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Review

Inflammatory response after laparoscopic versus open colonic resection: Review of the literature

Dimitrios Tsamis[1], George Theodoropoulos[1], V. Nikolaos Michalopoulos[1], Thalassini Delistathi[1], Nikolaos Nikiteas[2], Christos Tsigris[3] and Emmanuel Leandros[1]

[1]Propedeutic Surgical Department, Hippokration University Hospital, Athens Medical School, Athens, Greece.
[2]Propedeutic Surgical Department, Laiko University Hospital, Athens Medical School, Athens, Greece.
[3]Surgical Department, Laiko University Hospital, Athens Medical School, Athens, Greece.

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Surgical trauma may lead to immune dysfunction as a result of the intense inflammatory response which arises in order to restore tissue function. The inflammatory response after surgical trauma is mediated by a number of substances which are produced at the site of wounded and manipulated tissues or at more distant places and they can act locally and systematically. These substances are TNF, Interleukins, Heat shock proteins, etc. Laparoscopic surgery is associated with reduced surgical trauma, much less manipulation of tissues and an environment of CO_2 pneumoperitoneum comparatively with open procedures. All of these contribute to the theory that laparoscopic colonic resections are expected to be associated with less inflammatory and acute phase response than open resections. As indices of inflammation in colon surgery cytokines, such as TNF, Interleukins and CRP are the most studied ones. From the studies which are reviewed, comparing these cytokines in serum and peritoneal fluids in patients undergoing open versus laparoscopic colectomy, some showed that inflammatory response after laparoscopic colorectal resections seems to be slightly attenuated, as long as values of IL-6, IL-8 and CRP in peripheral blood are in lower levels in the first postoperative hours than open procedures. This phenomenon was not noticed in all studies and for other inflammatory and anti-inflammatory cytokines in the serum of the patients or in the peritoneal fluids.

Key words: Laparoscopic colectomy, open colectomy, inflammatory response.

INTRODUCTION

Surgical trauma has a major impact in patients under-going surgery especially in immune response and this is a possible predictive factor of patients' clinical outcome (Lujan et al., 2002; Jacob et al., 2005; Buunen et al., 2009; Barlehner et al., 2005; Barlehner et al., 2004). The immune dysfunction is a result of the intense inflam-matory response which arises after surgical trauma in order to restore tissue function and to control the infection eradicating the invading microorganisms (Brivio et al., 1998). The integrity of peritoneal and systemic immune response also prevents and protects from endoperitoneal or wound site spread and adherence of tumor cells. Major insults, as the big surgical wound in the open colectomy and time consuming tissue manipulations are associated with an overwhelming inflammatory response (Koerner et al., 2008; Gupta et al., 2001).

Theoretically, the advantage of laparoscopic tech-niques with the lesser surgical trauma, the smaller tissue manipulations, and the presence of CO_2 pneumo-peritoneum and the minimal exposure of the viscera to the air may be the cause of a much smaller inflammatory response and a lesser impact in immune response. This is extremely interesting in patients who undergo a colorectal resection for a malignant disease (Hartley et al., 2001; Carter et al., 2001) where an immune suppres-sion to them may exacerbate their disease. It is obvious that this theoretical advantage in inflammatory response of minimal invasive techniques in colorectal surgery must be elucidated, researching these data in medical literature.

The inflammatory response after surgical trauma is me-diated by a number of substances which are produced at the site of wounded and manipulated tissues or at more

*Corresponding author. E-mail: tsamisdim@hotmail.com. Tel: 0030 6937334858. Fax: 0030 2107792819.

distant places and they can act locally and systematically (Gupta et al., 2001). The potent mediators are cytokines, heat shock proteins, acute phase proteins, eicosanoids and many others. The most studied in the literature are the cytokines and C reactive protein and they are studied both in the serum and in the peritoneal fluid (Koerner et al., 2008; Hartley et al., 2001).

Cytokines appear to be the most potent mediators of inflammatory response. They are divided in two groups in order to characterize their function; the pro-inflammatory and the anti-inflammatory group. In general, they can act autocrine or paracrine to the producing cell, so as systematically.

The pro-inflammatory cytokines locally at the site of injury have an effect to immune cells and they can cause activation, proliferation and differentiation to them. The anti-inflammatory cytokines simply oppose the excessive actions of pro-inflammatory cytokines (Carter et al., 2001; Schwenk et al., 2000; Hewitt et al., 1998).

