, etc. (1). It is difficult to quantitatively measure the level of liver damage, and liver function tests, such as measuring the activity of aminotransferases and other specific enzymes, can evaluate liver damage (2). Regarding the type of anesthesia as a risk factor for liver damage, two types of TIVA anesthesia (TIVA= Total Intravenous Anesthesia) and inhalation anesthesia are used to maintain anesthesia in surgery (3).

As an inhalation anesthetic, isoflurane is a halogenated anesthetic, and some cases of liver toxicity following the use of this drug compared to previous generations have been reported (3-5). Hepatic blood flow decreases in a dose-dependent manner in all inhalation anesthetics, including isoflurane, which may lead to liver damage (4). In a study aimed at investigating changes in liver enzymes following isoflurane anesthesia, the results showed that isoflurane can increase within 24 to 48 days after surgery in patients (5).

TIVA with propofol is usually used as a balanced anesthesia. The use of continuous injection of propofol as a maintenance anesthetic is common and safe. The place of metabolism of this drug, which belongs to the family of alkylphenols, is the liver (6). It is a fat-soluble drug that reduces blood pressure and liver perfusion. One of its advantages is the rapid induction of anesthesia and the quick awakening of the patient after stopping its administration, as well as less incidence of nausea and vomiting after the operation (6, 7). Various studies have shown that in some cases, when continuous injection of propofol is used for long-term sedation, the patient suffers complications such as metabolic acidosis, fatty liver and hepatomegaly, rhabdomyolysis, and hyperlipidemia (5, 7).

Since different methods of anesthesia such as intravenous and inhalation have different effects on the activity of liver enzymes and cholecystectomy due to the nature of the operation and the laparoscopic surgery approach may cause some changes in the serum enzyme level due to manipulations in the liver area, the present study was conducted to compare the rate of changes in liver enzymes, which express the function of liver cells during anesthesia, using TIVA and isoflurane methods.

Methods

After being approved by the ethics committee of North Khorasan University of Medical Sciences with the code IR.NKUMS.REC.1395.14 and registered in the Iranian Registry of Clinical Trials with the code IRCT20200122046216N1, this double-blind randomized clinical trial was conducted on 70 patients aged 18 to 70 who were candidates for laparoscopic cholecystectomy in North Khorasan University of Medical Sciences in 2020. Patients aged between 18 and 70 years, class I and II ASA (American anesthesia classification), no history of surgery in the last 6 months, no liver disease and no alcohol use were included in the study. People who needed more drug therapy and cardiopulmonary resuscitation during surgery, inability to remove the tracheal tube at the end of surgery, bleeding during surgery and conversion of laparoscopic surgery to open cholecystectomy were excluded from the study.

Based on the pilot study and the formula for comparing the mean of two populations with a confidence level of 95% and a test power of 80% and with a 10% risk of sample drop, the number of samples was calculated to be 35 people in each group and a total of 70 people (Figure 1). At first, the patients were

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selected by non-probability sampling, and then randomized block design was used through the web system in www.randomlists.com in 7 blocks of 10: in each block, 5 people were in the first group (A), 5 people were in the second group (B). After the random sequence was determined in all blocks, cards with B and A letters were prepared to show which group each patient was assigned to, and by someone other than the research team, they were numbered from 1 to 70 in all blocks, and these cards were placed in non-transparent sealed envelopes. Then, in order to hide the random allocation, when the patient visited, the non-transparent sealed envelope was opened and then each sample was assigned to a group one by one. Patients were divided into TIVA and Isoflurane groups.

