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Histological Changes in the Intestinal Wall in Experimental Obstructive Ileus: Experimental Animal Study

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Abstract **Background:** Patients with obstructive bowel obstruction often develop severe infections, which can lead to death in 45-88% of cases. These complications are thought to be caused by bacteria in the intestine. However, treatments that affect these bacteria have not helped to reduce the number of complications. It is important to find other possible sources of infection in intestinal obstruction. The experiment was done to study how the intestinal wall changes during 48 hours of obstruction. **Methods:** The experiment was conducted on 13 white rats. The animals were separated into two groups. In the first (control) group, 5 rats experienced a laparotomy (abdominal incision) without affecting the intestines. In the second group, eight rats had their small intestine ligated after laparotomy to cause a complete blockage. Then the abdomen was sutured and after a specific time, the intestines were examined after 12, 24, 36 and 48 hours. **Results:** The results showed no changes in the control group. The histological examination revealed that the average thickness of the intestinal mucosa was 0.48±0.02 mm and the muscle layer was 0.92±0.02 mm. Healthy enterocytes with a clear structure were observed. In the group with intestinal obstruction, after 12 hours, the intestine dilated to 6-9 mm above the obstruction site and fluid appeared in the abdominal cavity. After 48 hours, the intestine became 2.5 times wider, blue-purple in colour and cloudy in fluid. The study showed that there were no changes in the control group. However, in the group with obstructive obstruction, purulent inflammation of the intestine began within 12 hours. It first appeared on the mucous membrane because the protective layer of the villi was damaged. Then, the inflammation spreads to the muscle and serous layers. Inflammation happened not only at the place of the blockage but also in the part of the intestine above it. **Conclusions:** The source of purulent complications in intestinal obstruction involves both intestinal microbes and structural damage to the bowel wall above the blockage. These findings underscore the need for early surgical intervention and strategies to protect the intestinal barrier, not just target the microbiota.

Key Words Obstructive Intestinal Obstruction, Intestine, Experiment, Complications, Histology, Bacteria

INTRODUCTION

Acute Bowel Obstruction (ABO) is a serious problem that often leads to complications and even death. Doctors and scientists are looking for new treatments to reduce patient risks.

After surgery, the mortality rate in patients with APN exceeds 17% and does not decrease [1,2]. One of the leading causes of complications is purulent infections, which occur in 45-88% of cases [3]. For example, postoperative peritonitis occurs in 35-56% of cases [3], anastomotic problems in 6.2-17.5% and postoperative wound suppuration in 2.7-37.8% [4-6].

Some studies indicate that purulent complications may be caused by the microflora in the intestine [5-9).

Doctors use various methods to reduce the number of purulent complications. These include naso-intestinal intubation, when a tube is inserted through the nose to remove the contents of the intestine, bowel lavage during surgery [7] and the administration of antibiotics through a probe [4,8,9]. Also, some researchers believe broad-spectrum antibiotics should be administered intravenously for prevention rather than treatment [7].

However, all these methods have some problems. For example, naso-intestinal intubation can damage the intestinal lining and it has not been proven to work well. The use of

antibiotics through a probe is also debated, as there is no agreement on which drugs and doses to use [2,3,4,6,9].

Because there is a high risk of death after surgery for APNs, more research is needed to understand why infections happen and to find better ways to stop them.

Postoperative intestinal obstruction is a common and serious problem. Researchers are studying how it happens with both clinical cases and animal studies. Many treatments have been tested to prevent or reduce this condition [8-11).

Ileus usually means food and liquids cannot move properly through the intestines. Most studies focus on patients after surgery [12]. Small bowel obstruction is one of the main reasons for emergency surgery [13,14]. If not treated, it can lead to serious problems like organ failure. It can also change the bacteria in the gut and damage the intestine [15,16].

Studies show that in intestinal obstruction, the cells in the intestine begin to break down. The mucous membrane becomes more permeable within 3 hours of the disease. First, peristalsis works quickly, but then it slows down [8,17].

Bacteria growing too fast in the small intestine can cause digestion problems. However, the exact process is not fully understood. Treatment often uses broad-spectrum antibiotics. For example, Saffouri *et al.* [18] showed that a low-fiber diet can change the gut bacteria and cause problems with digestion.

