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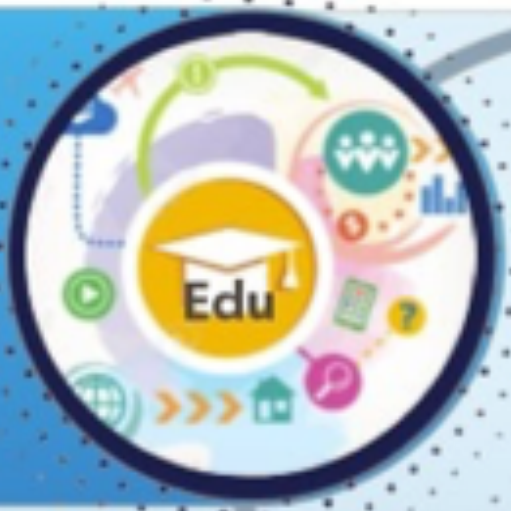

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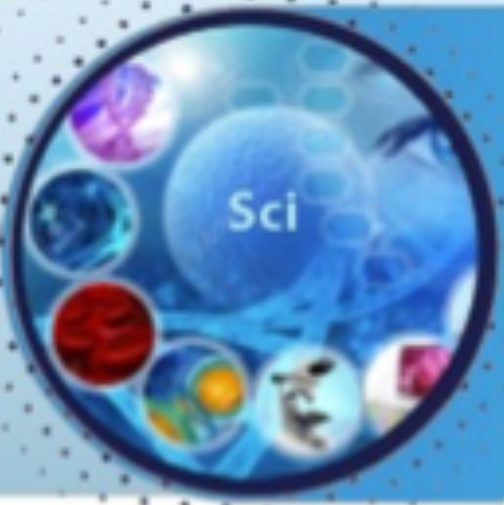

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Development and Comparative Evaluation of the Effectiveness of a New Experimental Model of Abdominal Sepsis

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ABSTRACT

Background. The main goal of modelling pathological processes is to solve the problem of an entire link of translational medicine, which is aimed at developing treatment methods and introducing them into clinical settings.

Material and methods. The work is experimental and was carried out on 40 beads of both sexes of the Wistar line. Various variants of abdominal sepsis were simulated in animals, including the original technique developed by us.

Results. Comparative characteristics of the reproducibility of various variants of experimental models of abdominal sepsis showed high values of positive results among animals of the C-series. The reproducibility rate of abdominal sepsis was 28.5% higher than among Series-A and Series-B animals. At the same time, lethality among the animals of the C-series was minimal.

Conclusion. The proposed version of the model of abdominal sepsis makes it possible to achieve the formation of several pathogenetic mechanisms that have a reasonable place in clinical practice.

Keywords: Abdominal sepsis, reproduction of the experimental model, peritonitis

INTRODUCTION

Abdominal sepsis is egalitarian because it remains a potential health threat to all people of all ages, races, and socioeconomic groups, regardless of how healthy. Worldwide, the combined burden of all pathologies that cause abdominal sepsis is enormous. Abdominal sepsis, which affects both developing and developed countries, is a huge source of lost lives, livelihoods and resources. Using data from the Global Prevalence Survey [17, 23].

B. Stewart et al. reported 896,000 deaths, 20 million years of life lost, and 25 million disability-adjusted life years lost per year, associated with a total of 11 general surgical emergencies [24].

The magnitude of DALYs lost due to this disease is also staggering [37].

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The overall incidence of abdominal sepsis is difficult to estimate, but large-scale epidemiological studies indicate that abdominal sepsis accounts for 1% of all hospital visits and is the second most important type of sepsis worldwide [27].

From a patient-centred practical perspective, peritonitis is most deserving of consideration as a marker of impending abdominal sepsis. Intra-abdominal infection is the most common cause of abdominal sepsis [33].

The high incidence of abdominal sepsis is accompanied by a high mortality rate, which can range from 7.6% to 36.0% [9].

Several studies have shown that the worsening prognosis in secondary peritonitis is due to some direct factors. Candida infection, severe organ dysfunction (SOFA≥7), severe pre-existing comorbidities, inadequate source control, and inappropriate antibiotic prescription play a role [3, 38].

