

# Comparison of metabolic and inflammatory stress response after laparoscopic and open cholecystectomy

M ZEA, A Anees, N Islam, K Zafar, T ASHRAF

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## Abstract

Surgical trauma by incision and dissection of tissue stimulates the body to respond proportionately to the extent of injury. This study was conducted to compare metabolic and inflammatory responses after laparoscopic and open cholecystectomy in terms of serum glucose, cortisol and C-reactive protein levels before and after operation, as non-randomized controlled trial a medical college of western India. It was found that metabolic responses like serum cortisol and glucose were significantly higher after open the procedure 6 hours and 48 hours postoperatively. Similarly, inflammatory response indicator C-reactive protein was raised significantly higher 48 hours after open as compared to laparoscopic cholecystectomy. On the basis of these findings, it can be hypothesized that open cholecystectomy causes more tissue responses as compared to its laparoscopic alternative.

## INTRODUCTION

Acute trauma, whether accidental or surgical, stimulates a series of hormonal, metabolic and inflammatory changes that together constitute the stress response<sup>1</sup>. The stress response depends directly on the extent of injury. Cholecystectomy, being an intra-abdominal procedure, may be regarded as a major surgical stress. Laparoscopic cholecystectomy reduces the extent of the peritoneal incision and is considered to be less stressful than the conventional procedure. The advantage of this new method compared to open cholecystectomies are: minimal postoperative pain, prompt postoperative bowel activity (6-24 hours), reduced postoperative infections, shorter hospitalization (1-3 days), diminished neuroendocrine metabolic response as well as earlier return to normal activity<sup>2</sup>. In our study, the systemic stress responses after laparoscopic and conventional open cholecystectomy were compared as a non-randomized prospective trial. The hypothesis is that laparoscopic cholecystectomy causes significantly less stress response as compare to open cholecystectomy.

## MATERIALS AND METHODS

This was a non-randomized, prospective and comparative study, conducted at the Department of Surgery, Department of Medicine and Department of Biochemistry, J.N. Medical College Hospital, AMU, Aligarh, from December 2004 to July 2006. One hundred patients were included in this study and were divided into two groups of open and laparoscopic

cholecystectomy. The allocation of patients in different groups was done on the basis of patient's choice after explaining the study procedure and taking informed consent.

## INCLUSION CRITERIA:

Patients with symptomatic cholelithiasis

Uncomplicated gall stone disease (acute cholecystitis, empyema, associated CBD stones, Mirizzi's syndrome, biliary fistulas, gall bladder mass were not included).

Age: 20 to 60 years.

## Exclusion Criteria

Patients with concomitant illness like hypertension, diabetes, pregnancy, chronic pulmonary disease, cardiac disease, and other associated abdominal disease.

Any need for conversion, peroperative cholangiography, or CBD exploration.

Duration of surgery more than 90 minutes.

Out of these 100 patients, 42 underwent open cholecystectomy and 58 laparoscopic cholecystectomy. Preoperative, intraoperative, postoperative and anaesthetic medications were standardized in all the patients. All patients were kept nil orally since midnight. Tab. alprazolam 0.5 mg was given at bedtime to all the patients. Intravenous fluids started half an hour before surgery. Inj. ceftriaxone

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was given to all patients intravenously half an hour before operation.

In the patients who underwent laparoscopic procedures, pneumoperitoneum was created with CO<sub>2</sub>, and the standard four-port method was used to carry out the procedure. In the patients subjected to open cholecystectomy, a subcostal incision was used varying from 10-14cm. In both approaches, cholecystectomy was carried out by dissection of Calot's triangle and ligating/clipping of cystic duct and artery. A drain was placed in the subhepatic space in all the patients.

In all the patients, till evening 3 units of fluids were given in the form of Ringer lactate and 5% dextrose. The postoperative antibiotic used was inj. ceftriaxone and inj. gentamycin. Postoperative analgesic inj. diclofenac was given. The antiemetic used was inj. metoclopramide. Fluid administration was stopped in the evening and all the patients were allowed oral fluid intake.

Premedication was done with inj. metoclopramide, inj. Tramadol and inj. diazepam. Induction of anesthesia was done with inj. succinyl choline followed by inj. vecuronium. Maintenance was done with Entonox and reversal with inj. Neostigmine.

In all the 100 patients, blood samples were collected half an hour before the operations from the antecubital vein for estimation of serum cortisol, and at 6 hours and 48 hours postoperatively for estimation of serum cortisol and C-reactive protein.