A search in the medical literature was conducted and several studies were found investigating the role of TNF-a, IL-1, IL-2, IL-6, IL-8 and IL-10 in inflammatory response in laparoscopic and open procedures in colorectal surgery. Special attention was given in the studies which were comparing the values of these aforementioned cytokines in serum and peritoneal fluid of patients who underwent conventional versus laparoscopic colectomies. Databases from medline were used. Manuscripts which were published between 1994 and 2009 were reviewed.

DISCUSSION

Tumor necrosis factor

Tumor necrosis factor-a (TNF-a) is among the earliest responders following injury. It is synthesized from monocytes, macrophages and T-cells which are abundant in the peritoneum and splachnic tissues. The half time of TNF is less than 20 min and its main effect is to activate other mediators in the inflammatory response, to have cytotoxic activity and to promote shock and catabolism. A prospective randomized trial that conducted by Wu et al. was designed to evaluate the difference of TNF-a in the serum and in the peritoneal drain fluid of patients with a primary carcinoma undergoing curative laparoscopic (n = 12) or conventional (n = 14) colon resection. TNF-a was measured before surgery and in several time intervals after. No differences were found between the two groups (Wu et al., 2003). Another study by Hu et al. which evaluated TNF-a in the serum of patients with rectal cancer undergoing laparoscopic (n = 20) and open (n = 25) total mesorectal excisions (TME) with anal sphincter preservation, before operation and in postoperative days 1 and 5, showed no difference also between the two groups (Hu et al., 2003).

Interleukin 1

There are two forms of IL-1; the IL-1a and the IL-1β. IL-1 is primarily released by monocytes, macrophages, T and B lymphocytes and endothelial cells. IL-1a is predominantly cell membrane associated and exerts its influence via cellular contacts. By contrast, IL-1β is detectable in the circulation and has a half-life of approximately 6 min.

Both forms of IL-1 have similar physiologic effects as TNF-a and this emphasize the synergistic roles of them. Moreover, IL-1 can induce the classic inflammatory febrile response to injury by stimulating local prostaglan-din activity in the anterior hypothalamus and promotes β-endorphin release from pituitary resulting in attenuated pain perception in patients after surgery. It is worth mentioning that there is a receptor antagonist of IL-1 (IL-1ra), an anti-inflammatory cytokine which also is released during injury and its main role is to regulate the IL-1 activity.

In 1994 Harmon et al. assessed the IL-1 levels in the serum of 12 patients who underwent a laparoscopic colon resection preoperatively and after surgery at 1, 2, 3, 4, 5, 12, 24, 72 h and compared these results with a group of patients (n = 12) who underwent open colon resection. The result was that the levels of IL-1 were undetectable in virtually all patients (Harmon et al., 1994). Later Schwenk et al. in a prospective randomized controlled trial measured the anti-inflammatory IL-1ra plasma levels several hours after laparoscopic and conventional colorectal resections and did not find any difference between the two groups. Overall, Schwenk et al. used two groups of 30 patients each and all of them proceeded to colorectal resection for cancer (Schwenk et al., 2000).

Interleukin 2

With IL-2 not many investigators proceeded to examine its role in minimal invasive procedures in colorectal surgery. Hu et al. in the same study for laparoscopic and open TME in 20 and 25 patients, respectively, also assayed serum IL-2 before operation and in postoperative days 1 and 5. As for TNF-a, no significant difference also was observed in two groups for IL-2. IL-2 is mainly produced by T lymphocytes (Hu et al., 2003). The half-life is less than 10 min and partly for that, is not readily detectable following acute injury. Attenuated IL-2 expression is associated with major injuries and major blood loss preoperatively. Its main role is to promote proliferation of lymphocytes, to regulate their apoptosis, to produce immunoglobin and to preserve the integrity of gut barrier.

It is imperative to mention that, an accelerated lymphocyte apoptosis due to injury may exacerbate immunocompromise as a result of diminished IL-2 stimulation and production.

Interleukin 6 - C reactive protein

The most studied interleukin in the medical literature is IL-6. IL-6 is elicited by virtually all immunogenic cells like macrophages, neutrophils, B lymphocytes, basophils, mast cells, endothelial cells, fibroblasts and many others and actually in every tissue including the gut. Inducers of IL-6 production are potentially TNF-a and IL-1. IL-6 levels in the circulation can be detected in 60 min after injury; they peak at approximately 300 min and are detectable even 10 days after the operation. The levels appear to be proportional to the extent of injury and the duration of the operative procedure.

