

# Review Article

## Immunological Response to Laparoscopic Surgery

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Laparoscopic surgery has gained rapid acceptance based on clinical grounds. Patients benefit from faster recovery, decreased pain and quick return to normal activities. Immune and metastatic response to laparoscopy are now being evaluated in relation to the present knowledge of immune responses to traditional laparotomy and surgery in general. A review of the published literature of immune and metabolic responses to laparoscopy was performed. Laparoscopic surgery is compared with traditional laparotomy on the basis of local and systemic immune responses and patterns of tumour growth. Impact of pneumoperitoneum and insufflation gases on the immune response is also reviewed. Systemic immune responses for surgery in general may not apply to laparoscopic surgery. Body's response to laparoscopy is one of lesser immune activation as opposed to immunosuppression.

**Key words:** Immune response, laparoscopic surgery

Surgical trauma induces haemodynamic, metabolic and immune response mediated by humoral agents such as catecholamines, glucocorticoids and cytokines produced at the site of injury by varied immune cells<sup>1</sup>.

Surgical trauma is associated with multifactorial immunosuppression. It is associated with a decreased neutrophil function, decreased lymphocyte macrophage interaction, depression of delayed hypersensitivity due to defective antigen presentation, reduced natural killer cell activity and decreased IL-2 production from T-lymphocytes.

In general, immune system is directed against the antigenic characteristics of micro-organisms and acts to destroy them and negate their effects. It is also required for the surveillance and destruction of tumour cells. Acute inflammatory response to surgery is a multi-factorial reaction some aspects of which rely on classical immune response. Therefore, immunosuppression in a surgical patient is associated with an increased incidence of post-operative infections and in patients with malignant disease an increased potential for seedling of metastasis.

Laparoscopic surgery has gained a rapid acceptance in the last decade. Laparoscopic surgery provides tremendous benefits in terms of immunized surgical trauma, faster recovery, shorter hospital stay, better cosmesis and greater patient satisfaction<sup>2</sup>.

In this review systemic, metabolic and immune responses to laparoscopic surgery studied to date are summarized.

### Local and systemic immune responses

While laparoscopy is minimally invasive, systemic immune responses are invariably activated. Overall responses to surgery are reflected in terms of cytokine function and cellular messenger systems. Immune response mediators which were evaluated in different studies were interleukin-1, interleukin-6, C-reactive protein, tumour necrosis factor, total leukocyte count, T-lymphocyte

population, delayed hypersensitivity, neutrophil function and macrophage activation<sup>3</sup>.

Surgical trauma provokes an acute phase protein response detected in peripheral blood. IL-1, protein is the key marker of acute phase proteins. It rises 4-12 hours after surgery, peaks at 24-72 hours and then remains elevated for two weeks. Degree of alteration of C-reactive protein was noted to be 20 folds after open and 5 folds after laparoscopic cholecystectomy.

IL-6 levels are early and sensitive markers of tissue damage. IL-6 alterations are directly correlated with the length of operation and blood loss during surgery<sup>4</sup>.

Table 1 Peak C-reactive protein levels comparing laparoscopic vs open surgery

Authors	Laparoscopic (mg/L)	Open (mg/L)	P value
CHO (1994) <sup>4</sup>	24	104	<0.06
Halvey (1995)	26.8	128.6	<0.001
Bolufer (1995)	49	95	<0.005
McMohan (1993) <sup>5</sup>	48	84	0.13
Redmond (1994)	69	53	NS
Mealy (1992)	20.6	106.9	<0.04
Perttala (1999)	61	89	0.064

Table 2. Peak IL-6 levels comparing laparoscopic vs general surgery.

Authors	Laparoscopic (pg/ml)	Open (pg/ml)	P value
Glaser (1995)	15	50	0.02
Maruzynski (1995)	12.5	48.8	<0.001
Suzuki (1994) <sup>6</sup>	21	18.6	<0.01
Cho (1994)	51	125	<0.001
Rouman (1992)	<20	<20	NS
Vander Velphen (1994)	800%	580%	NS
McMohan 1993)	14.2	135	-
Perttilla (1999)	142	29	0.075

Although several comparative studies that examine IL-6 in



open and laparoscopic surgical procedures are available no consensus has been reached as to its metabolic and immunological role. The IL-6 response may or may not accurately reflect an acute phase response as C-reactive protein responses appear to do. Further research in this area is warranted.

#### Peripheral leukocyte population and activation

Immunosuppression following surgical trauma has been described in terms of cellular components of systemic immune response<sup>7</sup>. It has been evaluated in terms of TLC, specific leukocyte population and leukocyte function and activation. Surgical trauma leads to an increase in overall peripheral leukocyte number, which is more significant in open procedures as compared to laparoscopy<sup>8</sup>. There is a transient increase in granulocyte count in open procedures but not in laparoscopic procedures. Neutrophilia in both open and laparoscopic procedure is mainly responsible for increase in peripheral leukocyte count. Following surgery lymphocytic count is decreased in both groups but to a greater extent in the open groups. Percentage of T-helper cells (CD-4) reduced and T-suppressor cells (CD-8) increased immediately after operation in both groups indicating immunosuppression, however, these changes were much more pronounced in cases of open as compared to laparoscopic group. Some of the studies also indicated decrease in number of  $\beta$ -lymphocytes indicating depression of humoral response. There was no significant difference in absolute CD-4 and CD-8 cell counts in both the groups. Phagocytosis by neutrophil was significantly lower for few hours after open but not laparoscopic surgery<sup>9</sup>. Better preserved phagocytosis/lytic activity and blunted activation in the laparoscopic groups helps in prevention of development of postoperative infection<sup>10</sup>.