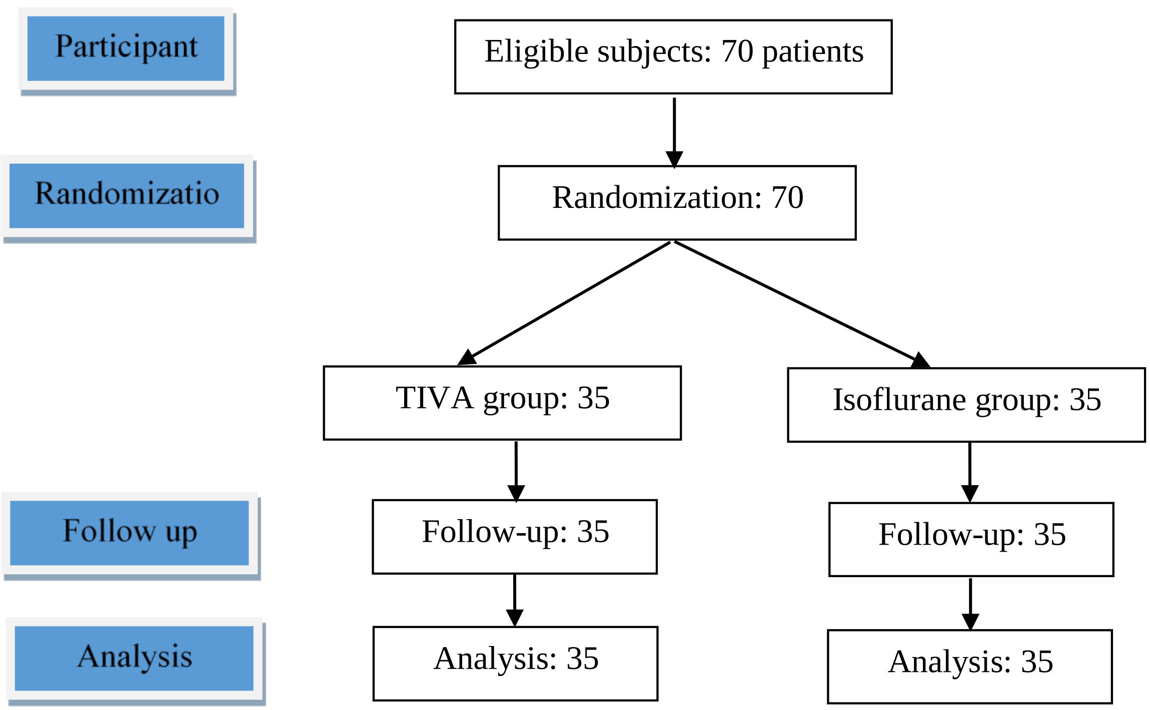

Figure 1. Flowchart of allocation process

After patients enter the operating room and establish the necessary monitoring and start fluid therapy with Ringer's solution, induction of anesthesia was done in all patients using fentanyl injection (1-2 µg/kg) and midazolam (2 mg) as a premedication for anesthesia as well as atracurium (0.5 mg) and propofol (2 mg/kg) drugs. After hyperventilating the patients with 100% oxygen for 3 minutes, the patients were intubated by an experienced anesthesiologist and connected to the anesthesia machine with a controlled mode. All patients received oxygen and N_2O in a ratio of 1:1 during anesthesia.

The intervention in the studied groups was carried out as follows: in the isoflurane group, to maintain anesthesia during surgery, the patients received isoflurane inhalation agent (Isoflurane 100 ml, Piramal Company, India) in an amount of 1.2 MAC by the anesthetic vaporizer (in this group, intravenous anesthetics were not used to maintain anesthesia) in addition to O_2 and N_2O.

In the TIVA group, in addition to O_2 and N_2O, patients received a continuous infusion of 100 micrograms/kg/minute propofol (propofol 10 mg/ml ampoule, Iran) along with 0.1 micrograms/kg/minute remifentanil (inhalation anesthetics were not used to maintain anesthesia in this group).

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Surgery was performed in all patients with a standard procedure by a skilled surgeon. At the end of the surgery, the patients' muscle relaxation was reversed with atropine and neostigmine drugs, the endotracheal tube was removed and the patients were transferred to recovery.

Measurement of the concentration of liver enzymes ALP, AST, ALT and coagulation tests PPT, INR were done in three stages: before administration of anesthetic drugs, immediately after the end of surgery, and 24 and 48 hours after the surgery by collecting venous blood samples and they were sent to the laboratory.

