*Research Article*

# Stress Response After open and Laparoscopic Retro-infundibular cholecystectomy in difficult cases

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## Abstract

**Background:** Laparoscopic cholecystectomy (LC) is now considered to be the gold standard therapy for symptomatic cholelithiasis. Surgery in general induces activation of sympathetic nervous system and hypothalamic-pituitary-adrenal axis leading to activation of adrenal cortex, promoting the release of neurohormonal transmitters that would affect the degree of postoperative pain postoperative ileus. The aim of this study was to evaluate the stress response after open and laparoscopic retro-infundibular cholecystectomy in difficult cases

**Patients and methods:** This study is a randomized controlled clinical trial, was conducted in Surgery Department, Minia University Hospital, Egypt, during a period between January 2017 and May 2017, and included 100 patients presented with chronic cholecystitis. Patients were divided into two groups. Group A was treated laparoscopic cholecystectomy by retroinfundibular (RI) approach, whereas the other group (group B) was treated by open cholecystectomy blood sample for evaluation of stress hormones were withdrawn at time of operation, 12 hours& 24hours postoperative. **Result:** From total 100 patients, 40 were females (40%) and 60 were males (60%). Age range between 35 years and 65 years with a mean (52.7± 6.3 years) and mean body weight of (62.4±5.61kg). Operative time was 79.6±19.5 and 96.8±13.8 for group A & B respectively. Postoperative hospital stay was 1.4±0.51, 2.4±0.6 days for group A & B respectively. At time 0, ACTH was (44.5 pg/ ml) and (46.5 pg/ml), at 12h postoperative, it was (219.6 pg/ml) & (65.7 pg/ml), at 24h postoperative, it was (40 pg/ml) and (137.8 pg/ml) for group A & B respectively. At time 0, the level of Insulin was (12.8µm/ml) and (9.3µm/ml), at 12h postoperative it was (26 µm/ ml) and (44.1 µm/ml) and At 24h postoperative, (101.1 µm/ml) (48.6 µm/ml) for group A & B respectively. At time 0, the level of NE was (46.6 ng/ml) and (48.8 ng/ml), at 12h postoperative, it was (65.8 ng/ml) and (89.2 ng/ml) and at 24h postoperative, it was (80.9 ng/ml) and (60.3 ng/ml) for group A & B respectively. **Conclusion:** In conclusion, laparoscopic RI cholecystectomy is associated with less neuroendocrinal and inflammatory responses than open cholecystectomy

**Key words:** Laparoscopic cholecystectomy**,** neurohormonal**,** and retroinfundibular

## Introduction

Acute trauma, either surgical or accidental lead to a series of hormonal, metabolic and inflammatory changes that constitute what is called the stress response, which related to the extent of injury. Cholecystectomy, being an intra-abdominal procedure, may be regarded as a major surgical stress(1). The magnitude of the peroperative and the immediate postoperative trauma response has an impact on the postoperative course with regard to pain; mobilization and duration of the hospital stay(2).

The stress of surgery leads to production of cytokines, increases in the levels of stress hormones, greater vascular permeability, and loss of muscle protein and changes in white cell count. Some of these responses are a homoeostatic defense mechanism, but others such as the catabolic state are thought to be deleterious and become harmful to the body, resulting in glucose intolerance, negative nitrogen balance, and immunologic impairment, which increase postoperative morbidity(3).

Laparoscopic cholecystectomy (LC) is now considered the gold standard treatment for gallstone and chronic cholecystitis because it had induced less tissue trauma response throughout the course of wound healing compared to open cholecystectomy. Surgery also induces neurohormonal events with activation of sympathetic nervous system and activation of hypothalamic-pituitary -adrenal axis. Then the adrenal cortex is stimulated, leading to release of neurohormonal transmitters that influence the intensity of postoperative pain and postoperative ileus.[4]

The superiority of laparoscopic cholecystectomy has justified its universal usage in recent years. Although laparoscopic cholecystectomy results in a favourable clinical outcome compared with open cholecystectomy, little is known about its impact on human homoeostasis and there were few studies concerning the difference between the two operative techniques in operative stress response and energy metabolism[5].

ACTH, catecholamine, cortisol, and glucagon all played important roles in the stress response. In response to sepsis and trauma, cortisol, catecholamine and glucagons are released, and insulin decrease relatively[6,7].

The stress response has been investigated in several studies comparing laparoscopic and open surgery in an effort to explore possible physiologic differences that might be of clinical importance. To date, no major differences in the endocrine, metabolic, or immune response have been observed in favor of the laparoscopic procedure[8].

This study aimed at evaluation of stress response after open and laparoscopic (RI) cholecystectomy in difficult cases to determine the least invasive surgical procedure by comparing the levels of stress hormones (ACTH , Norepinephrine and Insulin) and liver functions (ALT, AST, S.bilirubin, ALP, PC and albumin) in both procedures.

