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A STUDY OF ALTERATION IN COAGULATION PROFILE IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY

General Surgery

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ABSTRACT

Introduction: Laparoscopic cholecystectomy has become the gold standard for the treatment of cholelithiasis. It has many advantages such as better cosmetic, shorter hospitalization time, minimal postoperative pain, early return to normal life. However carbon dioxide pneumoperitoneum may cause alteration in the coagulation system and moreover the reverse Trendelenburg position adopted diring surgery can induce blood stagnation in the lower limbs leading to a hypercoagulable state. **Objective:** The aim of the study was to record the effect of carbon dioxide pneumoperitoneum on coagulation factors and fibrinolysis response during laparoscopic cholecystectomy and to assess if there is any risk of postoperative thromboembolic complications following laparoscopic cholecystectomy. **Methods:** The hospital based descriptive study of 50 patients undergoing elective laparoscopic cholecystectomy was designed to study alteration in Clotting time, Prothrombin time(PT), Activated partial thrombin time(aPTT), Fibrinogen and D-dimer, which were measured preoperatively and 6 hour postoperatively. **Results:** Out of 50 patients operated 38 were female and 12 were male. Significant decrease in PT and aPTT suggested activation of coagulation pathways while significant increase in d-dimer and fibrinogen suggested activation of fibrinolytic systems. None of the patients had any postoperative thromboembolic complications. **Discussions:** From the study we found that there was activation of coagulation and fibrinolysis after laparoscopic cholecystectomy leading to a hypercoagulable state which may be either due to carbon dioxide pneumoperitoneum or due to increased intra-abdominal pressure. Although none of the patients had any thromboembolic complications postoperatively, however there may be the need to use prophylactic measures for thrombosis in high risk patients.

KEYWORDS

INTRODUCTION

Laparoscopic cholecystectomy has replaced classic open cholecystectomy as the gold standard for the treatment of cholelithiasis after more than 100 years of initial introduction of Laparoscopy in1901 by Russian Gynaecologist, Dimitri Ott[1] .Once introduced, the evolution to laparoscopic cholecystectomy took place so suddenly and on such a large scale worldwide that, in the history of surgery, the last decade of the 20th century will certainly be remembered as that of the laparoscopic revolution.[1]

Laparoscopic Cholecystectomy has many advantages such as better cosmetic, shorter hospitalization time, minimal post-operative pain, early return to normal life and work.[2] In Laparoscopic Cholecystectomy a fundamental step is the insufflation of a gas inside the peritoneal cavity to allow the distention of the abdominal wall, to create a working cavity, to achieve better visibility of the surgical field. This cavity is commonly created by positive pressure pneumoperitoneum using carbon dioxide, as carbon dioxide is non-combustible and electrocoagulation is possible during surgery.[2]

Carbon dioxide pneumoperitoneum affects normal physiology. It may affect the coagulation system, cardiovascular system such as increase in systemic venous resistance and mean arterial pressure and decrease in venous return and cardiac output due to pressure on inferior vena cava.[1] In respiratory system it may result in decrease in lung volume and compliance, increase in airway resistance and an increase in ventilation perfusion ratio. If intraoperative carbon dioxide pneumoperitoneum lasts a long time renal artery flow decreases and results in decreased glomerular filtration rate. Thrombotic risks during laparoscopic surgery are mostly pneumoperitoneum related. The increase in intra-abdominal pressure during pneumoperitoneum causes mechanical compression on the inferior vena cava with a reduction in venous return. Moreover, the reverse Trendelenburg position adopted during surgery can induce blood stagnation in the lower limbs.[2] The effects of gas and the pathophysiological changes induced by CO2 have led to use of low pressure to avoid the onset of some complications such as venous thromboembolism. The usual pressure range of the pneumoperitoneum is between 12 and 14 mmHg.