Experimental modeling of abdominal sepsis has not lost its relevance for more than a century. Many scientists have tried not only to improve the technique of modeling the pathological process, but also to bring it closer to the realities of clinical conditions. Advances in the study of the pathogenetic mechanisms of sepsis have played an important role in this. In this section of the review, we present information on the history and achievements in the field of experimental modelling of abdominal sepsis.

Small laboratory animals (rats and mice) are now generally accepted for use in the reproduction of abdominal sepsis. In general, all known methods of reproducing abdominal sepsis can be safely divided into injection and surgical models.

The main goal of modeling pathological processes is to solve the problem of an entire link of translational medicine, which is aimed at developing treatment methods and introducing them into clinical settings.

At the same time, the mechanism of most models of abdominal sepsis is reduced to the reproduction of fecal peritonitis, the source of which is perforation (or acute traumatic injury) of the cecum. And although perforation (or acute traumatic injury) of a hollow organ has a certain share in the list of varieties of peritonitis, nevertheless, unfortunately, it cannot be similar to such causes as acute appendicitis, acute cholecystitis, pancreatic necrosis, diverticulitis, etc.

We believe that, based on the principles of translational medicine, when translating these values into clinical conditions, it is necessary to take into account all the subtleties of the mechanisms of modeling the pathological process in animals. Underestimation of these mechanisms will contribute to the formation of erroneous conclusions, which, in turn, can hinder scientific achievements.

The aim of our study was to develop an adequate model of abdominal sepsis, which would make it possible to create maximum conditions of pathogenetic mechanisms close to real clinical conditions of life

MATERIAL AND METHODS

The experiments were carried out on laboratory paints weighing 190-250 grams, of both sexes, Wistar lines, which were on a normal daily diet.

The preliminary protocol for experimental studies was approved, after review and discussion, by the Bioethics Committee under the Ministry of Health of the Republic of Uzbekistan.

The planned experimental studies, which included sampling, biopsies and autopsies, were based on the principle of the conditions specified in the Council of Europe Convention for the Protection of Animals of 1986.

RESULTS

We immediately excluded the widespread variant of intra-abdominal injection of animal autocal, since this approach to the formation of an experimental model corresponds to primary peritonitis, which is rare in clinical practice. In this regard, at the first stage, we used the method of modeling abdominal sepsis according to the CLD principle (series-A), proposed by a group of scientists led by H. Mutlak [15].

To do this, under anesthesia, laparotomy was performed in animals, the dome of the cecum was isolated, which was bandaged and crossed between two ligatures. In the abdominal cavity, according to the conditions of development, 2 mm^2 of the fecal mass of the animal itself was injected. The excised cecum stump was left in the free abdominal cavity, which was removed during the already therapeutic relaparotomy against the background of peritonitis.

This method, unlike others, where perforation or injury of the cecum dome was performed, made it possible to prolong the course of the pathological process, by reducing the frequency of lightning-fast development of septic shock. However, the mechanism of its reproduction did not always correspond to the development of peritonitis occurring in clinical practice.

On the one hand, the ingress of a large amount of feces into the abdominal cavity does not lead to the development of peritonitis and the corresponding clinical picture of sepsis, which would be manifested by signs of systemic inflammatory response syndrome, but to the development of septic shock, which led to death within 10 hours after the simulation of the pathological process.

On the other hand, in animals, the developed septic shock proceeded against the background of an unformed purulent-inflammatory focus, which excludes all stages of the pathogenesis of abdominal sepsis. The abdominal cavity, in this version of the model, acted as an entrance gate for the generalization of infection. In other words, we can observe the formation of the toxic phase of peritonitis, bypassing the reactive one, with a rapid transition to the terminal phase. Naturally, this cannot in any way be approximated to clinical conditions.

The reactive phase of peritonitis also, logically, rarely occurs against the background of the relatively complete "biological calm" of the body. As a rule, before the onset of peritonitis, the patient undergoes a process associated with the development of inflammation of the primary focus, and the initial period is considered to be aseptic inflammation.

It is necessary to create conditions for damaging the crypt and creating a pathway between the intestinal mucosa and serous membranes. Such a pathomorphological substrate leads to the involvement of all layers of the intestinal wall in the inflammatory process (similar to the primary affect of Ashof).