Scientists have found that bacteria in the intestines change during obstruction. In studies with mice, Bacillota decreased and Pseudomonadota and Bacteroidota increased [19]. When the obstruction is complete, Bacillota decreases even more, while Pseudomonadota, Verrucomicrobia and Bacteroidota increase. This harms the intestine's function and makes it more vulnerable to infection [15].

If the ileus continues, fluid and gas build up in the intestine. This causes the intestine to stretch and swell, leading to serious problems like inflammation, sepsis, or complete blockage. Wang *et al.* [20] found that the bacteria in the gut change during obstruction. This could help doctors choose the right antibiotics for patients with complications after surgery.

It is also known that certain receptors (TLR4) damage the intestinal barrier after surgery. If bacteria begin to grow uncontrollably, they can enter the blood and cause inflammation. This can happen in two ways: through gaps between the cells (paracellular route) or directly through the cells (transcellular route). In the transcellular way, bacteria enter cells using unique molecules or by diffusion [21].

Animal studies show that acute intestinal obstruction can allow bacteria to enter the blood. These bacteria can travel to the upper small intestine [22]. The central part of gram-negative bacteria, lipopolysaccharide (LPS), is a potent toxin that can cause sepsis. LPS can be found in the blood not only in bacterial infections but also in fungal infections. Infections damage the intestinal barrier [13,23]. Researchers have shown that the breakdown of the intestinal barrier and the entry of bacteria into the blood is an important factor in sepsis development during intestinal obstruction.

Many processes in the gut affect how the body reacts to toxins. One of the main ways is through inflammation, which can harm internal organs [13,24,25]. Other diseases can worsen these problems [26-29].

Current research seeks new ways to prevent and treat infections in patients with postoperative intestinal obstruction. For example, Hartmann *et al.* [30] showed that preparing the bowels before surgery can lower the risk of infection and inflammation. However, other studies, like Hegde *et al.* [19], show that antibiotics do not significantly affect inflammation during intestinal obstruction.

Research on postoperative intestinal obstruction aims to identify the factors that contribute to the development of complications, particularly infections and inflammation. In this context, special attention is given to changes in the gut microbiota and structural alterations in the intestinal wall [33]. Disruption of the mucosal, muscular and serous layers creates conditions for bacterial translocation into the bloodstream, which can lead to severe postoperative complications such as sepsis [34].

In animal studies, it has been found that significant morphological changes occur in the intestine just hours after obstruction [35]. Specifically, increased mucosal permeability allows bacteria and toxins to enter the bloodstream [36]. Additionally, inflammation leads to the disruption of normal intestinal function and changes in the microbiota composition, which may contribute to the development of serious infections [37].

These results highlight the importance of studying not only the microbiota but also the structural changes in the intestinal wall, as damage to the intestinal barrier function is one of the main mechanisms underlying postoperative complications [38]. A deeper understanding of these processes allows for the development of new strategies to improve the treatment of patients with postoperative intestinal obstruction and reduce the risk of sepsis and other severe complications [39].

In conclusion, postoperative intestinal obstruction can lead to profound changes in the intestine. It disrupts the balance of bacteria and causes inflammation. The bacteria in the large intestine are also greatly affected. More research is needed to find better ways to prevent and treat these complications.

The aim of the article is to study how the intestinal wall changes during obstruction and understand where infections might occur.

Objectives of the study:

- To achieve the goal, there is a need to:
- Induce intestinal obstruction in white rats in the laboratory
- Study how the structure of the intestine changes in this process
- Determine what changes occur in the intestinal wall
- Find out what causes purulent complications in obstruction
- To identify a causal relationship between these changes and the development of purulent complications

METHODS

The study was conducted on 13 white rats, divided into control (5 rats) and experimental (8 rats) groups. The division of subjects into these groups was based on the intended comparison of obstructive ileus versus healthy controls. However, the sample size was not calculated a priori, which limits the statistical power of the study. Rats with pre-existing gastrointestinal issues or other health conditions were excluded from the study to minimize confounding factors. The control and experimental groups were subjected to the same environmental conditions, including temperature and humidity, to ensure consistency throughout the experiment. The first group (5 rats) underwent an operation on the abdomen (laparotomy) but did not touch the intestines. The wound was then sutured.

