

## Single Dose Pre-Operative Dexamethasone in Laparoscopic Cholecystectomy—Evaluation of Stress Markers and Post-Operative Nausea and Vomiting

Mrigpuri Rahul<sup>1</sup>, Chandel UK<sup>2\*</sup>, Sodhi Surinder Singh<sup>3</sup>

<sup>1</sup>Senior Resident, Department of General Surgery, IGMC, Shimla, Himachal Pradesh, India

<sup>2</sup>Professor, Department of General Surgery, IGMC, Shimla, Himachal Pradesh, India

<sup>3</sup>Professor, Department of Anesthesiology, IGMC, Shimla, Himachal Pradesh, India

### Original Research Article

\*Corresponding author  
Chandel UK

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**Abstract:** Postoperative Surgical Stress, nausea and vomiting (PONV) continue to be highly undesirable outcomes of anesthesia and surgery. Therefore, multimodal approaches have been suggested in order to decrease PONV and surgical stress. The aim of this study was to evaluate stress markers (TLC & CRP) and antiemetic effect of a single dose injection of dexamethasone (8mg i.v.) on reducing postoperative surgical stress and PONV in laparoscopic cholecystectomy. In this prospective study, 60 patients aged 20-69 years, selected for laparoscopic cholecystectomy, were classified into study and control groups 30 patients in each group. The study group underwent general anesthesia with intravenous injection of dexamethasone. The Control group received general anesthesia and no intravenous injection of dexamethasone. TLC, CRP, Total dose of consumed analgesics and Ondansetron during first 24 hours were evaluated in both groups. Stress Markers (TLC & CRP) in study group were significantly less than control group after 6 and 24 hours of surgery. PONV and antiemetic requirement in study group was significantly less than control group after surgery. No significant difference existed between two groups regarding Hospital stay. Single dose of 8 mg of i.v. dexamethasone preoperatively is safe and effective and may be considered to minimize surgical stress response, PONV and antiemetic use.

**Keywords:** Laparoscopic Cholecystectomy; Post-Operative Nausea Vomiting (PONV); Postoperative Pain; Total leucocyte count (TLC), C Reactive protein (CRP) Dexamethasone; Ondansetron.

### INTRODUCTION

Among the abdominal surgical procedures, operations on the biliary tract are the most common and cholecystectomy is the commonest among them. Because of the proven advantages of Laparoscopic Cholecystectomy, it has become the “New Gold standard” for the management of symptomatic gall stone disease. However, a variety of metabolic, hormonal, inflammatory, and immune responses are activated during minimally invasive procedures, which may impair clinical recovery. Methods to attenuate these adverse physiologic responses to surgery may improve outcomes.

Surgery, “controlled deliberate injury”, for purpose of therapy, induces a series of biochemical and hormonal responses in the body, that include alteration in the expression of acute phase reactants, C-reactive protein (CRP) and total leucocyte count (TLC). In general, the magnitude of changes in CRP is apparently taken as proportional to the extent of overall surgical stress. Recent evidence indicates that trauma induced

stress hormone responses are insufficient to explain the broad spectrum of post injury defects, particularly in relation to immune system. Stress of injury leads to production of cytokines and acute phase proteins, which initiates increase in the levels of “Stress” hormones, loss of muscle proteins, greater vascular permeability and changes in white blood cell count. Some of these responses are homeostatic defense mechanism, but others such as catabolic state are thought to be deleterious [1].

Postoperative nausea and vomiting (PONV) continue to be a highly undesirable outcome of anesthesia and surgery. Although the precise etiology of PONV is unknown, experts suggest a multifactorial origin. Patient-specific (age, sex, motion sickness, smoking), anesthetic (inhalational agents, duration of general anesthesia) and surgical (duration of surgery, pneumoperitoneum) have all been identified as causes.

Systemic glucocorticoids have well known anti-inflammatory and antiemetic properties, and significant

post-operative beneficial effects have been documented. The effects of single-dose i.v. dexamethasone in reducing the risk for postoperative nausea and vomiting are well documented. [2–4] Dexamethasone may offer additional benefits over traditional antiemetics in improving surgical outcomes. Dexamethasone phosphate 8 mg i.v. given 60- 90 minutes before laparoscopic cholecystectomy has been demonstrated to significantly reduce postoperative fatigue, pain, and levels of C-reactive protein, in addition to reducing the incidence of PONV [5].