Thus, the development of an experimental model of abdominal sepsis, in the classical form of its origin, requires a special reactivity of the macroorganism in response to aggressive invasion of the microorganism. This corresponds to clinical data, in which it is possible to trace the development of an experimental model of abdominal sepsis, after the formation of a specific primary inflammatory focus (acute appendicitis, intestinal necrosis, pancreatic necrosis, etc.).

However, only under conditions of reduced reactivity of the macroorganism against the background of insignificant microbial aggression, it is possible to achieve generalization of the inflammatory process. In other words, the formation of an immunosuppressive state is required. This was pointed out by a number of Russian researchers when modeling various variants of surgical sepsis [28, 36].

The formation of an immunosuppressive state of the body and the creation of conditions for the development of destruction of the focus of inflammation can be considered the main factors in modeling surgical sepsis. At the same time, if possible, it is necessary to avoid "aggressive" surgical operations aimed at disrupting the integrity of the hollow organ. This approach excludes the possibility of postoperative peritonitis.

To change the reactivity of the macroorganism, it is currently actively recommended to use an injection of a 10% solution of calcium chloride, which is known to cause coagulation necrosis and aseptic inflammation [5].

But to what extent can such an approach with the introduction of calcium chloride, directly into the intestine, lead to the development of a change in the reactivity of the macroorganism?

The answer to this question was obtained in a new series of experiments (series-B), in which approximation to the clinical conditions for reproduction of the experimental model of abdominal sepsis was achieved by preliminary injection of antilympholin-Cr into the abdominal cavity at a dose of 0.03 mg per 100 grams of animal for 48 hours.

At the next stage of reproducing the experimental model of abdominal sepsis, the animal underwent a minilaparotomy under anesthesia in the right iliac region up to 1 cm long. This was done in order to provoke local coagulation necrosis and aseptic inflammatory process.

Signs of exclusion of technical errors during subserosal injection of 10% calcium chloride solution into the intestinal cavity were the absence of feces and air intake during the reverse vacuum of the syringe plunger, a relatively tight intake of injected fluid, as well as dilation of the subserosal capillaries of the intestine at the time of injection of the solution. The dome of the cecum was lowered into the abdominal cavity. The wound was sutured tightly.

Thus, the use of this technique for the reproduction of abdominal sepsis made it possible to achieve the goal by preserving the integrity of the intestine and made it possible to create the effect of inflammation of the primary focus. This made it possible to reduce the number of deaths compared to the series-A by more than 3 times. However, we have not been able to achieve the maximum amount of reproducibility of the process.

During the autopsy of B-series animals, in more than half of the cases (57.1%) we found no signs of diffuse peritonitis. Necrosis of the intestinal wall shrivelled (dry necrosis), limited to a local inflammatory process. In this case, the possible development of abdominal sepsis in 42.9% of cases was due to a decrease in the body's reactivity, rather than due to the aggressive effect of a microbial factor, which was insignificant. The use of a more

aggressive principle was required, which could cause a rapid progression of local necrosis, transferring it from coagulation to colliquation [6]. This prompted us to make changes to the technique of modeling abdominal sepsis by replacing a 10% calcium chloride solution with a 10% ammonia solution administered at a dose of 0.3-0.5 mL (series-C).

At the autopsy of the C-series animals, after 24 hours of observation, the focus of necrosis in the area of the dome of the cecum underwent autolysis with the leakage of purulent-fecal exudate into the free abdominal cavity.

Comparative characteristics of the reproducibility of different variants of experimental models of abdominal sepsis showed high values of positive results among animals of the C-series (Table). The reproducibility rate of abdominal sepsis was 28.5% higher than among Series-A and Series-B animals. At the same time, mortality among the C-series animals was minimal.

