Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL 14, ISSUE 12, 2023

Original research article

COMPARATIVE STUDY BETWEEN LOW PRESSURE AND STANDARD PRESSURE PNEUMOPERITONEUM IN LAPAROSCOPIC CHOLECYSTECTOMY ON ALANINE TRANSAMINASE

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Abstract

This study is a randomized control trail conducted in CSI Holdsworth Memorial Hospital, Mysore. Study was initiated after taking clearance from Scientific and Ethical committee. Study population consists of 60 patients requiring Laparoscopic Cholecystectomy for benign gall bladder disease. They were divided into two groups, Group-A and Group-B each group consisting of 30 patients. Pre-operative Alanine transaminase (ALT) level was measured in both the groups. Group-A was operated using Low pressure pneumoperitoneum (8-12 mmHg), Group-B was operated using Standard pressure pneumoperitoneum (12-15 mmHg) and duration of the procedure was also noted. Post-operative 24th hour Alanine transaminase (ALT) level was measured. Changes in ALT level in both the groups were compared and reasons for alteration in Liver enzymes were studied.

Keywords: Pneumoperitoneum, laparoscopic, cholecystectomy, alanine transaminase

Introduction

Modern surgery has evolved to be technically sophisticated and complex. During the past several decades, numerous individuals cultivated and promoted the access for laparoscopy. The big development in the field of laparoscopy was made by invention of computer chip television camera. This scientific modernization implement the means to program a magnified picture of the operation field on to the monitor, facilitating performance of complex laparoscopic procedures, better results with least damage [1].

Laparoscopy provides access to the peritoneal cavity for diagnosis and for many surgical interventions that were previously possible only by laparotomy [2]. Some of diseases which were not dealt due to fear of damage to surrounding structures during access are presently been treated easily with laparoscopic surgery [1].

Pneumoperitoneum is a crucial factor in laparoscopy. Insufflation with it, helps to maximize the working space in a limited contained cavity. Method of insufflation is usually intra peritoneal, wherein the abdominal wall gets elevated and the viscera gets

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suppressed [3].

Carbon dioxide (CO_2) is the preferred gas for establishing a pneumoperitoneum, and this method of creating pneumoperitoneum using CO_2 is referred to as capnoperitoneum. Although the mainstay for cholecystectomy is laparoscopy, it also has its own limiting factors. It produces elevated intra-abdominal pressure (IAP) and continuous compression on intra-abdominal organs with elevation of diaphragm, which might potentially influence the hepatic, pulmonary and renal functions [4].

Physiological changes due to pneumoperitoneum depend on amount of intra-abdominal pressure used intraoperatively and time taken to complete the surgery [5]. Pneumoperitoneum created with CO_2 for Laparoscopic cholecystectomy in head up position leads to greater risk of decrease in cardiac output and hence affecting hepatic perfusion [5, 8].

The intra-abdominal pressure of 12-14 mmHg of carbon dioxide (CO_2) traditionally used in laparoscopic surgery is higher than normal pressure values of the portal system (7-10 mmHg). This pneumoperitoneum value could therefore reduce portal flow and cause physiological alterations in liver function [5]. By using a pressure less than traditional pressure, there may be chances of visceral injury and prolonged time of procedure due to reduced operating space.

Despite other studies ideal pressure is not given for creating pneumoperitoneum in laparoscopic cholecystectomy considering alteration of liver function and injury to biliary structure. This study is to determine the reasons for elevation of liver function parameter at different insufflation pressure and to determine the best pressure for laparoscopic procedure considering patient safety and post-operative wellbeing.

Aim and Objectives

Aim

To correlate the effect of pressure and duration of intra-operative carbon dioxide pneumoperitoneum on the hepatic enzyme Alanine transaminase, in Laparoscopic cholecystectomy.

Objective

To identify possible reasons for changes in liver enzymes in relation to insufflation pressure, duration of procedure in patients undergoing Laparoscopic cholecystectomy.

Materials and Methods

Study site

The study was conducted in the department of general surgery, of CSI Holdsworth Memorial Hospital, located in Mysore of Karnataka state. This hospital is a multi-disciplinary hospital with exclusive beds allotted to surgical patients.

Study design

This study was a prospective double blinded randomized control trial.

Study population

The study population constituted of patients presenting to department of General surgery of CSI Holdsworth Memorial Hospital for Laparoscopic cholecystectomy. The

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study participants who fulfilled inclusion criteria were included in the study.

