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Original Article

A Study Of Effect Of Carbon Dioxide Pneumoperitoneum On Liver Function Tests Following Laparoscopic Cholecystectomy

Varun Deep Konda[1], Pippiri Satwi Bruhath[2], Nousheen Hameed[3], P. Sai Karthik Reddy[4]

[1]Assistant Professor, [2]Junior Resident, [3]Assistant Professor, [4]Senior Resident, Department of General Surgery, Malla Reddy Institute of Medical Sciences, Suraram, Hyderabad, Telangana, India

Corresponding Author:

Dr. Nousheen Hameed

Assistant Professor, Department of General Surgery, Malla Reddy Institute of Medical Sciences, Suraram, Hyderabad, Telangana, India

Email: nosh1229naaz@gmail.com

ABSTRACT:

Background: CO_2 pneumoperitoneum may be one of the primary causes of the alteration in blood liver enzyme levels. However, these findings suggest that laparoscopic surgery may not be the best option for treating cholelithiasis if the patient's preoperative liver function was very poor.

Objective: To determine prevalence and clinical significance of unexplained liver enzyme changes following laparoscopic cholecystectomy.

Methods: Prospective, observational study was conducted among 70 patients undergoing laparoscopic cholecystectomy. Laparoscopic cholecystectomy was done as per the standard operative procedure. The abdomen was inflated with carbon dioxide. Liver enzymes were measured before surgery, and post-operatively on day one, three and seven. Each patient was followed for seven days after surgery.

Results: Females were 49 (70.0%) and males were 21 (30.0%). Mean age of the patients was 40.1±8.6 years. Carbon dioxide insufflation had dramatic effect on the liver enzymes. All the liver enzymes values increased significantly ($P<0.05$) on postoperative day one. But over the period of one week, the values decreased slowly and steadily and almost returned to the baseline levels. 37 (52.9%) patients had duration of CO_2 Pneumoperitoneum < 70 minutes) and 33 (47.1%) had > 70 minutes. Duration of carbon dioxide pneumoperitoneum lasted 65 to 85 minutes, it was observed there was a significant change in liver function enzymes where duration lasted more than 70 minutes.

Conclusion: Carbon dioxide insufflation had dramatic effect on liver enzymes. All liver enzymes values increased significantly ($P<0.05$) on postoperative day one. But over week, the values decreased slowly and steadily and almost returned to baseline levels.

Key words: pneumoperitoneum, liver function tests, laparoscopic cholecystectomy

INTRODUCTION

Minimally invasive surgery, particularly laparoscopic surgery, refers to a field of surgery that transcends all traditional specialties and has altered the face of general surgery. The objective of laparoscopic surgery is to execute standard, classical open surgical operations using the

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laparoscope in order to make the operation more patient-friendly. This technology and its applications have expanded at an exponential rate, and it now accounts for a significant share of all surgical procedures. One of the primary benefits of laparoscopic cholecystectomy is the reduction in adhesion formation. The increasing popularity of laparoscopic cholecystectomy is largely related to studies indicating a decrease in patient morbidity, a shorter hospital stays, and an early return to regular activity. [1]

Throughout the last decade, numerous studies have reported 'unexplained' variations in postoperative liver function tests in patients who have undergone laparoscopic cholecystectomy. [2] Although laparoscopic cholecystectomy offers numerous advantages over laparotomy, new concerns arose regarding the cardiovascular and pulmonary implications of pneumoperitoneum. [3] The brief reduction in hepatic blood flow caused by pneumoperitoneum on the cardiovascular, respiratory, or renal insufficiency may induce undesirable outcomes due to hypercapnia or increased intra-abdominal pressure. [4, 5]

The pressure and duration of pneumoperitoneum have been proven to increase liver enzyme levels. [6, 7] These studies illustrate that a transitory increase in liver enzymes may occur following a surgery. These alterations may be attributable to hepatocellular dysfunction caused by one or more CO_2 pneumoperitoneum. CO_2 pneumoperitoneum may be one of the primary causes of the alteration in blood liver enzyme levels. However, these findings suggest that laparoscopic surgery may not be the best option for treating cholelithiasis if the patient's preoperative liver function was very poor. [8] Guven and Oral [9] observed that variations in liver enzymes do not appear to be clinically significant; thus, patients with hepatic insufficiency should exercise caution before undergoing laparoscopic cholecystectomy. Mehdat et al [10] have also noticed that an early increase in LFTs shortly after surgery should not be cause for alarm, as they typically revert to normal without intervention.