C-reactive protein (CRP) was measured by CRP ELISA kit with ELISA reader and spectrophotometry with automated analyzer was used to measure serum glucose in the department of biochemistry. Serum cortisol was measured by radioimmunoassay technique in the department of medicine.

### STATISTICAL ANALYSIS

Results were expressed in terms of mean with standard deviation. Statistical comparison was performed using Student's t-test. Statistical significance was accepted when the p-value was less than 0.05.

### OBSERVATIONS:

The average age of the patients was 39.36±6.24 yrs, with a range of 20 to 60 yrs. The average age of male patients was 42.6±5.82 yrs ranging between 26-58 yrs and for the female

patients it was 34.64±7.66 yrs. Among 100 patients, 78 patients were female and 22 were male. Male to female ratio was found to be 1:3.55. In the 58 patients who underwent laparoscopic cholecystectomy, male to female ratio was 12:46 and in the open group this ratio was 1:3.2.

SERUM CORTISOL: Normal range of serum cortisol was 0.16-0.81µmol/l. Serum cortisol was evaluated in both groups preoperatively, 6 hrs and 48 hrs after the operation. The details are shown in table 1.

### Figure 1

Table 1: Serum cortisol level at different intervals of time

Timing	Lap (Mean ± SD) N=58	Open (Mean ± SD) N=42	P-value
Preoperative	0.44 ± 0.05	0.42 ± 0.04	NS
6 hrs Postoperative	0.57 ± 0.03	1.4 ± 0.26	<0.001
48 hrs Postoperative	0.57 ± 0.05	0.97 ± 0.07	<0.001

Serum cortisol levels were expressed as mean with standard deviation, the mean preoperative level was 0.44±0.05µmol/l and 0.42±0.04µmol/l in the laparoscopic and in the open group, respectively, which was comparable and there was no significant difference. The level of mean serum cortisol was raised to 0.57±0.03µmol/l and 1.4±0.26µmol/l at 6 hours postoperatively. The rise of serum cortisol was significant in the open group at 6 hours after the operation. At 48 hours, the levels were 0.57±0.05µmol/l and 0.97±0.07µmol/l, which shows a fall in the level of cortisol in the open group as compared to the level at 6 hours. However, the level was still significantly higher as compared to the laparoscopic group at 48 hours after the operation. The level of serum cortisol was not significantly changed postoperatively in the laparoscopic group. The differences between the two groups were statistically significant at 6hrs. postoperatively (t=27.7, p<0.001) and at 48 hrs. postoperatively (t=33.3, p<0.001).

### SERUM GLUCOSE

The normal range of serum glucose is 90-126mg/dl. Serum glucose levels were evaluated preoperatively, and at 6 hrs. and 48 hrs. postoperatively. The mean serum glucose level was 99.27±8.76mg/dl and 104.56±10.47mg/dl preoperatively in the laparoscopic and in the open group, respectively, which was not statistically different. The mean serum glucose level was 114.43±11.85mg/dl and 128.26±11.59mg/dl at 6 hrs. postoperatively. After 48 hrs., the levels were 106.93±11.27mg/dl and 117.62±11.13mg/dl, respectively, in

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the laparoscopic and in the open group. The serum glucose level rose in both groups at different intervals although it remained within the normal range.

These raised levels of serum glucose were higher in open as compared to laparoscopic cholecystectomy. The difference was statistically significant at 6 hrs. ( $t=5.9$ ,  $p<0.001$ ) and 48 hrs. ( $t=4.8$ ,  $p<0.001$ ).

**Figure 2**

Table 2: Serum Glucose Level

Timing	Lap (Mean ± SD) N = 58	Open (Mean ± SD) N = 42	P-value
Preop. (mg/dL)	99.27±8.76	104.56±10.47	NS
6 hrs. PO (mg/dL)	114.43±11.85	128.26±11.59	<0.001
48 hrs. PO (mg/dL)	106.93±11.27	117.62±11.13	<0.001

C-reactive protein (CRP): C-reactive protein is an important marker of acute inflammatory response of the body system. Its level reflects the amount of stress due to any surgical procedure. The mean CRP level was  $15.35\pm 3.99$  in the laparoscopic group at 48 hrs. after the procedure and  $41.67\pm 10.57$  after open cholecystectomy as shown in table 3.

**Figure 3**

Table 3: C-reactive protein 48 hrs. postoperatively

Procedure	CRP (Mean ± SD)	P-value
Lap (n=58)	15.35±3.99	<0.001
Open (n=42)	41.67±10.57	

On analyzing, we found that the raised CRP level in open cholecystectomy was much higher than in laparoscopic cholecystectomy at 48 hrs. after procedure. The difference was statistically highly significant ( $t=17.6$ ,  $P<0.001$ ). This indicates that inflammatory stress is higher in open cholecystectomy.