However, there is no clear evidence of safety of use of low pressure and also low pressure could reduce the formation of a safety working chamber and thus international guidelines do not recommend operating at lower pressure value with the purpose of avoiding the potentially negative effects of pneumoperitoneum on heart and lungs.[3,4] In this study we aim to record the effect of carbon dioxide pneumoperitoneum on coagulation factors and fibrinolysis response during Laparoscopic Cholecystectomy.

Methodology :

This hospital based descriptive study was conducted over a period of one year. A total of 50 patients admitted in Department of Surgery, Fakhruddin Ali Ahmed Medical College & Hospital for elective Laparoscopic Cholecystectomy and meeting the inclusion and exclusion criterias were included in this study. Detailed clinical history and thorough examinations of all patients were done, and all relevant investigations were done like blood and radiological examination.

Inclusion criteria:

a) All patients operated for cholecystectomy laparoscopically were included in the study.
b) Patients of both sexes and age from 18 years to 60 years.
c) Patients with gallstones or gall bladder polyps.
d) Patients with chronic cholecystitis.
e) Patients who gave consent for study were included.

Exclusion Criteria:

a) Patients below age 18 and above the age of 60 years.
b) Surgery time exceeding three hours.
c) Patients with acute cholecystitis, cholangitis.
d) Patients with recent surgeries.
e) Patients with recent thromboembolic disorder.
f) Patients with haematological disorder.
g) Patients with known malignancies.
h) Patients with on anticoagulant therapy, Oral Contraceptive Pills,
I) Pregnancy.

Method of collection of data:

a) First 50 patients meeting the inclusion criteria were chosen serially.
b) Detailed history and clinical examination were done.
c) Basic routine investigations were done for all patients.
d) One sample was drawn prior to surgery.

e) One sample was drawn 6 hours after surgery.
f) Samples were processed for Clotting Time, Prothrombin time, Activated partial thromboplastin time(aPTT), Fibrinogen and D-Dimer.
g) Consent was obtained for inclusion under study and for surgery.

Method of Surgery :
Procedure was done under general anaesthesia. Surgery was done with standard laparoscopic equipment for all patients using carbon dioxide pneumoperitoneum.

The pressure of pneumoperitoneum was maintained at 13 mmHg +/- 1 mmHg.

Statistical Analysis Of Data:
All relevant data were documented in a tabular form. Analysis was statistically and interpretation was elicitated. For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analysed by using software. Data have been expressed in terms of mean and standard deviation for numerical variables and the counts for categorical variables. Chi-square test was used where relevant.

For statistically significant p-value was considered to be ≤ 0.05.

Ethical Clearance: Ethical clearance was taken from Institutional Ethics Committee, Fakhruddin Ali Ahmed Medical College and Hospital, Barpeta.

RESULTS:
Table: 1 Age Distribution Of The Study Patients

Age in Years	N	%
18-27	18	36.00%
28-37	18	36.00%
38-47	11	22.00%
48-57	2	4.00%
58-60	1	2.00%
Grand Total	50	100%

	Mean	SD
Age	32	10

In the study there was more number of cases in the age group of 18-27 and 28-37 years compared to other age group.

Table: 2 Sex Distribution Of The Study Participants

SEX	NUMBER	PERCENTAGE
Female	38	76%
Male	12	24%
Grand Total	50	100%

Out of 50 patients operated 38 were female and 12 were male.

Table: 3 Clotting Time

	Mean	SD	p-value
Pre Operative CT	10.30	1.91	0.745
6 h Postoperative CT	9.91	1.67	

The mean clotting time of the patients before surgery was 10.3 seconds with a standard deviation of 1.91.

The mean clotting time of the patients 6 hours postoperatively was 9.91 with a standard deviation of 1.67.

Some patients had elevated clotting time and some had decreased clotting time.

The difference between the two groups was 0.39. The p-value was 0.745. Hence the p-value was statistically not significant.

Prothrombin time:
Prothrombin time is an indicator of the concentration of prothrombin in the blood**.** The time required for coagulation to take place is known as the prothrombin time. The shortness of the time is determined mainly by prothrombin concentration. The normal prothrombin time is about 12 seconds.