IL-6 has a complicated physiologic role in the organism since it features pro-inflammatory and anti-inflammatory action. Mainly IL-6 is an important mediator of the hepatic acute phase response during injury, inducing hepatic cells to produce proteinase inhibitors, coagulation and complement proteins and transport proteins. Most useful biomarker representative of hepatic acute phase proteins is C-reactive protein (CRP). Clinically, CRP is the most consistently used as a marker of inflammation because it displays great accuracy, dynamic reflection of inflammation and does not affected by feeding but only of pre-existing liver compromise or failure. Other action of IL-6 is to activate neutrophils during injury and sometimes to delay the disposal of them. The anti-inflammatory role of IL-6 consists of promoting the release of soluble tumor necrosis factor receptors (sTNFRs) and IL-1ra and thereby attenuating TNF-a and IL-1 activity during injury.

From 1990 - 1999 in medical literature, there are no many studies comparing IL-6 and CRP response in patients undergoing laparoscopic or open colorectal resections. Harmon et al. compared IL-6 from serum of 12 patients (laparoscopic group) with 41 patients (open group) at preinduction and several hours postinduction to general anesthesia. Harmon et al. noticed that IL-6 levels of the laparoscopic cohort were significantly lower than those of the open cohort between 3 and 24 h postinduction ($p < 0.05$) (Harmon et al., 1994). In another study, Hewitt et al. concluded in a similar result for IL-6, noticing peak levels at 4 h and returning to preoperative levels at 48 h. This response appeared greater for open resection ($p = 0.25$). In this study 16 patients with colorectal cancer were randomized to undergo laparoscopic assisted resection or open (Hewitt et al., 1998).

From 2000 and thereafter, several studies have been published with the same results. Schwenk et al. in 30 laparoscopic and 30 open colorectal resections for tumors noticed postoperative peak concentrations of IL-6 ($p = 0.05$) and CRP ($p < 0.001$) and the overall postoperative plasma concentrations of IL-6 ($p = 0.03$) and CRP ($p = 0.002$) were lower in the laparoscopic than in the conventional group (Schwenk et al., 2000). A Spanish study from Delgado et al. included 97 patients; 58 received open colectomy and 39 laparoscopic assisted. In the Spanish study, the levels of IL-6 were higher with significant differences at 4, 12, 24 h in the patients submitted to open colectomy and CRP levels in the plasma were significantly lower at 72 h in patients receiving laparoscopic assisted colectomy (Delgado et al., 2001).

Some investigators analyzed also the peritoneal drain fluid for IL-6 to assess the local response and to compare it with the systemic pro-inflammatory response. A Japanese study from Ozawa et al. comprised of 8 patients who underwent open and 8 who underwent laparoscopic assisted colectomy. Peripheral blood samples were obtained before induction of anesthesia and several hours after the skin incision. Moreover, peritoneal fluid samples were collected at the same time intervals. In the serum the IL-6 levels at 4 h after the skin incision were significantly lower in the laparoscopic assisted group than the open group of patients ($p < 0.05$). In collected ascites samples, the IL-6 levels were not significantly different between the two groups (Ozawa et al., 2000). In the same results as concluded and a study from The Netherlands, Wu et al. measured IL-6 and CRP in the serum and IL-6 in peritoneal drain fluid preoperatively. CRP was not significantly differed between the 12 patients who submitted to laparoscopic colon resection and the 14 patients who submitted to open procedures. Nevertheless, serum levels of IL-6 were significantly lower 2 h after laparoscopic surgery than with the conventional procedures of colon resection. There was no difference between the two groups in peritoneal drain fluid samples; except that there were significantly higher levels of pro-inflammatory cytokines in the peritoneal drain fluid than in the circulation after both procedures (Wu et al., 2003).

However, two studies assessed pro-inflammatory cytokines (IL-6) and CRP in the serum of patients who underwent laparoscopic assisted colorectal resection and open surgery preoperatively, at first postoperative day and then at fifth or the seventh postoperative day. In both studies, the investigators did not found significant difference between the two groups. The first was a study from The Netherlands and included 30 patients who randomized for laparoscopically assisted or open bowel resection not for cancer but for Crohn's disease, ulcerative colitis and Familial Adenomatous Polyposis (FAP) (Dunker et al., 2003). The second was from China and concerned laparoscopic and open total mesorectal excisions (Hu et al., 2003).