**Patients and Methods**

This study was conducted in Surgery Department, Minia University Hospital, Egypt during a period between January 2017 and May 2017. This study was conducted on 100 patients presented with chronic cholecystitis. Patients were divided into two groups by random allocation. One group (group A) was treated laparoscopic cholecystectomy by retroinfundibular (RI) approach, whereas the other group (group B) was treated by open cholecystectomy. Detailed explanation of the procedure, its outcome, complications, expected improvement were included in an informed consent and signed by all included patients before management.

**Inclusion criteria:** Patients with Symptomatic chronic cholecystitis predicted to have a difficult cholecystectomy according to the score of difficulty as shown in the tables 1, 2[9]. **Exclusion criteria:** Patients unfit for surgery and those refused to be involved in the study.

Detailed history was taken from all patients especially history of any medical problems as DM, HTN and liver disease. Patients were subjected to complete clinical, laboratory, and radiological investigations (abdominal ultrasound was done to show site and size of gall bladder stones, gall bladder size ,gall bladder wall thickness, CBD diameter , pericholecystic collection, intrahepatic biliary radicals and any signs of pancreatitis).

**Table (1): Scoring factors used for grading the patient parameters.**

| | | score | Max score |
|---|---|---|---|
| **History** | | | |
| Age | ≤50 | 0 | 1 |
| | >50 | 1 | |
| Sex | Male | 1 | 1 |
| | female | 0 | |
| History of hospitalization for | Yes | 4 | 4 |
| Acutecholycystitis | NO | 0 | |
| **Clinical parameters** | | | |
| BMI | <25 | 0 | 2 |
| | 25-27.5 | 1 | |
| | <27.5 | 2 | |
| Abdominal scar | NO | 0 | 2 |
| | Infraumblical | 1 | |
| | supraumblical | 2 | |
| Palpable gall bladder | YES | 1 | 1 |
| | NO | 0 | |
| **Sonography** | | | |
| Wall thickness | Thin<4mm | 0 | 2 |
| | Thick≥4mm | 2 | |
| Pericholecystic collection | NO | 0 | 1 |
| | YES | 1 | |
| Impacted stone | NO | 0 | 1 |
| | YES | 1 | |

**Score 0-5 easy, 6-10 difficult , 11-15 very difficult.**

**Table (2): Intra operative assessment.**

| Parameters | Score | Grading |
|---|---|---|
| **Time taken<60 min&<br>NO bile spillage &<br>NO injury to duct** | 0-5 | Easy |
| **Time taken 60-120 min and\or<br>Bile or stone spillage and\or<br>Injury to duct** | 6-10 | Difficult |
| **Time taken> 120 min or conversion** | 11-15 | Very difficult |

**Both groups of patients was compared in the following:** Preoperative risks (obesity, DM, IHD, liver cirrhosis), operative time, postoperative pain assessment by using a linear visual analogue scale (VAS) ,explained for all patients preoperatively, with pain value ranging between 0 = no pain at all and 10 = intolerable pain, **postoperative analgesia,** duration of hospital stay which needed after operation, operative and postoperative complications( bile duct injury, uncontrolled bleeding, bile leak and postoperative jaundice), laboratory study at 24h and 48h postoperative involving( liver enzymes, prothrombin time, direct bilirubin, indirect bilirubin, stress hormones comparison at time 0, time 12h and time 24h postoperative using ELISA technique, insulin, Norepinephrine (NE) and ACTH.

**Techniques**

**Conventional open cholecystectomy.** Open cholecystectomy can be performed through either an upper midline or right subcostal (Kocher) incision. Identification and division of the cystic duct and artery initially limits bleeding from the gallbladder for the remainder of the dissection. With lateral traction on the gallbladder neck, the peritoneum overlying the triangle of Calot is incised, and the cystic duct is identified and ligated distally.

The cystic duct is then ligated proximally and divided. Similarly, the cystic artery is ligated and divided after carefully tracing it onto the gallbladder. The gallbladder is dissected out of the gallbladder bed by incising the overlying peritoneum with cautery[10].

**Laparoscopic cholecystectomy (Retroinfundibular approach):** The site of trocars was the same as for the standard laparoscopic cholecystectomy. After dissection of adhesion that may masking the GB, to reach the Hartmann pouch, Calot's triangle was scarred and frozen.

1. Incising the peritoneal covering on either side of the infundibulum and lower part of the body.
2. Dissection and separation of the lower third of GB body from its bed. Dissection continued downward till the narrowest part of GB (pedicle: duct and artery).
3. Mass ligation of the pedicle, by vicryl number 1 suture.
4. Division of GB above the ligature. During this step the cut end of the GB was grasped by forceps trying to prevent spillage of its content, if happened, stones were collected in a bag and extracted.
5. Then GB was dissected from its bed as usual and extracted in a bag.