The second group (8 rats) also underwent a laparotomy, but the intestine was additionally clamped with a thread to create an obstruction. The wound was then sutured.

After 12, 24, 36 and 48 hours of strong anaesthesia, the animals were removed from the experiment. The study was conducted in accordance with international standards "European Convention for the Protection of Pet Animals" [31] and the Law of Ukraine "On the protection of animals from cruelty" [32]. Postoperative pain management for experimental animals was carried out following ethical guidelines and established protocols to minimize discomfort and ensure animal welfare throughout the study.

At the end of the experiment, the condition of the intestine was checked: Its appearance, size, presence of fluid in the abdominal cavity and characteristics. Two pieces of intestine were taken from the animals of the second group: one 1 cm above the place of clamping, the other 1 cm below the duodenum. Changes in intestinal tissue were analysed after 12, 24, 36 and 48 hours. Intestinal samples were also taken from the control group for comparison. Inter-rater reliability in the histological assessments was ensured through blinded evaluations by multiple pathologists, who independently analyzed the tissue samples without knowledge of the group assignments. To minimize bias and ensure consistency, predefined histological scoring criteria were used and discrepancies in assessments were resolved through consensus meetings.

Data were analyzed using descriptive statistics. Histological data were compared between the control and experimental groups at each time point using appropriate statistical tests (ANOVA) to assess the significance of observed differences. A p-value of <0.05 was considered statistically significant.

RESULTS

In the control group, no pathological changes in the intestine were detected.

In animals with obstruction, after 12 hours, the intestine above the constriction expanded to 6-8 mm and the membrane was shiny. The intestine below the constriction was flattened. There was a small amount of clear fluid in the abdominal cavity; 24 hours later, the intestine above the constriction did not change in size but became cyanotic. Below the constriction, it remained turgid and shiny; 36 hours later, a cloudy, foul-smelling effusion appeared in the abdominal cavity. The intestine above the clamping point became blue-purple. Below the constriction, it expanded slightly but looked normal; 48 hours later, dark spots appeared on the intestine above the constriction and the membrane became dull. The abdominal effusion became thicker and cloudy, smelled of intestinal bacteria and contained fibrin.

Analysis of Intestinal Tissues

In the control group, the thickness of the mucous membrane was 0.48±0.02 mm and the muscle layer was 0.92±0.02 mm (Figure 1). The height of the villi was 2.5 times greater than the depth of the crypts. The primary cells of the crypts were cylindrical cells, including goblet cells and Paneth cells (5.02±1.04 per crypt). The crypts also contained dividing cells (4.52±0.51 per crypt).

The villi epithelium had 163.05±17.39 intraepithelial lymphocytes per 1000 epithelial cells. The lamina propria had mostly loose fibrous tissue with 16.02±4.52 small lymphocytes per villus.

After 12 hours of intestinal obstruction, the villi thickness increased to 0.137±0.012 mm. Compared to the crypts, their size decreased to 1.9:1 and the diameter of enterocytes with a brush border dropped to 28.68±0.52 µm.

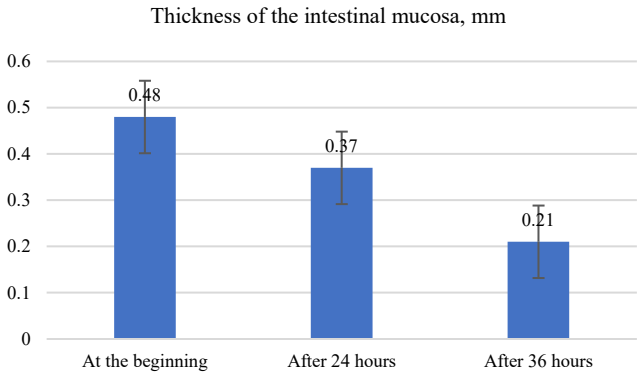

Figure 1: Changes in the thickness of the intestinal mucosa during the experiment