### **OBJECTIVES**

Aim of the study was to evaluate the role of single dose pre-operative dexamethasone in laparoscopic cholecystectomy with regards to stress markers (TLC & CRP) and PONV.

### **MATERIALS AND METHODS**

The present prospective randomized study was conducted in a period of one year. Patients of symptomatic cholelithiasis aged 18 years or more were planned for laparoscopic cholecystectomy. A total of 60 patients were included after consent. The patients were alternatively distributed among control and study group of 30 each. The study group was given 8mg Dexamethasone intravenously within one hour prior to induction of general anesthesia. Patients with severe Chronic obstructive airway disease/Cardiac diseases/unfit for general anesthesia, Acute Cholecystitis /pancreatitis, History of any acute attack within 6 weeks, History of Allergy, on Steroids, chronic use of NSAIDS, other analgesics and Chemotherapy, Pregnancy, Conversion of LC to OC, Intra operative injury, Surgery lasting for more than one hour, were excluded from the study. The selected patients were screened preoperatively by detailed history, general and systemic examination, complete haemogram, blood sugar, liver function test, renal function test, pulmonary function test, serum electrolytes, CRP, X ray chest, ECG, abdominal ultrasonography.

#### **C-reactive protein estimation**

The concentration of CRP was measured by nycocardcrp single test kit and using nycocard reader ii (AXIS– SHIELD PoC AS Norway).

#### **Total leucocyte count estimation**

TLC was measured by automated hematology cell counter (meletschloesing laboratories osny-france)

### **Operative procedure**

Patients were kept fasting a night before surgery and given one tablet of alprazolam 0.5mg to relieve anxiety. Study group was given 8 mg of dexamethasone i.v. in the pre anesthetic room, within one hour prior to surgery or before induction of general anaesthesia, whereas control group received 1ml of normal saline.

Patient was placed in the ordinary supine position on operation table. After attaching electrocardiographic monitoring, pulse oximetry, blood pressure measurement, capnography, and hydration with 10 mL/Kg of crystalloids in all subjects, general anaesthesia was administered with Thiopentone 5mg/kg body weight; Inj.Succinylcholine 1.5mg/kg for tracheal intubation. Maintenance was done with N<sub>2</sub>O:O<sub>2</sub> =2:1; Isoflurane 0.5%-1%; Atracurium 0.5mg/kg; Pentazocine 0.5mg/kg. Reversal of neuromuscular blockade was done with Neostigmine 2.5 mg and Glycopyrrolate 0.4 mg. No prophylactic antiemetic was given intraoperatively.

Pneumoperitoneum was created through a Veress needle with CO<sub>2</sub> insufflated to the pressure of 12 to 14 mm of Hg. Four port Laparoscopic Cholecystectomy was performed in all patients.

### **Parameters for patients analysis**

- Serial measurements of TLC and CRP was done in both study and control group by sampling blood which was collected at time of completion of surgery in recovery room, at 6 hrs and 24 hrs after surgery.
- Evaluation for Nausea (subjective feeling) and vomiting (number of episodes) was done in both study and control group post operatively at 4, 8, 12 and 24 hours.
- Antiemetic requirement was assessed in terms of number and frequency of administration of Inj. Ondansetron 4mg as per requirement of the patient.

### **Statistical analysis**

The cumulative data was analyzed statistically using student-t test, Paired-t test, chi-square test by SPSS-20.

### **OBSERVATIONS/RESULTS**

#### **Demographic and biochemical profile**

Demographic and Biochemical profile were comparable in both the groups and the difference between the two was statistically insignificant as shown in Table No.1.

