Basic Research in Open Abdomen

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2.1 Background

Basic research on open abdomen, especially using animal models, has recently developed around some important topics. The aim is to better understand this strategy and its pathophysiology and to allow its more effective use and prevent the complications of this procedure.

Actually the most studied topics in basic research are the immunological modifications caused by NPT (negative pressure therapy), the distribution of negative pressure in the abdominal cavity, its effects on bowel surface, and the development of means to protect intestinal anastomosis in the setting of open abdomen.

2.2 Immunological Modification

Basic research on open abdomen has focused on immunological modifications induced by NPT, not only in the peritoneal cavity but also in the systemic circulation. Recent preclinical studies have analyzed the role of the temporary abdominal closure systems that employ negative pressure in preventing multiple

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organ dysfunction syndrome (MODS) and in improving outcomes in animal models [1–4].

2.2.1 MODS Pathogenesis

MODS is the final and often lethal stage of the septic and hemorrhagic shock. The mechanism of MODS is thought to be the excessive systemic inflammation (SIRS, systemic inflammatory response syndrome) that affects a complex array of molecular pathways causing an overwhelming "cytokine storm" [1, 3].

Although there is no consensus about the organ system that generates MODS, it is well established that an injury in one organ system can cause injury to a second, distant organ system through the "cytokine storm" [5, 6].

It is likely that the gut is the initial motor of MODS, also during extra-abdominal sepsis. Indeed microcirculation in the gut is preferentially altered in both septic and hemorrhagic shock through hypoxic and inflammation-induced injury. This can lead to the loss of intestinal barrier function and to the increasing of permeability, resulting in intestinal edema and ascites formation. This fluid in the third space is rich in cytokines and inflammatory mediators that can reach the systemic circulation, perpetuate SIRS, and promote MODS [1].

Indeed it has been suggested by some studies that inflammatory mediators such as cytokines released during intestinal ischemia and reperfusion increase permeability in the lungs with subsequent lung injury [7]. To stress the important role of cytokines in causing distant organ system failure during MODS, in a study on animal models by Narita et al. [8], it has been demonstrated that the isolation of the intestine in a bag during ischemia and reperfusion reduced the degree of subsequent lung injury, probably due to the reduced absorption of locally produced cytokines via the parietal peritoneum [8].

So, in light of these studies, the local control of cytokines in the peritoneal cavity may be important in order to prevent MODS.

2.2.2 Preclinical Studies

In the study by Kubiak et al. [1], pigs with intra-abdominal sepsis were randomized to negative pressure peritoneal therapy versus passive drainage of the peritoneal cavity. The most important findings in this study were that peritoneal NPT reduced histologic damage to the lungs, intestine, kidney, and liver. The mechanism for this protection involved removal of inflammatory peritoneal ascites, causing a moderation of SIRS and a limitation of distant organ damage. The reduction in peritoneal inflammation was responsible for the blunted systemic inflammatory response in the NPT group, with plasma concentrations of TNF-α, IL 1-β, IL-6, and IL-12 diminished. Furthermore NPT, removing a larger volume of ascites, reduced intra-abdominal pressure (IAP), which may also play a role in the reduction of systemic inflammation and organ damage. These data suggest that inflammatory ascites, rather than bacterial translocation, is the motor driving organ damage.

Emr et al. [2] went further insight into the complex immunological response, through the use of "in vivo" and "in silico" studies. They found that only the concentrations of IL-8 and IL-6 were lowered significantly in NPT group, while all other inflammatory mediators remained at the same concentration. Given that IL-6 is the biomarker that typically distinguishes adverse outcomes in sepsis [9], probably NPT modifies inflammation in a favorable fashion by reducing the production of IL-6. There were differences neither in endotoxin concentration, and all animals had positive cultures for both aerobic and anaerobic bacteria. Thus, the simple removal of bacteria does not seem to be the mechanism underlying the protective effect of NPT.

Furthermore, in silico analysis, IL-10, which is inferred to be produced as a consequence of the core IL-6/TGF-β1/CRP motif in control group, is absent in NPT group. IL-10 is a key anti-inflammatory cytokine, so its absence suggests a more robust ability to control infection with NPT.

Norbury et al. [3] in 2015 developed these aspects analyzing in more details the immunological modifications induced by NPT in the septic swine model. Also in this study, the improved survival due to NPT was directly associated with a reduction of MODS. Analyzing the immunological response, in both groups (peritoneal NPT versus passive peritoneal drainage), the septic swine model displayed evidence of leukocytosis in the initial 12 h after injury, followed by immunoparalysis manifested as lymphopenia. This is the result of a compensatory anti-inflammatory response designed to protect against an uncontrolled hyperinflammatory response. While in the group treated with passive drainage there was a further decrease in the number of circulating lymphocytes as the experiment progressed, the NPT group showed a significant recovery by the end of the experiment, suggesting that NPT mitigated the further effects of systemic inflammatory injury and overcome the effects of immunoparalysis in this model.

In the NPT group also, the response by macrophages in producing ROS was demonstrably greater and peaked early with the effect being even greater at 3 h than at 6 h, again suggesting that the inflammatory response is more effective but finite and controlled.

So this study hypothesized that the effect of NPT on the inflammatory response is not only due to the active removal of inflammatory mediators from the peritoneal cavity before they enter in the systemic circulation but also due to a dynamic alteration of the microenvironment that allows a more robust, yet transient, innate antimicrobial response.

Regarding trauma setting, a recent study by Shi et al. [4] showed that in experimental pigs with blast injury in the abdomen and exposed internal organ, NPT can control the amount of bacteria; reduce the expression of TNF-α, IL-1, and IL-6; and promote the expression of growth factors.

