Effects of low and high intra-abdominal pressure on immune response in laparoscopic cholecystectomy

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ABSTRACT

Objective: Immunosuppression is directly related to the degree of trauma. The aim of this study is to compare the effects of low and high intra-abdominal pressure on immune response in moderate surgical trauma.

Methods: Twenty-two patients, scheduled for laparoscopic cholecystectomy, were randomly allocated to one of 2 groups according to intra-abdominal pressure: low and high intra-abdominal pressure. This study was conducted in the Hacettepe University Faculty of Medicine, Operation Room, Ankara, Turkey. Serum interleukin (IL)-2 and IL-6 levels were measured.

Results: Serum IL-2 showed a significant decrease before the incision in high intra-abdominal pressure group. The increase in serum IL-6 at the end of surgery and postoperatively was lower in low intra-abdominal pressure group.

Conclusion: These results, can be interpreted as the immune system, are less depressed when there is lower intra-abdominal pressure. This may have clinical implications in immunocompromised patients.

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Anesthesia and surgical trauma depress many normal functions of the immune system and lead to postoperative infection. Immunosuppression is directly related to the degree of trauma.[1] Cytokines are heterogeneous group of proteins and are the messenger molecules of the immune system.[2] Interleukin (IL)-2 is the major autocrine and paracrine growth factor for T lymphocytes,[2] while IL-6 is a mediator of acute phase response and a proinflammatory cytokine. The plasma concentration of IL-6 is the most sensitive cytokine marker of postoperative immune response. An increased level of IL-6 shows the degree of tissue trauma.[3] Immunoglobulins are the glycoproteins secreted by B-lymphocytes against antigenic stimuli. Immunoglobulin synthesis is depressed by anesthesia and surgery.[1] Surgical procedures may be divided into 3 groups depending on the degree of trauma: a) minor surgical trauma (cataract, biopsy, curettage and so forth), b) moderate surgical trauma (laparoscopic cholecystectomy and so forth), c) major surgical trauma (abdominal surgery and so forth). Although laparoscopy is thought to be a moderate surgical trauma, CO_2 insufflation may lead to further pathophysiological changes. Three main ventilatory problems may occur during laparoscopy: an increase in $PaCO_2$, pneumothorax and gas embolism.[4-6] Intra-abdominal pressures higher than 10 mm Hg induce significant alterations in hemodynamics. These disturbances are characterized by a decrease in cardiac output, an elevation of arterial pressure, and an increase in systemic and pulmonary vascular resistances. The decrease in cardiac output is proportional to the

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increase in intra-abdominal pressure.[7-9] All of these pathological changes caused by increased intra-abdominal pressure may affect the postoperative immune response. The effect of the degree of surgical trauma and different anesthetic agents on immune response have been studied previously, but there is a lack of information concerning comparisons of various levels of intra-abdominal pressure.[10] The aim of this study was to compare the effects of low and high intra-abdominal pressures on the immune response.

Methods. After obtaining institutional approval from the Local Ethical Committee, in the Operation Room of Hacettepe University Faculty of Medicine, Ankara, Turkey on March 2001 and April 2001, 22 adult patients, ASA grade 1-2 scheduled for laparoscopic cholecystectomy, were included in the study. Patients with endocrine or immune system disorders, malignant or chronic inflammatory disease, marked obesity, acute cholecystitis or kidney, liver disorders, and patients on immunosuppressive treatment were excluded. Patients undergoing laparoscopic cholecystectomy were randomly allocated to one of 2 groups according to the intra-abdominal pressure: low intra-abdominal pressure (10 mm Hg) n=11 and high intra-abdominal pressure (14-15 mmHg) n=11. The operative technique involves the intraperitoneal insufflation of carbon dioxide through a Veress needle inserted into a small infraumbilical incision with the patient in a 15-20 degrees Trendelenburg position. The electronic variable-flow insufflator terminates flow when a preset intra-abdominal pressure of 12-15 mm Hg has been reached. A cannula was inserted in place of the needle to provide and maintain insufflation adequate for surgery. A video laparoscope was inserted through the cannula and the operative field was visualized by high resolution television camera and monitor systems.[11,12] All patients were premedicated with diazepam 0.1 mgkg-1 orally 30 minutes preoperatively. General anesthesia was induced with thiopental 5-7 mgkg-1 and fentanyl 1 µg kg-1 administered intravenously over 30 seconds until loss of eyelash reflex in all patients. Tracheal intubation was facilitated with vecuronium 0.1 mgkg-1. Anesthesia was maintained with nitrous oxide in oxygen (at flows of 3 lt minute-1) and sevoflurane during controlled ventilation. Further fentanyl increments of 0.5 µgkg-1 and vecuronium 0.03 mgkg-1 were given when indicated. Manually assisted ventilation of the lungs was carried out to maintain end-tidal carbon dioxide concentration within the normal range.

