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Original Article

Surgery Section

Effect of Carbon Dioxide Pneumo-peritoneum in Coagulation Profile of Patients undergoing Laparoscopic Cholecystectomy: A Prospective Cohort Study

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ABSTRACT

Introduction: Laparoscopic Cholecystectomy (LC) is done under general anaesthesia with the patient in a reverse Trendelenburg position and with pressurised carbon dioxide in the peritoneum. This can induce venous stasis in the lower extremities and may affect the balance in the coagulation and fibrinolysis system, thereby thrombo-embolic complications.

Aim: To investigate the effects of carbon dioxide pneumo-peritoneum on the coagulation system of patients undergoing LC.

Materials and Methods: A prospective longitudinal study was carried out from January 2021 to June 2021 among patients aged 18 to 60 years who attended the Surgery Department at Regional Institute of Medical Sciences, Imphal, Manipur, India and were diagnosed with gallstone disease and subsequently underwent LC. Independent variables like age, sex, religion, pre-operative prothrombin time, platelet count, activated Partial Thromboplastin Time (aPTT), and International Normalised Ratio (INR). Outcome variables comprised complications, post-operative prothrombin time, platelet count, aPTT, and INR. Data collected were analysed using Statistical Package for Social Sciences (SPSS) version 21.0. Paired t-tests were employed to test the association between mean values of post-operative and pre-operative PT, aPTT, INR, etc. A p-value of less than 0.05 was considered statistically significant.

Results: The study enrolled 71 patients who encountered LC with carbon dioxide pneumo-peritoneum, including 18 male and 54 female patients. Maximum number of patients (28, 38.9%) fell into the 41 to 50 years age group. There was no significant difference in the mean value of prothrombin time (p=0.150) and INR (p=0.437) measured between the pre-operative and post-operative periods.

Conclusion: LC is a safe procedure without clinically significant changes in the coagulation profile.

Keywords: Capno-peritoneum, Fibrinolysis, Prothrombin time, Virchow's triad

INTRODUCTION

Laparoscopy has become one of the most common procedures used for diagnostic and therapeutic purposes. It offers the benefit of better cosmesis, milder post-operative pain, early discharge from the hospital, resume to normal life and work faster than traditional open methods [1]. The experience gained from approximately over 500,000 procedures annually has laid a strong foundation of knowledge for advanced laparoscopy, but the effect of carbon dioxide pneumo-peritoneum on the coagulation system needs further exploration [2].

The procedure of LC is done under general anaesthesia with the patient in a reverse Trendelenburg position and pressurised carbon dioxide in the peritoneum. Maintaining this position till the procedure can induce venous stasis in the lower extremities, leading to endothelial changes that affect the balance in the coagulation and fibrinolysis system [2,3]. Thus, all the components of Virchow's triad can be seen above which could ultimately lead to thrombo-embolic complications. Studies have described the effect of pneumo-peritoneum during LC in relation to coagulation and platelet activation, creating a state of hypercoagulability during the post-operative period [4-6]. The incidence of post-operative deep vein thrombosis among LC patients ranges from 0 to 55% [5]. Such variations in incidence and differences of opinion underscore the need for further studies.

The increasing use of laparoscopic techniques in modern surgery demands research on changes in blood coagulation following these operations. Thus far, the data was limited and marked by differences of opinion between those who argue against [7,8] and those who support [4,9] the effects of LC on patients' coagulation profiles.

The consequences of carbon dioxide pneumo-peritoneum need to be further studied with respect to individual systems. Thus, this study was initiated to study the effects of carbon dioxide pneumo-peritoneum on the coagulation system of patients undergoing LC and to make surgeons aware of any potential harmful effects.

MATERIALS AND METHODS

A prospective cohort study was conducted in Manipur at the Department of Surgery, RIMS, Imphal, Manipur, from January 2021 to June 2022 after obtaining ethical approval from the institutional Research Ethics Board (reference no. A/206/REB-Comm(SP)/RIMS/2015/752/94/2020).

Inclusion criteria: This study was conducted among patients aged 18 to 60 years who attended the Department of Surgery, were diagnosed with gallstone disease, and underwent LC.

Exclusion criteria: Those who refused to participate, were on anti-coagulation therapy, had a known case of Deep Vein Thrombosis (DVT), had co-existing malignancy, were pregnant, or had their procedure converted to open surgery were excluded from the study.