Inclusion criteria

1. Patients undergoing laparoscopic cholecystectomy procedures in, CSI Holdsworth Memorial Hospital, Mysore.
2. Age more than 18year.

Exclusion criteria

- Patients with coexisting liver disease, long term use of hepatotoxic drug and those who undergo ERCP within one week preoperatively.
- Patients with intraoperative, bile duct injury, obstruction, infection, leakage and high grade fever during surgery.
- Age less than 18year.
- Pregnancy, lactation.

Study duration

The total study duration was from October 2018 to May 2020.

Sample size determination

Sample size was calculated based on previous study of alteration in liver function tests following laparoscopic procedure.
We have considered, Prevalence -18%
Precision -10%
Confidence level -95%
Type 1 error - 0.05

The formula to this study for sample size calculation is

$N = [Z^2 P (1-P)] / d^2$
Where, n = sample size
Z = statistical level of confidence (2)
D = precision
$N = [2^2 \times 0.18(1-0.18)] / (0.1)^2$
N = 59

Total 60 number of patients will be selected for the study after application of inclusion and exclusion criteria and enrolled after taking informed and written consent. These patients will be divided into two equal group containing 30 subjects in each group.

Conduction of study

Randomization and blinding

Randomization used was a block randomization, so that every sampling unit got an equal chance of being included in it. Randomization of each patients was done into two groups one of which underwent Laparoscopic cholecystectomy at low pressure 10-12 mmHg and other group underwent Laparoscopic cholecystectomy at standard pressure 12-15 mmHg. Randomization was done using codes obtained from www.randomization.com using randomly permuted blocks with random block sizes

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and allocation ratio of 1:1. Blinding followed in the present study was a double blinding technique, neither the study participant nor the investigator knows about which patient gets operated at what pressure.

Sampling method

Once a patient General surgery department, CSI Holdsworth Memorial Hospital fulfils the above mentioned inclusion and exclusion criteria allocation to groups as per randomization to the current study was done. Patients were explained about the purpose of study verbally and in form of written patient information sheet in a language of their understanding ensuring strict confidentiality. Written informed consent were taken prior to undertaking for surgery. Following Helsinki declaration, they were given option not to participate in study if they wish to or opt out anytime from study (detailed sheets included in Annexure).

Patients were assigned a random number generated through a computer software and will be grouped as A and B. Group A - Patients undergoing Laparoscopic cholecystectomy at Low pressure pneumoperitoneum 8-12 mmHg. Group B - Patients undergoing Laparoscopic cholecystectomy at Standard pressure pneumoperitoneum 12-15 mmHg. All patients underwent surgery were measured pre-operative ALT and post operatively after 24 hr again ALT was measured. Level of ALT in both group were measured and tabulated. Only ALT was measured which is more specific for liver. Other routine pre-operative blood investigations like complete blood count, blood grouping and typing, bleeding time, clotting time, renal functional test, HIV, HBsAg, HCV, ECG were done.

Parameters included in the study

Primary outcome of interest was measuring changes in ALT and duration of the surgery and adverse effect associated in both the group.

Ethical consideration

The study, approved by ethical committee, was undertaken in Surgical department at CSI Holdsworth memorial hospital, Mysore.

1. Respondents participated in the survey voluntarily after giving informed consent in their language of understanding and was fully informed in presence of a senior specialist, about the aims and objectives of the study and associated possibility of any complications along with amount of risk of its incidence as supported by current literature, before participants in it.
2. The questionnaire did not contain any degrading, discriminating or any other unacceptable language that could be offensive to any members of the sample group.
3. The privacy of the research participants, anonymity of individuals and organisations participants in the research and adequate level of confidentiality of the research data will be ensured. The data obtained in the study and photograph, if taken will be published in the journal.
4. Falsification, fabrication and misinterpretation of data, deception or exaggeration about the aims and objectives of the research, as well as representation of primary data findings in a biased way will be avoided.
5. The researchers participating in the study don’t have any affiliations in any forms

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whatsoever to any institution, company or agency. There are not any known possible conflicts of interest.

6. Complete freedom to individuals to participate and to withdraw from research at any time without penalty or loss of benefits to which the subject would otherwise be entitled.

Consent of the study participants

Printed consent form was given to the participants if she could read, or it was to read out to him the presence of another person, after which the participant was asked to sign (or place thumb impression) on the form (Annexure IV). The confidentiality of the study participants was maintained at all points of the study.

Statistical analysis

Summary statistics was done by means of proportions for categorical/binary variables and mean, median, Standard deviation, Inter Quartile Range (IQR) for continuous variables.

