

Systemic Cytokine Response To Laparoscopic Versus Open Cholecystectomy. A Prospective Study.

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Abstract:

Surgical trauma elicits a characteristic response involving synthesis and release of acute phase proteins as interleukin-6 (IL-6) and C-reactive protein (CRP). The magnitude of trauma is directly proportionate to the concentration of these mediators. Laparoscopic cholecystectomy is now considered the gold standard for treatment of cholecystolithiasis. We aimed at comparing the magnitude of trauma elicited by laparoscopic versus open cholecystectomy.

Thirty cholecystectomies were divided into two groups; Laparoscopic group (15 cases) and open group (15 cases). Both groups were compared regarding demographic data, operative time, hospital stay, plasma CRP and IL-6 levels.

The two groups were comparable regarding demographic data. Open cholecystectomy had shorter operative time (68 vs. 57 min), but the difference was not significant. Laparoscopic group had significantly shorter hospital stay (1 vs. 4 days). No mortality or major morbidity was reported in both groups. Preoperatively, there were no differences in the levels of IL-6 or CRP. However, significantly higher levels of both IL-6 and CRP were found with open surgery compared to laparoscopic approach.

These results show that laparoscopic cholecystectomy is associated with higher cytokine response than open cholecystectomy. A difference that could be due to the less surgical trauma associated with laparoscopic technique.

Introduction:

The response to trauma involves complex inflammatory, neurological and metabolic alterations. The magnitude of the trauma response has an impact on the postoperative course of the patient regarding pain, mobilization and duration of hospital stay. Recent data suggest that laparoscopic approach is superior to open cholecystectomy regarding metabolic and respiratory changes (1).

Surgical trauma elicits a characteristic response involving synthesis and release of acute phase proteins such as C-reactive protein (CRP), increase in circulating stress hormones (cortisol and catecholamines), and synthesis and release of various mediators as cytokines, specially interleukin-6 (IL6). The synthesis and release of various inflammatory cytokines in response to trauma is a sequential process that involves systemic concentration of tumor necrosis factor (TNF) and, occasionally, interleukin-1 (IL1) within two hours. Afterwards, IL6 is usually detectable a few hours later, either through direct response of trauma or indirectly via effect on TNF and IL-1 (2).

It is apparent that the magnitude of the surgical trauma is directly proportionate to the systemic circulatory concentration of inflammatory mediators (3).

Since the introduction of laparoscopic surgery on a wide scale in the late eighties of last century, it was well recognized that laparoscopic approach leads to less postoperative pain, earlier mobilization and shorter hospital stay compared to open approach (4).

Several studies have investigated the magnitude of trauma represented by the inflammatory mediators of laparoscopic versus respective open approach. These studies were performed regarding cholecystectomy (1,5), fundoplication (6), colectomy (7) and rectosegmoidectomy (8).

Patients and Methods:

Thirty patients suffering from chronic cholecystitis, for each of whom cholecystectomy was indicated, were divided into two groups. Group 1 consists of 15 patients, who were subjected to laparoscopic cholecystectomy, whereas the other 15 patients were operated upon by the open approach. In group 2 open surgery is justified due to absence of needed laparoscopic instrumentation and/or experience.

All patients were ASA grades I or II. The two groups were matched regarding age, sex, white blood cell count, which indicates the severity of the inflammation, and sonographic findings.

Informed consent was obtained from each patient and the Ethics Committee of Assiut Faculty of Medicine approved the study protocol.

For all patients the technique of anaesthesia involved, premedication with intramuscular midazolam 5 mg 60 minutes before induction of anaesthesia. Anaesthesia was induced by 4-7 mg/kg thiopental followed by 1 µg/kg fentanyl. Endotracheal intubation was facilitated by 0.6 mg/kg atracurium. Incremental doses of atracurium can be used according to need. Nitric oxide was not used during anaesthesia. Mechanical ventilation was used in a rate of 12-14 breaths/min to maintain an end tidal carbon dioxide concentration of 35-45 mm Hg. Monitoring of all patients for ECG, non-invasive blood pressure, oxygen saturation, temperature and end tidal CO₂. At the end of surgery neostigmine 2.5 mg and atropine 0.1 mg/kg were given. All patients received one and half to two liters of Ringer's solution intraoperatively.

For group (1), laparoscopic cholecystectomy was performed by an experienced surgeon, using the standard four port technique, and CO₂ insufflation. Patients who needed conversion to open approach were excluded from the study.

For group (2), open cholecystectomy was performed by an experienced surgeon, using the standard right subcostal incision, and a peritoneal drain was left.

All patients were given prophylactic antibiotic in the form of intravenous injection of 1gm cefoperazone at the time of induction of anesthesia and two other doses postoperatively.

All laparoscopic and open incisions were infiltrated with a maximum of 10 ml of bupivacaine 5mg/ml at the end of procedure.

Postoperatively, all patients received intravenous fluids (Ringer's and glucose 5%) until oral feeding is restored. Pethedine was given intramuscularly in a dose of 50-100 mg on demand for the first one to two days after surgery.

Venous sampling for IL6 & CRP were obtained from all patients preoperatively. Postoperatively, one sample was taken at 4 hours after skin incision for IL6 and another at 24 hours for both IL6 & CRP. The samples were collected in tubes without additives. Sera were separated and stored at -70°C until they were analyzed. IL6 was determined by solid phase sandwich ELISA, using monoclonal antibody specific for IL6 in a specific kit (Biosource International Inc., Camarillo, California, USA). On the other hand, CRP was determined by semi-quantitative test using Avitex-CRP Latextest (Omega Diagnostics Limited, Scotland, UK) with series of doubling dilution of the patient serum in isotonic saline. CRP could be calculated by multiplying the dilution factor by detection limit. Normal value for this procedure is less than 6mg/L.

