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Peritonitis: Relevance and Choice of Adequate Experimental Model

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ABSTRACT

Peritonitis is characterized by high lethality, which indicates the need to elaborate adequate methods of its treatment. Non-surgical methods applied along with the surgery are elaborated after preliminary experimental studies on animals, that requires to choose the relevant model of peritonitis. The article highlights the issues of the peritonitis relevance, the formation of bacterial biofilm and the choice of methods for peritonitis modeling in the experiment.

Keywords: Diffuse Peritonitis; Lethality; Bacterial Biofilm; Models of Peritonitis

Introduction

The Relevance of the Peritonitis

Peritonitis continues to be one of the main topical problems of urgent abdominal surgery. This is mainly due to the lethality in diffuse peritonitis (DP), which remains high nowadays, despite the significant advances of modern medicine in the diagnostics and treatment of urgent surgical pathology. The progression of the inflammatory process inside closed and anatomically complex abdominal cavity, the rapid increase in intoxication resulting in severe hemodynamic and metabolic disorders, largely hinder the effective treatment of DP. Hence the high lethality. Thus, the overall lethality in DP, according to data of various authors, is about 27,8–37,2% [1-4]. However, lethality in DP due to acute mesenteric ischemia and pancreatic necrosis reaches around 70% [2], while lethality in DP due to acute appendicitis and perforated gastroduodenal ulcer as it's the most common causes [1,2,5] is 0-8,5% and 13,5-21%, respectively [1,2,4]. Lethality is high in DP due to cancer and non-cancer colon perforations – 47-52,4% [13, 28], perforations of the jejunum and ileum – 50% [4]. At the same time, the analysis of lethality showed that the absolute number of deaths is higher in DP due to perforations of the large intestine than due to acute mesenteric ischemia and pancreatic necrosis [2]. For the prediction of the disease, the time of patient admission is of great importance. According to Zhidkov S.A., about 34% of patients are admitted in toxic stage and 15,5% – in terminal stage of peritonitis [1]. The later patients with acute surgical pathology are admitted to hospital, the higher lethality rate.

Thus, among those who died from acute surgical diseases of the abdominal cavity, 20 % of patients were admitted before 6 hours from the onset of the disease, 23% of patients – within 6-24 hours, and 57% – after 24 hours [1]. It has also been established that the risk of death in patients with severe DP increases in case of delayed surgical treatment (later than 6 hours from the patient hospitalization) or antimicrobial therapy (later than 1 hour from the admission to the surgical department) and depends on the presence of multiple organ failure in the patient [6]. It is the multiple organ failure, along with septic shock, that are the most common causes of death in patients with DP [1,6] and that increases the lethality

in this pathology by 70% or more [7-10]. In addition, it is known that DP is one of eight risk factors in calculation of the Mannheim peritonitis index, which makes it possible to determine the severity of the pathology and, to a certain extent, predict lethality in a particular patient [11]. The index takes into account, along with the area of peritoneum damage, the nature of peritoneal exudate. Herewith, the fecal exudate is estimated at the maximum number of scores, which, compared with the purulent exudate, is 12 scores versus 6 points, indicating an extremely unfavorable prediction in fecal peritonitis.

Bacterial Biofilm in Peritonitis

Several types of microorganisms are detected in peritoneal exudate in peritonitis, and aerobic-anaerobic associations of microbes are identified in 90% of cases [12,13]. The dominant role among microorganism in peritonitis belongs to Escherichia coli [14-16]. However, there is a pattern of microflora in peritoneal exudate, depending on the level of gastrointestinal tract perforation. So, according to (Kupchenko AM [16]), in DP due to perforations of stomach and duodenum, *E. coli* (34%) and gram-positive aerobic microorganisms are detected in the peritoneal exudate, *B. fragilis* is identified only in 20,3% of cases [16]. In small intestine perforation, gram-negative microflora predominates among aerobic microorganisms, mainly *E. coli* (65,2%), the participation of anaerobic microorganisms reaches 69,6%. Gram-negative aerobic microflora, *E. coli* mainly (55,4%) and Klebsiella spp. (16,1%), is determined in colon perforation, with the dominance of the anaerobes (58,3% – Bacteroides fragilis), which reaches 88,7% [16]. Well known, the course of anaerobic peritonitis is much more severe than aerobic one. Numerous metabolites of anaerobic microorganisms possess pronounced toxic effect on cells, their pathogenicity factors affect tissue structures not only in the focus of inflammation, but also beyond it, causing severe intoxication of the body [17]. According to modern concepts, the persistence of the infectious process in DP is provided by a biofilm formed by pathogens in the abdominal cavity. A biofilm is not a simple accumulation of bacteria, but consists of a cellular component – microorganisms – and an extracellular matrix, which is a complex biochemical mixture of polysaccharides, glycopeptides, nucleic acids and lipids [18]. The bacterial biofilm maintains the level of systemic inflammation, which is manifested as an increase in fever duration, leukocytosis persistence, lengthening the time for complete sanitation of the abdominal cavity and an increase in the 7-day lethality rate in DP [6].