**Table-1: statistical analysis of demographic and biochemical data**

	GROUP	Mean	Std. Deviation	Std. Error Mean	P Value
AGE	CONTROL	46.4000	10.78505	1.96907	0.320
	STUDY	43.6000	10.84245	1.97955	
SEX	CONTROL	1.17	.379	.069	0.723
	STUDY	1.13	.346	.063	
FBS	CONTROL	88.4667	9.17919	1.67588	.361
	STUDY	90.6667	9.34154	1.70552	
RBS	CONTROL	104.60	7.85032	1.43327	0.581
	STUDY	105.83	9.28136	1.69454	
TOTAL PROTEINS	CONTROL	6.5567	.64791	.11829	0.70
	STUDY	6.9000	.78740	.14376	
ALBUMIN	CONTROL	4.0900	.35071	.06403	0.135
	STUDY	4.2267	.34734	.06341	
AMYLASE	CONTROL	58.1000	14.48983	2.64547	0.112
	STUDY	52.0667	14.48408	2.64442	
BILIRUBIN TOTAL	CONTROL	.6933	.23916	.04366	.369
	STUDY	.7467	.21613	.03946	
BILIRUBIN CONJUGATE	CONTROL	.1767	.14547	.02656	.264
	STUDY	.2167	.12888	.02353	
AST	CONTROL	30.1333	10.12247	1.84810	.763
	STUDY	30.9000	9.50263	1.73494	
ALT	CONTROL	31.9000	10.58740	1.93299	.594
	STUDY	33.4000	11.10949	2.02831	
ALP	CONTROL	59.8667	24.80925	4.52953	.663
	STUDY	62.7667	26.41797	4.82324	
UREA	CONTROL	25.2000	5.89213	1.07575	0.091
	STUDY	22.7000	5.36367	0.97927	
CREATININE	CONTROL	0.6467	0.11366	0.02075	0.094
	STUDY	0.6000	0.09826	0.01794	

**Pre-operative TLC**

As expected, the preoperative levels of the TLC and CRP were comparable in the two groups. The mean pre-operative TLC was  $7.1023 \pm 1.7385$  m/mm<sup>3</sup>. In the

study group, mean pre-operative TLC was  $6.936 \pm 1.532$  m/mm<sup>3</sup>. In the control group, pre-operative TLC mean was  $7.2683 \pm 1.934$  m/mm<sup>3</sup>. The result was comparable in both the groups (p = 0.412). Table No. 2.

**Table-2: Pre-operative tlc in study and control group**

	RANGE (m/mm <sup>3</sup> )	MEAN (m/mm <sup>3</sup> )	STD. DEVIATION	STD. ERROR OF MEAN	p-VALUE
TOTAL	4.44 – 10.56	7.1023	1.73852		.464
STUDY	4.44 – 9.97	6.9363	1.53295	.27988	
CONTROL	4.44 – 10.56	7.2683	1.93446	.35318	

**TLC at time of completion of surgery**

The mean TLC at completion of surgery was  $7.6767 \pm 1.9582$  m/mm<sup>3</sup>. In the STUDY group, the mean TLC at completion of surgery was  $8.0717 \pm 2.2121$

m/mm<sup>3</sup>. In the CONTROL group, the mean TLC at completion of surgery was  $6.842 \pm 1.375$  m/mm<sup>3</sup>. The result was comparable in both the groups (p = 0.120). Shown in Table No.3.

**Table-3: Talc at time of completion of surgery**

	RANGE (m/mm <sup>3</sup> )	MEAN (m/mm <sup>3</sup> )	STD. DEVIATION	STD. ERROR OF MEAN	p-VALUE
TOTAL	4.48 – 12.44	7.6767	1.9582		.120
STUDY	4.54 – 10.81	7.2817	1.60798	.29358	
CONTROL	4.48 – 12.44	8.0717	2.21210	.40387	

**TLC at 6 hrs of surgery**

The TLC 6hrs post operatively was markedly increased in CONTROL group ( $10.217 \pm 2.948 \text{ m/mm}^3$ ) when compared to the STUDY group

( $8.234 \pm 1.5344 \text{ m/mm}^3$ ). Statistical analysis shows significantly higher postoperative counts in CONTROL group ( $p < 0.002$ ) as Shown in Table No. 4

**Table-4: TLC AT 6 HRS of surgery**

	RANGE (m/mm <sup>3</sup> )	MEAN (m/mm <sup>3</sup> )	STD DEVIATION	STD ERROR OF MEAN	p-VALUE
TOTAL	4.46 – 16.02	9.225	2.535		
STUDY	4.46 – 11.34	8.234	1.53441	0.28041	0.002
CONTROL	5.55– 16.02	10.217	2.94836	0.53829	

**TLC at 24 hours after surgery**

The TLC, 24 hr after surgery in control group was markedly increased ( $11.510 \pm 3.410 \text{ m/mm}^3$ ) when compared to the study group ( $8.9447 \pm 1.953 \text{ m/mm}^3$ ).