## DISCUSSION

Elective surgical wounds and trauma elicit similar physiological responses; these include increased stress hormone release, interaction of intermediary metabolism and fluid balance, negative nitrogen balance and increased hepatic production of acute-phase proteins. These responses are mediated by both afferent neural stimuli and circulating factors such as catabolic hormones and cytokines that are released by wounds. Attention has now focused on

attenuating these responses. Blockage of these circulating factors is potentially more difficult to achieve as compared to attenuating neural responses.

Minimally invasive surgery has presented an alternative approach to diminishing metabolic responses by avoidance of a substantial abdominal incision, reduced tissue manipulation and faster patient recovery<sup>3,4</sup>.

Serum cortisol is one of the most important hormone rises after acute stress. Its level reflects the extent of stimulation of the hypothalamic-pituitary-adrenal axis. Cortisol acts directly or indirectly on different homeostatic mechanisms of body to attenuate the stress. Corticosteroid increases extracellular osmolarity to provide the driving force for fluid shift from intracellular to extracellular space in conditions like haemorrhage<sup>5</sup>. It also inhibits glycogenolysis, stimulates gluconeogenesis and inhibits protein synthesis.<sup>6,7</sup>

In different previous studies it has been clearly demonstrated that the level of serum cortisol rises significantly after open cholecystectomy as compared to laparoscopic cholecystectomy from postoperative day one up to day three<sup>8,9</sup>.

In the present study, we found a marked increase in the serum cortisol level after open cholecystectomy. The rise of serum cortisol was significant in the open group at 6 hours after the operation as compared to the laparoscopic group. This level showed a slight fall at 48 hours as compared to the level at 6 hours. However, this level was still higher as compared to the laparoscopic group. At both intervals of time, 6 hours and 48 hours, the serum cortisol level was significantly higher in the open group.

A prominent feature of the response to injury or sepsis is hyperglycemia. The initial increase in blood glucose after injury is due to mobilization of liver glycogen. After that, hyperglycemia is maintained by increased production of glucose from the liver by gluconeogenesis and decreased clearance of glucose by peripheral tissue due to insulin resistance<sup>10</sup>. These responses occur as a composite response of different hormones like insulin, glucagon, catecholamines, cortisol and growth hormones<sup>9,11,12</sup>. These hormones affect, directly or indirectly, the serum glucose level leading to postoperative hyperglycemia.

The mean glucose level was significantly higher after open cholecystectomy as compared to laparoscopic cholecystectomy, which was also reported in previous

studies<sup>8,13,14,15</sup>.

Similarly, in this study postoperative raised levels of serum glucose of different intervals of time were higher in open as compared to laparoscopic cholecystectomy.

The systemic stress response is also mediated by inflammatory mediators originating from the surgical wounds. Of these mediators, IL-6 has a crucial role in the induction and control of acute-phase protein synthesis, particularly of CRP, by human hepatocytes<sup>13</sup>. Hepatic acute-phase protein production, especially of CRP, is a sensitive marker of inflammatory response<sup>16</sup>. The level of IL-6 raises, parallel to CRP, more in open cholecystectomy.<sup>13,14,15,17</sup>

The result of the present study confirms previous reports in the literature indicating that open cholecystectomy causes more significant stress response in the form of raised CRP as compared to laparoscopic cholecystectomy at 48 hours after the operation<sup>8,9</sup>.

This may result from decreased release of IL-6 from a smaller wound surface of laparoscopic cholecystectomy as compared to open cholecystectomy, which leads to a diminished rise of the CRP level after laparoscopic cholecystectomy.

Conclusion: Metabolic and inflammatory stress responses of human body are higher after open as compared to laparoscopic cholecystectomy, because the body faces more trauma in open procedures.

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**Author Information**

**Mohammad Iqbal ZEA, M S**

Senior Resident, Department of Surgery, J N Medical College

**Afzal Anees, M S, FAIS, FAIGES, FMAS**

Lecturer, Department of Surgery, J N Medical College

**Najmul Islam, M D**

Lecturer, Department of Biochemistry, J N Medical College

**Khwaja Saifullah Zafar, M D**

Senior Resident, Department of Medicine, J N Medical College

**Tarique Hussain ASHRAF, M S**

Senior Resident, Department of GI Surgery, CSSMM College