RESULTS:

Table (1): Demographic Characteristics, Duration of surgery, and Hospital stay in Both Groups. [Mean (SE)]

<i>Data</i>	Lap. Group	Open Surgery Group
Age	45.4 (5.2)	47.8 (6.1)
Sex (M/F)	4/11	3/12
Height	172 (38.9)	169 (34.1)
Weight	78 (11.1)	76 (10.5)
Operative time in min.	68.3 (29.6)	57.5 (18.3)
Hospital stay in days [Mean (Range)]	1 (6 hours-3 days)	4 (3-8 days)**
Mortality	0	0
Major Morbidity	0	0

* P<0.05

** P<0.01

*** P<0.001

Table (2): Plasma C-reactive protein in mg/L of both groups [Mean (SE)]

<i>CRP</i>	Lap. Group	Open Surgery Group
Preoperative	11.6 (5.6)	12.8 (6.3)
24 hours after skin incision	18.8 (5.2)	78.1 (12.1)**

* P<0.05

** P<0.01

*** P<0.001

Table (3): Plasma IL6 concentrations (pg/ml) in patients undergoing Lap. and Open Cholecystectomy [Mean(SE)]

IL6	Lap. Group	Open Surgery Group
Preoperative	2.1 (0.24)	3 (0.29)
4 hours after skin incision	51.2 (9.6)	124.6 (18.3)***
24 hours after skin incision	14.5 (4.6)	38.7 (7.3)**

* P<0.05

** P<0.01

*** P<0.001

Demographic characteristics

Table (1) summarizes the demographic characteristics, duration of surgery, hospital stay in days in both groups, mortality and morbidity.

There was no significant difference as regard age, height, weight and duration of surgery between both groups. However, laparoscopic group had a shorter hospital stay than open surgery group; 1 versus 5 days respectively (p<0.05). There was no mortality in both groups. Additionally, both groups showed no major complications as bile duct injury, intestinal injury or major bleeding.

CRP concentration:

There was no significant difference at preoperative values of serum CPR between both groups. Postoperative serum CRP increased in both groups, but the increase was significantly less marked in laparoscopic group 18.8 (5.2) mg/L versus 78.1 (12.1) mg/L in open group (P<0.01) at 24 hours after skin incision. See Table (2).

IL6 concentration:

There was no significant difference at preoperative values between both groups. At 4 hours after skin incision the rise in IL6 was significantly higher in open surgery group than laparoscopic group with values of 51.2 (9.6) pg/ml versus 124.6 (18.3) pg/ml respectively (P<0.001). After 24 hours the concentration decreased to reach 14.5 (4.6) versus 38.7 (7.3) pg/ml in laparoscopic and open surgery patients, a difference which was less significant (P<0.01). See Table (3).

Discussion:

IL6 appears to be rapidly released into the circulation in response to injury. It can be detected within 60 minutes of trauma (9). It is also detected in patients after elective biliary operations (10). IL6 promotes synthesis of numerous acute phase proteins including C-reactive protein (11). Consequently, the increase in CRP synthesis is related to the extent and severity of tissue damage. CRP synthesis in hepatocytes requires a minimum of 6-12 hours before an increase in plasma concentration is expected. Thus, CRP level can be normal within the first 12 hours of trauma (12).

The present study reveals that cholecystectomy has an influence on the IL6 and CRP responses to trauma. Both were raised throughout the study period whether with open or laparoscopic technique. The increase in IL6 and CRP was significantly higher in open cholecystectomy compared to laparoscopic procedure.

These findings are in agreement with the results of some other previous studies (13, 3, 14, 5). Additionally, Jess et al in 2000 found that the surgical trauma of laparoscopic repair of inguinal hernia is less than that of similar open technique, expressed by the circulatory mediators of postoperative inflammatory response (15). Also laparoscopic fundoplication resulted in levels of IL-6 that are significantly lower than that of open technique (16). Moreover, Leung et al in 2000 found significantly higher levels of IL6 and CRP after open rectosegmoid resection in comparison to laparoscopic-assisted technique (8).

Our results, on the other hand, were in contrast to those reported by of Vander Velpen et al in 1994, who did not find any differences in systemic IL6 concentration between patients undergoing laparoscopic and open cholecystectomy (17). In another study by Bozkurt et al in 2000, they found that the surgical stress and trauma imposed by laparoscopy seems similar to that caused by open surgery in children undergoing emergency abdominal surgery (18).

The duration and extent of elective surgery have been related to the magnitude of IL6 and CRP response (12). In the present study the duration of surgery did not significantly differ between the two techniques, which in turn implies that the severity and the extent of trauma are more important than operating time alone.

A shorter duration of hospital stay in laparoscopic group is supported by previous studies (13, 19).

Elective surgical wounds and trauma elicit similar physiological responses. These include increase stress hormone release, and increased hepatic production of acute phase proteins. It appears that both afferent neural stimuli and circulating factors are responsible (20).

Laparoscopic cholecystectomy is considered as a minimally invasive surgery, which diminishes metabolic responses by the avoidance of substantial abdominal incision, which in elective surgery is frequently the site of maximum tissue damage.

Conclusion:

Tissue trauma, reflected by the level of systemic cytokine in the form of IL6 and CRP, was significantly less after laparoscopic than open cholecystectomy. This difference may have implications on convalescence and hospital stay.

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