In order to collect data, a researcher-made checklist was used, which contained the demographic information of the patients, the duration of anesthesia and surgery, and the duration of fasting, and its content validity was confirmed. Furthermore, for the measurement of liver enzymes and coagulation tests, a standard laboratory device and liver enzyme testing kits (Paacdo company kits, Iran) and coagulation tests (Pacific Hemostasis kit, USA) were used. These devices are calibrated and their reliability was measured every morning by the calibration solution.

None of the participants in the study were aware of the randomization list, and in order to hide the randomization process, the name of groups was placed in sealed envelopes in the reception department and were assigned to the eligible people who entered the study. Therefore, the study was double-blind in a way that the patients and the specialist evaluating the outcome were not aware of the allocation status of the two study groups.

In order to check the normal distribution of quantitative data, the Kolmogorov-Smirnov test was used, and to check the variables between the two groups, the independent t-test and chi-square test were used. To compare dependent variables during the study in the two groups, statistical test of repeated measures ANOVA was used and $p<0.05$ was considered significant.

Results

The mean age of people in TIVA group was 46.2±5.7 and in isoflurane group was 48.4±6.9 years. The duration of anesthesia was 55.1±8.4 minutes in the TIVA group and 51.6±7.5 minutes in the isoflurane group. Based on statistical tests, there was no significant difference between the two groups in terms of age, weight, duration of surgery and duration of anesthesia (Table 1).

Table 1. Comparison of demographic characteristics in the two study groups

Variable	Groups		p-value
	TIVA Mean±SD	Isoflurane Mean±SD	
Age (years)	46.2±5.7	48.4±6.9	0.57*
Weight (kg)	85.4±11.3	87.1±9.8	0.65*
Duration of surgery (m)	55.1±8.4	51.6±7.5	0.24*
Duration of fasting (hours)	10.9±1.1	9.5±0.8	0.72*
Gender			0.20**
Male (number)	15	18	
Female (number)	20	17	

***Independent t-test, **Chi-square test**

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The level of AST and ALT enzymes in TIVA group increased from 20.2±5.5 (AST) and 17.6±10.7 (ALT) in the pre-operative stage to 35.8±16.8 and 21.2±14.2 within 48 hours after the operation. This value in isoflurane group increased from 21.3±6.8 (AST) and 16.7±9.4 (ALT) to 39.5±14.7 and 28.4±16.1, respectively. Based on the statistical test of repeated measures ANOVA, there was a significant difference between the ALT enzyme levels between the two groups in different evaluation stages ($p<0.05$). But this difference was not significant in the case of AST and ALP enzymes. Moreover, the findings showed that there is no significant difference between PTT and INR coagulation tests between the two groups in different stages of evaluation (Table 2).

Table 2. Comparison of mean liver enzymes and coagulation tests in different stages of evaluation

Enzymes and groups	Before anesthesia (baseline) Mean±SD	Immediately after the operation Mean±SD	24 hours after the operation Mean±SD	48 hours after the operation Mean±SD
AST (U/L)				
TIVA	20.2±5.5	43.5±12.7	40.4±11.2	35.8±16.8
Isoflurane	21.3±6.8	48.7±15.4	45.6±17.5	39.5±14.7
ALT (U/L)				
TIVA	17.6±10.7	32.2±11.6	22.8±9.7	21.2±14.2
Isoflurane	16.7±9.4	25.4±14.8	26.9±12.8	24.8±16.1
ALP (U/L)				
TIVA	205.4±52.4	192.4±61.5	200.0±58.2	207.5±72.5
Isoflurane	198.2±67.2	184.8±78.2	190.3±64.3	194.1±59.4
PTT (Sec)				
TIVA	25.55±4.1	27.1±4.2	26.2±5.5	26.7±6.1
Isoflurane	27.8±4.9	29.4±5.6	28.4±5.4	28.1±4.9
INR				
TIVA	1.09±0.2	1.15±0.7	1.13±0.5	1.11±0.5
Isoflurane	1.08±0.4	1.15±0.5	1.14±0.6	1.11±0.4

Discussion

The results of the study showed that the level of AST and ALT enzymes in the isoflurane and TIVA groups immediately after the operation, 24 and 48 hours after the operation increased compared to the pre-surgery stage, and this increase was higher in the isoflurane group. Although the change in AST levels was not statistically significant in TIVA and Isoflurane group, ALT levels increased significantly in both groups. Furthermore, the results of this study showed that the use of isoflurane and propofol has no significant effect on PTT and INR coagulation tests.