Table

Comparative Characteristics of Reproducibility of Different Variants of Experimental Models of Abdominal Sepsis

	SERIES OF EXPERIMENTS		
	A (n=7)	B (n=7)	C (n=7)
Reproducibility of the primary focus	0 (0)	4 (57,1%)	7 (100%)
Reproducibility of peritonitis	7 (100%)	3 (42,9%)	6 (85,7%)
Reproducibility of sepsis	3 (42,9%)	3 (42,9%)	5 (71,4%)
Start of reproducibility (hours)	3,5±2,7	18,9±5,9	24,6±2,1
Process regression	0 (0)	4 (57,1%)	1 (14,3%)
Mortality within 24 hours	7 (100%)	2 (28,6%)	1 (14,3%)

DISCUSSION

At the turn of the last century, the German scientist R. Pfeiffer was the first to isolate the products of pathogenic microorganisms – endotoxins. However, their activity and role in the development of inflammation were determined only in the 1940s by the French microbiologist André Boivin [8].

It has been determined that the so-called "endotoxins" are chemical compounds of fat, protein and carbohydrate substrates that have been found in the membrane membranes of gram-negative bacteria. They are called "lipoprotein carbohydrate complexes". The isolation of these complexes allowed scientists to study their effect on the development of sepsis. In particular, various groups of scientists led by Borden et al. and Braude et al. were able to identify a direct correlation between gram-negative endotoxins and the development of sepsis. The resulting component, which provokes the development of an experimental model of sepsis, is called "lipopolysaccharide" [10, 29].

This model, based on the application of lipopolysaccharides, was the first attempt to develop a model of sepsis. The model is based on the concept that sepsis may not be caused by the pathogen itself, but is the end result of a host's response to bacterial products or endotoxins that have been administered intraperitoneally or intravenously. Endotoxins serve as a reasonable surrogate for bacteria, making the model easy to use and reproducible. However, the therapeutic drugs studied using this model were ineffective when introduced into clinical settings [31].

To understand why this occurs, it is necessary to consider that the innate immune system of rats and mice is activated after intraperitoneal or intravenous injections by an interaction between the bacterial product of lipopolysaccharides and the cell receptor CD14, which activate the "lost" receptors of monocytes and macrophages of the host. This process initiates both cellular signaling and transcription of inflammatory genes, leading to the production of inflammatory cytokines such as TNF-α, IL-1, and IL-6. The way in which lipopolysaccharides activate the cell receptor is very specific. Rodents, cats, and dogs are relatively resistant to endotoxins, while humans, rabbits, sheep, and primates show an increased response.

When the dose of lipopolysaccharides is large enough, rats/mice exhibit biochemical and physiological changes that resemble some fulminant human forms of gram-negative bacterial infections. This acute endotoxicemia occurs in rats/mice as systemic hypotension, impairs myocardial contractility, and increases circulating levels of TNF-α, IL-6. This reaction is the same as in human endotoxicosis, except for different temporal kinetics and magnitude of physiological changes. Compared to humans, rodents are significantly less sensitive to the toxic or lethal effects of lipopolysaccharides, and therefore need higher doses of lipopolysaccharides to exert effects. Some factors present in rodent serum can neutralize cytokine production, which could explain the differences, but the nature of these factors is still unclear [39].

Thus, the discrepancy in lipopolysaccharide sensitivity between rats and humans suggests that the findings from such models of sepsis may not be applicable to human disease.

Another fundamental difference between the lipopolysaccharide model and human sepsis is the cytokine release profile. In animals, bolus injection of endotoxin usually causes an acute but transient increase in pro-inflammatory cytokines such as TNF-α, IL-1, and

IL-6. At the same time, in the reproduction of the experimental model, in which ligation and perforation of the cecum is performed, the septic reaction of the body is already caused directly by live bacteria. This leads to a lower, but at the same time, long-lasting detection of the level of pro-inflammatory cytokines in the blood. The same reaction occurs in abdominal sepsis and in clinical settings. However, in the evaluation of hemodynamic disorders, in animals with this experimental model of abdominal sepsis, hypodynamic states with a decrease in cardiac output and an increase in peripheral resistance were revealed. At the same time, in clinical practice, from the point of view of the development of sepsis as a result of endotoxicosis, we deal with hyperdynamic states of the body [32].

Thus, the results obtained in the simulation of abdominal sepsis with the lipopolysaccharide effect of endotoxins, by ligation and perforation of the cecum dome, do not allow us to accurately reflect the pathogenetic mechanisms of sepsis development that take place in clinical practice.

