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EFFECT OF CARBON DIOXIDE PNEUMOPERITONEUM ON LIVER FUNCTION TESTS AFTER LAPAROSCOPIC CHOLECYSTECTOMY

General Surgery

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ABSTRACT

Introduction: Laparoscopic cholecystectomy (LC) is the gold standard treatment option for symptomatic gall stones. Changes in liver function tests (LFT) following laparoscopic cholecystectomy has been documented by several studies in the past. Altered splanchnic circulation leading to pan-hepatic hypoperfusion secondary to carbon dioxide (CO_2) pneumoperitoneum is attributed as the probable cause. The present study was conducted to observe the changes in LFT after laparoscopic cholecystectomy. The study was also intended to observe the relationship of post-operative changes in LFT with the duration of CO_2 insufflation and its clinical significance.

Methods: Blood samples of 142 patients who underwent LC were collected pre-operatively and at 6 hours, 24 hours and 48 hours interval post-operatively. The collected samples were analysed for serum Bilirubin (total), serum Aspartate Transaminase (AST), serum Alanine Transaminase (ALT) and serum Alkaline phosphatase. The pre-operative and post-operative values of the above mentioned LFT values were compared.

Duration of CO_2 pneumoperitoneum required during LC was recorded to analyse the relationship between the changes in LFT and the duration of CO_2 insufflation.

Results: A statistically significant change in the post-operative levels of serum Bilirubin (total), serum AST, serum ALT and serum alkaline phosphatase was observed after LC.

The elevation from the baseline values in LFT observed after 6 hours and 24 hours of surgery was weakly associated with the duration of pneumoperitoneum required during LC.

The changes in LFT had no apparent effect on the clinical outcome of the patient as measured in terms of post-operative hospital stay duration.

Conclusion: After LC an elevation from pre-operative value is observed in the LFT for a short duration of time post-operatively, having a weak association with the duration of CO_2 insufflation and no apparent clinical significance.

KEYWORDS

CO_2 pneumoperitoneum, Laparoscopic Cholecystectomy, Liver function tests.

INTRODUCTION

Minimal access surgery (MAS) has developed strong roots in surgical field and has changed the face of general surgery. This advancement has now extended into the super-speciality branches of general surgery too.

Within the last 20 years, open cholecystectomy has been taken over by laparoscopic cholecystectomy in benign gallbladder conditions and has been labelled gold standard in cases in cases of cholelithiasis.

Laparoscopic cholecystectomy, though a boon to the surgeon, is not without challenges. Apart from the disease-related complications, there are certain complications in laparoscopic cholecystectomy that are due to the differences in access approaches used and the prerequisite pneumoperitoneum which has to be created, exclusive to laparoscopic surgery ,to name a few.

The increased intra-abdominal pressure due to gas insufflation during laparoscopic surgery has been attributed to hemodynamic, [2, 3, 4] metabolic, [5,4] respiratory, [2,3,4] renal [4] and hepatic dysfunctions [6,7,8,9,10,11,12] during and after the procedure.

Few studies observing the effect of CO_2 pneumoperitoneum on hepatic functions have been reported from the southern part of India. No such studies have been conducted in our Vindhya region. In this study, the effect of CO_2 pneumoperitoneum on hepatic function was analysed by observing the changes in liver function tests at 6 hours interval, 24 hours interval and 48 hours interval after laparoscopic cholecystectomy. This study is also intended to observe the clinical significance of such changes in hepatic functions in a prospective way.

MATERIALS AND METHODS:

The present study ***"Effect of carbon dioxide pneumoperitoneum on liver function tests after laparoscopic cholecystectomy"*** was conducted in the Department of General Surgery, Sanjay Gandhi Memorial Hospital associated with Shyam Shah Medical College, Rewa, (M.P.) from 1st June 2019 to 31st May 2020.

All patients who reported to surgical OPD in Department of General Surgery; referred and transferred from related departments were seen by faculty members and patients in whom there was an indication for laparoscopic cholecystectomy, were investigated, screened and hospitalised.

SELECTION CRITERIA:

All the patients selected for the study had normal range values of liver function tests prior to the laparoscopic cholecystectomy.