Statistical analysis shows significant rise in postoperative counts for patients in control group ( $p < 0.001$ ). Shown in table no. 5

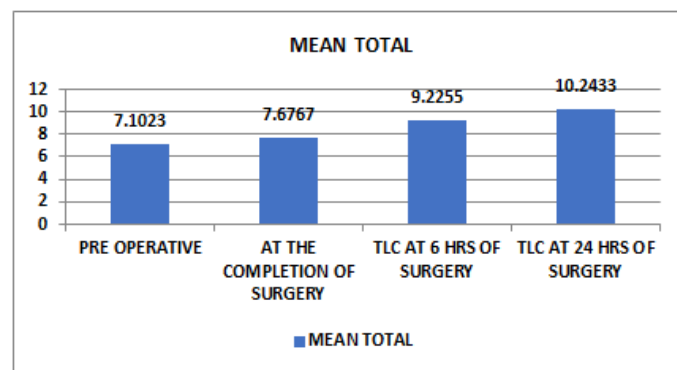
**Table-5: TLC AT 24 HOURS AFTER SURGERY**

	RANGE (m/mm <sup>3</sup> )	MEAN (m/mm <sup>3</sup> )	STD. DEVIATION	STD. ERROR OF MEAN	p-VALUE
TOTAL	4.48 – 18.67	10.2433	3.044		
STUDY	4.48 – 14.34	8.9447	1.95393	0.36098	0.001
CONTROL	5.33 – 18.67	11.510	3.41055	0.62268	

**CUMULATIVE DATA OF TLC**

**Table-6: TLC – TOTAL**

SR NO	TIMING OF SAMPLE	RANGE (m/mm <sup>3</sup> )	MEAN (m/mm <sup>3</sup> )
1	PRE-OPERATIVE	4.44 – 10.56	7.1023
2	AT THE COMPLETION OF SURGERY	4.48 – 12.44	7.6767
3	TLC AT 6 HRS OF SURGERY	4.46 – 16.02	9.2255
4	TLC AT 24 HRS OF SURGERY	4.48 – 18.67	10.2433



**Fig-1**

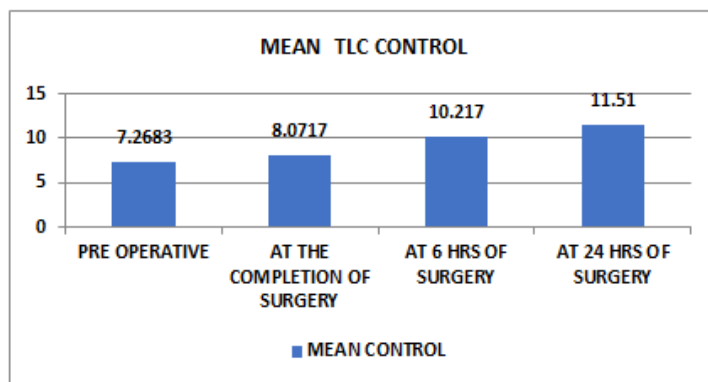


Fig-3

Table-8: TLC – CONTROL GROUP

SR NO	TIMING OF SAMPLE	RANGE (M/MM <sup>3</sup> )	MEAN (M/MM <sup>3</sup> )
1	PRE-OPERATIVE	4.44 – 10.56	7.2683
2	AT THE COMPLETION OF SURGERY	4.48 – 12.44	8.0717
3	AT 6 HRS OF SURGERY	5.55– 16.02	10.217
4	AT 24 HRS OF SURGERY	5.33 – 18.67	11.510

**PRE-OPERATIVE CRP**

The mean pre operative CRP was  $5.15 \pm 0.547$  mg/dl . In the study group mean pre operative CRP was  $5.03$  mg/dl  $\pm 0.183$  mg/dl. In the control group, mean pre operative CRP was  $8.0717 \pm 2.2121$  mg/dl. The result was comparable in both the groups ( $p = 0.103$ )