Since the first half of the mid-20th century, the attention of scientists has shifted from the endotoxic theory of the origin of sepsis to the bacterial one. More and more often there were publications describing cases of modeling abdominal sepsis by intra-abdominal injection of fecal granules. These granules were inoculation into gelatin capsules of fecal matter and adjuvant substances, which were placed in the abdominal cavity. Adjuvant substances, in particular barium sulfate, acted as a barrier to the rapid degradation of the seed, which prolonged the reaction of the macroorganism. It should be noted that these techniques were first used to study the differences between peritonitis and abdominal abscesses.

In the process of modeling abdominal sepsis using fecal granules, a phase process occurs. In the first phase, after inoculation of the gelatin capsule into the abdominal cavity, the animals develop septic shock. The mortality rate in this phase is up to 40% during 1-3 days of modeling. At the same time, during the study of hemoculture, mainly aerobic bacteria (E. coli and Enterococcus) were obtained. In the following 24 hours, the second phase of the experimental model developed, in which the presence of abscesses in the abdominal cavity could be detected in animals for 6-7 days. Microbiological inoculation of abscesses revealed a predominance of anaerobic bacteria, in particular B. fragilis and F. varium [1].

In general, the model using fecal granules allows for studies of abdominal abscesses after peritonitis, which in reality does not correspond to the purpose of modeling abdominal sepsis. [4]. It has also been proven that mortality under the conditions of reproduction of this experimental model depends on the type of feces, which in turn depends on the diet and feeding regime of the animal [1].

Therefore, in terms of achieving an experimental model of abdominal sepsis, this model is unmanageable and non-reproducible.

Thus, there was still a need for scientists to develop new models of abdominal sepsis that took advantage of certain qualities and numbers of bacterial populations, which prompted researchers to look for new models. Since then, well-established models of bacterial culture have been developed.

Certain models of bacterial inoculum involve intraperitoneal inoculation of known amounts of bacteria mixed with fecal material or adjuvant substances [2].

The mortality of these models depends on the number of bacteria administered, the route of administration (intravenous, intratracheal, or intramuscular), and the fluids and antibiotics used. Even though these models are controllable and reproducible, they have drawbacks [7].

For example, when high doses of bacteria are administered, they do not colonize and cannot multiply in the host because they are immediately lysed by the complement system. Thus, endotoxemia rather than sepsis is created, so the bacterial culture must be administered with adjuvant substances that prevent its degradation [18].

Coliform bacteria and anaerobes, which are already defined by fecal patterns, play different roles. In 1976, Onderdonk and his colleagues implanted mice with different types of bacteria, either individually or in combination. They demonstrated that only E. coli resulted in fulminant sepsis with early mortality, while mice treated with a combination of E. coli and B. fragilis developed more intra-abdominal abscesses [26].

This result was confirmed in subsequent experiments, e.g., by Verweij et al. in 1991 [20].

In 2011, a group of scientists led by Bauer developed a model of peritonitis, in which the pathology of the cecum played a leading role [16].

In an attempt to overcome the shortcomings of different models, they characterized a rat model of abdominal sepsis based on an intra-abdominal injection of a certain volume of feces that was obtained from three healthy non-vegetarian donors. To standardize the protocol, they used aliquots from only one processed batch of frozen human stool to conduct all experiments, resulting in relatively low variability in terms of source of infection.

Technically, the model is relatively simple to perform, which reduces the internal variability of the surgical procedure. In the first step, a stool suspension at a dose of 1.75 ml/kg body weight was diluted (1:4) in saline and a 21G cannula was injected into the abdominal cavity. Animals in the comparison group received the same volume of saline. Survival analysis, clinical status assessment, hemodynamic assessment, blood count, cytokine determination, rotational thromboelastometry, intravital microscopy, and liver histology were performed. 40 hours after the simulation of abdominal sepsis, none of the animals survived.