Models of Peritonitis

High lethality in DP becomes a stimulus to search a new or improve an existing methods of its treatment. As known, the putting of new achievements into clinical practice is impossible without previous carrying-out of experiments. At the same time, before elaboration of therapeutic methods, it is necessary to model an experimental peritonitis (EP) that is closest to actual course of the pathology. To date, many models of peritoneal inflammation have been proposed, which can be grouped as follows:

1. Putting of foreign bodies [19] or injection of chemicals [20] into abdominal cavity of experimental animals.
2. Bacterial contamination of the abdominal cavity with various cultures of pathogenic microorganisms [14,21-23], fecal suspension [24] or by perforation of any part of the gastrointestinal tract [25-27].
3. Combined methods for EP modeling. For example, the injection of microbial suspension along with putting of foreign body (gauze swab) into abdominal cavity [28]. However, when peritonitis is induced such way, acute abdominal sepsis develops rapidly and animals often die within the first day.

Regarding the first group of methods, it should be noted that in surgical practice, peritonitis resulting from putting of foreign bodies into abdominal cavity is rare. An example is gossypiboms, a surgical gauze dressing material forgotten after surgery in cavities or tissues of the body, which are most often found after abdominal surgery. According to (Yagmur Y [29]), the incidence rate of gossypiboms in abdominal surgery is around 52% [29]. However, among all performed intra-abdominal surgeries, they are detected with a frequency of 1:1000-1500 [30]. It is assumed that the true number of such cases exceeds the number published in press [31,32]. In aseptic peritonitis, which is developed as a result of peritoneum irritation by chemicals (for example, gastric juice), peritoneal exudate cultures are usually sterile in first hours after stomach perforation, later, when infection is joined, *E. coli* and gram-positive aerobic microflora are most often determined [16]. From the given data on the statistics of peritonitis, the conclusion follows that the second group of methods for peritonitis modeling is more relevant. This is primarily due to the fact that peritonitis occuring in disruption of gastrointestinal tract integrity is the most common, as well as due to significant number of deaths due to perforations of the stomach or intestine. Special attention is for fecal DP, which is characterized by significant microbial contamination of the abdominal cavity and significantly determines the prediction in peritonitis. It should also be noted that the model of fecal DP induced to study the effects of therapeutic agents, should reflex the lethality corresponding to that in clinic, where a complex of surgical and therapeutic measures is performed. Models of DP based on injection of microbial suspension into abdominal cavity through the polyvinyl-chloride catheter are proposed. For example, models with the injection of *E. coli* suspension as a monoorganism [23], suspensions of *E. coli*, Staph. spp., Ps. aeruginosae and Peptococcus

spp. in equal proportions [22], *E. coli* and Staph. aureus in a ratio of 3:1 [14] or a suspension consisting of aerobic (*E. coli*) and anaerobic (*B. fragilis*) components [21]. Obviously, with these methods, use of *E. coli* is mandatory as, in most cases, the dominant pathogen in peritonitis. Models allow to evaluate the effectiveness of various antibacterial drugs.