If the GB was hugely distended, it was aspirated to facilitate its grasping. Also in cases of Mirizzi syndrome we were obligated to open the GB direct on the stone to remove it, to facilitate grasping of GB then we continued as described above (Figure 1).

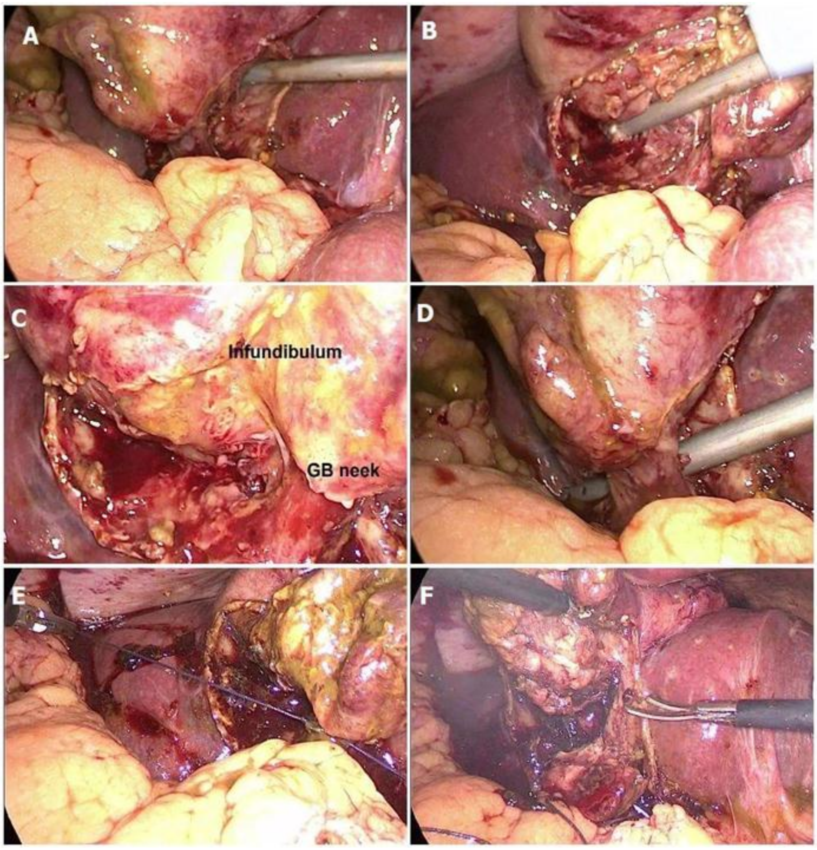


**Figure (1) Steps of laparoscopic cholecystectomy retroinfundibular approach.**

**Statistical analysis**

Data were collected, revised, verified, coded, then entered PC for statistical analysis done by using SPSS statistical package version 20. **Descriptive statistics:** for qualitative data: number (N) and percentage (%), for quantitative data: mean (X~) and standard deviation (SD). Kolmogorov- Smirnov for normality test was used to differentiate between parametric data and non-parametric data.

**Analytical statistics:** Normally distributed variables (parametric) between two study groups were analyzed using: paired (t) test for analysis of quantitative variables, Independent sample (t) test for analysis of quantitative variables, Chi – square ($x^2$) for analysis of qualitative data.

**For all tests probability (p) was considered:** Non-significant if ≥ 0.05 and significant if < 0.05

**Results**

This study included 100 patients, 40 females (40%) and 60 males (60%) with age range 35-65 years. Group A included 50 patients with 23 males (46%) and 27 females (54%) and age range between 35 years and 65 years with a mean (52.7± 6.3 years) and mean body weight of (62.4 ± 5.61kg). Group B included 50 patients with 20 males (40%) and 30 females (60%) and age mean (50.7±5.5 years) and body weight (60.4±5.61kg).

In this study ,there is no significant difference between two groups as regards preoperative predictors of difficult cholecystectomy (age, male sex ,obesity, post ERCP, upper abdominal scar, pericholecystic collection,thick gall bladder wall) (Table 3).

Difficulty as a result of difficult grasping or retracting of GB and non visualization of GB appeared to be increased in laparoscopic procedure than open procedure, However difficulty as a result of abnormal anatomy or difficult clipping of duct or dissection of calot triangle appeared to be increased in open procedure but not present in laparoscopic (RI) procedure (Table 4).

Operative time and postoperative hospital stay appeared to be increased during open than laparoscopic (RI) procedure and these differences were statistically significant (Table 5).

Operative complications “bleeding” appeared to be increased in open than laparoscopic procedure but post-operative complications “jaundice” was not observed after laparoscopic or open procedure, however CBD injury occurred in one case of open group and not occurred with the laparoscopic procedure (Table 6).