Table 4: Prothrombin Time

	Mean	SD	p-value
Pre Operative PT	12.7	0.5	0.001
6 h Postoperative PT	11.9	0.3	

The prothrombin time of the patients before surgery ranged from 11 to 13 seconds with the mean at 12.7 seconds. The standard deviation was 0.5.

The prothrombin time of patients 6 hr after surgery ranged from 11.1 to 12.7 seconds with the mean at 11.9 seconds. The standard deviation was 0.3.

Some patients had decreased prothrombin time while some showed elevated prothrombin time and few showed no change at all.

The difference in the mean between the two groups was 0.2 seconds. The p-value was 0.001. Hence the value was statistically extremely significant.

D-dimer:
D-Dimer levels have been used as a marker of intravascular clot formation. D-Dimer is a cross-linked fibrin degradation product, which forms as a result of a breakdown of fibrin.[5]

The reference value is less than 250 ng/ml or 0.5 ug/ml fibrinogen equivalent units.

D-dimer serves as a valuable marker of activation of coagulation and fibrinolysis. D-dimer has been extensively investigated for the diagnosis of venous thromboembolism (VTE),for determining the optimal duration of anticoagulation in VTE patients, for diagnosing and monitoring disseminated intravascular coagulation, and as an aid in the identification of medical patients at high risk for VTE.[6]

Table 5: D-dimer Values

	Mean	SD	p-value
Pre Operative D-dimer	178.29	32.84	0.036
6 h Postoperative D-dimer	436.10	111.47	

The preoperative d-dimer values of 50 patients ranged from 94.25 ng/ml to 269 ng/ml with a mean at 178.29 ng/ml. The standard deviation was at 32.84.

The d-dimer values of 50 patients 6 hrs after surgery ranged from 94.25 ng/ml to 609.73 ng/ml with the mean at 436.1 ng/ml. The standard deviation was 111.47.

The d-dimer values of all the 50 patients showed a drastic increase after surgery. The difference in mean between the two groups was 257.71.

The p-value of the d-dimer analysis was at 0.036 i.e less than 0.05 and hence it was statistically significant.

Activated Partial Thrombhoplastin Time:
Partial thromboplastin time (PTT) is the time it takes for a patient's blood to form a clot as measured in seconds. It is used to measure the activity of the intrinsic pathway of the clotting cascade. PTT tests the function of all clotting factors except factor VII (tissue factor) and factor XIII (fibrin stabilizing factor).

PTT is commonly used in clinical practice to monitor patient response to unfractionated heparin infusion, to target therapeutic anticoagulation, and as part of a "coagulation panel" to help elucidate causes of bleeding or clotting disorders.[7,8,9,10]
The normal value is 25 to 35 seconds.

Table:6 Activated Partial Thromboplastin Time

	Mean	SD	p-value
Pre Operative aPTT	1.01	0.01	0.041
6 h Postoperative aPTT	0.91	0.04	

The preoperative APTT values of 50 patients ranged from 0.99 to 1.04 min with the mean at 1.01 min. The standard deviation was 0.01.

The 6 hour post operative APTT values for the 50 patients ranged from 0.84 to 0.99 min with the mean at 0.91 min. The standard deviation was 0.04.

The difference in mean of the two groups was 0.1 min. The APTT values of all the patients showed a decrease post surgery. The p-value of the APTT analysis was at 0.041(<0.05) and hence it was statistically significant.

Fibrinogen:
It is formed in the liver and is essential for clot formation. Following vascular injury, fibrinogen is cleaved by thrombin to form fibrin which is the most abundant component of blood clots.[11] The plasma concentration is 100 to 700 mg/dl.

Table : 7 Fibrinogen

	Mean	SD	p-value
Pre Operative Fibrinogen	350.48	113.04	0.021
6 h Postoperative Fibrinogen	445.38	79.44	

The pre operative fibrinogen values for the patients ranged from 99.71 to 531.95 mg/dl with the mean at 350.48 mg /dl. The standard devition was 113.04.