This study aims to determine the prevalence and clinical significance of unexplained liver enzyme changes following laparoscopic cholecystectomy, as well as their relevance during the post-operative recovery phase.

PATIENTS AND METHODS:

Study design: This was a prospective, observational study

Settings: Present study was conducted in the department of General surgery, at the Malla Reddy Institute of Medical Sciences, Hyderabad

Study duration: Present study was conducted from January 2021- July 2022

Sample size: Present study was carried out among 70 patients undergoing laparoscopic cholecystectomy.

Inclusion criteria: All patients undergoing laparoscopic cholecystectomy at our hospital who have given written consent to be part of the study group were included.

Exclusion criteria: Any patient with preoperative abnormality in liver enzymes, having suspected chronic liver diseases, common bile duct pathology, conversion to open cholecystectomy, recent elective retrograde cholangiopancreatography and intra operative bile leakage were excluded.

Ethical considerations: Ethical committee approval was taken. Scientific committee approval was taken. Informed consent was taken from individual participants

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Methodology:

All patients undergoing laparoscopic cholecystectomy were contacted. Detailed history, thorough clinical examination and all necessary investigations needed for surgical profile were carried out as per the standard guidelines. The pre-anesthetic check-up was carried out to ascertain the fitness of the patient for the surgery.

Laparoscopic cholecystectomy was done as per the standard operative procedure. The abdomen was inflated with the help of carbon dioxide. The liver enzymes were measured before surgery, and post operatively on day one, three and seven. All blood investigations were done with all standard aseptic precautions and as per the standard guidelines using the standard equipment in the NABL accredited laboratory of the hospital. Thus, each patient was followed for seven days after surgery from the day of his admission.

STATISTICAL ANALYSIS:

All the data was collected in approved proforma and entered in MS excel and was subjected to statistical analysis. Descriptive data was analysed using proportions. Analysis of variance (ANOVA) test was used to compare mean values in more than two groups. For comparison of mean values in only two groups, independent samples t test was used. P value <0.05 was considered statistically significant.

RESULTS

Table 1: Distribution of study subjects as per age and sex

Variables		Number	%
Gender	Females	49	70
	Males	21	30
Age (years)	≤ 30	7	10
	31-40	36	51.4
	41-50	19	27.2
	> 50	8	11.4

In present study, females were 49 (70.0%) and males were 21 (30.0%). Mean age of the patients was 40.1±8.6 years (Range: 27 – 66 years). Majority of the patients were from the age group of 31 – 40 years – 36 (51.4%) followed by 19 (27.2%) patients from 41 – 50 years, 8 (11.4%) patients age was > 50 years and 7 (10.0%) patients age was ≤ 30 years. (Table 1)

Table 2: Comparison of liver enzymes from pre-operative to postoperative 7th day

Liver enzyme	Pre-operative	Post-op day 1	Post-op day	Post-op day 7	F	p
Bilirubin	0.78±0.2	1.69±0.28	1.34±0.23	0.8±0.16	310.08	< 0.001
AST	23.3±8.5	40.4±10.5	31.3±6.5	25.7±4.8	72.655	<0.001
ALP	105.5±18.6	142.1±17.7	126.8±15.6	110.2±11.5	83.98	<0.001
ALT	20.8±3.9	50.2±14.2	42.2±7.3	32.2±5.7	166.696	<0.001

The carbon dioxide insufflation had dramatic effect on the liver enzymes. All the liver enzymes values increased significantly (P<0.05) on postoperative day one. But over the period of one week, the values decreased slowly and steadily and almost returned to the baseline levels. (Table 2)

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Table 3: Distribution of study subjects as per the duration of carbon dioxide insufflation

Duration of carbon dioxide insufflation (min)	Number	%
≤ 70	37	52.9
> 70	33	47.1

37 (52.9%) patients had duration of CO_2 Pneumoperitoneum < 70 minutes) and 33 (47.1%) had > 70 minutes. (Table 3)

Table 4: Effect of duration of carbon dioxide insufflation on liver enzyme values

Liver enzymes	Duration of carbon dioxide insufflation (min)		t	p
	> 70	≤ 70		
Bilirubin	0.92±1.0	0.65±0.14	8.193	<0.0001
AST	52.8±15.0	44.5±17.3	2.149	0.035
ALP	86.3±14.1	74.2±18.9	3.012	0.0004
ALT	56.1±11.4	46.0±15.0	3.136	0.0003