Hemodynamic analysis showed a decrease in mean arterial pressure, baseline arterial excess, and $PaCO_2$ with a concomitant increase in lactate levels. This biological profile clearly indicated the presence of respiratory-compensated metabolic acidosis. Liver analysis revealed marked hepatocellular dysfunction with decreased serum albumin levels in rats with abdominal sepsis, followed by degradation of hemostatic capacity. Parallel intravital liver microscopy revealed sinusoidal perfusion 5 h after reproduction of abdominal sepsis, but a 3-fold increase in the number of non-perfusion sinusoids was observed, which was probably due to the interaction of leukocytes with the endothelium. As expected, the reproduction of the experimental model of peritonitis ended with an increase in the levels of IL-6 and IL-10.

The proposed model demonstrated key features: it showed hemodynamic and physiological changes similar to those in human abdominal sepsis, it is reproducible, independent of the researcher, and can be standardized. In a similar method, a model of cecum ligation in intra-abdominal feces obtained during autopsy of healthy rats is suspended in liquid form and injected into the abdominal cavity. The results showed hemodynamic and physiological changes comparable to sepsis occurring in clinical practice. This model was also investigated by Lee et al., who analyzed the effects of increasing the volume of peritoneal injections of cecum suspension and demonstrated dose-dependent mortality [19].

Polymicrobial sepsis is induced by intraperitoneal injection of cecum contents in the form of a suspension obtained from various donor rats. The total volume of such cecum suspension (5.0, 7.5, 10 and 15 ml/kg) is administered through an incision along the midline of the abdomen, up to 0.5 cm long, and the survival rates occurring at different doses are compared. Animals of the comparison group are injected with the same amount of saline. Polymicrobial sepsis was confirmed by blood cultures of the recipient, which showed the presence of Enterococcus faecalis or Enterococcus gallinarum. All rats in the 0.5 mL/kg group survived for 14 days, while all rats given 15 mL/kg died within 24 h. In addition, 5 of the 30 rats (16.7%) treated with 7.5 mL/kg died within 48 h, with an overall mortality of about 40% within 14 days. These data support the dose-dependent mortality of this model of abdominal sepsis with intestinal contents.

The first surgical models of abdominal sepsis were developed in the late 1960s and early 1970s. Bacterial contamination of the abdomen is the most common cause of abdominal sepsis in humans. This may be a consequence of the failure of the intestinal anastomosis sutures after surgery with an intraperitoneal outpouring of a large number of microorganisms present in the intestine (for this reason, such an infection is in principle considered polymicrobial). Abdominal sepsis is characterized by extensive peritoneal infiltration of neutrophils and macrophages, which constitute the first line of defense to kill bacteria. However, if they fail to limit the diffusion of peritoneal bacteria, they can enter the bloodstream and activate a cascade systemic immune response through the production of pro-inflammatory mediators such as cytokines, often leading to multi-organ dysfunction, septic shock, and death [22].

There is also an experimental model of abdominal sepsis based on devascularization of the intestinal segment (modeling of necrosis of the intestinal segment). The technique consisted of ligating the cecum below the ileocecal valve, while avoiding interruption of the intestinal patency. The devascularized cecum undergoes necrosis followed by transmural infection and the establishment of a septic scenario, but the results in terms of sepsis are not very clear [11].

The stability of the model has been questioned and is not very reproducible due to the uncontrolled number of bacteria in the gut, as well as the exact timing of intestinal damage.

In 1979, S. Keith et al. [34] demonstrated that cecum ligation alone did not lead to sepsis, but to abdominal abscesses without sepsis in 71 mice. To solve this problem, they proposed a new model of ligation and puncture of the cecum to improve on previous models. This technique is based on puncture of the cecum after its ligation below the ileocecal valve to obtain continuous bacterial contamination of the abdominal cavity. Their experiment showed that with the help of this model, it is possible to obtain the effective development of abdominal sepsis. In addition, this approach leads to polymicrobial bacteremia, which is consistent with the same bacteria isolated at the site of infection and with the clinical signs of

abdominal sepsis (fever, lack of appetite, and lethargy). This model shows the onset of peritonitis with polymicrobial flora as well as devitalized/ischemic tissue, thus mimicking clinical conditions such as appendicitis and diverticulitis [30].

All subsequent models were inspired by the puncture and ligation of the cecum, which still represents the gold standard of abdominal sepsis models. The lethality in this model and the increase in inflammatory mediators (IL-6 and TNF-α) depend on various factors, such as the diameter of the needle, the number of perforations, the length of the bound cecum, possible infusion, and antibiotic therapy [35].