In Group A, score of pain < 3 was recorded in 47 patients (94%) in day of surgery, in 49 patients (98%) in 1 st postoperative day. Score of pain 3-6 was recorded in 2 patients (4%) in the day of surgery, and in one patient (2%) in the 1 st postoperative day. Score of pain 6-9 was only recorded in one patient (2%) in the day of surgery. In Group B, score of pain < 3 was recorded in 35 patients (70%) in day of surgery, in 43 patients (86%) in 1 st postoperative day. Score of pain 3-6 was recorded in 9 patients (18%) in day of surgery, in 5 patients (10%) in 1 St postoperative day. Score of pain 6-9 was recorded in 5 patients (10%) in day of surgery and in 2 patients (4%) in 1 postoperative day. Maximum score of pain 10 was recorded in one patient (2%) (Table 7).

As regards stress hormones, at time 0, level of ACTH is nearly equal in both open group (44.5 pg/ml) and laparoscopic group (46.5 pg/ ml). At 12h postoperative, level of ACTH increased in both groups but more in open (219.6 pg/ ml) than laparoscopic group (65.7 pg/ ml). At 24h postoperative, level of ACTH nearly returned to normal in laparoscopic group (40 pg/ ml) but still increased in open group ( 137.8 pg/ml ) (Table 8, figure 4).
At time 0 , Level of NE is nearly equal in both open (46.6 ng/ ml ) and laparoscopic group (48.8 ng/ml ). At 12h postoperative, level of NE increased in laparoscopic group (65.8 ng/ ml) but less than open group (89.2 ng/ml) but still within normal level. At 24h postoperative, level of NE

still increased in both open (80.9 ng/ ml) and laparoscopic group (60.3 ng/ ml) but within normal level (Table 8, figure 5).

At time 0, Level of Insulin is nearly equal in both open (12.8µm/ml) and laparoscopic group (9.3µm/ ml). At 12h postoperative, level of Insulin increased in laparoscopic group (26 µm/ ml) but less than open group (44.1 µm/ml). At 24h postoperative, level of Insulin still increased in both groups but more in open (101.1 µm/ ml ) than laparoscopic group (48.6 µm/ ml) (Table 8, figure 6).

As regards liver functions (Table 9), nearly no change in level of AST between two groups at 24h postoperative. At 48h postoperative level of AST in open group (45.7) is more than laparoscopic group (29.4) but within normal level. No difference in levels of ALT at time 24h and 48h postoperative in both groups. No difference in levels of PC, total bilirubin, albumin, Alkaline phosphatase at time 24h and 48h postoperative in both groups. There was a significant difference between 2 groups in direct bilirubin at time 24h postoperative (Table 8).

**Table (3): possible predictors of difficulty:**

| Possible predictors of difficulty | Group A N=50 | Group B N=50 | P-value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| **Old age** | 25(50%) | 20(40%) | 0.653 |
| **Male Sex** | 23(46%) | 20(40%) | 0.2 |
| **Obesity** | 10(20%) | 15(30%) | 0.606 |
| **Liver cirrhosis** | 10(20%) | 15(20%) | 1 |
| **Previous Upper Abdominal Surgery** | 10(20%) | 15(30%) | 0.606 |
| **Previous ERCP** | 5(10%) | 15(30%) | 0.264 |
| **Pericholecysticcollection** | 5(10%) | 6(12%) | 0.390 |
| **Thick GB wall** | 7(14%) | 7(14%) | 1 |
| **History of hospitalization** | 6(12%) | 4(8%) | 0.783 |

**Table (4): Intra-operative difficulties.**

| Type of difficulty | Group A N=50 | Group B N=50 | P-value |
|---|---|---|---|
| | Freq. (%) | Freq. (%) | |
| **Difficult Grasping and Retraction of the GB** | 5(10%) | 0(0%) | 0.305 |
| **Difficult Dissection of CalotTriangle** | 0(0%) | 30(60%) | <0.001* |
| **Abnormal Anatomy** | 0(0%) | 15(30%) | <0.001* |
| **Difficult Retrieval of the Specimen** | 0(0%) | 0(0%) | NA |
| **Difficult Access/ Pneumo-peritoneum** | 5(10%) | 0(0%) | 0.305 |
| **Non visualization of gallbladder** | 10(20%) | 0(0%) | 0.136 |
| **Difficulty in duct clipping** | 0(0%) | 20(40%) | 0.025* |