Sample size calculation: A sample size of 72 was calculated using the formula $N=(u+v)^2 (s_1^2+s_2^2)/(m_1-m_2)^2$, where u=0.84 (at 80% power), v=1.96 (at 5% significance level), and the following values were taken from a study by Milic DJ et al., [6]:

m_1=mean of APTT value at the pre-operative level=26.8276

m_2=mean of APTT value at the post-operative level (24 h)=25.8704

s_1=standard deviation of APTT value at the pre-operative level=2.2876

s_2=standard deviation of APTT value at the post-operative level (24 h)=1.7809

Procedure

Patients were enrolled by convenient sampling in this study. Independent variables included age, sex, pre-operative prothrombin time, platelet count, aPTT, INR, etc. Outcome variables were complications, post-operative prothrombin time, platelet count, aPTT, and INR.

Data collection: A detailed structured proforma was used. Those with gallstones who underwent LC at 12 mmHg pressured pneumo-peritoneum were included in the study as per the inclusion and exclusion criteria. Written informed consents were taken from all the participants. After collecting the socio-demographic profile of the patients, a detailed clinical history was obtained, followed by a thorough physical examination. Basic routine examinations were done for all patients. A blue top tube with 3.2% sodium citrate was used to collect 1.8 ml of the patient's blood for studying the coagulation profile. Similarly, a lavender top tube containing Ethylene Diamine Tetra-Acetic Acid (EDTA) was used to collect 1 mL of the patient's blood to determine platelet counts.

For each patient, one blood sample was collected prior to surgery, and another sample was collected after 24 hours from the onset of pneumo-peritoneum. All the blood samples were examined for Prothrombin Time (PT), aPTT, INR, and platelet count values. The participants were assured of their anonymity at the time of data collection, and the importance of providing honest answers was stressed. Collected data were checked for completeness and consistency before the patient was discharged, and necessary rectifications were made.

STATISTICAL ANALYSIS

The collected data were collated and analysed in SPSS (IBM) version 21.0. Summaries of the data were carried out and presented as mean, standard deviation, and percentages. The paired t-test was employed to test the association between the mean values of post-operative and pre-operative PT, aPTT, INR, etc. A p-value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, 72 patients who underwent LC using carbon dioxide pneumo-peritoneum were enrolled in the study, of which 18 were male and 54 were female patients, as shown in [Table/Fig-1]. The maximum number of patients, 28 (38.9%), were in the age group of 41 to 50 years. The mean age of the study participants was 42.5±10.3 years. A total of 46 (63.9%) of the patients were exposed to pneumo-peritoneum for 1-2 hours during surgery. Similarly, 60 (83.33%) patients had no complications, and 13.89% of the patients had post-operative port site infection. Only 2 (2.78%) of the patients had bile leakage [Table/Fig-1].

No significant difference in the mean value of prothrombin time (p=0.150) and INR (p=0.437) measured between the pre-operative period and the post-operative period was seen in the study population [Table/Fig-2].

The mean value of aPTT before surgery was higher than the mean value of aPTT after surgery, and it was found to be statistically significant (p=0.004). Similarly, the mean value of platelet count before surgery was higher than the mean value of platelet count after surgery, and it was found to be statistically significant (p<0.001) [Table/Fig-3].

S. No.	Characteristics		No. of patient	Percentages
1.	Gender	Male	18	25
		Female	54	75
2.	Age	20-30 years	12	16.7
		>30-40 years	17	23.6
		>40-50 years	28	38.9
		>50 years	15	20.8
		Mean age±Standard deviation (Years)		42.5±10.3
3.	Duration of surgery	<1 hour	6	8.3
		1-2 hours	46	63.9
		>2 hours	20	27.8
4.	postoperative complication	No complication	60	83.33
		Port site infection	10	13.89
		Bile leak	2	2.78

[Table/Fig-1]: Distribution of patients by demographic profiles, duration of surgery and postoperative complications (N=72).