Table-9: PRE-OPERATIVE CRP

	RANGE (mg/dl )	MEAN (mg/dl )	STD. DEVIATION	STD. ERROR OF MEAN	p-VALUE
TOTAL	5 – 8	5.15	0.547		
STUDY	5 - 6	5.03	0.183	0.033	.103
CONTROL	5 - 8	5.27	0.740	0.135	

**CRP at completion of surgery**

The mean CRP at completion of surgery was  $6.250 \pm 2.955$ mg/dl. In the STUDY group, the mean CRP at completion of surgery was  $5.16 \pm 0.461$ mg/dl. In

the CONTROL group, the mean CRP at completion of surgery was  $7.30 \pm 3.889$  mg/dl. The result was comparable in both the groups ( $p = 0.09$ ). Shown in Table No. 10.

Table-10: CRP at completion of surgery

	RANGE (mg/dl)	MEAN (mg/dl)	STD. DEVIATION	STD. ERROR OF MEAN	p-VALUE
TOTAL	5 – 9	5.333	0.795		
STUDY	5 – 7	5.100	0.40258	0.07350	0.09
CONTROL	5 - 9	5.566	1.0063	0.18372	

**CRP at 6 hours after surgery**

The mean CRP 6 hrs post operatively was  $8.86 \pm 4.87$  mg/dl. In the STUDY group, the mean CRP 6 hrs post operatively was  $6.43 \pm 1.73$  mg/dl. In the CONTROL group, the mean CRP 6 hrs post operatively was  $11.30 \pm 5.75$  mg/dl. The rise in plasma CRP was more marked in CONTROL group ( $11.30 \pm 5.75$  mg/dl)

than in the study group ( $6.43 \pm 1.73$  mg/dl). Six hours after surgery slight increase in CRP was noted in the study group ( $5.03$  mg/dl  $\pm 0.183$  mg/dl vs.  $6.43 \pm 1.73$  mg/dl) and a more remarkable increase was noted in control group ( $8.0717 \pm 2.2121$  mg/dl vs.  $11.30 \pm 5.75$  mg/dl). This rise in CRP 6 hrs postoperatively in study and control groups was statistically significant

(p=0.000); this has also been observed by other investigators[5,6] shown in Table No. 11.

**Table -11: CRP AT 6 hours after surgery**

	RANGE (mg/dl)	MEAN (mg/dl)	STD. DEVIATION	STD. ERROR OF MEAN	p-VALUE
TOTAL	5 – 32	8.86	4.87		
STUDY	5 – 11	6.43	1.73570	0.31689	.000
CONTROL	5 - 32	11.30	5.75446	1.05062	

**Crp at 24 hours after surgery**

The rise in plasma CRP was more marked in control group (20.76 ± 14.82 mg/dl) than in study group (9.10± 3.34 mg/dl) after 24 hours of surgery. Pre-operative serum CRP levels were not statistically different in the two groups, but a slight postoperative increase in CRP was noted in the STUDY cases (preoperative 5.03 mg/dl ± 0.183 mg/dl vs 9.10± 3.34 mg/dl 24 hrs post operatively) and a more remarkable increase was noted for CONTROL cases (preoperative

8.0717 ± 2.21 mg/dl vs. 20.76 ± 14.82 mg/dl 24 hrs postoperatively as shown in Table No. 16. There was statistically significant rise in CRP 24 hours after the surgery in study groups (p=0.000).Sistla S *et al.*[6] observed that serum CRP levels increased significantly in both dexamethasone receiving (D) and placebo (P) groups after surgery. However, this increase was significantly greater in the P group compared with the D group both at 24 and 48 hours postoperatively. Similar results were also reported by other studies[5].