Duration of carbon dioxide pneumoperitoneum lasted 65 to 85 minutes, it was observed there was a significant change in liver function enzymes where duration lasted more than 70 minutes. (Table 4)

DISCUSSION

In our study, in the 70 patients who constituted the study population, 49 subjects were female (70%) and 21 subjects were male (30%). In a similar study conducted by Bendre et al of 60 patients 45 were female and 15 were male. [8] In our study, the mean age of the patients was 40.1±8.6 years (Range: 27 – 66 years) and median age was 39 years. Majority of the patients were from the age group of 31 – 40 years – 36 (51.4%) followed by 19 (27.2%) patients from 41 – 50 years, 8 (11.4%) patients age was > 50 years and 7 (10.0%) patients age was ≤ 30 years. In a similar study conducted by Bendre et al [8] patients were between 24 and 75 years of age, with majority of cases [33.3%] in age group of 30 – 40 years.

In our study, in all patients the levels of serum bilirubin, serum AST, serum ALT and serum ALP was checked preoperatively once and post operatively on day 1, day 3 and day 7. In details, on post-operative day 1, bilirubin was significantly increased from preoperative (Pre Op vs. Day 1; 0.78±0.2 vs. 1.69±0.28) (p = 0.0001). At post-operative day 3, (1.34±0.23) bilirubin was significantly increased from preoperative (0.78±0.2) (p = 0.0001) whereas at day 7 (0.8±0.16) there was no significant difference observed from preoperative (p = 0.172). Similarly, bilirubin was significantly decreased at day 3 and 7 from day 1 as well as at day 3 from day 1 (p = 0.0001). Thus it was found that there was a significant rise (P=0.001) in the serum bilirubin levels in the immediate post-op period which came down to near pre-op values within 1 week postoperatively. Similar findings were also reported by Bendre et al [8], Godara et al study [6], Syed Ibrahim et al study. [11]

Similarly, at day 1, AST was significantly increased from preoperative (Pre Op vs. Day 1; 23.3±8.5 vs. 40.4±10.5) (p = 0.0001). At post-operative day 3 (31.3±6.5) the levels increased compared to pre-operative and on post-operative day 7 (25.7±4.8) AST was significantly decreased and reached close to preoperative values (p < 0.05). Similarly, AST was significantly decreased at day 3 and 7 from day 1 as well as at day 7 from day 3 (p = 0.0001).

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Similar findings were also reported by Bendre et al [8], Godara et al study [6], Syed Ibrahim et al study. [11]

Furthermore, At post-operative day 1, ALP was significantly increased from preoperative (Pre Op vs. Day 1; 105.5±18.6 vs. 142.1±17.7) (p = 0.0001). At day 3 (126.8±15.6) ALP was significantly increased from preoperative (p = 0.0001). Whereas, at day 7 (110.2±11.5) there was no significant difference observed from preoperative (p = 0.102). Similarly, ALP was significantly decreased at day 3 and 7 from day 1 as well as at day 7 from day 3 (p = 0.0001). Similar findings were also reported by Bendre et al [8], Godara et al study [6], Syed Ibrahim et al study. [11]

Furthermore, at postoperative day 1, ALT was significantly increased from preoperative (Pre Op vs. Day 1; 20.8±3.9 vs. 50.2±14.2) (p = 0.0001). At post-operative day 3 (42.2±7.3) and 7 **(32.2±5.7)** ALT was significantly increased from preoperative (p = 0.0001). Similarly, ALT was significantly decreased at day 3 and 7 from day 1 as well as at day 7 from day 3 (p = 0.0001). Similar findings were also reported by Bendre et al [8], Godara et al study [6], Syed Ibrahim et al study. [11]

In our study, 37 (52.9%) patients had duration of CO_2 Pneumoperitoneum < 70 minutes) and 33 (47.1%) had > 70 minutes. Duration of carbon dioxide pneumoperitoneum lasted 65 to 85 minutes, it was observed there was a significant change in liver function enzymes where duration lasted more than 70 minutes.

In surgeries which lasted < 70 minutes the mean value of bilirubin was (0.65±0.14) when compared to surgeries which lasted >70 minutes with a mean value of (0.92±1.0). There is a significant change in the level of bilirubin in surgeries which lasted more than 70 minutes showing an association between the duration of pneumoperitoneum and derangement of bilirubin.