Inferential statistics was done by using Chi square test/fisher exact test, Independent t test, and Mann Whitney test.

All the statistical methods were done using SPSS 21.0 version for windows. $p<0.05$ was considered statistically significant.

Chi square test/fisher exact test are used comparing two or more independent proportions. Fisher exact is used when the number of expected numbers in >25% cells is <5.

Independent t test was used to compare means between independent groups/mutually exclusive groups.

Mann Whitney test was used to compare the continuous variable which is not normally distributed/ ordinal variables between two independent group

Results

Total patients studied were 60 among which 24 were male and 36 were female. 17 and 19 females are operated at low and standard pressure respectively. 13 and 11 males are operated at low and standard pressure respectively.

Table 1: Sex distribution in study population

		Pressure			
		Low		Standard	
		Count	Column N %	Count	Column N %
Sex	Female	17	56.7%	19	63.3%
	Male	13	43.3%	11	36.7%

P=0.6, chi square test

The groups were similar with respect to gender as it is statistically insignificant.

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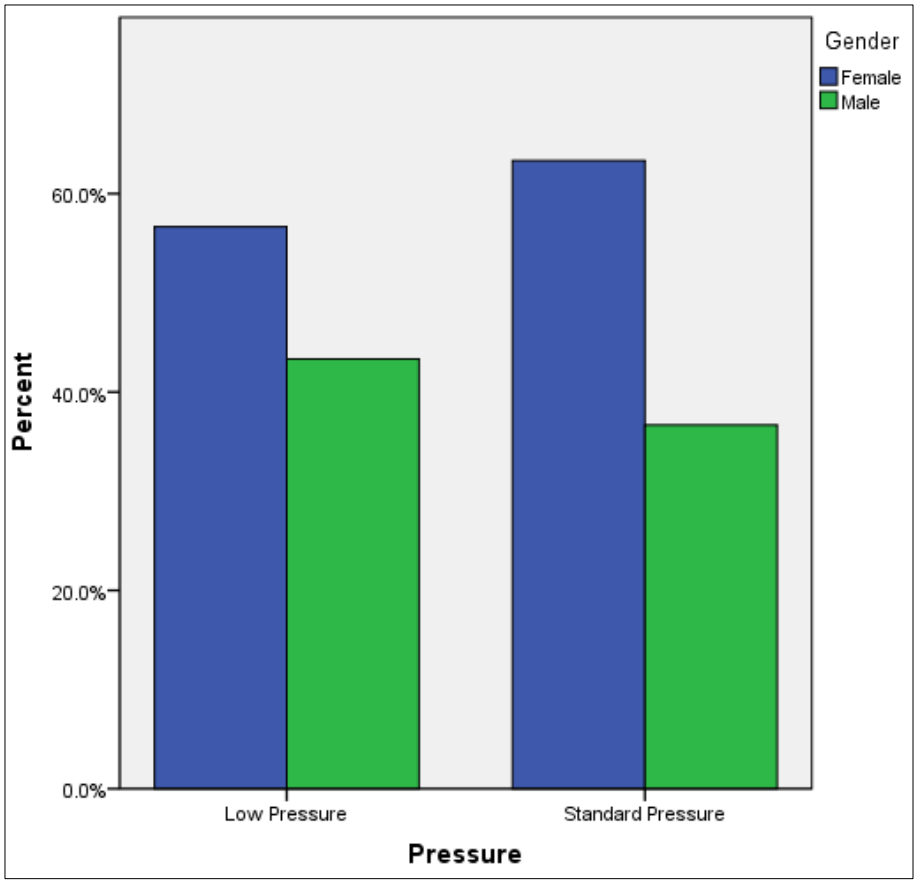

Fig 1: Bar chart showing sex distribution in study population

The population operated at low pressure is 43.87±12.73years and standard pressure is 44.93±11.81years.

