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Impact of Carbon Dioxide Pneumoperitoneum on Liver Function Tests in Laparoscopic Cholecystectomy, A Prospective Study

Muhammad Shahbaz Nazir, Maria Nawaz*, Afzal Saeed Awan, Hafiza Ayesha Nawaz, Laiba Iqbal***, Muhammad Irfan******

Department of General Surgery, Combined Military Hospital, Multan/National University of Medical Sciences (NUMS) Pakistan, *Department of Pathology, Children Hospital, Faisalabad Pakistan, **National University of Sciences & Technology, Islamabad Pakistan, ***Department of General Surgery, District Headquarters Hospital, Sargodha Pakistan, ****Department of General Surgery, Combined Military Hospital, Sialkot/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To evaluate the impact of carbon dioxide pneumoperitoneum on liver function tests in patients undergoing laparoscopic cholecystectomy for a benign disease as an elective surgery.

Study Design: Prospective longitudinal study.

Place and Duration of Study: Army Liver Transplant Unit, Pak Emirates Military Hospital Rawalpindi, Pakistan from Mar 2021 to Feb 2024.

Methodology: The study included 455 patients who underwent elective laparoscopic cholecystectomy in a tertiary care hospital in accordance with the inclusion and exclusion criteria. All patients of 18-80 years of age with normal LFTs were included and those with liver and associated diseases that could affect the LFTs were excluded. The detailed medical history and laboratory findings were recorded preoperatively and post operatively on the 1st, 3rd, and 7th post operative day and evaluated for any significant change in values.

Results: ALP and LDH showed a rise in serum values after surgery. The mean values before surgery for ALP and LDH were 88.09±30.19 U/L and 201.11±42.46 U/L respectively. After seven days of surgery, the mean values of ALP and LDH were 91.69±32.86 U/L and 212.16±44.31 U/L respectively with *p*-value <0.05. However, no significant change in the mean values of serum levels of ALT, AST, bilirubin and albumin was observed during the preoperative and post-operative period.

Conclusion: A temporary rise of liver enzyme levels, such as ALP and LDH may be seen in patients undergoing laparoscopic cholecystectomy due to CO2 pneumoperitoneum, but these values return to normal after one week with no adverse effects.

Keywords: Carbon dioxide, Cholelithiasis, Laparoscopic Cholecystectomy, Liver Function Tests, Pneumoperitoneum.

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INTRODUCTION

Gallstones disease is the most common disease of the biliary system and the best treatment for symptomatic gallstones is the surgical removal of gall bladder.[1] The modern time shift from minimally invasive surgery (MIS) to minimally access surgery (MAS) has led to perform most of the surgeries laparoscopically. The laparoscopic cholecystectomy (LC) has now become the gold standard procedure due to less post-operative pain, shorter hospital stay, rapid return to daily routine life, and being minimally invasive as well.[2,3] All laparoscopic procedures have a key element of pneumoperitoneum that provides space for surgery, visual magnification, clarity, and safety. For this purpose, the intraabdominal pressure is raised to 14-15 mm Hg with carbon dioxide whereas the normal value of intra-abdominal pressure is 5 mmHg.[4,5] Different gases can be used for this purpose like carbon dioxide, argon, and helium but carbon dioxide is the preferred gas being non-combustible and highly soluble and it is rapidly absorbed in serum and excreted from lungs.[6,7]

With the technique becoming more popular, difficulties associated with it are also becoming challenging. Some of the challenges can be overcome by proper instrument handling, well-trained medical practitioners, and early detection of complications.[8] The establishment of pneumoperitoneum has raised concerns regarding its effects on the respiratory and cardiovascular systems, specifically with regards to hemodynamic changes. One notable effect is a temporary reduction in hepatic blood flow, which may result in hepatic hypoperfusion and ischemia. This, in turn, can lead to damage to the Kupffer and endothelial cells within the hepatic sinusoids, induced by the presence of free radicals. Furthermore, studies indicate that there is a correlation between the