The post operative fibrinogen values of the patients ranged from 272.18 to 662.04 mg/dl and the mean was at 445.38 mg/dl. The standard deviation was 79.44.

Post operatively the fibrinogen values for all the 50 patients has showed drastic increase.

The difference in mean of the two groups was 94.9 mg/dl. The p-value of the fibrinogen analysis was at 0.021 and it was statistically significant.

DISCUSSIONS
The values of clotting time,prothrombin time, d-dimer,aPTT and fibrinogen of 50 patients were analyzed. The inferences derived from them were compared with other similar studies.

There was a higher incidence of female patients undergoing cholecystectomy i.e 76% compared to male which was 24%. This matches the rates in India which also shows a higher female predisposition towards gall bladder pathologies. Other studies which had similar finding are Natkaniec M et al[12], Garg PK et al[11], Lauro A et al[13] . The majority of the patients who underwent surgery were in the age group of 18-27 and 28-37 years. The mean age was 32 years. These constituted about 72% of the cases showing that the disease incidence was higher in the age group of 18-37 years.

In Martinez-Ramos C et al[14] study the mean age in years was 59.4 years and in Natkaniec M et al[12] study the mean age was 48.3 ± 14.6 years, this showed that the disease incidence increased after 40 years which was not the case in our study.

The clotting time of the patients when analysed showed that the difference between the preoperative and postoperative values was not statistically significant (p-value=0.745).

The prothrombin time of patients when analysed showed that majority of the patients i.e 64% of them had an decrease in prothrombin time postoperatively indicating a state of hypercoagulability and 39% of the patients had an elevation of prothrombin time after surgery showing a state of hypocoagulability.

The mean of prothrombin time before surgery was 12.7 seconds and the prothrombin time after surgery was 11.9 seconds. When theses values were charted the decrease in the mean of prothrombin time was found to be statistically extremely significant i.e p-value was 0.001. Thus our study showed activation of Coagulation Profile after laparoscopic cholecystectomy with respect to prothrombin time and hence there is hypercoagulability of blood post laparopscopic cholecystectomy.

Similarly when the aPTT values were analysed showed that all the patients had a decrease in aPTT values post operatively indicating activation of coagulation pathways resulting in hypercoagulation.

The mean of aPTT before surgery was 1.01 min and postoperatively the mean was 0.91 min. The p-value of the aPTT analysis was at 0.041(<0.05) and thus the difference in mean was statistically significant. Thus our study showed alteration in Coagulation Profile after laparoscopic cholecystectomy leading to a state of hypercoagulation.

The study goes in line with other studies by Amine Buhe et al[15] where they found decrease in prothrombin time and aPTT post operatively in 50 patients and concluded that pneumoperitoneum leads to post operative hypercoagulation.

I.M.Gudz et al[15] found decrease in PT and aPTT values of 70 patients after laparoscopic cholecystectomy and supported hypercoagulation state postoperatively.

However, Garg PK et al[11] observed no statistically significant postoperative changes in the values of PT but they observed significant postoperative decrease in aPTT suggesting activation of coagulation pathways.

When the D-dimer values were analysed, all the patients were seen to have a drastic increase in D-dimer values postoperatively. The mean of the D-dimer preoperatively and postoperatively calculated to be 178.29 ng/ml and 436.10ng/ml respectively. Statistically the values were found to be significant with p-value of 0.036. Thus our study suggests activation of fibrinolytic systems.

In our study the postoperative fibrinogen values of all patients have shown a drastic increase. The difference in mean of the two groups was 94.9 mg/dl with p-value of the fibrinogen analysis at 0.021. Hence it was statistically significant and suggested activation of fibrinolysis.