Table 2: Age distribution in study population

	Pressure			
	Low		**Standard**	
	Mean	**SD**	**Mean**	**SD**
Age	43.87	12.73	44.93	11.81

P=0.7, independent t test

There was no statistically significant difference in age between the two groups

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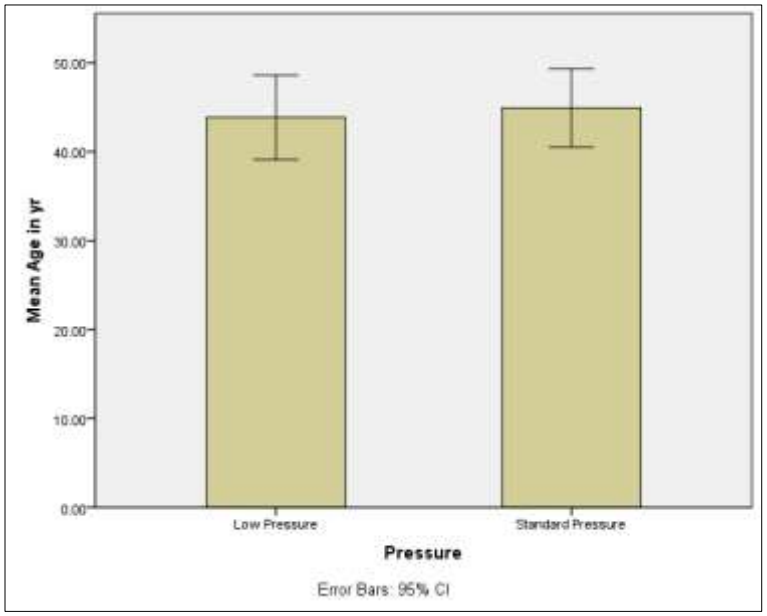

Fig 2: Age wise distribution in study population

There are 5 subjects in both low and standard pressure group were below 30 years of age. 9 and 5 were between 31to 40years, 11 and 14 were between 41 to 50years, 5 and 6 were above 51years respectively.

Table 3: Comparison of age between low and standard pressure group

		Pressure			
		Low		Standard	
		Count	Column N %	Count	Column N %
Age groups	<30 yr.	5	16.7%	5	16.7%
	31-40 yr.	9	30.0%	5	16.7%
	41-50 yr.	11	36.7%	14	46.7%
	>51 yr.	5	16.7%	6	20.0%

P=0.66, chi square test

There was no statistically significant difference in age groups between the two groups. In other words age was similar in both groups and groups are comparable w r t age groups.

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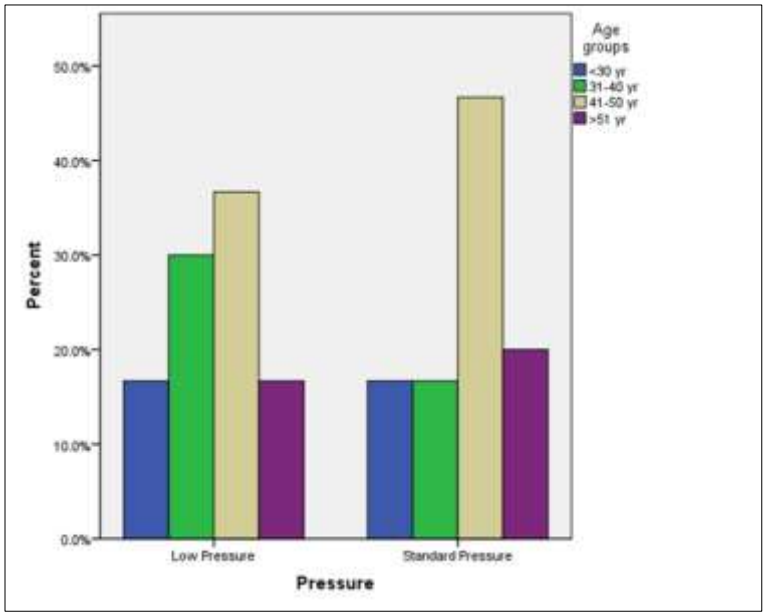

Fig 3: Different age distribution in each group

Duration of laparoscopic cholecystectomy using low pressure pneumoperitoneum is 91±13.09 minutes and using standard pressure pneumoperitoneum is 86.17±10.96 minutes.

Table 4: Duration of procedure in both group

	Pressure			
	Low		**Standard**	
	Mean	**SD**	**Mean**	**SD**
Duration in minutes	91.00	13.09	86.17	10.96

P=0.12

Independent t test

There was no statistically significant difference in duration of surgery between the two groups.