The ability to modulate the severity of abdominal sepsis using these multiple variables was evaluated as an advantage of the model. However, in order to obtain consistent results, there was a need to standardize procedures. Versatility also represented a weakness of the model due to the lack of controllability due to the large number of variables. It has also been criticized for causing either fulminant sepsis or intra-abdominal abscesses in survivors, not always providing the clinical picture of generalized peritonitis [15].

Since the first model of cecum puncture and ligation described in 1979, various versions have followed, highlighting that it is still the gold standard despite the fact that 45 years have passed [13].

In 1997, Zantl et al. developed a model of abdominal sepsis with an ascending colon stent based on the insertion of a stent into the ascending colon. The idea behind this model is based on the principle of the failure of anastomotes, which lead to peritonitis followed by septic shock and death. It has been observed that as the diameter of the stent increases, so does the mortality rate. The 14-gauge (G) stent resulted in 100% mortality, while the 18-G stent caused 68% mortality, and the 22-G stent was fatal in 25% of experimental animals [21].

The model of abdominal sepsis with an ascending colon stent leads to organ dysfunction, as in patients with sepsis, and causes damage to the kidneys, lungs, and medullaries with the production of IL-1 or IFN-γ, as well as independent survival of TNF-α [25].

Maier et al. compared models of abdominal sepsis with ascending colon stent and puncture with cecal ligation, and demonstrated that mortality was directly proportional to the diameter of the stent, but not to the number of punctures. In addition, in the model of abdominal sepsis with an ascending colon stent, there is a high, persistent increase in cytokines compared to puncture and ligation of the colon. Laparotomy performed 24 h later showed that in the model of abdominal sepsis with an ascending stent of the colon, fecal loss persists for a long time, while in puncture and ligation of the cecum, there is buffering of the focus with the formation of early iliac adhesions. The results obtained again revealed the pattern of intra-abdominal abscess formation with minor signs of systemic inflammation [14].

The disadvantage of the ascending colon stent model of abdominal sepsis, however, is that the bacterial contamination is continuous and uncontrollable.

To further investigate the pathophysiological mechanisms of abdominal sepsis, Zantl et al. later refined their model by creating a model of surgery after colon stenting surgery to determine whether surgical removal of the septic lesion would prevent death after induction of peritonitis, and if so, for how long. In this model, a relaparotomy is performed with stent removal and suturing of the defect on the cecum at a standard time (after 3, 5 and 9 hours), which mimics what is actually done in clinical practice for peritonitis. Removal of the stent after 3 hours resulted in a 100% survival rate, while relaparotomy after 9 hours showed a 100% mortality rate. Surgery after five hours resulted in average mortality rates. These results clearly showed that critical pathophysiological events occur between 3 and 9 hours after the simulation of abdominal sepsis and develop independently of continuous bacterial contamination of peritoneal drainage [21].

In 2009, Scheiermann et al. created a model of ligation and incision of the cecum to reflect severe sepsis, characterized by acute onset and high mortality. In this model, a cecum ligation is performed and a 1.5 cm incision is made to establish continuous leakage of feces, which is directly inspired by the model of puncture and ligation of the cecum. They also wanted to get acute and severe abdominal sepsis, as in endotoxin models, while overcoming their artificiality [12].

In 2013, a model of ligation and dissection of the cecum was created, based on clamping of 2 mm of the terminal part of the cecum and its section after binding. A standardized amount of faeces (2 mm^2) is excreted in the abdominal cavity. The stump is left in the abdominal cavity and then a relaparotomy is performed, with the removal of a piece of cecum, which by this point is necrotic, followed by antibiotic therapy. This model was aimed at simulating what is happening in clinical reality as accurately as possible. According to the guidelines, abdominal sepsis caused by intestinal perforation or failure of anastomosis sutures should be treated surgically with concomitant antibiotic therapy. This model is very

novel in that it has a standardized amount of loose stool in the abdomen and a free necrotic stump that cannot be encapsulated [15].