Venous blood samples were taken immediately before the induction of anesthesia, immediately before the skin incision after CO_2 insufflations for the desired intra-abdominal pressure, at the end of surgery, and 24 hour postoperatively. Blood samples (10 ml each) from all tested patients were taken via an indwelling catheter inserted into a forearm vein. After centrifugation of the blood at 4°C, separated plasma samples were stored at -80°C. Plasma levels of IL-2 (using Biosource Cytoscreen™ hIL-2) and IL-6 (using Biosource Cytoscreen™ hIL-6) were measured with enzyme-linked immunoassay (ELISA) kits.

In addition to the clinical signs, continuous electrocardiographic display, heart rate, respiratory rate, and peripheral oxygen saturation (using a pulse oximeter) were monitored noninvasively throughout the operation. Noninvasive systolic, diastolic and mean arterial pressure measurements using the intermittent oscillometric method were obtained at 5 minutes interval.

Statistical analyses of the various parameters observed and cytokine levels were performed (expressed as mean ± SD). The data were analyzed using student's t-test, paired t-test and repeated measurement analysis of variance. A value of $p<0.05$ was considered statistically significant.

Results. There were no significant differences between the 2 groups in terms of demographic data, ASA grade, duration of anesthesia, time from induction to skin incision and time from skin incision to the end of surgery (**Tables 1 & 2**). Vital signs were stable during anesthesia in the 2 groups. Interleukin-2 levels were higher before the incision and at the end of anesthesia and surgery in the low intra-abdominal pressure group, and IL-6 levels were lower at the end of anesthesia and 24 hours postoperatively in the low intra-abdominal pressure group (**Table 3**). Interleukin-2 showed a significant decrease before the incision and a significant increase after surgery and 24 hours postoperatively to reach pre-induction levels in the low abdominal pressure group ($p<0.001$) (**Figure 1**). In both groups IL-6 showed a significant increase before the incision, at the end of surgery and 24 hours postoperatively to reach a maximum level. However, the increase in IL-6 at the end of surgery and 24 hours postoperatively was higher in the high abdominal pressure group ($p<0.001$) (**Figure 2**).

Discussion. Laparoscopic cholecystectomy is known to have many advantages over open conventional cholecystectomy, including shorter hospital stay, better patient comfort and good homeostasis.[13] The laparoscopic approach allows for a reduction in the acute phase reaction. The plasma concentration of IL-6, which reflects the extent of tissue damage, is significantly lower in laparoscopy than laparotomy.[14] Surprisingly, while laparoscopy allows for a reduction in surgical trauma, the stress responses during laparoscopic and

Table 1 - Characteristics of patients. Values are mean (SD) or number (proportion) (p>0.05)

Characteristics	**High intra-abdominal pressure (N=11) n (%)**	**Low intra-abdominal pressure (N=11) n (%)**
Age (year)	48.36 ± 7.28	48.64 ± 6.93
Weight (kg)	70.82 ± 7.39	72.45 ± 8.17
Gender		
Male	6 (54.5)	6 (54.5)
Female	5 (45.5)	5 (45.5)
ASA		6 (54.5)
I	6 (54.5)	5 (45.5)
II	5 (45.5)	

ASA - American Society of Anesthesiologists

Table 2 - Duration of anesthesia surgery according to groups (p>0.05) (X±SD).

Duration of anesthesia	**High intra-abdominal pressure(N=11)**	**Low intra-abdominal pressure (N=11)**
Duration of anesthesia (minutes)	73.55 ± 8.24	73.82 ± 7.36
Time from induction to skin incision (minute)	9.27 ± 2.76	8.55 ± 2.02
Time from skin incision to the end of surgery (minute)	64.27 ± 6.13	65.27 ± 5.61

X+SD = mean ± standard deviation

Table 3 - Measured immunologic parameter levels at any time intervals according to groups (X±SD).