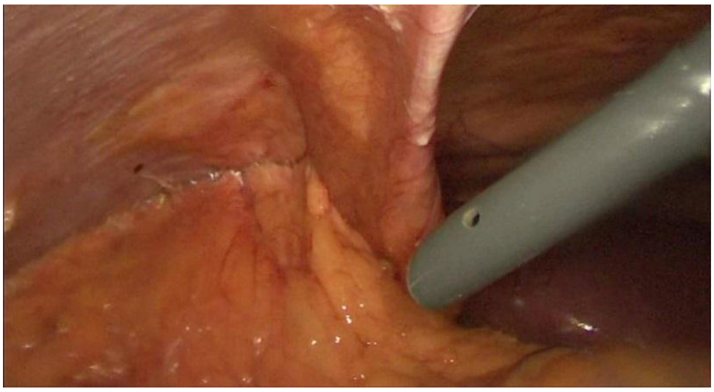

**Figure (2) Gall bladder completely covered by omentum.**

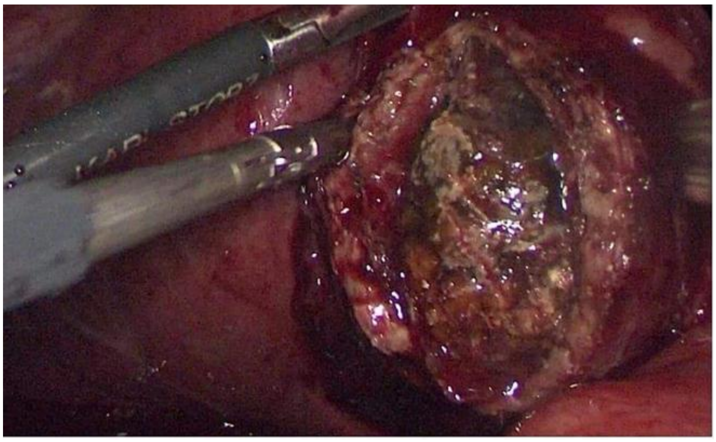

**Figure (3) Laparoscopic view showing Mirrizi syndrome.**

**Table (5): Operative time and hospital stay in both procedures:**

| | Group A N=50 | Group B N=50 | P-value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Operative time | 79.6±19.5 | 96.8±13.8 | 0.036* |
| **Hospital stay** | 1.4±0.51 | 2.4±0.6 | 0.002* |

**Table (6): Operative and postoperative complications in both procedures:**

| Complications | Group A N=50 | Group B N=50 | P-value |
|---|---|---|---|
| | Freq. (%) | Freq. (%) | |
| **Bleeding** | 5(10%) | 20(40%) | 0.121 |
| **Postoperative jaundice** | 0(0%) | 0(0%) | NA |
| **CBD injury** | 0(0%) | 1(2%) | 1 |

**Table (7): Score of pain in both groups.**

| Score of pain | Day of surgery | | First postoperative day | |
|---|---|---|---|---|
| | Freq. | (%) | Freq. | (%) |
| **Group A** | | | | |
| **<3** | 47 | 94 | 49 | 98 |
| **3-6** | 2 | 4 | 1 | 2 |
| **6-9** | 1 | 2 | 0 | 0 |
| **9-10** | 0 | 0 | 0 | 0 |
| **Group B** | | | | |
| **<3** | 35 | 70 | 43 | 86 |
| **3-6** | 9 | 18 | 5 | 10 |
| **6-9** | 5 | 10 | 2 | 4 |
| **9-10** | 1 | 2 | 0 | 0 |
| **P-value** | 0.019 | | 0.079 | |

**Table 8: Stress Hormones:**

| Stress Hormones | Group A N=50 Mean ± SD | Group B N=50 Mean ± SD | P-value |
|---|---|---|---|
| **ACTH** | | | |
| **Just Preoperative (Time 0)** | 44.5± 7.8 | 46.5±6.5 | 0.544 |
| **12 hours Postoperative** | 65.7±4.03$^{\#}$ | 219.6±104.5$^{\#}$ | <0.001* |
| **24 hours Postoperative** | 40±13.9 | 137.8±56.6$^{\#}$ | <0.001* |
| **Norepinephrine** | | | |
| **Just Preoperative (Time 0)** | 46.6±11.5 | 48±10.3 | 0.779 |
| **12 hours Postoperative** | 65.8±16.7$^{\#}$ | 89.2±7.7$^{\#}$ | 0.001* |
| **24 hours Postoperative** | 60.3±8.8$^{\#}$ | 80.9±7.8$^{\#}$ | <0.001* |
| **Insulin** | | | |
| **Just Preoperative (Time 0)** | 9.3±7.1 | 12.8±8.2 | 0.323 |
| **12 hours Postoperative** | 26±11.4$^{\#}$ | 44.1±19.6$^{\#}$ | 0.022* |
| **24 hours Postoperative** | 48.6±18.3$^{\#}$ | 101.1±12.03$^{\#}$ | <0.001* |