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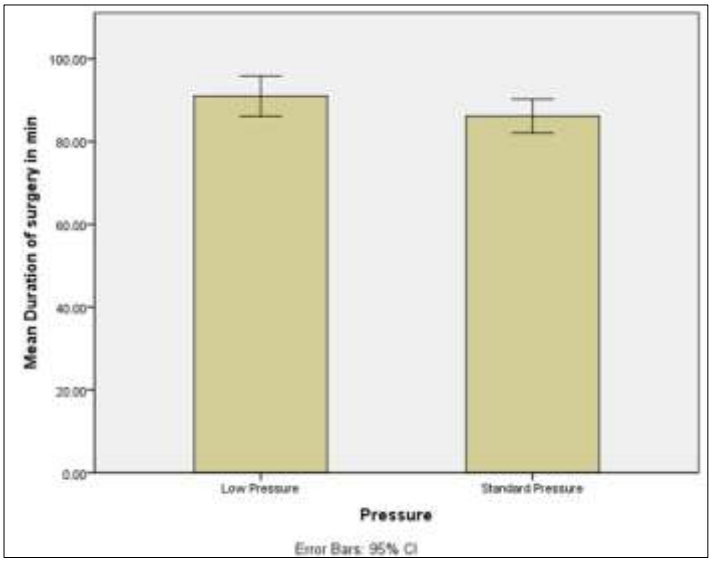

Fig 4: Graph showing duration of procedure in Low and Standard pressure pneumoperitoneum

The pneumoperitoneum pressure used for low pressure group is 11.8±0.7mmhg and for standard pressure is 15±0 mmhg

Table 5: Pressure difference in both groups

	Pressure			
	Low		Standard	
	Mean	SD	Mean	SD
Pressure in mmHg	11.8	0.7	15.0	.0

p<0.0001, independent t test

There was statistically significant difference in pressure between two groups. Standard pressure group had 3.2 mm of Hg higher compared to low pressure group.

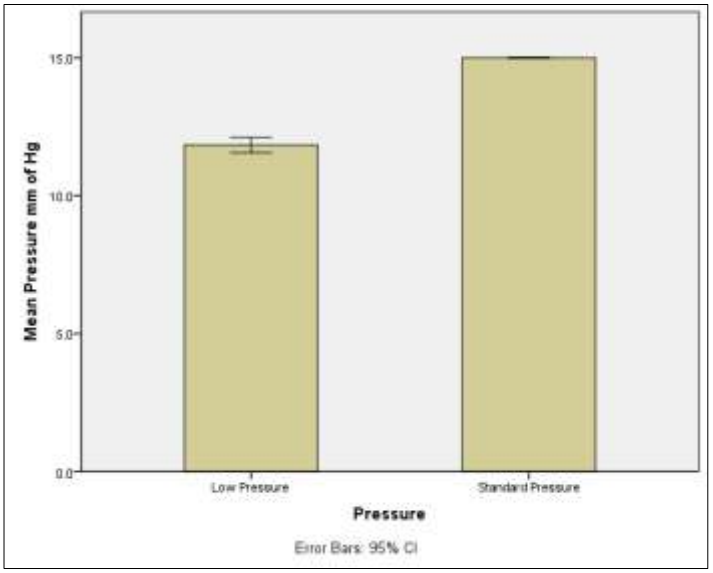

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Fig 5: Graph showing pressure difference in both group

The pre-operative Alanine transaminase (ALT/SGPT) value are 44.27±21.14units/liter in low pressure and 57.97±21.14 units/liter in standard pressure pneumoperitoneum group.

Table 6: Comparison of pre-operative ALT (SGPT) in both group

	Pressure			
	Low		Standard	
	Mean	SD	Mean	SD
Pre-operative ALT U/ltr	44.27	21.14	57.97	52.00

P=0.2, Independent t test

There was no statistically significant difference in pre surgery ALT in both groups. The pre surgery ALT was similar in both groups.

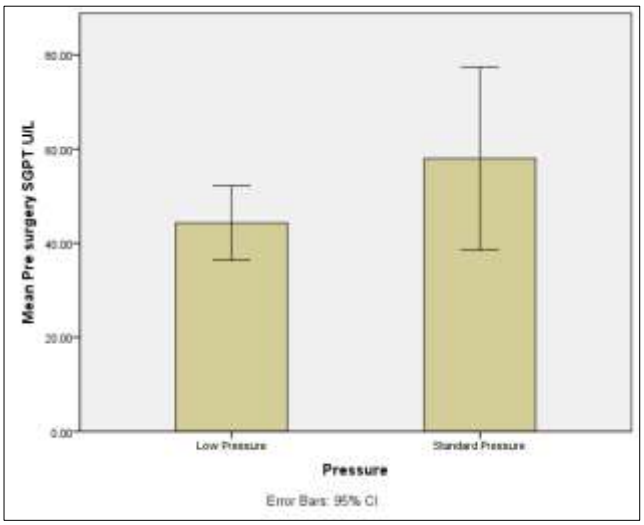

Fig 6: Pre-operative ALT (SGPT) in both groups

The elevation of ALT (SGPT) in first post-operative day is 56.23±23.33 Unit/liter in low pressure and 77.67±51.38Unit/liter in standard pressure pneumoperitoneum.