In a study by Kuethe et al. [9], peritoneal cytokines and cells of mice with abdominal sepsis were analyzed. Mice that survived had decreased peritoneal IL-6 levels, decreased peritoneal bacterial loads, decreased systemic IL-10, and increased peritoneal monocyte numbers and phagocytosis. All these are the observed effects of NPT in the septic swine model in the previously mentioned studies.

2.3 Distribution of Negative Pressure in the Abdominal Cavity and Its Effects on Bowel Surface

Some preclinical studies focused on pressure distribution in abdominal cavity and its effects on microvascular blood flow in the intestinal wall using different open abdomen dressing systems [10–15].

2.3.1 Pressure Distribution

In a recent in vitro study by Delgado et al. [10], assessing pressure mapping and fluid extraction efficiency of three open abdomen dressing systems (ABThera™ Active Abdominal Therapy System, VAC® Abdominal Dressing System, and Barker's vacuum pack technique), pressure distribution of ABThera Therapy and of VAC Abdominal Dressing System was significantly superior to Barker's vacuum pack technique in all peritoneal evaluated zones. There were no pressure distribution differences in the zone closest to negative pressure source between ABThera Therapy and VAC Abdominal Dressing System. In the zone immediately outside of manifolding material edge and in the area most distant to negative pressure source, ABThera Therapy pressure was significantly superior to VAC Abdominal Dressing System one.

2.3.2 NPT Effects on Intestinal Wall

In the study by Bjarnason [11], pressure propagation at the bowel surface was investigated on a porcine model. The negative pressure observed at the bowel surface was substantially reduced, compared to the applied pressure, for all NPT settings, indicating that the visceral protective layer effectively isolates the bowel from the negative pressure. Furthermore in this study, the observed pressure at the bowel surface did not correlate with the level of applied NPT.

Lindstedt et al. conducted many studies on pigs about pressure transduction on intestinal wall, fluid evacuation, and protection of intestinal loops during open abdomen. They showed that the use of NPT in open abdomen induces a decrease in the blood flow in the small intestinal wall lying close to the dressing and beneath the anterior abdominal wall. Furthermore, in spite of Bjarnason's results, the decrease in blood flow became greater with increasing negative pressure applied. The blood flow could be restored by inserting a protective thin plastic disc over the intestine but could not be prevented by inserting four layers of paraffin gauze between the visceral protective layer and the intestine [12, 13]. Macroscopic changes in the small intestine lying close to the NPT dressing were studied in another preclinical trial [14]. Slight petechial bleeding was seen in the small intestinal loop in this area after 24 h, but especially after 48 h. In contrast, hardly any petechial bleeding was seen in pigs treated with the protective disc over the intestines [14]. Furthermore, abdominal drainage was significantly better using NPT with the protective disc than

with conventional NPT system, and the pressure transduction was more even at all pressure levels using NPT with protective disc than with conventional NPT [13].

Comparing VAC Abdominal Dressing System and ABThera Therapy, there were no differences in the decrease in microvascular blood flow in the intestinal wall lying close to the visceral protective layer. So the decrease in the blood flow was related to the amount of negative pressure applied and not to the type of dressing [15]. These results are very interesting if applied to humans, and the use of the protective plastic disc over the intestine could be a useful tool to prevent intestinal injury in these patients.

2.4 Means to Protect Intestinal Anastomosis in Open Abdomen

Zhou et al. conducted a study to evaluate the effect of platelet-rich plasma (PRP) gel, a blood-derived biomaterial, on the healing of colon anastomosis and anastomotic strength in the open abdomen [16]. There is a growing body of evidence indicating that blood-derived biomaterials such as platelet-rich plasma gel promote wound healing in a variety of clinical fields via release of chemoattractants and growth factor, such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β). These molecules synergize to facilitate regeneration of injured tissue through acceleration of cell proliferation and matrix formation [17]. They observed that the hydroxyproline levels (amino acid found almost exclusively in collagen, used as an indicator of collagen synthesis and wound healing) were statistically higher in patients with open abdomen that were treated with PRP on anastomosis than in patients with traditional open abdomen. They analyzed the anastomotic bursting pressure that reflects the balance between collagen deposition and lysis, and it's a predictor of outcome of gastrointestinal anastomoses. In anastomoses in open abdomen patients treated with PRP, after day 7, the bursting pressure was similar to anastomoses in patients without open abdomen and higher than in patients treated with traditional open abdomen technique without PRP. Furthermore, colonic anastomoses sealed by PRP gel showed significantly increased inflammatory cell infiltration, anastomotic fibroblast ingrowth, anastomotic neovascularization, and collagen deposition compared to standard anastomoses [16].

Other substances were tested in other studies with the same aim. In a study in rat models, tannin acid–polyethylene glycol adhesive seems to give good results in this context [18].

Conclusion

Basic research on open abdomen and NPT is in constant evolution.

NPT in septic animal models seems to offer better outcomes in terms of mortality and morbidity. This advantage can be explained by the local and systemic immunologic modification caused by removing abdominal fluids rich in inflammatory mediators. This results in more effective and more limited local inflammatory response, in lower levels of circulating cytokines, and in decreased risk

of distant organ injury and MODS. Evidence obtained from animal models can potentially be applied to clinical research, thus providing new insight in the pathophysiological basis of NPT.

Basic research also focuses on complications of negative pressure on intestinal wall and anastomotic leaks. Recent reports have shown promising results on how to prevent those complications.

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