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Original Article

A Prospective Study of Altered Inflammatory Response and Its Clinical Outcome Following Laparoscopic and Open Cholecystectomy

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What's Known

- Any surgical trauma produces alterations in the hemodynamic, metabolic, and immune response of patients in the postoperative period. The initial pro-inflammatory immune response, mediated primarily by the cells of the innate immune system, is followed by a compensatory anti-inflammatory or immunosuppressive phenotype, mediated primarily by the cells of the adaptive immune system.

What's New

- Study gives an objective assessment of pro-inflammatory IL-1 and TNFα and anti-inflammatory IL-10 at postoperative 4 hours and 24 hours in laparoscopic and open cholecystectomies. Study compares the clinical outcome of a differential rise in these cytokines regarding postoperative pain.
- Inflammatory cytokines can be a future target for reducing surgical stress.

Abstract

Background: Inflammatory response following surgical trauma has long been a matter of study. Results, however, have been varied. We sought to assess changes in the levels of proinflammatory and anti-inflammatory cytokines in patients undergoing laparoscopic and open cholecystectomy and their impact on the clinical outcome of patients concerning the postoperative pain score.

Methods: The study involved 90 cholecystectomies (55 laparoscopic and 35 open) for chronic cholecystitis. Blood samples were collected 2 hours preoperatively and at 4 and 24 hours post surgery. Sera were evaluated for the levels of interleukin-1β, interleukin-10, and tumor necrosis factor-alpha. The independent sample *t*-test was used to compare the means of a variable between the 2 groups. Statistical analysis was done using SPSS, version 17.

Results: The rise in the levels of interleukin-1β, interleukin-10, and tumor necrosis factor-alpha was significantly more in the open cholecystectomy group at 4 hours ($P<0.00$). At the 24th postoperative hour, the levels of all 3 cytokines were also higher in the open cholecystectomy group ($P<0.001$ for interleukin-1β, $P=0.185$ for interleukin-10, and $P<0.001$ for tumor necrosis factor-alpha). At the 4th postoperative hour, the patients in the laparoscopic cholecystectomy group had a significantly lower pain score ($P<0.001$) than the open group.

Conclusion: Both laparoscopic and open cholecystectomy procedures altered the inflammatory milieu of our patients in the postoperative period. Inflammation caused by the laparoscopic procedure was significantly less. More research is needed to target specific inflammatory and anti-inflammatory cytokines to reduce surgical stress and improve patient outcomes.

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Keywords • Cholecystectomy • Laparoscopic • Open cholecystectomy • Inflammatory response interleukins • Tumor necrosis factor

Introduction

Any degree of surgical trauma leads to changes in the hemodynamic, metabolic, and immune response of patients during the postoperative period. The initial proinflammatory immune response is mediated by the cells of the innate immune system.[1] The initial proinflammatory response is followed by the compensatory anti-inflammatory response. This anti-inflammatory response is mediated by the cells of the adaptive immune system, which—if uncontrolled—may predispose the host to various postoperative septic complications.[2] The protective immunity of the body is critically dependent on adequate cytokine balance as well as macrophage cell interaction. Surgical trauma-induced immune dysfunction results from the disruption of these homeostatic mechanisms.[3] The restoration of balance between inflammatory and anti-inflammatory forces using interferon gamma (a monocyte deactivator), indomethacin (a PGE2 inhibitor), and granulocyte colony-stimulating factor (G-CSF) or pentoxifylline (inhibitors of the initial hyperinflammatory response) is currently under research.

Gallstone disease is a major health problem worldwide, particularly in the adult population. Its prevalence rate is varied in different populations. Around 6% of the adult population in Northern India suffers from this disease.[4] Since the performance of the first open cholecystectomy by Carl Langebuch of Germany (1846–1901) and the first laparoscopic cholecystectomy by Prof. Erich of Germany (1882), the management of cholelithiasis and cholecystitis has undergone a major breakthrough. Numerous studies have since then proven the supremacy of laparoscopic cholecystectomy over open cholecystectomy in terms of lesser degrees of surgical stress and inflammatory response, shorter hospital lengths of stay, lower morbidity, and substantially lower overall costs.[5]

The purpose of the present study was to objectively measure changes in the levels of proinflammatory and anti-inflammatory cytokines in the serum of patients undergoing laparoscopic and open cholecystectomy and to study their impact on the postoperative outcome of the patients in terms of postoperative pain.