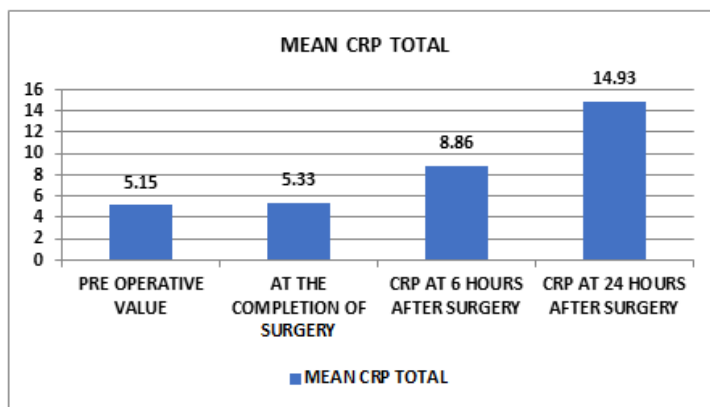
**Table-12: CRP AT 24 hours after surgery**

	RANGE (mg/dl)	MEAN (mg/dl)	STD. DEVIATION	STD. ERROR OF MEAN	p-VALUE
TOTAL	5– 63	14.93	12.17		
STUDY	5 – 16	9.10	3.34	0.61092	.000
CONTROL	5 - 63	20.76	14.82	2.70745	

**CUMULATIVE DATA OF CRP**

**Table-13: CRP – TOTAL**

SR NO	TIMING OF SAMPLE	RANGE	MEAN
1	PRE-OPERATIVE VALUE	5 – 8	5.15
2	AT THE COMPLETION OF SURGERY	5 – 9	5.33
3	CRP AT 6 HOURS AFTER SURGERY	6 – 14	8.86
4	CRP AT 24 HOURS AFTER SURGERY	5-63	14.93



**Fig-4**

**Table-14: CRP – STUDY GROUP**

Sr no	Timing of sample	Range	Mean
1	Pre-operative value	5 – 6	5.03
2	At the completion of surgery	5 – 7	5.10
3	CRP at 6 hours after surgery	5 –11	6.43
4	CRP at 24 hours after surgery	5 - 16	9.10

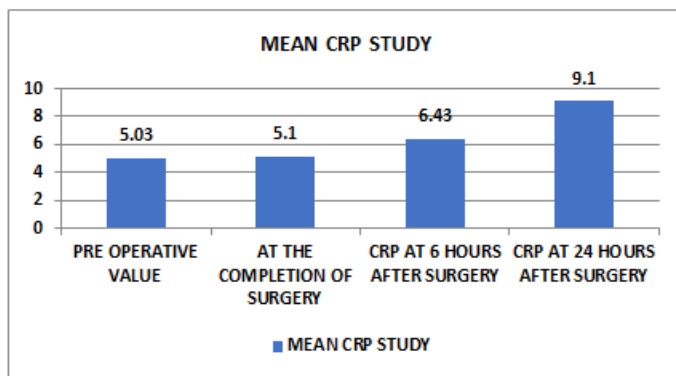


Fig-5

Table-15: CRP – CONTROL GROUP

SR NO	TIMING OF SAMPLE	RANGE	MEAN
1	PRE-OPERATIVE VALUE	5 – 8	5.27
2	AT THE COMPLETION OF SURGERY	5 – 9	5.56
3	CRP AT 6 HOURS AFTER SURGERY	5– 32	11.30
4	CRP AT 24 HOURS AFTER SURGERY	5-63	20.76