Correspondence: Dr Muhammad Shahbaz Nazir, Department of General Surgery, Combined Military Hospital, Multan Pakistan
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pressure and duration of pneumoperitoneum and increased levels of liver enzymes, highlighting the potential impact of these factors.[9] Additionally, damage to the biliary duct, liver compression, liver bed cauterization, and increased intra-abdominal pressure can also contribute to this issue. Following laparoscopic cholecystectomy, a temporary increase in liver enzymes may occur, but this is usually a self-limiting phenomenon and does not require intervention in individuals with normal pre-operative liver function. In such cases, the elevated enzyme levels typically resolve on their own without necessitating further action.[10] But in patients with underlying liver diseases and other metabolic conditions, laparoscopy may not be considered the best option.[1] This prospective observational study aimed to examine the effects of CO^2 pneumo-peritoneum on liver enzymes in patients undergoing laparoscopic cholecystectomy, taking into account other potential factors that may contribute to elevated liver enzymes postoperatively.

METHODOLOGY

This prospective longitudinal study was conducted in the Army Liver Transplant Unit, Pak Emirates Military Hospital, Rawalpindi for 03 years from March 2021 to February 2024. Sample size was calculated using WHO sample size calculator, with test value of population proportion 0.43 and anticipated value of population proportion 0.5, keeping confidence level 95% and power of test 90%.[11] A total of 455 patients were recruited in this study who underwent elective laparoscopic cholecystectomy. Ethical approval from the ethical committee of the hospital (letter no. A/28/1840) was obtained before starting the study. All the patients taking part in this study were informed about the nature of the study and their consent was taken.

Inclusion Criteria: All patients from the age of 18 to 80 years presenting in tertiary care hospital OPD for elective cholecystectomy with symptomatic cholelithiasis, normal values of LFTs, and BMI before operation were included in the study.

Exclusion Criteria: Patients with altered or elevated values of LFTs before the operation, any underlying and coexisting chronic liver disease, complicated surgery, bile duct injury, pancreatitis, CBD pathology, open cholecystectomy, diagnosed biliary cancer or any other malignancy in the body were excluded. Patients with porcelain GB, primary sclerosing cholangitis, uncontrolled diabetes or hypertension and GB polyps were also excluded from the study.

Patients' medical history, personal information, demographic data, socioeconomic status, smoking and exercise status, USG findings, routine and specific investigations i.e. LFTs including AST (Aspartate Aminotransferase), ALT (Alanine Aminotransferase), ALP (Alkaline Phosphatase), albumin, LDH and bilirubin levels were recorded 24 hours pre-operatively. Counselling sessions were carried out about the disease and procedure, laparoscopic surgery with informed consent to convert to open if required. During the preoperative assessment, patients were given routine medications and prophylactic antibiotic treatment (Ceftriaxone, 1g) in accordance with hospital protocols. All eligible patients underwent laparoscopic cholecystectomy, where CO_2 pneumoperitoneum was established using the open method. This involved the insertion of four standard ports, and a constant pressure of 12 mmHg was maintained during the procedure. Patients who required conversion to open cholecystectomy were excluded from the study. Surgical parameters like duration of surgery, difficult dissection, spillage of bile/stone, intra-operative bleed and placement of drain were recorded. Liver function tests were repeated on the 1st, 3rd and 7th day after undergoing cholecystectomy from the same laboratory of Armed Force Institute of Pathology and the data was compared.

All data was entered into Statistical Package for Social Sciences (SPSS) software version 27 for Windows and used to review and analyze the data through its statistical package. The repeated measures Anova Test was used to compare the studied parameters with Liver Function Tests, including ALT, AST, ALP, LDH, bilirubin, and albumin, which were presented as Mean±SD. The *p*-value of ≤0.05 was taken as significant.

RESULTS

A total of 455 patients who underwent elective laparoscopic cholecystectomy in three years were included in the study. The descriptive parameters of the patients are shown in Table-I. Among the total, 41.3 % of patients were male while females were 58.7 %. A comprehensive comparison was made between all parameters including age, gender, symptom duration, hepatitis presence, co-morbid conditions (diabetes, hypertension, smoking), surgery duration, pre-operative ultrasound findings, intra-operative

bleeding, drain placement, gallstone/bile spillage, and liver bed dissection and their impact on liver function tests (ALT, AST, ALP, Bilirubin, Albumin, and LDH) at multiple time points (24 hours preoperatively and postoperatively on days 1, 3, and 7). However, no significant association or difference was found.