Patients and Methods

This prospective interventional study was conducted in the Department of Surgery in collaboration with the Department of Biochemistry of Jawaharlal Nehru Medical College, Aligarh Muslim University. The study involved patients with symptomatic cholelithiasis with chronic cholecystitis undergoing either laparoscopic or open cholecystectomy in this institute. Patients with acute cholecystitis, common bile duct stones, preoperative deranged leukocytes count or interleukin levels, and laparoscopic cholecystectomy converted to open cholecystectomy were excluded from the study.

A well-informed consent was taken from the patients before inclusion in the study. Approval was obtained from the institutional ethics committee. Preoperatively, all the patients were kept nil orally since midnight. Alprazolam (0.5 mg) was given at bedtime to all the patients. Intravenous fluids were started half an hour before surgery. Intravenous ceftriaxone was given to all the patients half an hour before surgery.

In the patients who underwent the laparoscopic procedure, pneumoperitoneum was created with CO2, and a standard 4-port procedure was used in all the patients. In the patients subjected to open cholecystectomy, a subcostal incision, varying from 5 to 8 cm, was used. In both approaches, cholecystectomy was carried out by the dissection of the Calot triangle and the ligating/clipping of the cystic duct and artery. Subhepatic suction drains were placed in all the patients. Postoperatively, all the patients were given 15 mg/kg of intravenous acetaminophen every 8 hours.

Postoperatively, pain relief in the patients was measured using a 1D pain intensity scoring scale at 4 and 24 hours. Pain intensity was given a score ranging from 0 to 10 by the patients. Zero denoted no pain, 1 to 3 denoted mild pain, 4 to 6 denoted moderate pain, and 7 to 10 denoted severe pain.

Blood samples were collected 2 hours preoperatively and at 4 and 24 hours postoperatively. Sera were obtained after centrifuging the blood and were stored at -80 ºC. The sera were evaluated for the levels of interleukin-1β (IL-1β), interleukin-10 (IL-10), and tumor necrosis alpha (TNF-α). The plasma concentration of human TNF-α was determined using the enzyme-linked immunosorbent assay (ELISA) (Quantikine; R&D System Minneapolis, Minn, USA). ELISA methods similar to TNF-α were also used for IL-1 (T cell Diagnostics, Cambridge, Mass, USA) and IL-10 (Serotec, Oxford, UK). The statistical analyses were conducted using SPSS, version 17. The continuous variables are expressed as means, SDs, and ranges. The independent sample *t*-test was used to compare the means of a variable between the 2 groups.

Results

Totally, 90 patients were allocated to 2 groups of laparoscopic cholecystectomy (n=55) and open cholecystectomy (n=35). The study population comprised 13 (14.4%) males and 77 (85.6%) females. The average age of the patients was 40.9±12.4 years (range=12–70 y). The mean age in the laparoscopic cholecystectomy group was 38.6±11.3 years, while the mean age in the open cholecystectomy group was 44.6±13.3 years. The maximum incidence of cholelithiasis and subsequent cholecystectomy was in the age group of 30 to 50 years old. There was no significant difference between the 2 groups in respect to average age. The mean operating time in the cases of laparoscopic cholecystectomy in this study was 50±16.6 minutes (range=15–90 min). The mean operating time for open cholecystectomy was 94.3±35 minutes (range=50–200 min). Chronic cholecystitis was the most common histopathological diagnosis in the gall bladder specimen of the patients included, present in 79 out of the 90 patients (87.7%).

Postoperative Proinflammatory Cytokine Response in the Laparoscopic and Open Cholecystectomy Groups

IL-1β: The mean preoperative level of IL-1β (pg/mL) in the open cholecystectomy group was 34.36±6.18 pg/mL, which rose to 47.49±6.43 pg/mL at the 4th postoperative hour (a rise of 38.21%) and to 62.61±6.82 pg/mL at the 24th postoperative hour (a rise of 82.21%). In the laparoscopic cholecystectomy group, the mean preoperative level of IL-1β was 34±3.99 pg/mL, which rose to 37.19±5.79 pg/mL at the 4th postoperative hour (a rise of 9.38%) and to 39.36±5.34 pg/mL at the 24th postoperative hour (a rise of 15.76%) (table 1).