EXCLUSION CRITERIA:

- Cases with pre-operative abnormal liver function tests or known case of chronic liver disease or common bile duct pathology;
- Patients with severe co-morbid conditions like cardio-respiratory and renal disease;
- Gall bladder empyema, gangrene or perforation;
- Immunocompromised patients;
- Conversion of laparoscopic surgery to open surgery;
- Haematological disorders;
- Patients who develop biliary complications;
- Pregnant and lactating females;
- Patients who did not give consent for the study.

The protocol for anaesthesia was uniform for all patients as using drugs of low hepatic metabolism. 1 dose of 1.5 g Ceftriaxone plus Sulbactam was given with the induction of anaesthesia as a prophylactic antibiotic and continued post-operatively till the day of discharge.

During laparoscopic cholecystectomy, the intra-abdominal pressure (IAP) was maintained at 12-14 mmHg and the time duration of CO_2 insufflation was recorded.

In all selected patients, the effect of CO_2 pneumoperitoneum on liver function tests was assessed by measuring the levels of Serum Bilirubin, Serum Alkaline Phosphatase, Serum Aspartate Aminotransferase (AST or SGPT) and Serum Alanine Aminotransferase (ALT or SGOT) pre-operatively and then the above mentioned blood/ serum levels were collected 6 hours, 24 hours and 48 hours post-operatively and their levels recorded. The correlation of time duration of CO_2 insufflation with the changes in blood and serum levels of liver enzymes was also analysed.

All data were expressed as the mean ± standard deviation (SD). The data was analysed for finding the significance of the effect of CO_2 pneumoperitoneum on hepatic function by using the students paired t test and one-way Anova test. Pearson correlation coefficient was used to analyse the association of mean difference in serum levels of Bilirubin, AST, ALT and alkaline phosphatase pre-operatively and 6 hours, 24 hours & 48 hours post-operatively with the duration of CO_2 insufflation. P value <0.05 was considered to be statistically significant.

Sample size: 142 patients

RESULTS

Age:

The mean age of the patients in this study was 38.29 (+/- 12.3) years. Mean age among female patients was 37.47 (+/- 10.96) years and among male patients was 41.92 (+/- 16.11) years. The highest prevalence, 50 patients (35.21%) was seen in 31 years to 40 years of age group followed by 37 patients (26.05%) in 21 years to 30 years of age group.

Sex:

Among the patients in our study, around 116 patients (81.69%) were female and 26 patients (18.31%) were male.

LFT changes after LC:

An elevation from the baseline value in the serum levels of bilirubin, AST, ALT and alkaline phosphatase was seen at 6 hours interval and 24 hours interval after laparoscopic cholecystectomy which tapered over next 48 hours but did not reach the pre-operative level. This post-operative change in serum bilirubin, serum AST, serum ALT and serum alkaline phosphatase value was statistically significant ($p < 0.0001$). [Table 1]

Table 1:Changes in liver function tests after Laparoscopic Cholecystectomy

n = 142

S. NO	LIVER FUNCTION TEST (Mean +/- SD)	TIME OF ASSESSMENT				MEASURES OF ONE-WAY ANOVA TEST	
		PRE-OPERATIVE	POST-OPERATIVE			F	P
			6 hours	24 hours	48 hours		
1.	Average Serum Bilirubin value (in mg/dl)	0.6 (+/- 0.23)	0.86 (+/- 0.20)	0.79 (+/- 0.16)	0.64 (+/- 0.18)	**55.16068**	**<0.00001**
2.	Average Serum AST Value (In IU/L)	42.39 (+/- 8.93)	45.98 (+/- 8.29)	45.55 (+/- 8.52)	44.41 (+/- 8.09)	**5.10509**	**0.001713**
3.	Average Serum ALT Value (In IU/L)	42.47 (+/- 8.98)	47.38 (+/- 10.88)	43.85 (+/- 10.62)	41.92 (+/- 10.32)	**19.42977**	**< 0.00001**
4.	Average Serum Alkaline Phosphatase Value (In IU/L)	52.97 (+/- 12.32)	60.68 (+/- 13.98)	55.40 (+/- 12.40)	51.47 (+/- 13.21)	**13.68457**	**< 0.00001**

Serum bilirubin:

The mean difference in serum bilirubin value between pre-operative level & 6 hours post-operative level; pre-operative level & 24 hours post-operative level and pre-operative level & 48 hours post-operative level was found to be highly significant ($p < 0.0001$). [Table 2]

Serum AST:

When the association between the pre-operative serum AST value with the post-operative values at 6 hours interval, 24 hours interval and 48 hours interval after laparoscopic cholecystectomy was studied, a significant rise was noted in serum AST level post-operatively in comparison to the pre-operative value ($p < 0.05$). [Table 2]

Table 2: Association of pre-operative and post-operative LFT values (n = 142)

S.No	Association between	Paired T – Test Value	Inference
Serum Bilirubin level			
1.	Pre-operative and 6 hours post-operative	16.611869	P < 0.00001 (Significant)
2.	Pre-operative and 24 hours post-operative	11.545139	P < 0.00001 (Significant)
3.	Pre-operative and 48 hours post-operative	3.963037	P = 0.00012 (Significant)
Serum Aspartate Transamainase level			
1.	Pre-operative and 6 hours post-operative	4.998167	P < 0.00001 (Significant)
2.	Pre-operative and 24 hours post-operative	3.612748	P = 0.00042 (Significant)
3.	Pre-operative and 48 hours post-operative	2.511861	P = 0.01314 (Significant)
Serum Alanine Transaminase value			
1.	Pre-operative and 6 hours post-operative	5.184288	P < 0.00001 (Significant)
2.	Pre-operative and 24 hours post-operative	1.382719	P = 0.16894 (Insignificant)
3.	Pre-operative and 48 hours post-operative	-0.596733	P = 0.55164 (Insignificant)
Serum alkaline phosphatase value			
1.	Pre-operative and 6 hours post-operative	7.844248	P < 0.00001 (Significant)
2.	Pre-operative and 24 hours post-operative	2.444323	P = 0.01575 (Significant)
3.	Pre-operative and 48 hours post-operative	-1.51833	P = 0.13117 (Insignificant)

Serum ALT:

There was a significant rise in serum ALT level at 6 hours interval post-operatively in comparison to the pre-operative value. But the correlation between the differences in serum ALT value pre-operatively vs. 24 hours post-operatively ($p = 0.16$) and pre-operatively vs. 48 hours post-operatively ($p = 0.55$) was found to be statistically insignificant. [Table 2]

Serum alkaline phosphatase:

The rise in serum alkaline phosphatase levels at 6 hours interval and 24 hours interval post-operatively in comparison to the pre-operative values was significant. But the differences in serum alkaline phosphatase value pre-operatively versus 48 hours post-operatively ($p = 0.13$) was observed to be statistically non-significant. [Table 2]

Duration of CO_2 insufflation:

The maximum duration of CO_2 insufflation during laparoscopic cholecystectomy was 55 minutes and the minimum duration was 30 minutes with an average of 39.78 (+/- 6.1) minutes.

When the correlation of the duration of CO_2 insufflation and the rise in level of serum Bilirubin, serum AST, serum ALT and alkaline phosphatase after 6 hours and 24 hours of LC was studied by Pearson correlation coefficient, the association was observed to be weak. [Table 3-6]

Table 3: Change in serum Bilirubin value in relation to duration of CO2 insufflation

n = 142

S. No	Average Serum Bilirubin Value (In mg/dl) (Mean +/- SD)	Duration of CO_2 insufflation (in minutes)					
		≤ 30 (n =12)	31-35 (n = 46)	36-40 (n = 38)	41-45 (n = 33)	46-50 (n = 08)	51-55 (n = 05)

1.	**Pre-operative**	0.60 (+/0.18)	0.54 (+/0.23)	0.68 (+/-0.21)	0.56 (+/0.23)	0.68 (+/-0.26)	0.68 (+/-0.25)
2.	**6 hours post-operative**	0.85 (+/0.17)	0.83 (+/0.17)	0.89 (+/-0.17)	0.89 (+/0.27)	0.86 (+/-0.17)	0.94 (+/-0.28)
3.	**24 hours post-operative**	0.73 (+/0.14)	0.78 (+/0.18)	0.80 (+/-0.13)	0.82 (+/0.17)	0.8 (+/-0.15)	0.74 (+/- 0.11)
4.	**48 hours post-operative**	0.63 (+/- 0.16)	0.61 (+/- 0.16)	0.71 (+/- 0.20)	0.61 (+/- 0.17)	0.65 (+/- 0.23)	0.7 (+/- 0.18)