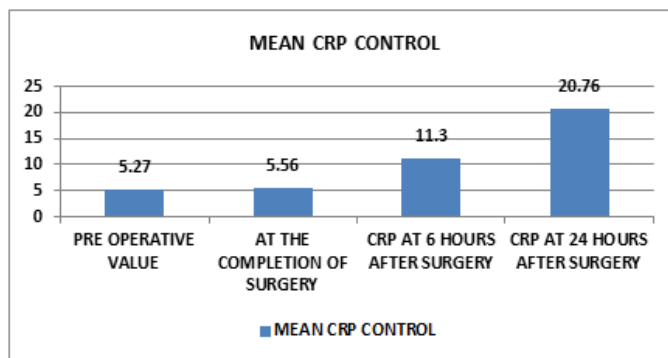


Fig-6

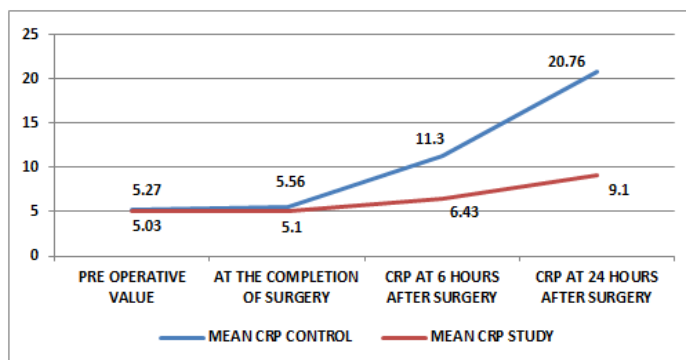
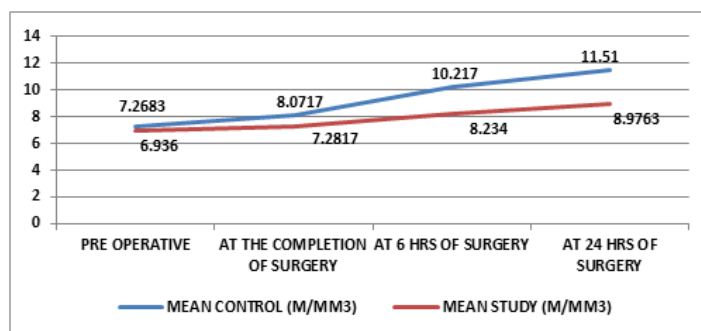


Fig-7: Graphical Representation of means of CRP in study and control group



**Fig-8: Graphical representation of means of TLC in study and control group**

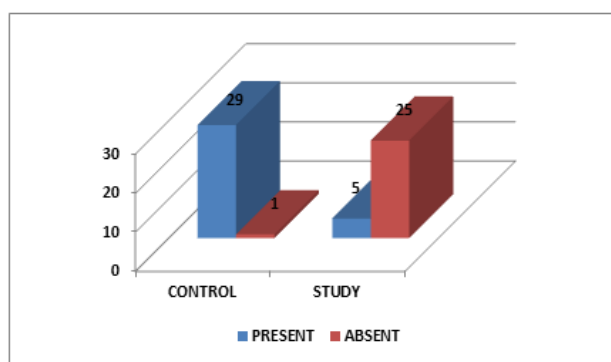
**Postoperative nausea and vomiting (PONV)**

The patients were given general anaesthesia by a standardized technique and drugs known to cause nausea and vomiting were not given. In study group 8.33 % ( n=30) patients had nausea, out of which 6.66 % ( n=30) had vomiting (one episode) whereas 91.37 % ( n=30) didn't have nausea or vomiting. In control group, nausea was present in 96.66 % ( n=30) patients, out of which 43.33% ( n=30) had vomiting (one to four episodes), whereas 3.33% ( n=30) didn't have nausea or vomiting. In study group, 93.33% ( n=30) didn't have vomiting and 6.66% ( n=30) had one episode of

vomiting. In control group 66.66 % ( n=30) had vomiting (1-4 episodes) and 33.33 % ( n=30) didn't had vomiting. The effects of single-dose i.v. dexamethasone in reducing the risk for postoperative nausea and vomiting are well documented. This study is consistent with other studies [7]. Though smaller doses of Dexamethasone i.e. 2.5 – 5 mg. have also been found effective in reducing PONV [8-9], their effect on stress markers like Total Leucocyte Count and C-Reactive Protein etc. needs further evaluation. Details of Nausea and vomiting in both the groups are as shown in Table No.16, 17 and Figure No. 9 and 10.