TNF-α: The mean preoperative level of TNF-α (pg/mL) in the open cholecystectomy group was 45.74±5.87 pg/mL, which rose to 60.00±6.0 pg/mL at the 4th postoperative hour (a rise of 31.17%) and to 89.86±6.79 pg/mL at the 24th postoperative hour (a rise of 96.45%). In the laparoscopic cholecystectomy group, the mean preoperative level of TNF-α was 46.77±6.37 pg/mL, which rose to 52.32±6.50 pg/mL at the 4th postoperative hour (a rise of 11.86%) and to 64.38±5.45 pg/mL at the 24th postoperative hour (a rise of 37.65%) (table 2).

Postoperative Anti-Inflammatory Cytokine Response in the Laparoscopic and Open Cholecystectomy Groups

IL-10: The mean preoperative level of IL-10 (pg/mL) in the open cholecystectomy group was 32.14±5.63 pg/mL, which rose to 43.55±6.28 pg/mL at the 4th postoperative hour (a rise of 35.50%) and to 64.25±5.77 pg/mL at the 24th postoperative hour (a rise of 99.9%). In the laparoscopic cholecystectomy group, the mean preoperative level of IL-1 was 27.52±5.98 pg/mL, which rose to 32.20±5.07 pg/mL at the 4th postoperative hour (a rise of 17%) and to 61.90±9 pg/mL at the 24th postoperative hour (a rise of 126.09%) (table 3).

Postoperative Severity of Pain in the Laparoscopic and Open Cholecystectomy Groups on 1D Pain Intensity Scales

In the laparoscopic cholecystectomy group, the average pain score was 2.8 (mild pain) at the 4th postoperative hour and 1.6 (mild pain) at the 24th postoperative hour. In the open cholecystectomy group, the average pain score was 5.1 (moderate pain) at the 4th postoperative hour and 2.4 (mild pain) at the 24th postoperative hour (table 4).

Discussion

Several studies have shown that surgical trauma produces alterations in the immune responses

Table 1: Postoperative IL-1 levels and their percentage rise in the laparoscopic and open cholecystectomy groups

IL-1 Level	OC	LC	P value
Mean preoperative IL-1 (pg/mL)	34.36±6.18	34.00±3.99	P=0.851
Mean IL-1 at the 4th postoperative hour (pg/mL)	47.49±6.43	37.19±5.79	T=5.737, P<0.001*
Percentage rise at the 4th postoperative hour	38.21%	9.38%	
Mean IL-1 at the 24th postoperative hour (pg/mL)	62.61±6.82	39.36±5.34	T=11.478, P<0.001*
Percentage rise at the 24th postoperative hour	82.21%	15.76%	

OC: Open cholecystectomy; LC: Laparoscopic cholecystectomy

Table 2: Postoperative TNF-α levels and their percentage rise in the laparoscopic and open cholecystectomy groups

TNF-α Level	OC	LC	P value
Mean preoperative TNF-α (pg/mL)	45.74±5.87	46.77±6.37	P=0.445
Mean TNF-α at the 4th postoperative hour (pg/mL)	60.00±6.0	52.32±6.50	t=7.64, P<0.001*
Percentage rise at the 4th postoperative hour	31.17%	11.86%	
Mean TNF-α at the 24th postoperative hour (pg/mL)	89.86±6.79	64.38±5.45	t=5.64, P<0.001*
Percentage rise at the 24th postoperative hour	96.45%	37.65%	

OC: Open cholecystectomy; LC: Laparoscopic cholecystectomy

Table 3: Postoperative IL-10 levels and their percentage rise in the laparoscopic and open cholecystectomy groups

IL-10 Level	OC	LC	P value
Mean preoperative IL-10 (pg/mL)	32.14±5.63	27.52±5.98	P=0.065
Mean IL-10 at the 4th postoperative hour (pg/mL)	43.55±6.28	32.20±5.07	t=7.701, P<0.001*
Percentage rise at the 4th postoperative hour	35.50%	17.00%	
Mean IL-10 at the 24th postoperative hour (pg/mL)	64.25±5.77	61.90±9.00	t=1.335, P=0.185*
Percentage rise at the 24th postoperative hour	99.9%	126.09%	

OC: Open cholecystectomy; LC: Laparoscopic cholecystectomy

Table 4: Postoperative average severity of the pain score in the laparoscopic and open cholecystectomy groups

Severity of pain	OC	LC	P value
Average severity of the pain score at 4 hours	5.1±1.8	2.8±1.6	P<0.001
Average severity of the pain score at 24 hours	2.4±1.2	1.6±0.9	P=0.007