Table-I: Descriptive Parameters of Patients Undergoing Laparoscopic Cholecystectomy (n=455)

Study Parameters	n(%)
Gender	
Male	188(40.9%)
Female	267(58.0%)
Age(years)	
Less than 50	224(48.7%)
Greater than 50	231(50.2%)
Duration of symptoms	
Less than 1 year	295(64.1%)
Greater than 1 year	160(34.8%)
Hepatitis	
B & C both negative	343(74.6%)
B Positive	28(6.1%)
C positive	83(18.0%)
B & C both positive	1(0.2%)
Smoking	
Non-smoker	416(90.4%)
Smoker	39(8.5%)
Hypertension	
Normotensive	389(84.6%)
Hypertensive	66(14.3%)
Ultrasound findings of liver	
Healthy liver	422(91.7%)
Cirrhotic liver	33(7.2%)
Bleeding during surgery	
Less than 5 ml	322(70.0%)
5-10 ml	96(20.9%)
Greater than 10 ml	35(7.6%)
Spillage of bile/stone	
Nil	349(75.9%)
Yes	106(23%)
Difficult dissection	
No damage to the Gall Bladder bed	381(82.8%)
Damage to Gall Bladder bed	73(15.9%)
Placement of drain	
Nil	394(85.7%)
Yes	61(13.3%)
Duration of surgery	
Less than 30 min	374(81.3%)
30-60 min	45(9.8%)
Greater than 1 hour	36(7.8%)

Table-II displays the mean and standard deviation of ALT, AST, ALP, bilirubin, albumin, and LDH levels 24 hours before surgery, as well as on the 1st, 3rd, and 7th postoperative days (POD). A comparison of the values was made between the preoperative period and postoperative periods (24 hours, 3rd day, and 7th day) to assess changes in liver function test results (Table-II). After 24 hours of surgery there was a significant rise in ALP and LDH levels. In the case of ALP, the value increased after 24 hours and then gradually decreased to the normal range while for LDH, the value gradually increased in a normal range till the 7th POD. The mean values before surgery for ALP and LDH were 88.09±30.193 U/L and 201.11±42.464 U/L respectively. After seven days of surgery, the mean values of ALP and LDH were 91.69±32.868 U/L and 212.16±44.315 U/L respectively. No significant change in the mean values of serum levels of ALT, AST, bilirubin and albumin was observed during the preoperative and post-operative period.

Table-II: Pre- and Postoperative Liver Function Tests in Laparoscopic Cholecystectomy (n=455)

Enzymes	Pre-operative Mean±SD	24 hours post op Mean±SD	3rd post op day Mean±SD	7th postop day Mean±SD	*p*-value
ALT U/L	25.74±8.38	25.48±4.35	25.60±4.30	25.46±4.40	0.94
AST U/L	22.89±8.06	22.93±7.14	23.29±7.21	23.46±7.58	0.88
ALP U/L	88.09±30.19	99.00±31.05	96.39±34.14	91.69±32.86	0.0001
Bilirubin µmol/L	9.72±5.56	10.27±5.66	10.11±5.83	10.22±5.76	0.17
Albumin g/dL	42.16±4.90	42.04±4.87	42.15±5.19	41.42±4.50	0.61
LDH U/L	201.11±42.46	206.21±42.40	211.49±43.19	212.16±44.31	0.01

AST :Aspartate Aminotransferase, ALT:Alanine Aminotransferase, ALP: Alkaline Phosphatase, LDH :Lactate Dehydrogenase, Post op: Post operative

DISCUSSION

The findings of our study showed that a transient increase in liver enzymes ALP and LDH may occur in patients undergoing laparoscopic cholecystectomy due to CO_2 pneumoperitoneum, but these values typically return to normal within one week without any adverse effects. Laparoscopy has become the first line of treatment for symptomatic gallstones as this technique offers more advantages over the previously used open surgical method.[12,13] The use of CO_2 pneumoperitoneum may be the cause of elevated serum values of liver enzymes after undergoing surgery.[14]