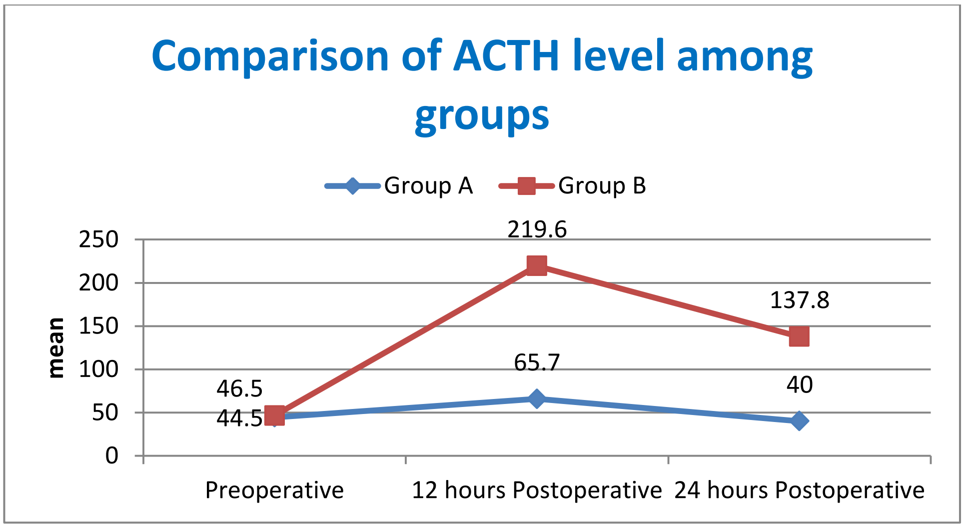


**Figure (4) level of ACTH at time 0 and postoperative at 12h , 24 h in both groups.**

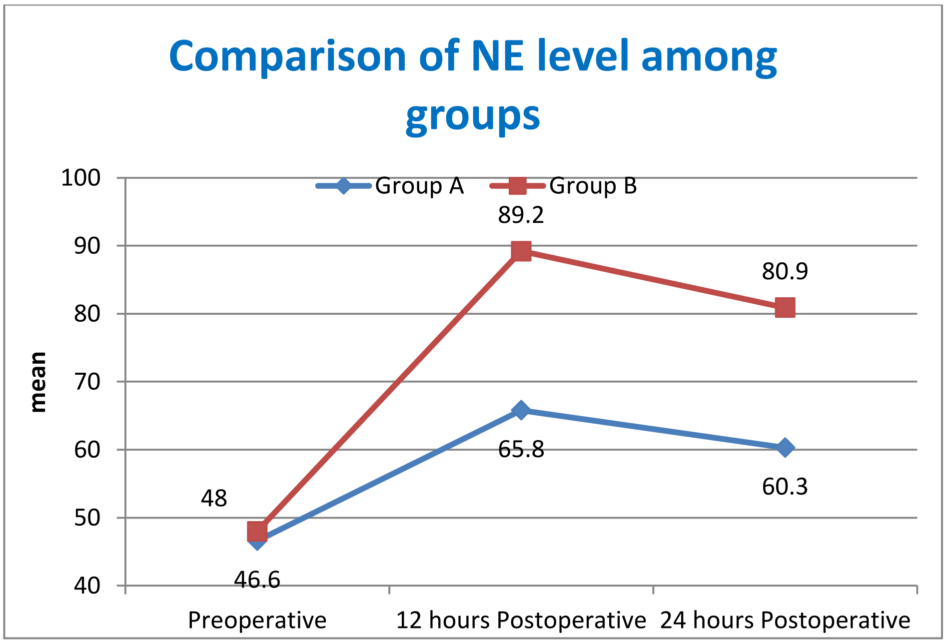


**Figure (5) level of Norepinephrine (NE) at time 0 and postoperative at 12h , 24 h in both groups.**

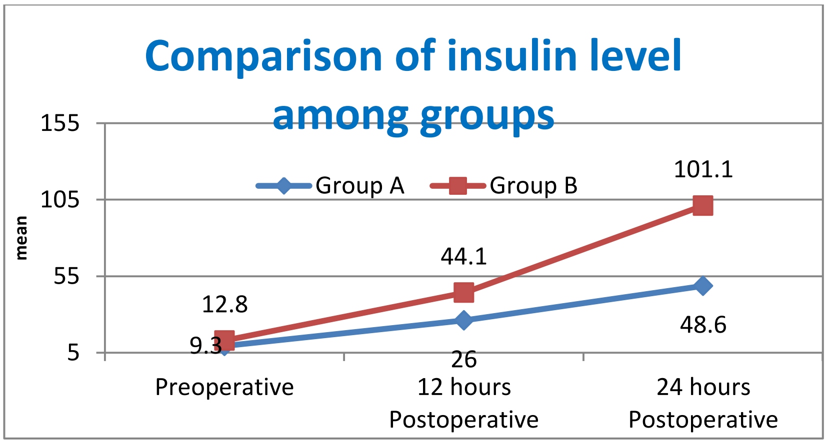


**Figure (6) level of Insulin at time 0 and postoperative at 12 h, 24 h in both groups.**

**Table 9: Liver functions in both groups:**

| Liver functions | Group A N=50 | Group B N=50 | P-value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| **AST** | | | |
| **24 hours Postoperative** | 40.6±25.6 | 41.1±9.8 | 0.955 |
| **48 hours Postoperative** | 29.4±15.9 | 45.7±23.3 | 0.085 |
| **ALT** | | | |
| **24 hours Postoperative** | 27.7±17.7 | 30.9±4.2 | 0.568 |
| **48 hours Postoperative** | 26.7±23.3 | 30.6±12.8 | 0.649 |
| **PC** | | | |
| **24 hours Postoperative** | 92.6±6.3 | 95.5±5.6 | 0.297 |
| **48 hours Postoperative** | 97.2±3.8# | 97.8± 3.3 | 0.718 |
| **Total bilirubin** | | | |
| **24 hours Postoperative** | 0.7±0.4 | 0.8±0.1 | 0.548 |
| **48 hours Postoperative** | 0.6±0.5 | 0.94±0.4 | 0.126 |
| **Direct bilirubin** | | | |
| **24 hours Postoperative** | 0.1± 0.03 | 0.4± 0.1 | 0.020* |
| **48 hours Postoperative** | 0.2±0.04 | 0.46±0.2 | 0.112 |
| **Albumin** | | | |
| **24 hours Postoperative** | 3±0.66 | 3.3±0.5 | 0.218 |
| **48 hours Postoperative** | 3.7± 0.67 | 3.7±0.4# | 0.938 |
| **Alkaline phosphatase** | | | |
| **24 hours Postoperative** | 68.7±30.3 | 92.2±39.8 | 0.155 |
| **48 hours Postoperative** | 60.6±28.7 | 78.6±40.1# | 0.263 |

## Discussion

All previous studies compared between stress response after OC and LC in easy cases, till now no study compared between stress response after OC and LC as regards difficult cases. Our study involved 100 patients with a difficult cholecystectomy.

Different predictive risk factors for difficult laparoscopic cholecystectomy were analyzed. There is no significant difference between two groups as regards preoperative predictors of difficult cholecystectomy. Old age (age > 50 years) has been found to be a significant risk factor for difficult LC in many studies(11). Male sex makes surgery difficult as being reported in studies(12). Obesity has been considered as another risk factor for difficult LC as observed by Rosen et al., 2002(13). Patient who require hospitali-zation for repeated attacks of acute cholecystitis, carry more chances of difficult cholecystectomy , probably due to dense adhesions at calot's triangle and gall bladder fossa(14), after previous upper abdominal surgery there may be adhesions present between viscera or omentum and abdominal wall. There may be chances of injury to these structures during insertion of first port.