OC: Open cholecystectomy; LC: Laparoscopic cholecystectomy

of patients in the postoperative period. The initial proinflammatory immune response, mediated primarily by the cells of the innate immune system, is followed by a compensatory anti-inflammatory or immunosuppressive phenotype, mediated primarily by cells of the adaptive immune system. Dunham[2] as early as 1900 observed that after surgery of any magnitude, the leukocyte count increased as a rule and every case examined within a few hours postoperatively showed a marked rise, corresponding closely with the duration of the operation. Cytokines, both proinflammatory and anti-inflammatory, form an indispensable part of homeostasis during the postoperative period. The systemic inflammatory response, mediated by cytokines, is complex. An excessive proinflammatory response may cause injury to the host, while an excessive anti-inflammatory response may render the host immunocompromised.[6]

Menger et al.[7] observed that the initial hyper inflammatory response following surgical trauma was mediated by TNF-α, IL-1, and IL-6—resulting in neutrophil activation and uncontrolled polymorphonuclear and macrophage oxidative burst. The authors reported that this resulted in surgical, trauma-induced, immunosuppression and proposed that imbalance between pro- and anti-inflammatory cytokines decided the outcome of any disease and, as such, should be kept in mind for planning a therapeutic strategy.

Cholecystectomy, whether open or laparoscopic, is the treatment of choice for cholelithiasis with chronic cholecystitis. Numerous studies have proven the supremacy of laparoscopic cholecystectomy over open cholecystectomy in terms of lesser degree of surgical stress and inflammatory response, shorter hospital lengths of stay, lower morbidity, and substantially lower overall costs.[5] However, a certain patient group in the Indian subcontinent prefers to undergo surgery via the open method. A false impression that laparoscopic cholecystectomy is associated with greater incidence of bile duct injuries is a common notion among these patients; subsequently, a number of open cholecystectomies are being performed at general surgical centers in the Indian subcontinent.

A number of studies conducted previously have provided varied results vis-à-vis postoperative changes in the levels of proinflammatory and anti-inflammatory cytokines. The results are extremely complex and lack significance because of the absence of correlation with clinical outcomes.

Proinflammatory Cytokine Response to Open and Laparoscopic Cholecystectomy

IL-1β: We observed a highly significant (P<0.001) rise from the preoperative levels in the mean IL-1β at 4 and 24 hours following both laparoscopic and open cholecystectomy procedures. At 24 hours, a net rise of 82.21% and 15.76%, respectively (from the baseline), was observed in the mean IL-1β level following open and laparoscopic cholecystectomy. In other words, a much greater rise occurred in the open cholecystectomy group. Though the baseline (preoperative) mean level of IL-1β was comparable between both groups (P=0.851), a highly significant difference (P<0.001) was noted between the open and laparoscopic cholecystectomy groups in the postoperative levels at 4 hours (47.49 ± 6.43 vs. 37.19±5.79 pg/mL, respectively) and 24 hours (62.61±6.82 vs. 39.36±5.34 pg/mL). The finding of a significant rise in IL-1β in both open and laparoscopic cholecystectomy procedures associated with a comparatively significant lesser rise of IL-1β in the laparoscopic group has also been reported by several other authors. Schietroma et al.[8,9] observed that the serum IL-1 and IL-6 levels began to significantly increase as early as 1 hour from the beginning of the operation, revealing a peak at the 6th in the open cholecystectomy group. The authors concluded that the cytokine surge correlated with hypercoagulability and that there was a positive correlation between the IL-6 level and hypercoagulability. However, this finding of an increase in the level of IL-1 after open cholecystectomy is contrary to the observations made by Lausten et al.[10] and Helmy et al.,[11] who reported a reduction in the IL-1 level after the open procedure.