Our study was comparable with R Vecchio et al[16] study where the D-dimer values increased postoperatively and concluded activation of coagulation and fibrinolytic pathways after laparoscopic cholecystectomy. Also D Prisco et al[17] found in their study a significant increase in fibrinogen and D-dimer values in patients undergoing videolaparoscopic cholecystectomy.

Nikos Tsiminikakis et al[18] concluded from their study a lower degree of hypercoagulability in patients undergoing laparoscopic cholecystectomy. Papaziogas B et al[19] did not find any significant alterations in PT and aPTT but significant elevation in D-dimer values after laparoscopic cholecystectomy suggesting activation of hemostatic mechanism. The findings of the study though contradicts the studies by Rahr et al[20] where they concluded Carbon dioxide pneumoperitoneum doesn't enhance the activation of coagulation and

fibrinolysis associated with laparoscopic cholecystectomy. They found coagulation and fibrinolytic systems were activated during and after gasless as well as conventional laparoscopic cholecystectomy.

A study by Martinez-Ramos C et al[14] found no greater activation of plasma coagulation than low risk surgery. On the contrary, the increase of fibrinolytic activity in plasma would extend a certain degree of hypocoagulability during surgery, maintaining it for 24 hours and thus possibly reducing thromboembolic risk in patients undergoing this type of surgery.

The alteration in Coagulation Profile can be due to surgery and may not be specifically only due to Carbon dioxide pneumoperitoneum as other studies by Papaziogas B et al[19] and Schietroma M et al[21] have shown similar rise in values after open surgeries too.

Some studies have shown that the effect of increased abdominal pressure have a role in the alteration of coagulation profile. Increase in intra-abdominal pressure during pneumoperitoneum compresses the inferior vena cava leading to decreased venous return from the extremities resulting in increase risk of deep vein thrombosis.

Turgut Donmez et al[22] concluded in their study that higher pressure pneumoperitoneum has a more negative effect on coagulation factors and fibrinolysis than lower pressure pneumoperitoneum although they did not encounter clinical or ultrasonographic DVT.

Similarly Intaglita Eva et al[2] found that a higher abdominal pressure is linked to a hypercoagulable state. F Lindberg et al[23] found that the average rate of reported deep vein thrombosis was 0.03%. They concluded that laparoscopic cholecystectomy is a safe procedure, and the rate of clinically evident postoperative thromboembolic complications is probably lower than after conventional cholecystectomy. The risk is not negligible, though, and some authors thus have recommended thromboembolism prophylaxis.

Regineld V N Lord et al[24] demonstrated in their study that despite the possible presence of all 3 of Virchow's factors for thrombosis formation during the performance of laparoscopic cholecystectomy , DVT detectable by color duplex examination was infrequent (2%) after laparoscopic cholecystectomy or minilaparotomy methods if thromboprophylaxis regimen which is preoperative and postoperative subcutaneous low-molecular-weight heparin (LMWH), graduated compression stockings, and intraoperative intermittent calf compression is employed.

In the study by Anna-Maria Blake et al[25] no clinically detectable evidence of DVT existed in despite the lack of any perioperative DVT prophylaxis and they questioned whether DVT prophylaxis is indicated for routine laparoscopic cholecystectomy.

The analysis of all the factors shows that none of the patients had any postoperative thromboembolic complications however there was alteration of coagulation n fibrinolysis pathways of patients after laparoscopic cholecystectomy using CO2 pneumoperitoneum. Hence there may be the need to use prophylactic measures for thrombosis in high risk patients.

CONCLUSION:

From our study we concluded that there is activation of coagulation and fibrinolysis after laparoscopic cholecystectomy leading to a hypercoagulable state which may be either due to CO2 pneumoperitoneum or due to increased intra-abdominal pressure. There was no statistical significance in the clotting time mean difference. The mean difference of prothrombin time and aPTT were statistically significant indicating activation of coagulation pathways. Drastic increase in D-dimer values and fibrinogen post operatively indicated activation of both coagulation and fibrinolysis. However none of the patients had any thromboembolic complications postoperatively.

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