Table 4: Change in serum AST value in relation to duration of CO2 insufflation

n = 142

S. No	Average Serum AST Value (in IU/L) (Mean +/ SD)	Duration Of Co_2 Insufflation (In Minutes)					
		≤ 30 (n = 12)	31-35 (n = 46)	36-40 (n = 38)	41-45 (n = 33)	46-50 (n = 08)	51-55 (n = 05)
1.	**Pre-operative**	39.75 (+/9.80)	41.69 (+/8.71)	42.81 (+/9.10)	44.51 (+/9.07)	40.12 (+/7.97)	41.6 (+/9.04)
2.	**6 hours post-operative**	46.33 (+/8.28)	44.84 (+/6.46)	46.63 (+/11.03)	47.24 (+/6.59)	44.75 (+/10.62)	44.4 (+/7.43)
3.	**24 hours post-operative**	45 (+/5.46)	45 (+/6.16)	46.89 (+/11.58)	44.84 (+/8.14)	43.25 (+/10.40)	50.2 (+/5.31)
4.	**48 hours post-operative**	42.66 (+/8.33)	44.93 (+/6.28)	45.18 (+/10.05)	43.57 (+/7.95)	42.87 (+/10.19)	46 (+/4.52)

AST: Aspartate Transmainase

Table 5: Change in Serum ALT value in relation to duration of CO2 insufflation

n = 142

S. NO	Average Serum ALT Value (in IU/L) (Mean +/- SD)	Duration of CO_2 Insufflation (in minutes)					
		≤ 30 (n = 12)	31-35 (n = 46)	36-40 (n = 38)	41-45 (n = 33)	46-50 (n = 08)	51-55 (n = 05)
1.	**Pre-operative**	40.16 (+/11.01)	42.10 (+/- 7.98)	41.71 (+/- 7.57)	46.18 (+/10.08)	36.37 (+/11.07)	42.6 (+/-5.41)
2.	**6 hours post-operative**	48.41 (+/- 6.82)	45.76 (+/-6.39)	48.84 (+/16.52)	47.93 (+/-9.48)	44.75 (+/11.62)	49.2 (+/-5.35)
3.	**24 hours post-operative**	45.41 (+/- 5.83)	43.80 (+/- 7.11)	45.05 (+/16.22)	43 (+/-8.34)	38.62 (+/11.01)	45.6 (+/-4.77)
4.	**48 hours post-operative**	41.83 (+/- 7.0)	41.13 (+/- 8.30)	42.36 (+/14.62)	43.24 (+/-9.23)	38.25 (+/-8.64)	43.2 (+/-0.83)

ALT: Alanine Transaminase

Table 6: Change in Serum Alkaline Phosphatase value in relation to duration of CO2 insufflation

n = 142

S. No	Average Serum Alkaline Phosphatase Value (In IU/L) (Mean +/- SD)	Duration Of Co_2 Insufflation (In Minutes)					
		≤ 30 (n = 12)	31-35 (n = 46)	36-40 (n = 38)	41-45 (n = 33)	46-50 (n = 08)	51-55 (n = 05)
1.	**Pre-operative**	50.83 (+/12.25)	52.21 (+/9.76)	52.73 (+/12.16)	53.51 (+/8.90)	58.25 (+/30.9)	55 (+/10.6)
2.	**6 hours post-operative**	59.16 (+/- 8.33)	59.17 (+/6.93)	61.18 (+/10.57)	61 (+/19.25)	69.75 (+/32.76)	57.80 (+/8.75)
3.	**24 hours post-operative**	55.16 (+/- 8.23)	54.13 (+/7.59)	55.63 (+/11.94)	54.90 (+/12.73)	63.25 (+/31.37)	56.6 (+/9.93)
4.	**48 hours post-operative**	51.08 (+/-10.98)	49.54 (+/9.71)	51.94 (+/11.37)	52.30 (+/12.08)	60 (+/33.73)	47.6 (+/12.60)

Table 7: Pearson correlation between elevation in liver function test value and duration of CO_2 insufflation