Table 7: Post-operative elevation in ALT (SGPT) in both groups

	Pressure			
	Low		Standard	
	Mean	SD	Mean	SD
@24HR SGPT U/l	56.23	23.33	77.67	51.38

P=0.04, independent t test

There was statistically significant higher ALT (SGPT) level in standard pressure group; however this increase of nearly 20 U/L is not clinically significant. (Table 7).

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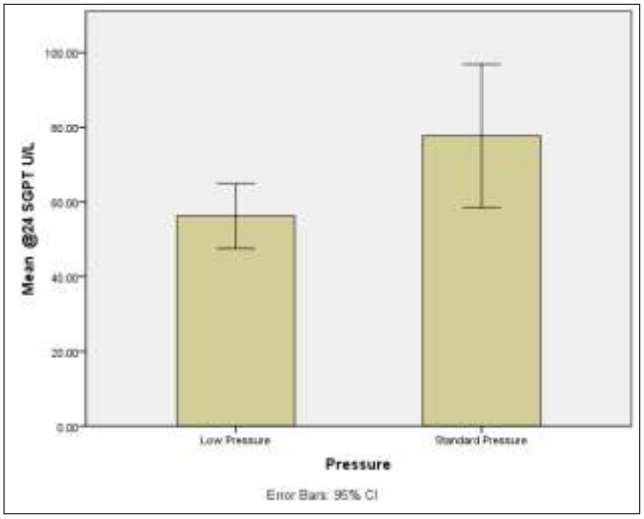

Fig 7: Graph showing first post-operative day changes in ALT (SGPT) in both groups

Table 8: Comparison of elevation in ALT/SGPT in low and standard pressure pneumoperitoneum group

	Pressure									
	Low					Standard				
	Mean	SD	Median	Q1	Q3	Mean	SD	Median	Q1	Q3
Increase of SGPT U/l	11.97	10.55	8.00	6.00	16.00	19.70	30.56	21.50	6.00	39.00

P=0.021, Mann Whitney test

The low pressure group had lesser increase [8, 6-16] compared to standard pressure [21.5, 6-39], as shown in the table 8. This difference in increase of SGPT was statistically significant, but not clinically relevant.

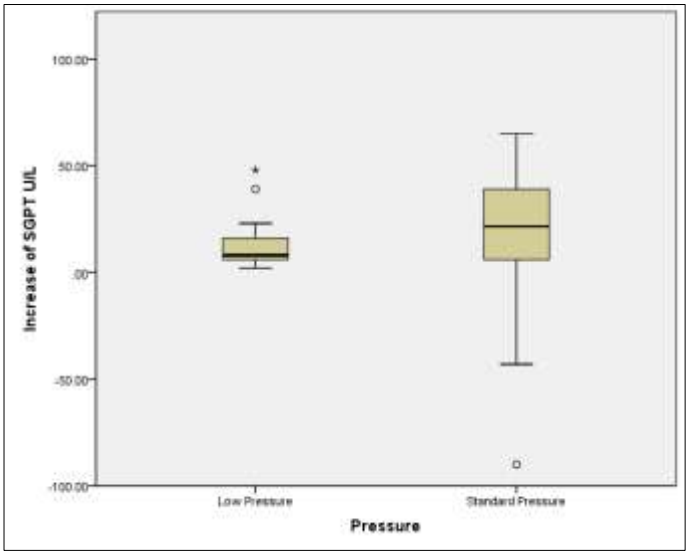

Fig 8: Graph showing elevation in ALT (SGPT) in low and standard pressure pneumoperitoneum group

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Percentage increase in ALT (SGPT) is low pressure group is 20.10, 10.26, 42.59 Unit/liter and in standard pressure pneumoperitoneum is 44.12, 9.88, 105 Unit/liter.

Table 9: Percentage increase in ALT (SGPT) in both groups

	Pressure					
	Low Pressure			Standard Pressure		
	Median	Q1	Q3	Median	Q1	Q3
% Increase of SGPT U/L	20.10	10.26	42.59	44.12	9.88	105.00

P=0.2, Mann Whitney test

The difference in percentage increase of ALT (SGPT) is statistically insignificant before removing the outliers.