TNF-α: A highly significant rise ($P<0.001$) from the preoperative level was observed in the mean TNF-α at 4 hours following surgery in both groups. The rise in the levels from the baseline to 24 hours postoperatively was also statistically significant in both the laparoscopic ($P=0.021$) and open ($P<0.001$) cholecystectomy groups. At 24 hours, a net rise of 96.45% and 37.65%, respectively (from the baseline), was observed in the mean TNF-α level following open and laparoscopic cholecystectomy. In other words, a much greater rise occurred in the open cholecystectomy group. Although the baseline (preoperative) mean level of TNF-α was comparable between both groups ($P=0.445$), a highly significant difference ($P<0.001$) was noted between the open and laparoscopic cholecystectomy groups in the postoperative levels at 4 hours (60.00±6.00 vs. 52.32±6.50 pg/mL, respectively) and 24 hours (89.86±6.79 vs. 64.38±5.45 pg/mL, respectively). The finding of a significant postoperative rise in the level of TNF-α in both groups with a comparatively higher rise in open cholecystectomy has been reported by several other authors (Redmond et al.[12] and Chaudhary et al.[13]). Redmond et al.[12] reported the rise in the levels of TNF-α to be positively correlated with significantly higher postoperative septic complications in the open cholecystectomy group. Boo et al.,[14] however, reported that in patients with acute cholecystitis, the postoperative TNF-α level in the open group was significantly lower than that in the laparoscopic cholecystectomy group. Abu-Eshy et al.[15] reported no significant difference in the levels of IL-1 and TNF-α in patients undergoing either laparoscopic or open cholecystectomy.

Anti-Inflammatory Cytokine Response to Open and Laparoscopic Cholecystectomy in Our Study

IL-10: A highly significant ($P<0.001$) rise from the preoperative level was observed in the mean IL-10 at 4 and 24 hours following both laparoscopic and open cholecystectomy procedures. At 24 hours, a net rise of 99.9% and 126.09%, respectively (from the baseline), was observed in the mean IL-10 level following open and laparoscopic cholecystectomy. In other words, a much greater rise occurred in the laparoscopic cholecystectomy group. The baseline (preoperative) mean level of IL-10 was comparable between both groups ($P=0.065$). At the 4th postoperative hour, the level was significantly higher ($P<0.001$) in the open cholecystectomy group than in the laparoscopic cholecystectomy group (43.55±6.28 vs. 32.20±5.07 pg/mL). However, at 24 hours post surgery, the level of IL-10 was not statistically different ($P=0.185$) between the open and laparoscopic cholecystectomy groups (64.25±5.77 vs. 61.90±9.00 pg/mL). The levels of anti-inflammatory cytokine IL-10 have yet to be extensively studied as compared to proinflammatory cytokines. Lausten et al.,[10] however, reported that IL-10 was significantly higher after laparoscopic cholecystectomy than following open cholecystectomy.

Clinical Implication of the Difference in Immune Response between the Laparoscopic and Open Cholecystectomy Groups

We sought to observe the clinical implications of the altered immune response of patients in our 2 groups using postoperative pain as the parameter. This was done by measuring the severity of pain using 1D pain intensity scales,[16] in which pain severity had to be given a number from 0 to 10. Pain scoring was done at 4 and 24 hours post surgery, time points at which the levels of serum interleukins were studied. In the laparoscopic cholecystectomy group, the average pain was 2.82.8±1.6 (mild pain) at 4 hours and 1.6±0.9 (mild pain) at 24 hours. In the open cholecystectomy group, the average pain was 5.1±0.9 (moderate pain) at 4 hours and 2.4±1.2 (mild pain) at 24 hours. The difference in the pain score between the 2 groups was statistically significant at 4 hours ($P<0.001$). This significant difference in the level of pain with the same amount of analgesics is the clinical proof of altered immune responses in the 2 groups.

Johansson et al.[17] reported no significant difference between laparoscopic and open cholecystectomy procedures in terms of postoperative pain, sick leave, and other postoperative complications. Nevertheless, their study population comprised patients with acute cholecystitis and pain scoring was done at discharge.

The current study has limitations. We utilized only postoperative pain scoring as the clinical outcome of an altered inflammatory response following cholecystectomy. In addition, we could not include the patients' total hospital admission time and wound healing time as markers of the difference in the levels of inflammation due to nonuniformity in discharge protocols and antibiotic use. Another drawback of note is that our study is not a double-blind trial.

Summary

Our results demonstrated that both laparoscopic and open cholecystectomy procedures altered the serum interleukin milieu of the whole study population. This interleukin response can be targeted in the future to reduce the levels of surgical stress and lessen unfavorable outcomes. Research is already ongoing for the use of interferon gamma to counteract monocyte deactivation and for the use of indomethacin for PGE2 inhibition. Additionally, various other anti-inflammatory substances such as G-CSF, hydroxyethyl starch, and pentoxifylline are currently under investigation. We investigated the clinical outcome of altered interleukin levels in terms of postoperative pain in our study. Laparoscopic cholecystectomy has a definitely significantly milder degree of proinflammatory response than conventional open cholecystectomy and should, therefore, be the procedure of choice for chronic cholecystitis.

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