The method with the injection of aerobic-anaerobic association [21] is the closest to actual conditions. However, the composition of the microbial suspension in practice turns out to be much more diverse than in the above models, and in case of fecal peritonitis due to colon perforations, the peritoneal exudate can contain up to 16 different types of pathogens [16]. At the same time, standard inflammation of the peritoneum is not always modeled due to variability of pathogenicity and virulence of the flora used for modeling. In addition, these methods are quite laborious, and animals often have a severe course of the disease and early death, which is explained by the rapid resorption of microbial suspension from the abdominal cavity. Bacterial contamination of the abdominal cavity after the incision of the abdominal wall can be carried out, for example, by cross-section of the duodenum [33], the perforation of the head of blind colon with subsequent omentum resection [26], the cruciform incision in the anterior wall of the appendix and eversion of its mucous membrane [25]. The proposed models are close to real conditions, but at the same time, they are laborious and significantly impact on the emotional state of experimental animals. It is also possible to model the DP by means of perforation of the hollow organ of gastrointestinal tract without laparotomy and anesthesia. For example, the insertion through the probe into a selected intestinal section of the ice capsules containing coiled elastic double-edged nichrome rod, that after capsule melting under the body temperature straightens and damages the intestinal wall [27]. This approach allows to simplify the technique and makes the method closer to the clinical course of perforated ulcer. Modeling of peritonitis by mechanical damage to the gastrointestinal tract with disruption of its integrity without adequate treatment results in death within few days, therefore additional surgical intervention to restore the integrity is required. The infliction of mechanical injury to animal changes the studying parameters, that reduces the reliability of the obtained results. In our opinion, the most acceptable is the EP model proposed by Lazarenko V.A. et al., that's carried out by injection of fecal suspension of intact animals into abdominal cavity of experimental rats [24].

In this case, the suspension is obtained by mixing 0,9% NaCl solution and feces from the caecum of two or three intact animals, followed by filtering it twice through a double layer of gauze. Not later than 20 minutes after preparation, the fecal suspension is injected to intact animals under anesthesia by puncturing the ventral wall in the center of the midline of the abdomen, 0,5 ml/100 g of body weight. The end of the needle is alternately directed to the right and left hypochondria, then to the right and left iliac regions, thus resulting in spreading of the inflammatory process inside the abdominal cavity. To avoid damage to the internal organs, the animals are positioned vertically, caudal end up. Lethality when using filtered 10% fecal suspension on day 1 is 20%, by the 14th day it reaches 60% [24]. According to the authors, clinical, laboratory and pathomorphological changes in peritonitis modeling in this way are similar in all experimental animals [24]. The microbial composition of the peritoneal exudate, if necessary, can be determined at different time intervals after the modeling of the inflammatory process in the abdominal cavity. The positive effect of peritonitis modeling in this way is as follows:

- In experimental animals, a generalized inflammatory process of the abdominal cavity develops, which is important for the experiment due to the high lethality in this pathology.
- Induced fecal peritonitis is characterized by severe course, which is unfavorable for the prediction of the disease and emphasizes the relevance of the method.
- Lethality in the experiment, which is 60%, is close to that in intestinal perforations in the clinic and, thus, mimics peritonitis with all therapeutic measures; this is important for the study of the properties of drugs for the corrective therapy of peritonitis.
- The injection of fecal suspension into abdominal cavity of experimental animals almost immediately after receiving of feces from the caecum makes it possible to preserve the pathogenic and virulent properties of microbial associations.
- In the model, there is no surgical injury to animal, which definitely affects the behavior of the animal and clinical and laboratory parameters.
- The method allows to observe clearly the dynamics of the peritonitis course at the required time intervals.
- The adequacy of the peritonitis induction in experimental animals determines the possibility of its pathogenetic therapy elaboration.
- The model is easy to implement. Standardization of fecal suspension can be achieved by two-stage filtration through a filters of a larger and then a smaller diameter and subsequent performing of spectrophotometric and densitometric analysis [34,35]. At the same time, 15% filtered fecal suspension spectrophotometrically corresponds to 2,8 units of optical density and densitometrically – to 11,3 McFarland units, 3396 x 106 bacteria/ml (λ=550 nm). The method allows to obtain solutions with the same extinction coefficient, which makes it possible to compare the results in different experimental animals.

Conclusion

The literature describes many ways to model peritonitis in the experiment. These EP models, despite their shortcomings, were elaborated for certain purposes and are acceptable to carry out certain experiments. The model of EP, carried out by injection of filtered fecal suspension of intact animals into the abdominal cavity of experimental rats, makes it possible to represent the development of DP similar to clinical conditions and to observe the changes in studying parameters in peritoneal exudate over time. Representation in the experiment lethality close to that in the clinic is important for studying the effect of corrective therapy drugs on the course of peritonitis. Also, in our opinion, it is necessary to focus on the following:

- Basing on the statistics of the patients admission into surgical hospitals, therapeutic measures on the experimental animals aren't recommended to be started before or immediately after EP induction and must be performed at a later date.
- It is important to perform clinical trial of new drugs effect on the bacterial biofilm formed during DP, which is the cause of the persistence of the inflammatory process in the abdominal cavity.

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