Interleukin 8

The least studied cytokines in minimal invasive techniques in colorectal surgery are the interleukins IL-8 and IL-10. The activity of IL-8 is similar to that of IL-6 in the surgical trauma, but it does not produce the hemodynamic instability of IL-1 and TNF and as well has

a chemoattractant act for neutrophils, lymphocytes, basophils and eosinophils. IL-8 is mainly produced by macrophages, monocytes, T lymphocytes, basophils, mast cells, platelets, etc. Wu et al. found significantly, lower serum levels of IL-8 2 h after laparoscopic colon resections than after open resections. In the peritoneal drain fluid they noticed no differences between the two groups (Wu et al., 2003).

Interleukin 10

In the other hand, IL-10 shows an anti-inflammatory action, emerging a role as a modulator of TNF-a activity. It also seems to attenuate the systemic inflammatory response and reduce mortality during septic peritonitis. T and B lymphocytes, macrophages and basophils are some of the producing cells of IL-10. Schwenk et al. did not observed any difference in the IL-10 serum levels between the laparoscopic and open colorectal resection groups (Schwenk et al., 2000).

CONCLUSION

Reviewing the medical literature, the result which someone is exerting is that the inflammatory response in laparoscopic colorectal resection is an issue which has not been studied extensively. Nevertheless, the results of the studies which are reviewed by the authors seem to correlate each other with small deviation.

The cascade of pro-inflammatory cytokines seems to activate in patients undergoing a colorectal resection with minimal invasive techniques just like in the open procedures (Brivio et al., 1998). But some studies has shown that this reaction may be lesser and attenuated in laparoscopic colectomies. This is elicited by the fact that in these studies, some cytokines such as IL-6 and IL-8 and CRP are tending to develop smaller augmentation in serum of the patients undergoing laparoscopic colorectal resections comparing with the patients undergoing open procedures. But, this fact seems also to be temporary as long as this is being observed in the serum of the patients only in the first postoperative hours. From 2 h after surgery until 48 h, IL-6 in laparoscopic groups is much less than open groups of patients. This is also observed for IL-8 at the first 2 h after surgery and until the first 72 h postoperatively for CRP. In contrast, this smaller augmentation which is observed in the serum in the laparoscopic colectomy groups of patients and represents the systematic inflammatory response, it is not observed in peritoneal fluid samples. Regarding the anti-inflammatory cytokines, IL-1ra and IL-10, the studies show that there are no differences postoperatively in the serum of patients submitted to laparoscopic and open colorectal resections.

Furthermore, lack of sufficient evidence is still apparent in regards to long term inflammatory response modulation following both approaches for colectomies for cancer patients, since studies focus on the first three postoperative days outmost, with one exception for rectal cancer from Hu et al. (2003). Further investigation on the inflammation cytokines changes during the late days postoperatively may be necessary. If the inflammatory disorders are more subtle or have subsided earlier at the laparoscopic colectomy group of patients, this may further add to the value of laparoscopic approach on accelerating the beginning of any needed adjuvant treatment, as chemotherapy or radiation therapy.

This inclination for attenuated inflammatory response in minimal invasive techniques in colorectal surgery seems not to correlate clearly with a respective attenuated immune response and a clear clinical effect. Results of many studies are controversial (Tang et al., 2001; Ordemann et al., 2001). Conversely, this phenomenon is not standing for animal studies comparing laparoscopic and colonic resections and for other laparoscopic surgeries less invasive, like cholecystectomy, Nissen fundoplication, hysterectomy and inguinal hernia repair. In the other laparoscopic surgeries, lesser inflammatory response and less cell mediated immune compromise are clearly observed (Hartley et al., 2001; Kuntz et al., 1998; Buunen et al., 2004; Grande et al., 2002; Redmond et al., 1994; Holub, 2002; Malik et al., 2001; Yuen et al., 1998; Perttila et al., 1999; Uzunkoy et al., 2000). This phenomenon is mainly based on the fact that laparoscopic colorectal resections are representing extensive laparoscopic procedures with great operative times, much more time in CO_2 pneumoperitoneum and exten-sive traumatic tissue manipulations, probably because of small familiarity and experience of the surgeons with these operative techniques (Sietses et al., 2000).

There is strong evidence in the animal setting that laparoscopic cancer resection methods may be associated with improved long term oncologic outcome based mainly in better preservation of immune response and lesser cell mediated immune compromise (Hartley et al., 2001; Carter et al., 2001). Such a postulate remains established in humans in colorectal surgery and to manifest minimal invasive techniques and laparoscopic surgery as a great weapon in warfare with cancer.

Eventually, it is really important to know if all the well known advantages of laparoscopic techniques are attributed to the smaller inflammatory response they actually proclaim, this is an area that is not well studied and needs more research.

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