In surgeries which lasted < 70 minutes the mean value of AST was (44.5±17.3) when compared to surgeries which lasted >70 minutes with a mean value of (52.8±15.0). There is a significant change in the level of AST in surgeries which lasted more than 70 minutes showing an association between the duration of pneumoperitoneum and derangement of AST.

In surgeries which lasted < 70 minutes the mean value of ALP was (74.2±18.9) when compared to surgeries which lasted >70 minutes with a mean value of (86.3±14.1). There is a significant change in the level of ALP in surgeries which lasted more than 70 minutes showing an association between the duration of pneumoperitoneum and derangement of ALP.

In surgeries which lasted < 70 minutes the mean value of ALT was (46.0±15.0) when compared to surgeries which lasted >70 minutes with a mean value of (56.1±11.4). There is a significant change in the level of ALT in surgeries which lasted more than 70 minutes showing an association between the duration of pneumoperitoneum and derangement of ALT.

Bendre et al study [8] also demonstrated that there was a significant change in liver function enzymes (serum bilirubin, AST, ALP, ALT) where duration lasted more than 70 minutes.

In a study that was very similar to this one, which was carried out by Medhat et al [10] involved 198 patients, it was found that postoperatively, there was a statistically significant increase in ASP, ALT, total bilirubin, and indirect bilirubin, as well as a significant decrease in ALP. There was a mean increase of 48.4% in the total bilirubin value, and there was a mean increase of up to 100% in both the ASP and ALT readings.

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In a similar study, done by Godara et al [6] which in involved 100 patients compared liver enzyme derangement in laparoscopic cholecystectomy versus open cholecystectomy. The results concluded that at 24 hrs in laparoscopic cholecystectomy group there was statistically significant rise in ALT and AST level rather than preoperatively. The mean before surgery ALT, AST values were (18.3+ 10.4 U/L and 20.6 +12.8 IU/L) in laparoscopic cholecystectomy group vs (19.6 + 10.9 and 18.6 +11.3 U/L) in open cholecystectomy group respectively. Post operatively at 24 hours, ALT and AST increased to 92.6 +20.2 U/L and 89.6 +24.2 in LC group ($p<.001$). In open surgery group serum value of ALT and AST increased at 24 hrs post operatively but not to significant level compared to preoperative level (ALT 41.4 + 11.3 U/L and AST 43.1+ 7.3 U/L, $p>0.05$).

On 7th postoperative day, value of ALT and AST returned to almost normal level in both groups. The serum values of bilirubin, GGT and alkaline phosphatase did not show any significant rise in postoperative period compared to preoperative value which demonstrates that CO_2 pneumoperitoneum can be a cause for alteration in hepatic enzymes when compared to open cholecystectomy where pneumoperitoneum is not created.

In 2005, a study by Sakorfas et al [12] concluded that 24 hours after the procedure SGOT and SGPT raised statistically significant. Levels returned to normality occurred 7-10 days after the procedure. In 2007, a study by Guven et al [9] performed in 86 patients who underwent Laparoscopic cholecystectomy to investigate the alterations in serum enzymes levels. He concluded that the differences between elevations of enzymes preoperatively and postoperatively were significant. In 2015 a study by Singhal et al 13 concluded that all types of laparoscopic procedures can cause transient elevation of hepatic enzymes and serum bilirubin for which CO_2 pneumoperitoneum is the causative factor.

Guven et al [9] studied alterations in liver enzymes after laparoscopic surgeries. The possible mechanism included increased intra-abdominal pressure, squeeze pressure effect on the liver, pulling on the gall bladder, excessive use of diathermy". Vast investigation was done to evaluate the causes of this elevation and concluded that low pressure pneumoperitoneum was combined with lesser side effects on liver function.

Within seven days of surgery, the enzyme levels of all of the patients who had experienced a momentary spike in their activity reverted to levels that were comparable to those found before the procedure. According to the follow-up observations and the input from these patients, the surgical procedure did not result in any of the patients presenting with clinical signs of hepatic dysfunction. Alterations in the serum levels of liver enzymes have been documented in the past following laparoscopic surgery as opposed to open surgery.