In the study of Xu et al. on 40 patients who underwent TIVA anesthesia with propofol, there was no significant change in the level of liver enzymes such as AST and ALT, which is consistent with the results of the present study in terms of changes in the level of AST enzyme. However, differences with our results in terms of ALT enzyme at the mentioned times may be due to the use of isoflurane anesthetic along with drugs such as midazolam, which affect liver function (8). In another study conducted by Jose et al., the results showed that propofol causes a temporary increase in the serum levels of AST, ALT and lactic

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dehydrogenase in patients undergoing coronary artery bypass surgery, which is consistent with our study (9). Another study conducted by Hasan et al. showed that halothane causes an asymptomatic increase in aminotransferases. Aminotransferase levels remain elevated for one to two weeks after exposure and return to baseline without treatment. The acute and irreversible reaction is acute hepatitis, which is often fatal and occurs due to acute liver failure. In this study, the average ALP level in the hours after the operation was not significant between the two groups (10). Similar results were obtained in a study by Xu et al. (8). Therefore, it seems that maybe more time is required to observe the change in ALP level.

A study conducted by Mohammed et al. on the effect of general anesthesia and spinal anesthesia on kidney and liver function and hemodynamic parameters in women undergoing cesarean surgery showed that the level of liver enzymes affected by general and spinal anesthesia showed no significant difference. The results in terms of the effect of general anesthesia on liver enzymes are consistent with the results of our study (11). The results of the study by Dabir et al. showed that the level of liver enzymes increased due to the use of isoflurane and propofol, but there was no significant difference between the two groups and it is consistent with our study (12).

In another study conducted by Hosseini Gohari et al. in patients undergoing neurological surgery with the aim of investigating the activity of liver enzymes after general anesthesia with isoflurane inhalation, it was indicated that there was no significant difference in the levels of AST and ALP enzymes, but there was a significant increase in ALT and GGT enzymes, which is in line with the results of our study (13).

In the study of Chen et al., it was found that propofol has a dose-dependent effect in reducing the activity of enzymes involved in the conjugation process of liver tissue, but such an effect was not observed in non-hepatic tissues. Considering the above study, it can be argued that isoflurane and propofol do not have a significant effect on the change of AST and ALT levels, and these results are similar to our study and the studies of other researchers (14).

The study of Abdel Tawab et al. showed that the level of liver enzymes after the use of isoflurane and propofol decreased significantly compared to pre-operative stage and caused an increase in coagulation tests, which is not consistent with the results of the present study, and this can be due to the difference in the use of drugs along with isoflurane and propofol (15).

The results of the study indicated that despite the non-significance of changes in liver enzymes between the isoflurane and propofol groups, the rate of increase compared to the pre-operative state was higher in the isoflurane group. In the study of Flamée et al., who used propofol in chronic liver patients, propofol was completely effective and without complications (16). Therefore, it can be concluded that propofol has less effects on liver enzymes compared to isoflurane. Therefore, this can be taken into consideration when prescribing liver medicines.

Based on the results of the present study, it can be said that there is a possibility of parenchymal liver damage and blockage of the bile ducts as a result of exposure to anesthesia with the mentioned drugs. However, in this study, during the 48 hours that the liver enzymes of the patients were examined, no specific liver disorders were observed that required action. Therefore, due to the mentioned reasons and the importance of the level of liver enzymes in its function and the health of the liver of patients after inhaling the common anesthetics isoflurane and propofol, it seems that the measurement of these enzymes in the measurement of the liver function among patients can provide useful information for future actions.

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