Thus, the main reason for investigating different animal models of abdominal sepsis is to develop treatments in a clinical setting. However, clinical trials should take into account all possible caveats of the model used. Animal models are essential to scientific progress in many areas of human health, but if they are not well characterized and understood, erroneous conclusions can be drawn that hinder scientific progress and result in the loss of animal life.

A well-designed animal model requires a thorough understanding of the similarities and differences in human and animal physiology and should incorporate knowledge into the objectives of the study. It must be remembered that any use of experimental animals must take into account the welfare of the animals. All of this points to the need to provide a systematic basis for the development of more appropriate experimental models for the study of abdominal sepsis.

CONCLUSION

Thus, the model of abdominal sepsis developed by us made it possible to achieve the formation of a number of pathogenetic mechanisms that have a reasonable place in clinical practice: achieving the development of the primary focus of the purulent-inflammatory process without opening or puncturing the intestinal cavity, in which only feces enter the abdominal cavity and toxic shock develops; To achieve a change in the body's reactivity, which made it possible to achieve the development of all phases of sepsis (from systemic inflammatory response syndrome to severe sepsis), without regression of the inflammatory process, as a result of its limitation.

Ethical component - The planned experimental studies, which included sampling, biopsies and autopsies, were based on the principle of the conditions specified in the Council of Europe Convention for the Protection of Animals of 1986.

Conflict of interest – no

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ABDOMINAL SEPSISNING YANGI EKSPERIMENTAL MODELI ISHLAB CHIQISH VA SAMARADORLIGINI BAHOLASH

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ABSTRAKT

Dolzarbligi. Patologik jarayonlarni modellashtirishdan asosiy maqsad – davolash usullarini ishlab chiqish va klinik moslamalarga kiritishga qaratilgan translyatsion tibbiyotning butun bog'lanish muammosini hal qilishdan iborat.

Material va usullar. Tadqiqot eksperimental bo'lib, Wistar liniyasining ikkala jinsining 40 ta kalamushda amalga oshirilgan. Hayvonlarda qorin bo'shlig'ining turli xil abdominal sepsis, shu jumladan biz tomonidan ishlab chiqilgan usul bilan solishtirildi.

Natijalar. Abdominal sepsis eksperimental modellarining turli xil variantlarini takrorlanishining solishtirma xususiyatlari C-seriyali hayvonlar orasida ijobiy natijalarning yuqori qiymatlarini ko'rsatdi. Qorin bo'shlig'i sepsisning takrorlanish darajasi Series-A va Series-B hayvonlariga nisbatan 28,5% ga ko'p bo'lgan. Shu bilan birga, C-seriyali hayvonlarning o'limga olib kelishi minimal edi.

Xulosa. Qorin bo'shlig'i sepsis modelining taklif qilingan varianti klinik amaliyotda oqilona o'ringa ega bo'lgan bir qator patogenetik mexanizmlarning shakllanishiga erishish imkonini beradi.

Tayanch iboralar: Qorin bo'shlig'i sepsis, tajriba modeli, peritonit

РАЗРАБОТКА И ОЦЕНКА ЭФФЕКТИВНОСТИ НОВОЙ ЭКСПЕРИМЕНТАЛЬНОЙ МОДЕЛИ АБДОМИНАЛЬНОГО СЕПСИСА

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АБСТРАКТ

Актуальность. Основная цель моделирования патологических процессов сводится к решению проблемы целого звена трансляционной медицины, которая направлена на разработку методов лечения и внедрения их в клинические условия.

Материал и методы. Работа носит экспериментальный характер и была проведена на 40 крысах обоего пола линии Вистар. У животных моделировали различные варианты абдоминального сепсиса, включая разработанную нами методику.

Результаты. Сравнительная характеристика воспроизводимости различных вариантов экспериментальных моделей абдоминального сепсиса показала высокие значения положительных результатов среди животных серии-С. Уровень воспроизводимости сепсиса был выше на 28,5% чем среди животных серии-А и серии-В. При этом летальность среди животных серии-С была минимальной.

Заключение. Предложенный вариант модели абдоминального сепсиса, позволяет достичь формирования ряда патогенетических механизмов, имеющих обоснованное место в клинической практике.

Ключевые слова: Абдоминальный сепсис, воспроизведение экспериментальной модели, перитонит