Parameter	**High intra-abdominal pressure (N=11) n (%)**	**Low intra-abdominal pressure (N=11) n (%)**	***p* value**
IL-2 (u ml-1)			
Before induction	0.167 ± 0.025	0.154 ± 0.023	>0.05
Before incision	0.148 ± 0.022	0.184 ± 0.022	<0.001
At the end of the operation	0.155 ± 0.023	0.181 ± 0.017	<0.001
Postoperative (24 hours)	0.167 ± 0.025	0.156 ± 0.021	>0.05
IL-6 (pg ml-1)			
Before induction	3.61 ± 1.00	3.46 ± 0.91	>0.05
Before incision	5.11 ± 1.25	4.86 ± 1.02	>0.05
At the end of the operation	8.06 ± 1.29	5.25 ± 1.04	<0.001
Postoperative (24 hours)	15.57 ± 2.62	7.39 ± 1.22	<0.001

X+SD = mean ± standard deviation

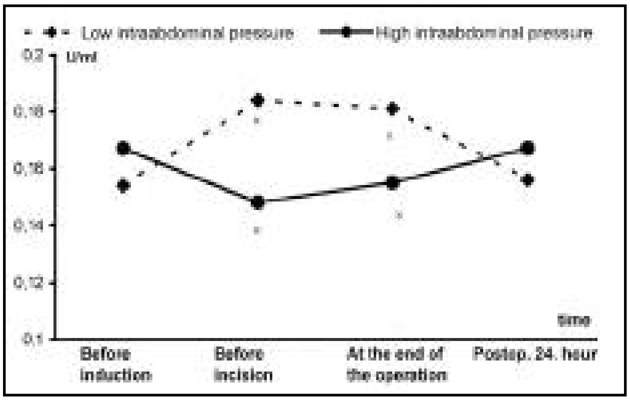

Figure 1 - The changes of IL-2 levels according to time. x = p<0.001, postop - postoperative

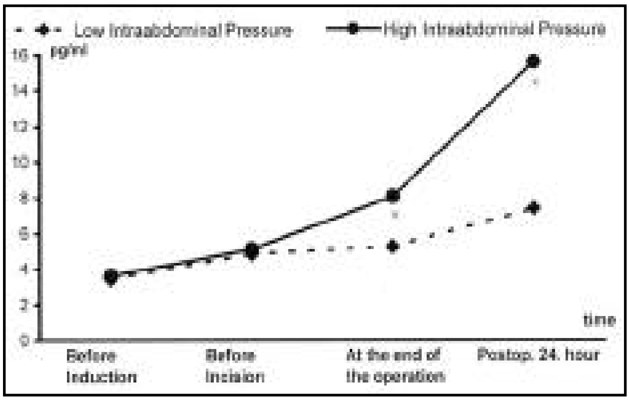

Figure 2 - The changes of IL-6 levels according to time. x = p<0.001, postop - postoperative

open cholecystectomy do not differ significantly. Plasma concentrations of cortisol and catecholamines, urinary concentrations of cortisol and catecholamine breakdown products and anesthetic requirements are similar.[14] Combined general and epidural anesthesia for laparoscopic cholecystectomy does not result in a decreased stress response compared with general anesthesia alone.[15] Several hypothesis might explain these observations. Pain and discomfort secondary to stretching of the peritoneum, hemodynamic disturbances, and ventilatory changes induced by pneumoperitoneum might contribute to the stress response. According to this hypothesis, increased intra-abdominal pressure caused by CO_2 insufflation affects the postoperative immune response. Increased intra-abdominal pressure during pneumoperitoneum, in upper abdominal laparoscopies, would also be expected to decrease venous return to the heart.[16] Although there are several studies of intra-abdominal pressure and immune functions, we could not find any effect of various degree of intra-abdominal pressure during laparoscopic cholecystectomy. We aimed to show this effect by measuring the level of serum interleukins and preferred to detect IL-2, which was the major autocrine and paracrine growth factor for T-lymphocytes[2] and IL-6 which was one of the mediator of acute phase response. Plasma concentration of IL-6 is the most sensitive cytokine marker of postoperative immune response.[3] Increased level of IL-6 shows the degree of tissue trauma.

In our study, IL-2 levels decreased significantly in the high intra-abdominal pressure group and increased in the lower intra-abdominal pressure group before the incision. Faist et al[17] reported that the decrease in IL-2 production was the most striking abnormality in trauma-induced immunodeficiency.[17] Interleukin-6 showed a significant increase perioperatively in the high intra-abdominal pressure group, whereas the increase in the IL-6 level was lower in the low intra-abdominal pressure group. Since laparoscopy is a moderate surgical trauma, the impairment of immune system function did not last more than 24 hours.

Interleukin-2 showed a significant increase before incision and IL-6 showed a lower increase perioperatively in the low intra-abdominal pressure group, we might conclude that during laparoscopic cholecystectomy as a moderate surgical trauma the degree of intra-abdominal pressure may affect the postoperative immune response and this may have clinical implications in immunocompromised patients. We need detailed studies concerning effects of various degrees of intra-abdominal pressures on immune response in laparoscopic surgeries.

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