As regards type of difficulty, difficult grasping and retraction of gallbladder is considerd to be a significant factor for intra operative difficulty in some studies(14), difficult dissection at calot triangle was a significant factor for intra operative difficulty as in Randhawa et al., study 2009[15]. Non visualization of gallbladder, abnormal anatomy and difficult retrieval of specimen are considered as a significant factors for difficulty as in kama et al., study, 2001 and palanivelu et al., study, 2006. Jongsiri et al., 2009 study Considered difficult duct clipping as a significant factor for intra operative difficulty (p=0.025)[16-18].

In this study, there is no significant difference between two groups as regards intraoperative predictors of difficult cholecystectomy (Gall bladder grasping and retraction). Also in this study difficult dissection at calot triangle and abnormal anatomy were not considered as intra operative factors for difficulty in laparoscopic group as RI approach away from the structures of calot triangle.

The results reflected a significant reduction in the operative time in cases operated by RI approach (79.6 ± 10 min.) compared to cases operated by open cholecystectomy (96 ± 13.8 min), due to spared time that spent in the dissection of Calot's triangle and time to deal with intraoperative complications. In a study of Lengyel et al., the mean of operative time for difficult LC was 123 min. while LO et al., reported mean operative time of 135 minutes in early laparoscopic cholecyst-ectomy for acute cholecystitis[19]

In this study, the incidence of biliary injuries with RI approach was 0% compared to 2% with the open procedure. In a study of Georgiades et al., they found the risk of (bile duct injury) BDI for difficult LC (acute inflammation) was 3.5 times as for normal GB,[20].The main cause of BDI during SLC, even with CVS, was the misidentification of anatomic structures. However, in RI approach, this misperception was not an issue as we shifted the dissection into the retroinfudibular area and away from the biliary tree.

In a study of Neri et al., the mean hospital stays for difficult cholecystectomy was 3 days[21]. In meta-analysis done by Henneman et al, the hospital stay for difficult cholecystectomies was 4.5 days [22]. In our study, there was a significant reduction in the mean of hospital stay with RI laparoscopic cholecystectomy (1.4 ± 0.51 day) compared with the open procedure (2.4 ± 0.6).