**Table-16: Postoperative nausea**

NAUSEA	GROUP		Total(n=60)
	CONTROL(n=30)	STUDY(n=30)	
PRESENT	29(96.66%)	5(16.66)	34(56.66%)
ABSENT	1(3.33%)	25(83.33)	26(43.33%)
Total(n=60)	30(50%)	30(50%)	60(100%)



**Fig-9: Postoperative nausea**



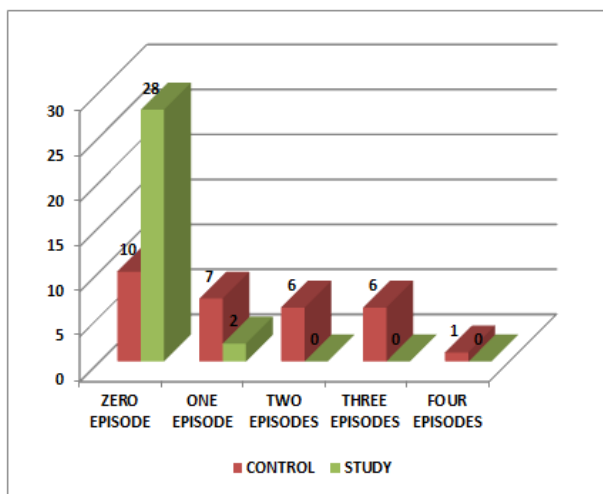


Fig-10: Postoperative vomiting

Table-17: Postoperative vomiting

VOMITING			
NUMBER OF EPISODES	CONTROL (n=30)	STUDY (n=30)	TOTAL (n=60)
0	10	28	38
1	7	2	9
2	6	0	6
3	6	0	6
4	1	0	1
Total	30	30	60

**Antiemetic**

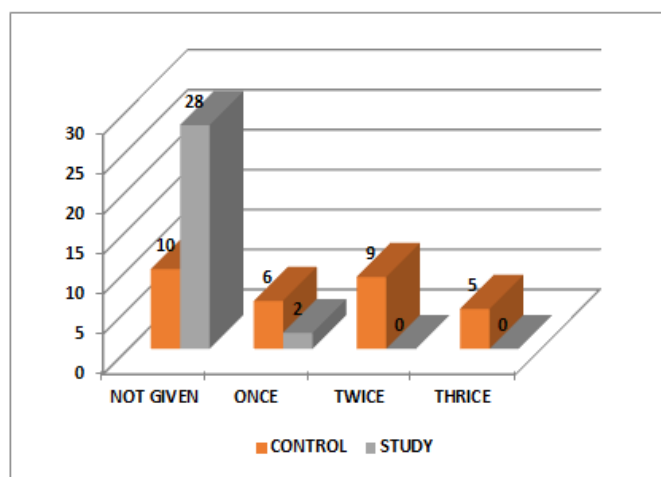


Fig-11: USE of ANTIEMETIC

Antiemetic (Ondansetroni.v. 4mg) was given to the patient as per requirement. Overall 63.33% (n=60) didn't required antiemetic post operatively however 35% (n=60) were given as per requirement. In Study group 93.33% (n=30) didn't require antiemetic whereas 6.66% (n=30) required one dose postoperatively. In Control group 33.33% (n=30) didn't require antiemetic whereas 66.66% (n=30) required 1 to 3 doses of antiemetic. This is in consistency with other studies [10-14].

**DISCUSSION**

Laparoscopic cholecystectomy (LC) is one of the most common surgery performed worldwide. The supplementation of dexamethasone preoperatively to reduce; surgical stress, PONV, antiemetic use and Hospital stay, is attributed to anti-inflammatory, immunomodulatory and antiemetic effect of dexamethasone.

Following inferences were derived from present study.

- The magnitude of the acute-phase response was less pronounced following administration of single dose of 8 mg of i.v. dexamethasone preoperatively.
- This study documents the substantial beneficial impact of administration of single dose of 8 mg of i.v. dexamethasone preoperatively with regards to reduced PONV and postoperative antiemetic requirement.
- It is concluded that single dose of 8 mg of i.v. dexamethasone preoperatively is safe and effective and can be considered to minimize surgical stress response, PONV and antiemetic use.

Therefore, the rise of markers of inflammation (TLC & CRP) is much less when 8mg of preoperative i.v. dexamethasone is given. Also, the incidence of PONV and requirement of antiemetic in post-operative period is reduced. However, the study period lasted 24 hrs only, the studies involving monitoring of inflammatory response for 48-72 hrs may be warranted, to evaluate the further duration of suppression of inflammatory response with single dose of 8 mg of dexamethasone. Also, anti-inflammatory effect of smaller doses (2.5-5 mg) of dexamethasone, which are known to decrease PONV, may be further evaluated.

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