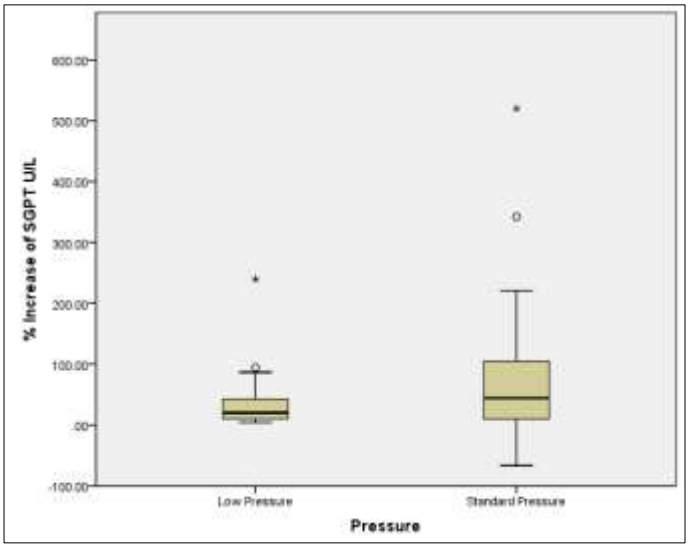

Fig 9: Percentage increase in ALT (SGPT) in both group before removing the outliers
Percentage increase in ALT (SGPT) in low pressure pneumoperitoneum is 19.51, 10.26, 40 and in standard pressure pneumoperitoneum is 27.27, 8.70, 84.62.

Table 10: Percentage increase in ALT (SGPT) in both group after removing the outliers

	Pressure					
	Low Pressure			Standard Pressure		
	Median	Q1	Q3	Median	Q1	Q3
% Increase of SGPT U/L	19.51	10.26	40.00	27.27	8.70	84.62

P=0.4, Mann Whitney test

The difference in percentage increase of ALT (SGPT) is statistically insignificant after removing the outliers.

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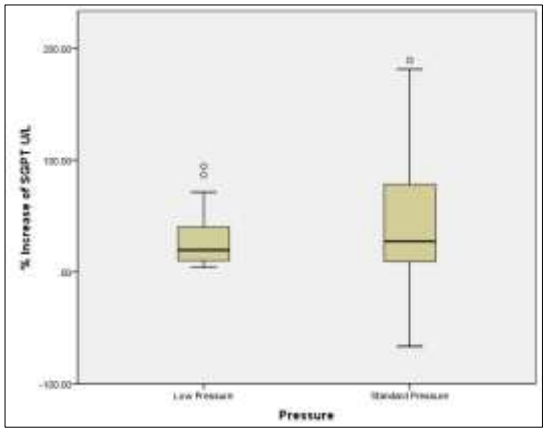

Fig 10: Percentage increase in ALT (SGPT) in both group after removing the outliers.

Out of 30 subjects in low pressure group only 2 subjects experienced shoulder tip pain and out of 30 subjects in standard pressure pneumoperitoneum group 7 subjects experienced shoulder tip pain.

Table 11: Shoulder tip pain experienced by subjects in low and standard pressure group

		Pressure			
		Low		Standard	
		Count	Column N %	Count	Column N %
Shoulder Tip Pain	NO	28	93.3%	23	76.7%
	YES	2	6.7%	7	23.3%

P=0.07, chi square test

The shoulder tip pain was low (2, 6.7%) in low pressure group compared to standard pressure group (7, 23.3%). However this difference was not statistically significant. This non significance may be due to lower sample size.

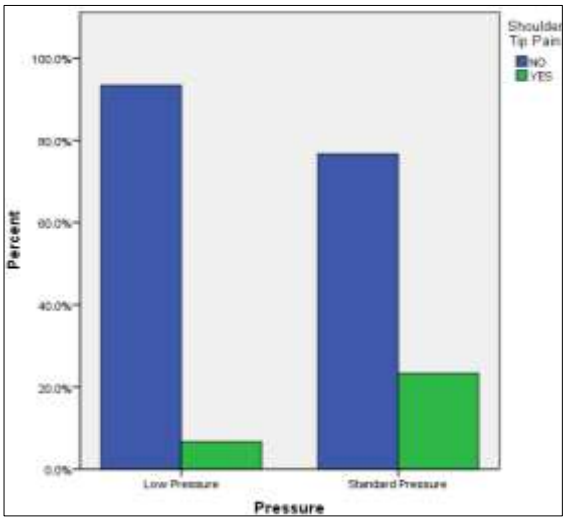

Fig 11: Bar graph showing shoulder tip pain in subjects underwent laparoscopic

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cholecystectomy in low and standard pressure pneumoperitoneum

Discussion

The present study was done to correlate the effect of pressure and duration of Carbon dioxide pneumoperitoneum on liver enzyme and to study the reasons for changes in liver enzyme in relation to different insufflation pressure of pneumoperitoneum and duration of procedure, in patient undergoing Laparoscopic cholecystectomy. There were two groups, group A operated at Low pressure pneumoperitoneum (8-12 mmHg) and group B operated at Standard pressure pneumoperitoneum (12-15 mmHg).