The CO_2 pneumoperitoneum must initially be taken into consideration in this scenario. All of the patients who participated in our research were given CO_2 pneumoperitoneum while they were having surgery, and after the procedure, their serum levels of liver enzymes exhibited considerable variations. This finding is consistent with those found in other research that are quite similar to this one. The intra-abdominal pressure of 12-14 mmHg that was employed in our investigation was greater than the typical portal blood pressure of 7-10 mmHg. As a result, the procedure may lower the portal blood flow and create a change in the function of the liver.

On the other hand, the rapid rise and fall in intra-abdominal pressure that occurred during the laparoscopic operation may have also been a contributing factor. It is possible for the portal

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blood flow to undulate as a result of an abrupt change in the pressure inside the abdomen that occurs during a laparoscopic surgery. This undulation and "re-irrigation of organs" and blood flow may give rise to "ischaemia and re-irrigation" damage of tissues and organs, particularly the Kupferr and endothelial cells of hepatic sinusoids. This can lead to the production of free radicals. [14] But it should be evident that the involvement of total surgical harm during open surgery is far more significant than the function played by the reperfusion-related mechanisms following laparoscopy and the creation of free radicals.

Additionally, during the course of our research, we discovered that the elevation in liver enzymes rose in proportion to the length of time that the CO_2 pneumoperitoneum procedure was carried out. Therefore, it is believed that the primary explanation behind these alterations is the elevation of intra-abdominal pressure caused by CO_2 pneumoperitoneum. [8]

Comparable clinical investigations in humans are uncommon, and when they do exist, they often involve just a limited number of participants. The effects of high pressure CO_2 pneumoperitoneum on the splanchnic circulatory system were investigated in a work which states that because of the rise in intra-abdominal pressure, the blood flow to the stomach decreased by 40-54%, the blood flow to the jejunum decreased by 32%, the blood flow to the colon decreased by 44%, the blood flow to the liver decreased by 39%, and the blood flow to the peritoneum increased by 60%. In the meantime, it was also discovered that, despite there being no change in the intra-arterial pressure, the splanchnic blood flow dropped as the operating time progressed. [15]

The neurohumoral response of the vasopressin, renin, angiotensin, and aldosterone system can be triggered by an increase in intra-abdominal pressure as well. Vasopressin and norepinephrine both play an important part in the pathophysiology that leads to impairment to the liver's function. The "squeeze pressure" effect on the liver is a second putative reason for variations of blood liver enzymes after laparoscopic cholecystectomy. This effect occurs after the liver is compressed during the procedure. It's possible that pulling on the gall bladder will allow liver enzymes to escape into the bloodstream. However, this does not hold any significance because the same traction is applied during open cholecystectomy.

The third option is that there was a local effect caused by the prolonged application of diathermy to the liver surface during laparoscopic cholecystectomy and the subsequent transfer of heat to the liver parenchyma. Several pieces of research lend credence to this hypothesis. On the other hand, a method very similar to diathermy is utilised during open cholecystectomy. [16]

The presence of hypercapnia during these treatments is also a potential contributing factor. In addition to these discoveries, it was shown that patients can experience a temporary dysfunction of the liver after receiving some form of general anaesthesia. [3] This consequence is linked to the alterations in splanchnic blood flow and oxygen consumption that are generated by the anaesthetic. However, anaesthesia cannot be the only factor responsible for these shifts because a large number of studies have demonstrated that open procedures performed under general anaesthesia do not result in modifications of this kind.

CONCLUSION

The key advantages of laparoscopic surgery are less tissue stress, a decrease in patient morbidity, and a decrease in patient hospital stay. This expansion of laparoscopic surgery has increased tremendously over the past few decades. Despite this, a large number of studies

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have shown that this surgery is associated with a transient increase in postoperative liver enzymes. New concerns have been raised regarding the effects of carbon dioxide pneumoperitoneum, which causes a decrease in the hepatic blood flow. This decrease in blood flow is accountable for the shift in liver enzymes. Given the limited number of similar studies that have been conducted in India, the present investigation, which was carried out at the Malla Reddy Institute of Medical Sciences on a total of seventy patients, was designed to provide confirmation of the findings of the previous research. The majority of patients demonstrate a transient rise of serum bilirubin and liver enzymes such as AST, ALT, and ALP, according to the findings of our research. It appears that the CO_2 pneumoperitoneum is primarily responsible for this rise. Although this alteration did not appear to have any therapeutic implications in patients with normal liver function, we conclude that those with poor liver function may not benefit as much from laparoscopic surgery as those with normal liver function.

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