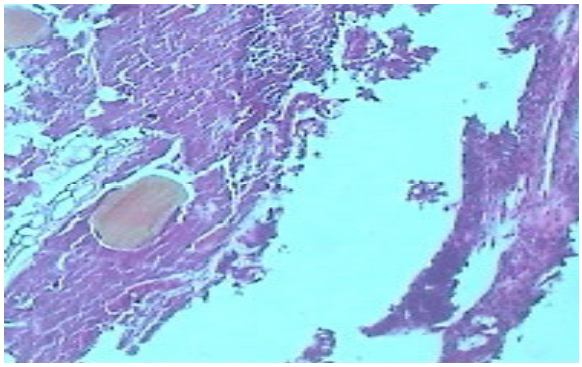

Figure 2: Intestinal wall structure after 48 hours: complete necrosis of a part of the wall. Hematoxylin and eosin staining, magnification ×100

The muscle layer stayed the same at 0.92±0.04 mm. The brush border was hard to see and bacteria began to gather on the epithelium. Goblet cells were found only at the bottom of the villi and were fewer than enterocytes, with a ratio of 1:3. Mitoses in the crypts were 5.62±0.19 and Paneth cells were 5.68±0.11. Lymphocytes in the mucosa increased to 185.02±29.05 per 1000 epithelial cells. Severe edema separated the villi from the epithelium and neutrophilic leukocytes appeared, some of which penetrated the villi.

After 24 hours, the intestinal mucosa thinned to 0.37±0.05 mm due to the intestine stretching above the obstruction. The villi thickened, but their epithelium was damaged and many bacteria appeared on their surface.

After 36 hours, the mucosa was severely damaged. The epithelium was almost gone and bacteria were everywhere. Leukocytes penetrated the villi and bacteria reached the submucosal layer. The mucosa thickness dropped to 0.21±0.12 mm. Microvessels were dilated in the submucosa and serosa with leukocytes at the edges, blood stagnation and leukocyte-fibrin thrombi.

After 48 hours, the villi were almost impossible to measure due to the complete loss of epithelium, heavy leukocyte presence and bacteria spreading into the submucosal layer. Ulcers formed, destroying much of the muscle layer, surrounded by dense leukocyte infiltration. The serosa was swollen with many leukocytes and the vessels had blood clots of leukocytes and fibrin. Large amounts of fibrin, leukocytes and bacteria were on the serous surface, indicating damage to the intestinal wall. Some vessels in the serosa had bacterial colonies.

Two animals had the most severe inflammation after 48 hours (Figure 2). All layers of their intestines were destroyed, with many ulcers and necrotic areas.

The severity of inflammation and tissue damage increased progressively with time, with significant degradation of the intestinal mucosa and epithelial layers observed by 48 hours. The extensive leukocyte infiltration, bacterial presence and ulceration of the intestinal wall suggest that bacterial translocation and the breakdown of the intestinal barrier contribute significantly to the observed purulent complications in obstructive ileus.

DISCUSSION

A global study (1990-2020) showed intestinal obstruction is a common acute surgical condition. The incidence has increased from 56.9% to 86.7% [3]. The authors say that older people are at higher risk of illness and death. They also note that intestinal obstruction puts a heavy burden on the healthcare system. In the United States, 350,000 patients with ileus are hospitalised each year: 65% of cases are caused by adhesions, 10% by hernias, 5% by tumours and 20% by other causes [2].

The literature shows that purulent complications are the main cause of death in obstructive ileus. Some authors believe that this is caused by bacteria in the intestine. Therefore, researchers have proposed treatments to reduce the number of bacteria in the intestine [6,9]. However, these methods have not reduced the number of complications or improved treatment outcomes.

Treatment methods should be based on experiments. Many studies have shown that during mechanical ileus, the intestinal mucosa is the first to be damaged [6,9]. In one experiment, scientists gave animals probiotics to protect the mucosa. After 24-48 hours, they removed the intestinal obstruction and continued giving them probiotics. In animals without probiotics, bacteria entered the intestinal wall more easily, showing the importance of this research.

Experiments showed that the mucosa starts to break down within 3 hours of intestinal obstruction. Over time, this makes the intestine more permeable to proteins and slows down peristalsis [8,9].

To learn more about these changes, scientists created a model of progressive ileus. A key process in acute intestinal obstruction is the loss of normal intestinal microflora [1].