S.No	Time duration	Pearson correlation coefficient (r)	P value
A.	**Serum Bilirubin**		
1.	6 hours post-operative	-0.0065	0.943505 (insignificant)
2.	24 hours post-operative	-0.0482	0.570539 (insignificant)
B.	**Serum AST**		
1.	6 hours post-operative	-0.052	0.538825 (insignificant)
2.	24 hours post-operative	-0.039	0.644938(insignificant)
C.	**Serum ALT**		
1.	6 hours post-operative	-0.0239	0.78586 (insignificant)
2.	24 hours post-operative	-0.109	0.196615 (insignificant)
D.	**Serum Alkaline phosphatase**		
1.	6 hours post-operative	-0.0004	1(insignificant)
2.	24 hours post-operative	-0.0137	0.877964(insignificant)

AST: Aspartate Transmainase, ALT: Alanine Transaminase

Post-operative hospital stay duration:

Amongst the total number of 142 patients who underwent laparoscopic cholecystectomy, maximum patients (64 patients) were discharged on 3rd post-operative day. Discharges on the 2nd, 4th and 5th POD were 57 patients, 20 patients and 1 patient, respectively. The average post-operative hospital stay duration was 2.76 (+/- 1.46) days following laparoscopic cholecystectomy.

DISCUSSION

Laparoscopic surgery has become the established method of treatment of many surgical conditions in the present era. The evolution from traditional open surgery to Minimal Access Surgery has been due to the large acceptance and increasing demand by the patients and treating doctors, attributable to its many advantages over open surgery.

Apart from the general complications common to all the surgical procedures, there are certain complications in laparoscopic surgery that are due to the differences in access approaches used and the prerequisite pneumoperitoneum which has to be created, exclusive to laparoscopic surgery, to name a few. During the last decade, many studies have reflected upon unexplained alterations in the liver function tests following laparoscopic surgery. [6,7,8,9,10,11,12]

Age:

Our report on the age distribution of study subjects is comparable to the observations made by Avadhani GK et al [13], Ibrahim AMS et al [14], Omari et al [15], Singal R et al [16]and Bellad A et al [17]. This is because of the fact that the disease cholelithiasis for which laparoscopic procedure is most commonly performed is more prevalent among women of reproductive age (15-50 years).

Sex:

The study by AvadhaniGK et al [13], Singal R et al [16], Chandrasekaran K [18], Omari et al [15] and Bellad et al [17] also reported more number of female patients than male patients which similar to our observation. The obvious observation is that the surgical pathology (cholelithiasis) per se is encountered routinely with a female predominance and therefore the laparoscopic treatment which is offered is more common in women than men.

The study sample of Ibrahim AMS et al [14]had 34 male and 26 female subjects which differs from our observation. This may be probably due to less number of female patients approaching hospital and very few opting surgical management in that demographic region.

Changes in liver function tests after LC:

AvadhaniGK et al [13] concluded from their study that when compared to the pre-operative value, the mean value of serum bilirubin, serum AST, serum ALT and serum alkaline phosphatase increased significantly ($p < 0.001$) by post-operative day 1 and they came down to near pre-operative value by post-operative day 5.

Ibrahim AMS et al [14] reported that when correlated to pre-operative

levels, serum bilirubin, serum AST, serum ALT and serum alkaline phosphatase values increased in post-operative day 1 (p = 0.0001) which was highly significant.

Omari A et al [15] observed a statistically significant increase of serum bilirubin, serum AST, serum ALT and serum alkaline phosphatase value 24 hours after laparoscopic cholecystectomy (P < 0.0005) which correlates with our analysis.

Singal R et al [16] observed a significant rise in the mean value of serum bilirubin, serum AST, serum ALT and serum alkaline phosphatase after 24 hours of surgery (P = 0.0001), followed by a fall to near normal value after 72 hours of surgery, a finding close to our study.

Bellad A et al [17] described a significant difference between the pre-operative and 24 hours post-operative serum bilirubin, serum AST, serum ALT and serum alkaline phosphatase value and a P value < 0.0001 much similar to our observation.

A study by Chandrasekaran K[18] on the effect of carbon dioxide as pneumoperitoneum on liver functions in laparoscopic cholecystectomy in 2016 on 50 patients did not observe any significant alterations in liver function tests after surgery. This can be attributed to the small sample size of the study.