In our study, Alanine transaminase is measured to find the effect of pressure and duration of pneumoperitoneum on liver enzyme because it is more specific.

In this study we measured changes in ALT (Alanine transaminase) in both low pressure and standard pressure pneumoperitoneum group on first post-operative day. It showed transient elevation of ALT in both group. The elevation is more in standard pressure pneumoperitoneum group (77.67±51.38 unit/liter) when compared to low pressure pneumoperitoneum (56.23±23.23 unit/liter).

In our study, duration of the procedure was slightly more for Low pressure group (91±13.09 minutes) when compare to Standard pressure group (86.17±10.96 minutes) but it was statistically insignificant.

Thus elevation in liver enzymes during Laparoscopic cholecystectomy is not only dependent on pressure and duration of Carbon dioxide pneumoperitoneum. It depends on other factors also.

The first factor to be considered is carbon dioxide pneumoperitoneum itself. All the patients in our study were subjected to carbon dioxide pneumoperitoneum and they showed changes in post-operative serum liver enzymes level irrespective of the group.

Many studies, have unexplained changes in post-operative liver function in patients undergoing laparoscopic procedures. CO_2 pneumoperitoneum might be one of the main reasons for this change in serum liver enzymes, as this is the main difference between laparoscopic surgeries and open surgeries [2].

Lai H *et al.*, [6] stated that the elevated intra-abdominal pressure due to pneumoperitoneum may be responsible for the increase in liver enzymes after laparoscopic abdominal surgery.

According to a study *et al.*, intraperitoneal pressure used for laparoscopic procedures are higher than the pressure in the portal venous system which impedes portal circulation, in turn reduces portal flow up to 50%, hence causes depression of the hepatic reticular endothelial system which causes elevation of liver enzymes.

Morino M *et al.* [5] concluded that change in liver function tests is directly proportional to duration & pressure used for pneumoperitoneum.

P Rama Rao *et al.* [2] also stated that during laparoscopic surgery, there is an elevation and depression of intra abdominal pressure (IAP) in a short time, this sudden alteration of IAP could cause undulation of portal blood flow. This undulation in blood flow and re-irrigation of organs may give rise to ischemia and re-irrigation damage of tissues and organs, especially the Kupffer and endothelial cells of hepatic sinusoids by free radicals generated at the end of a laparoscopic procedure which results in elevation of liver enzymes.

Other unmeasured confounding factors may also be responsible for elevation of liver enzymes, such as extended liver traction in large laparoscopy procedure that lead to

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hepatocyte damage, and the intraoperative ‘‘squeeze’’ pressure effect on the liver that free liver enzymes into the blood stream. The increased IAP also triggers Neurohumoral responses of the vasopressin renin–angiotensin–aldosterone system. Vasopressin and norepinephrine play a significant role in causing damage to the hepatic function [2].

The local effect of prolonged use of diathermy to the liver surface in laparoscopic cholecystectomy and the spread of heat to liver parenchyma may alter hepatic enzymes [2].

Thus our study findings supported by previous studies reported, we could conclude that

- The carbon dioxide pneumoperitoneum itself.
- Insufflation pressure of the carbon dioxide pneumoperitoneum both Low and Standard pressure which are more than normal portal pressure.
- The duration of carbon dioxide pneumoperitoneum.
- Surgical techniques used during dissection of gall bladder from liver bed.
- Prolonged use of diathermy.
- Other unmeasured confounding factors are responsible for elevation of liver enzymes.

Conclusion

On comparing values of ALT at different pressures and duration of procedure, the study showed pneumoperitoneum pressure affects on the function of the liver. The changes in ALT is not significant on comparing low and standard pressure pneumoperitoneum. Hence both Low and Standard pressure pneumoperitoneum causes elevation of ALT, that is any insufflation pressure more than normal portal pressure causes alteration in liver function. The elevation of ALT is transient and none of the subjects showed features of hepatic dysfunction.

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