Plasma levels of ACTH, Insulin and Norepinephrine were measured to assess the stress responses after open and laparoscopic (RI) cholecystectomy. As regards plasma ACTH level, the preoperative base line values were similar in both groups. It increased significantly (P<0.001) following open and laparo-scopic (RI) cholecystectomy. The significant increase in plasma ACTH level following laparoscopic cholecystectomy indicates that considerable activation of the neuro endocrine axis occurs after laparoscopic cholecystectomy despite the absence of a substantial skin incision and minimal postoperative pain, as demon-strated by the low pain scores and analgesic requirements in our study.

Furthermore, the creation of the pneumoperitoneum has been suggested as a possible stimulus for the sympathetic stress response. The most important finding in this study is that the post-operative increase in plasma ACTH level was significantly lower and its return to baseline value more rapid after laparoscopic cholecystectomy suggesting a reduced neuroendocrine response to laparoscopic (RI) cholecystectomy compared with the open procedure.

The mean plasma ACTH level just preoperative for open and laparoscopic (RI) cholecystectomy were (46.5±6.5) and (44.5±7.8) pg/mL respectively. The mean values of peak ACTH level of (219.6± 1.04) pg/mL for OC and (65.7±4.03) pg/mL for laparoscopic cholecystectomy occurred 12 hours after surgery. However 24 hour post operative, level of ACTH fall progressively and returned to preoperative values in laparoscopic cholecystectomy (40 ± 13.9) and still raised after OC ( 137± 56.6 ). In different previous studies it has been clearly demonstrated that the level of serum ACTH rises significantly (P<0.001) after OC as compared to LC for easy cases. Luo et al., 2003 investigated serum ACTH and blood glucose and found that there was no difference between OC and LC for easy cases.(23)

As regards plasma level of norepinephrine (NE), In our study, preoperative NE levels were similar in both groups. Their levels increased significantly (P<0.001). With mean [( 65.8 ±6.7) and (89.2±7.7) ng/mL] for laparoscopic and open group respect-tively by 12 hours after surgery. However these levels were significantly lower after laparoscopic (Ri) cholecystectomy than after OC [(60.3±8.8) and (80.9±7.8) ng/mL respectively]. In this study, the systemic stress response is significantly reduced after laparoscopic (RI) cholecyst-ectomy compared with OC.

As regard plasma glucose levels, Insulin is known to ameliorate postoperative hyperglycaemia and therefore the higher levels of this hormone observed after open and laparoscopic cholecystectomy. In our study the preoperative values of insulin level were similar in both groups. Plasma insulin levels increased significantly (P<0.001) 12 hours post operative in both laparoscopic and open group with mean [(26±11.4) and (44.1±19.6) µm/mL respectively]. However insulin level at 24 hours postoperative was significantly lower after laparoscopic (RI) cholecyst-ectomy (48.6±18.3 µm/mL) than after OC (101.1 ± 12.03 µm/mL).These findings suggested a reduced neuroendocrine response to laparoscopic (RI) cholecyst-ectomy.

As regards liver functions ,this study approved that there is no significant difference in levels of liver functions between two groups., Guven et al., 2007 study showed no significant difference ( P-0.005 ) in AST, ALT, ALP and S.bilirubin levels after laparoscopic and open cholecystectomy, Tan et al., 2003 found statistically significant increased levels of ALT, AST, S.bilirubin and ALP during first 48 hrs after LC compared to OC.(24,25)

In this study, the systemic stress response is significantly reduced after LC compared with OC. However, Mealy et al., 2006 reported that the duration, course and magnitude of the metabolic response (ACTH, Insulin and Catecholamines) were similar in both groups. Yoshida et al., 2000 investigated serum ACTH, Insulin and Catecholamines (NE) level in their study, and reported no difference among the two groups.(26,27)

The possible explanation for the difference between our results and the above mentioned findings could be due to either the small sample size, difference in patient's selection and in the duration of anaesthesia and surgery, as well as the pre –impetive analgesia which blunt the stress response.

The results of our study meets those of Glerup et al., 1995 and Kehlet et al., 1999 who measured ACTH and Insulin level in a similar designed study and these of Luo et al., 2003 who confirmed the results of Janicki et al., 2001 and concluded that laparoscopic cholecystectomy results in a diminished stress response. Haque et al., 2004 in another randomized study measured the same parameters and reported less postoperative pain and shorter hospital stay in laparoscopic group. These finding are nearly similar to this study and explain why patients underwent laparoscopic cholecystectomy had the advantages of shorter hospitalization, less post-operative pain, and an earlier return to normal activities and hence an economic aspect(8,23,28-31)

Patients operated by laparoscopic (RI) approach need more lenghthy close follow up to answer the question of safety of this procedure.

**Conclusion**

In conclusion, laparoscopic (RI) chole-cystectomy is associated with less neuro-endocrinal and inflammatory responses than open cholecystectomy.

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