Association of CO_2 insufflation duration and changes in liver function tests:

In our study, the average duration of CO_2 insufflation observed during laparoscopic cholecystectomy was 39.78 (+/- 6.1) minutes.

Omari A et al [15] described a statistically significant increase (p < 0.0005) of ALT, AST, total bilirubin and direct bilirubin 24 hours after LC which had no correlation with the duration of surgery. This was identical to the observation in our study.

Bellad A et al [17] observed that there was more increase in liver function tests (LFTs) when the surgeries were prolonged for more than 80 minutes, however the rise was non-significant which was in favour of our observations.

The study by Chandrasekaran K[18] concluded that the duration of CO_2 pneumoperitoneum had no significant effect on liver function tests.

Singal R et al [16] reported that after LC, patients with minimum duration of surgery (40 minutes) had less elevation in liver enzymes as compared to the patients with maximum duration (90 minutes) of surgery. In our study, laparoscopic cholecystectomy was completed on an average of 39.78 (+/- 6.1) minutes, which according to Singal R et al [16] was minimum duration of surgery with less elevation in liver enzymes.. Thus it can be concluded that since the subjects in our study underwent surgery with minimum duration of CO_2 insufflation duration, there was no significant correlation between the duration of CO_2 insufflation and changes in liver function tests.

Ibrahim AMS et al [14] reported a statistically significant correlation between the CO_2 insufflation duration and elevated liver enzyme levels. This observation differed from our study.

Many studies during the last decade have reported alterations in the liver function tests following laparoscopic surgery. [6, 7, 8, 9, 10, 11, 12] A transient "squeeze pressure" effect on liver by traction on gall bladder, transient kink in the extra hepatic ducts due to pulling of gall bladder, inadvertent clipping of the right branch of hepatic artery or any other aberrant arterial branch supplying blood to liver and prolonged use of diathermy on the liver surface and adjacent structures are suggested to be a cause of LFTs changes after laparoscopic surgery. However their effect is debatable since changes in LFTs is also observed after other laparoscopic surgeries whose focus is far away from liver.

There are two main factors that can cause changes in LFTs after laparoscopic surgeries: Increased intra-abdominal pressure (IAP) and CO_2 as pneumoperitoneum.

Elevated IAP mechanically compresses capillary beds, decreases splanchnic microcirculation and thus impairs oxygen delivery to the intra-abdominal organs. The cellular damage leading to pan-hepatic hypo-function after laparoscopic surgeries can be explained by decrease supply of O_2 and nutrients to the liver cells or to the release of toxins from the gut as a result of splanchnic ischemia. Many experimental studies have published a pressure related reduction in portal blood flow. [19,20,21,22] On the other hand, head-up positioning in the presence of pneumoperitoneum appears to be a cause of decreased hepatic perfusion. [15] CO_2 employed to induce pneumoperitoneum has a vaso-constrictive effect which can reduce the visceral blood flow.

The level of pneumoperitoneum is also seen to play an important role in such changes in LFTs after laparoscopic surgeries. Tripathi V et al [23] in July 2020 and a meta-analysis by Hua J et al [24] concluded that low-pressure pneumoperitoneum had least hemodynamic & physiological effects than standard pressure pneumoperitoneum and better tolerated in people with cardiovascular and pulmonary insufficiencies.

A sudden inflation and deflation of IAP may result in ischemia-reperfusion injury and release of free radicals at the end of laparoscopic surgery, damaging the liver cells especially the reticulo-endothelial cells of the hepatic sinusoids. [15]

CONCLUSION:

In the present study, a transient post-operative elevation in the serum bilirubin, serum AST, serum ALT and alkaline phosphatase levels was observed after different laparoscopic surgeries. It had no apparent effect on the clinical outcome of the patient as measured in terms of post-operative hospital stay duration. Therefore, as its benefits outweigh its limitations, laparoscopic approach is recommended in patients with normal pre-operative LFTs. Laparoscopic surgery will be emerging to be a gold standard approach in many surgical conditions in times to come. However, surgeons must take precautions in patients with hepatic dysfunction prior to the surgery and the biochemical markers should be continued to be assessed at least 7 days post-operatively till they reach the baseline value.

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