Histological studies showed that 12 hours after intestinal obstruction, inflammation appears in the mucous membrane. The protective layer of villi is destroyed, bacteria enter and the body responds with inflammation. This is accompanied by swelling and poor circulation. Bacteria and leukocytes in the intestinal wall indicate the onset of a purulent process. Purulent inflammation spreads to the entire intestine above the obstruction.

After 24 hours, the inflammation becomes purulent. After 36 hours, it reaches the muscle layer but does not touch the serous membrane.

After 48 hours, all layers of the intestine are destroyed and fibrinous-purulent peritonitis appears on the serous membrane.

Experiments have shown that in obstructive ileus, inflammation covers the entire intestine above the site of obstruction. As the disease progresses, phlegmonous enteritis develops.

Previously, researchers have studied only the intestinal wall near the site of obstruction [8,9]. Our study showed that purulent inflammation covers the entire proximal intestine.

Purulent inflammation begins after the brush border, which protects the intestine, is destroyed. Within 36 hours, it spreads to the submucosal and muscle layers. The serous membrane remains uninvolved. However, after 48 hours of experimental ileus, inflammation spreads to it.

Thus, the primary source of purulent complications in obstructive ileus is the microflora inside the inflamed intestinal wall, not the intestinal lumen. This is important because antibiotic therapy should be directed at the intestinal wall, not the lumen, in such patients.

After the cause of obstructive ileus is eliminated, the altered intestinal wall, not the microflora in its lumen, is the main source of purulent complications.

Thus, the primary source of purulent complications in obstructive ileus is the microflora inside the inflamed intestinal wall, not the intestinal lumen [40]. This is important because antibiotic therapy should be directed at the intestinal wall, not the lumen, in such patients [41]. Studies have demonstrated that bacterial translocation in obstructive ileus correlates with the degradation of the intestinal wall, with bacteria migrating from the intestinal lumen into the bloodstream as the intestinal barrier becomes compromised [42]. The progressive destruction of the intestinal wall creates favorable conditions for bacterial translocation, which contributes significantly to systemic infection and septic complications [43]. Furthermore, the timing of these changes is crucial, as bacterial translocation and wall degradation begin early in the course of ileus, highlighting the importance of early therapeutic intervention [44].

In addition to the observed histological changes and the progression of bacterial translocation in the model, better integration of these findings with established studies on postoperative complications and bacterial translocation is crucial [45]. Previous research has shown that bacterial translocation plays a pivotal role in the development of systemic infections, particularly in postoperative patients with intestinal obstruction [46]. However, further investigation into treatments such as antioxidants, probiotics, or specific antibiotics targeting intestinal inflammation is needed [47]. These interventions could potentially reduce the severity of complications by preserving the integrity of the intestinal barrier and reducing bacterial load, which would improve outcomes for patients with obstructive ileus [48]. The integration of such therapeutic approaches could provide valuable insights into potential strategies for reducing postoperative morbidity and mortality [49].

CONCLUSIONS

In the obstructive ileus experiment, the intestine's protective layer above the blockage is the first to break down. This allows normal bacteria to enter the wall of the intestine and cause harmful inflammation.

In cases of obstructive ileus, inflammation starts in the wall of the intestine above the blockage. Within 48 hours, it spreads through all the layers of the intestine, including the outer membrane. After the blockage is removed, the damaged intestine can still lead to serious infections. Early identification of intestinal damage and appropriate treatment can significantly reduce the risk of severe complications, including purulent inflammation and sepsis, ultimately improving patient outcomes.

Availability of Data and Material

The data will be available with the corresponding author and will be made available up on request via email.

Authors' Contributions

The authors confirm contribution to the paper as follows: study conception and design: Valentin Nepomnyashchy, Tamara Tamm, Konstantin Kramarenko; data collection: Ivan Mamontov, Olena Shakalova, Konstantin Kramarenko andrey Ustinov; analysis and interpretation of results: Valentin Nepomnyashchy, Tamara Tamm, Ivan Mamontov, Olena Shakalova; draft manuscript preparation: Valentin Nepomnyashchy, Tamara Tamm andrey Ustinov. All authors reviewed the results and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Statement

All animal experiments were conducted in accordance with the EU Directive 2010/63/EU for animal experiments. All efforts were made to minimize animal suffering and reduce the number of animals used, following the 3R principles (Replacement, Reduction and Refinement).

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