S. No.	Characteristics		Mean±SD	p-value*
1.	Prothrombin Time (seconds)	Pre-operative	12.9±1.03	0.150
		Post-operative	12.6±1.20	
2.	INR (International Normalised Ratio)	Pre-operative	1.249±0.139	0.437
		Post-operative	1.264±0.117	

[Table/Fig-2]: Association between mean PT and mean INR, before and after surgery (N=72).
*paired t-test and p-value <0.05 is statistically significant

S. No.	Characteristics		Mean±SD	p-value*
1.	aPPT (activated Partial Prothrombin Time) (seconds)	Pre-operative	32.53±2.80	**0.004**
		Post-operative	31.51±3.01	
2.	Platelet count (lac per cu.mm)	Pre-operative	2.182±0.393	**<0.001**
		Post-operative	2.012±0.403	

[Table/Fig-3]: Association between mean aPPT and mean platelet count before and after surgery (N=72).
*paired t-test and p-value <0.05 is statistically significant

DISCUSSION

In this study, out of 72 patients who underwent LC, 54 (75%) were females, and the remaining 18 (25%) were males. Similarly, in a study by Amin B et al., female patients (56%) were more than male patients (44%) [4]. In a study by Garg PK et al., most of the patients were females, with 88%, and males were only 12% [5]. In a similar study by Natkaniec M et al., they also found that 80% of the patients were females, and only 20% were males [7]. Thus, females predominated the study population in most of the studies; it may be due to the fact that females are more commonly affected with cholelithiasis than males [10].

The mean age of the population was 42.5±10.3 years in this study, with a comparable mean age between males and females. In a similar study by Natkaniec M et al., the mean age of their study population was 48.3±14.6 years, which is slightly higher than in this study [7]. Another study by Amin B et al., reported the mean age to be 56.7±11.5 years, which is also higher than in this study [4]. But in a study by Garg PK et al., the mean age of their study population was 36.0±10.7 years, which is slightly lower than in this study [5]. Thus, the commonest age group for LC was during the period of midlife, which was similar to the findings of this study, with the maximum cases reported in the age group of 41 to 50 years.

The duration of the operation, which correlates with the exposure to pneumo-peritoneum, was observed to be between 1 to 2 hours for 69.3% of the patients in this study, and 27.8% of the patients were exposed for more than three hours. In a study by Amin B et al., the average time of exposure to pneumo-peritoneum was 64.6±24.4 minutes, which falls within the range of 1 to 2 hours, similar to this study

Studies	Year	Place	Sample size	Procedure done	Test done at	Prothrombin time (sec)	aPPT (sec)	Platelet count (lakh per cu.mm)	INR
Donmez, T et al., [1] at 10 mmHg	2016	Turkey	25	Laparoscopic Cholecystectomy	Pre-operative	11.94±0.64	22.80±1.48	-	1.00±0.05
					24 h post-operative	12.43 ±0.86	24.54±2.16	-	1.04±0.07
					p-value	**0.048**	<0.001	-	0.067
Donmez, T et al., [1] at 14 mmHg	2016	Turkey	25	Laparoscopic Cholecystectomy	Pre-operative	11.66±0.79	22.01±0.99	-	0.98±0.06
					24 h post-operative	12.56±0.66	25.01±1.65	-	1.05±0.05
					p-value	**<0.001**	**<0.001**	-	**<0.001**
Panda BB, et al., [2]	2021	Bhubaneswar	50	Laparoscopic Cholecystectomy	Pre-operative	11.83±1.008	-	-	-
					24 h post-operative	11.7±0.898	-	-	-
					p-value	**<0.05**	-	-	-
Amin B et al., [4]	2014	China	50	Laparoscopic Cholecystectomy	Pre-operative	10.5±0.8	31.6± 3.6	-	-
					8 h post-operative	10±1.0	27.9± 4.7	-	-
					p-value	**<0.05**	**<0.05**	-	-
Garg PK et al., [5]	2009	New Delhi	50	Laparoscopic Cholecystectomy	Pre-operative	-	1.01±0.01	-	1.01±0.2
					24 h post-operative	-	0.95±0.3	-	0.99±4.65
					p-value	-	**< 0.05**	-	0.07
Natkaniec M et al., [7]	2014	Poland	35	Laparoscopic Cholecystectomy	Pre-operative	-	34.54±6.32	-	1.11± 0.14
					5 h post-operative	-	34.4±7.13	-	1.17±0.11
					p-value	-	**>0.05**	-	**<0.001**
Present study	2023	Manipur	72	Laparoscopic Cholecystectomy	Pre-operative	12.9±1.03	32.53±2.80	2.182±0.393	1.249±0.139
					24 hr post-operative	12.6±1.20	31.51±3.01	2.012±0.403	1.264±0.117
					P value	0.150	**0.004**	**<0.001**	0.437

[Table/Fig-4]: Comparison of coagulation profile among different studies [1,2,4,5,7].