The first study regarding the rise of liver enzymes in patients undergoing LC showed a statistically significant rise in AST and ALT after surgery but this elevation in serum levels was proved to be harmless and clinically insignificant with enzymes returning to their normal values within 72 hours.[15] Another study conducted in 2020 comparing the results of open vs laparoscopic cholecystectomy showed a significant rise in ALT and AST values after laparoscopic cholecystectomy on 1st POD but our study showed a temporary rise of ALP and LDH instead of ALT and AST values.[6]

Various studies have been conducted to investigate the effect of serum levels of liver enzymes in patients undergoing elective laparoscopic cholecystectomy compared with open cholecystectomy which revealed that low-pressure CO_2

pneumoperitoneum during laparoscopic cholecystectomy is safe for patients.[16] This pressure can be a source of transient rise in hepatic function enzymes but the short-term rise of these enzyme levels proved that it can never be a source of any kind of adverse effect on patient's health and post-operation recovery.[10,17]

The findings of our study are in alignment with a study conducted by Hameed *et al*., who compared hepatic function between laparoscopic cholecystectomy and open cholecystectomy. Their findings showed that Laparoscopic Cholecystectomy group patients had a significant rise in ALT and AST levels nearly double, but this effect was transient and clinically silent.[18] Anilkumar et al studied the liver function tests 24 hours before and after laparoscopic procedures in 100 patients. This revealed that the levels of bilirubin, AST, ALT and ALP increased temporarily while total proteins and serum albumin levels decreased with no clinically significant effect.[19]

A study conducted in India has also investigated the role of CO_2 pneumoperitoneum on liver function enzymes including 100 patients. They compared the levels of liver enzymes at 24 hours and seven days after surgery concluding that the levels of liver enzymes returned to normal range at the 7th post operative day with no apparent clinical effects.[6] Another prospective randomized study has investigated the pressure of CO_2 during laparoscopic cholecystectomy and data has shown that low-pressure CO_2 pneumoperitoneum is better and safe for laparoscopic cholecystectomy considering post-operative pain and recovery conditions.[13] A study conducted in Iran in 2019 showed an increase in AST and ALT levels compared to their base levels, which is not consistent with our study but a rise in LDH is comparable to our study.[20] Results of our study are comparable to a local study, conducted in LGH Lahore that demonstrated a substantial rise in ALT,AST LDH and bilirubin but no significant rise in ALP after Laparoscopic cholecystectomy.[12]

In our study of 455 subjects including both genders from the age of 18 to 80 years, a significant rise in serum levels of ALP and LDH was observed with no change in the levels of ALT, AST, bilirubin and albumin. The rise of ALP occurred at 24 hours and returned to normal on the 7th POD, but LDH levels progressively increased till the 7th POD within normal limits. In this study, we had not recorded values for more than 7th POD but these changes showed no clinically significant impact of carbon dioxide pneumoperitoneum on the levels of liver enzymes. Our findings in this study are consistent with the previous studies. Nevertheless, this slight effect is only temporary and self-limiting, provided that the patients do not have any preexisting imbalance in enzyme levels, liver disease, or other complications prior to the surgery.

However, this slight effect is proved to be temporary and self-limiting considering the patients have no preoperative imbalance of enzyme levels and any other liver disease or complications.

LIMITATIONS OF STUDY

Laparoscopic cholecystectomies were performed by three surgeons and cases of per-operative bleeding and electrocautery over the liver bed were also included in the study. The study is limited to the 7th POD and could not analyze the trends of LDH beyond the 7th POD. In order to distinguish the effects of CO_2 from other factors that can affect liver enzymes, it is important to include only those cases in the study that involve clean surgeries performed by a single surgeon with consistent CO_2 pressure. This will help to eliminate the potential influence of factors such as cautery, liver parenchyma damage, per operative bleeding, and variations in CO_2 pneumoperitoneum pressure. By focusing on a large number of patients meeting these criteria, the study can provide more accurate results into the specific impact of CO_2 on liver enzymes

CONCLUSION

A temporary and reversible rise in liver enzymes specifically ALP and LDH may take place due to higher pressure of the pneumoperitoneum after Laparoscopic cholecystectomy. This effect has no clinical significance for patients without any underlying liver diseases.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MSN & MN: Data acquisition, data analysis, critical review, approval of the final version to be published.

ASA & HAN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

LI & MI: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

of any part of the work are appropriately investigated and resolved.

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