Another study concluded that HLA-DR surface molecules on monocytes that are required for antigen presentation are decreased to a lesser extent in laparoscopic procedure, thereby these procedures interfere less with immune defences. Many other supportive studies have shown that laparoscopic procedures result in lower adrenocortical hormone release.

It has also been suggested that following conventional surgery there is more down regulation of T-helper type I immune response and more altered proinflammatory and antiinflammatory T-cell cytokine balanced as compared to laparoscopic procedures. These disturbances of pro and anti inflammatory cytokine balance by open procedures may result in increased susceptibility to septic complication.

#### Tumour spread and laparoscopy

There is a heightened awareness recently that laparoscopic surgery may have an impact on spread of intraperitoneal malignant disease. Laparoscopic surgery for malignancy must maintain the principles of surgical oncology i.e.

sufficient resection margins and adequate excision of node bearing tissue<sup>11</sup>. Most of the research in this regard has been done on animals. These studies have been conducted by Jones (1995), Bessler (1994), Jacobi (1996), Mutter (1996), Allendorf (1995) and Bouvy (1996).

As immunosuppression is associated with a high incidence of malignancy it has been suggested that application of laparoscopic techniques to patients with cancer who are already compromised may help to avoid further immunosuppression. Clinical trials have shown that laparoscopy may actually limit tumour spread compared to open procedure<sup>13</sup>. More manipulation of tumour during open procedures significantly increases tumour growth and spread. In a study conducted by Muller and Hajri in 1997 to compare laparoscopy and laparotomy as regards tumour growth and spread in rat model, it was concluded that tumour manipulation increased tumour growth significantly in laparotomy group but not laparoscopy group. There was no difference in tumour growth and spread in both groups when tumour manipulation is not carried out. Beneficial effect of laparoscopic surgery may be related to a better preservation of immune function in early postoperative period. On the other hand there are reports of abdominal wall and peritoneal recurrences after a laparoscopic resection for malignancy. It has been suggested that frequent instrument changes through trocar site promotes seedling<sup>12</sup>. In the study mentioned above (Muller and Hajri) there was no portsite or conventional wound seedling as only one laparoscopic grasper was used. It has also been suggested that in case of laparoscopic procedures pneumoperitoneum may detrimentally effect tumour growth. This question still remains unanswered.

#### Influence of CO<sub>2</sub> pneumoperitoneum on immune response

A pneumoperitoneum is usually required for laparoscopic surgery. Physiology of pneumoperitoneum is complex with local and systemic effects of a gas instilled under pressure. Different gases such as helium, argon and nitrous oxide have been evaluated as alternatives to CO<sub>2</sub>. The question has naturally arisen whether CO<sub>2</sub> pneumoperitoneum influences systemic metabolic and immune response to laparoscopic surgery.

Insufflation of CO<sub>2</sub> causes local and systemic effects. Local defence and immune mechanisms might be suppressed by altered pH in the subcutaneous tissue<sup>14</sup>.

In one of the studies macrophage TNF and IL-1 response to bacterial endotoxin was lower for macrophages inculcated in CO<sub>2</sub> rather than air or helium. It was inferred that drop in macrophage function is caused by a more acid environment due to CO<sub>2</sub>.

Most of the studies have also suggested that it is the suboptimal technique and instrumentation which lay a decisive part in the implantation of tumour cells rather than CO<sub>2</sub> pneumoperitoneum<sup>15</sup>. However there are certain



studies which suggest abdominal wall and peritoneal recurrence after a laparoscopic reaction for malignancy which led to speculations that pneumoperitoneum may detrimentally affect tumour growth. Another comparative study in animal model has suggested that tumour growth may be affected by the type of gas used during pneumoperitoneum<sup>16</sup>. Total intraperitoneal tumour growth was greater in CO<sub>2</sub> group in a rat model having colonic adenocarcinoma after insufflation with CO<sub>2</sub> and helium. However this did not reach statistical significance.

In another interesting study conducted comparison of immunological and physiological effects of CO<sub>2</sub> at room and body temperature was done. Pneumoperitoneum with CO<sub>2</sub> at room temperature supplies gas 15-16°C below core temperature. This is associated with visible hyperaemia of peritoneum and peritoneal exudation which may provide tumour cells with better chances of growing. Warming insufflated gas to body temperature reduces hyperaemia of peritoneum. There is decreased production of  $\alpha$ -TNF and TL-1. This may be associated with lower rate of post op wound infection and less transfusion requirements<sup>17</sup>.

Studies have also suggested that increased intra-abdominal pressure of pneumoperitoneum compromises splanchnic blood flow and afferent circulation of liver. Portal blood flow is important as regards liver function and cell conveyed immunoresponse. Therefore reduced portal blood flow due to pneumoperitoneum may suppress cell conveyed immunoresponse.

However, there are certain limitations of these trials. Half of these trails on human models are not randomized owing to rapid acceptance of laparoscopic surgery. Moreover, animal models may not be directly applicable to clinical human situations.

Clinical relevance of the changes noted in immune function after open operations remains to be determined. So further experimental studies about metabolism and immunology are necessary to support the suggested advantages of laparoscopic surgery.

In further studies all factors of invasiveness under certain surgical method must be considered. Total ivnasiveness of surgical procedure does not depend on size of incision for access. Duration of procedure, local tissue damage and general effects of operative method must also be considered.

However, based on the limited clinical data we have todate we can conclude that laparoscopic surgery leads to a decreased acute inflammatory response and to a lesser degrees of cell mediated immunosuppression as compared

to open surgical procedures but the clinical relevance of these findings remain to be determined.

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