[4]. Another study by Garg PK et al., found that the mean duration of pneumo-peritoneum exposure was 74.20±19.57 minutes [5].

Prothrombin time assesses the extrinsic pathway (factor VII) and common pathway protein factors (fibrinogen, prothrombin, Factor V and X) of the coagulation mechanism [11]. In this study, it was observed that there were variations in prothrombin times among the study patients. The reason for some patients being hyper-coagulable or hypo-coagulable may be due to other underlying conditions which were not considered in this study. This study showed no significant perioperative reduction in PT (p-value >0.05), which could indicate hypercoagulability. However, in a study by Natkaniec M et al., the mean PT value of the post-operative sample was higher than the pre-operative, and it was statistically significant (p=0.0009) [7]. In contrast, in a study by Amin B et al., the mean PT value of the post-operative sample was lesser than the pre-operative sample, and it was statistically significant (p<0.05) [4]. Similarly, in a study by Garg PK et al., the mean prothrombin time in the post-operative sample was lesser than the pre-operative sample, but it was not significant (p=0.07) [5]. Thus, PT could not be concluded to have an association with pneumo-peritoneum. Similarly, in this study, there were similar mean values of INR between the pre-operative and post-operative samples. This means that there was no major coagulation cascade abnormality during LC.

The aPTT assesses the intrinsic pathway (factor XII, XI, IX, VIII) and common pathway factors (fibrinogen, prothrombin, Factor V, and X) of the coagulation mechanism [11]. In this study, there was a significant difference in the mean value of aPPT between the pre-operative and post-operative samples. The mean value of aPPT before surgery was higher than the mean value of aPPT after surgery, and it was found to be statistically significant. Garg PK et al., also found in their study that the mean aPTT pre-operatively was significantly (p-value <0.001) higher than the post-operative sample [5]. Similarly, in a study by Amin B et al., the mean aPPT pre-operatively was higher than the post-operative sample, and this was found to be statistically significant (p-value <0.05) [4].

The observed decrease in aPTT indicates an active coagulation. Coagulation activity is commonly enhanced after surgery as a normal response to surgical insult [12]. For that reason, it is not easy to differentiate the cause as it can be either by pneumo-peritoneum or surgical trauma. In a contrast study by Larsen JF et al., between LC using CO_2 pneumo-peritoneum and gasless LC using lifting devices, no differences were seen between the two groups, suggesting CO_2 pneumo-peritoneum has no role in triggering the coagulation and fibrinolysis mechanism [13]. Another study by Ntourakis D et al., revealed that PT, aPTT, INR, D-dimer, fibrinogen, and Fibrinogen-Degradation Product (FDP) levels were elevated during the post-operative period in a statistically significant way [14]. This study also observed an insignificant elevation of INR during the post-operative 24th hour. This elevation in INR levels is believed to reduce the DVT risk associated with LCs [1].

In this study, there was a significant decrease in the mean value of platelet count between the pre-operative value and the post-operative value. Dabrowiecki S et al., also found that there was a significant difference in platelet value between the pre-operative and post-operative (first post-operative day) LC, where the platelet values of post-operative cholecystectomy were lower than the pre-operative values, which was similar to the findings in this study [15]. This may be due to intra-operative haemodilution and increased peri-operative platelet consumption [16]. A comparison of the coagulation profile among different studies can be found in [Table/Fig-4] [1,2,4,5,7].

Limitation(s)

In this study, only two coagulation markers were measured. If the levels of coagulation markers D-dimers and fibrinogen were considered, a more thorough and in-depth outcome could have been derived in terms of the post-operative risks of thrombosis. Secondly, a larger sample size may reveal the occurrence of thrombotic events.

CONCLUSION(S)

The blood serum levels of aPPT and platelet count in the post-operative sample, when compared with the pre-operative sample, were found to be significantly reduced after LC using carbon dioxide pneumo-peritoneum, but there was no clinical evidence

of hypercoagulability. There were no significant differences in prothrombin time and INR values between the pre-operative and post-operative samples. Since there were few post-operative complications and no significant changes in the coagulation profile, it can be assured that LC using carbon dioxide pneumo-peritoneum is a safe procedure. A multi-center study with a larger sample size and randomised controlled clinical studies are needed to shed light on and explore the risks of post-operative venous thrombosis after LC.

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