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PREVENTION OF ADHESIVE FORMATION UNDER EXPERIMENTAL CONDITIONS

ZAPOBIEGANIE POWSTAWANIU ZROSTÓW W WARUNKACH DOŚWIADCZALNYCH

Igor Deykalo[1(A,B,C,D)], **Roman Gorbatyuk**[2(A,B,C,E)], **Volodymyr Bukata**[1(A,C,D,E)],

Iryna Volch[3(B,D,E,F)], **Igor Grygus**[4(B,D,E)]

[1] Department of General Surgery, Ivan Horbachevsky Ternopil National Medical University, Ternopil, Ukraine
[2] Department of Mechanical Engineering and Transport, Ternopil Volodymyr Hnatiuk National Pedagogical University, Ternopil, Ukraine
[3] Department of Microbiology, Virology and Immunology, Ivan Horbachevsky Ternopil National Medical University, Ternopil, Ukraine
[4] Institute of Health, National University of Water and Environmental Engineering, Rivne, Ukraine

Authors' contribution
Wkład autorów:
A. Study design/planning
zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
wyszukiwanie i analiza literatury
G. Funds collection
zebranie funduszy

Summary

Background. Prevention of adhesions remains an urgent problem of abdominal surgery, despite the significant amount of research in this area. There are four areas in the prevention of adhesions: reduction of peritoneal injury, reduction of the inflammatory reaction in the area of operation, the effect of remedial drugs on the balance of formation and destruction of fibrin, and delimitation of damaged serous membranes by the formation of protective films on the mesothelium.

Material and methods. 84 laboratory mature white male rats, which were divided into 8 groups, were studied. The adhesion process was simulated with some groups using an anti-adhesive based on hyaluronic acid. On the 4th, 10th, and 30th day after the beginning of the experiment, the experimental animals were euthanized, the abdominal cavity was opened, and the visceral and parietal peritoneum and adhesions were examined through standard macroscopic and microscopic methods.

Results. During the correction of the simulated pathological process by Defensal, the number of adhesions decreased by 42.8%. The thickness of the adhesions under the influence of the above drug decreased by 3.5 times compared to the control group.

Conclusions. Studies and results show that a barrier drug such as Defensal has a positive effect on the course of experimental adhesive disease. During the use of this drug, the number of adhesions in the abdominal cavity significantly decreased, and the vast majority were filamentous, loose, easily separated, did not deform the lumen structure and almost did not change the digestive tract.

Keywords: macroscopy, morphometry, tissue adhesions, preventive medicine, experiment

Streszczenie

Wprowadzenie. Zapobieganie powstawaniu zrostów pozostaje pilnym problemem chirurgii jamy brzusznej, mimo znacznej ilości badań w tym zakresie. W profilaktyce zrostów można wyróżnić cztery obszary: zmniejszenie urazu otrzewnej, ograniczenie reakcji zapalnej w miejscu operacji, wpływ stosowanych w terapii leków na równowagę tworzenia i niszczenia fibryny oraz odgraniczenie uszkodzonych błon surowiczych poprzez tworzenie filmów ochronnych na mezotelium.

Materiał i metody. Badaniom poddano 84 dojrzałe samce białych szczurów laboratoryjnych, które podzielono na 8 grup. Proces tworzenia zrostów był symulowany, przy czym w niektórych grupach stosowano przeciwdziałające tworzeniu zrostów środki na bazie kwasu hialuronowego. W dniu 4, 10 i 30 od rozpoczęcia doświadczenia zwierzęta doświadczalne poddawano eutanazji, otwierano jamę brzuszną, a otrzewną trzewną i ścienną oraz zrosty badano standardowymi metodami makroskopowymi i mikroskopowymi.

Wyniki. Podczas korekty symulowanego procesu patologicznego za pomocą Defensal liczba zrostów zmniejszyła się o 42,8%. Grubość zrostów pod wpływem powyższego leku zmniejszyła się 3,5-krotnie w porównaniu z grupą kontrolną.

Wnioski. Badania i wyniki wskazują, że lek barierowy jakim jest Defensal ma pozytywny wpływ na przebieg powstawania zrostów w warunkach doświadczalnych. W trakcie stosowania tego leku w jamie brzusznej znacznie zmniejszyła się liczba zrostów, a zdecydowana większość była nitkowata, luźna, łatwo oddzielająca się, nie zniekształcała struktury światła i prawie nie zmieniała przewodu pokarmowego.

Słowa kluczowe: makroskopia, morfometria, zrosty, medycyna zapobiegawcza, eksperyment

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Address for correspondence / Adres korespondencyjny: Igor Grygus, Institute of Health, National University of Water and Environmental Engineering, 11 Soborna St., 33028 Rivne, Ukraine, e-mail: grygus03@ukr.net, phone: +38 (036) 263-30-98
ORCID: Igor Deykalo https://orcid.org/0000-0002-0095-4862, Roman Gorbatyuk https://orcid.org/0000-0002-1497-1866, Volodymyr Bukata https://orcid.org/0000-0001-9638-1052, Iryna Volch https://orcid.org/0000-0002-7333-3354, Igor Grygus https://orcid.org/0000-0003-2856-8514

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Introduction

The process of adhesions is a protective reaction of the body aimed at distinguishing the pathological process in the abdominal cavity [1-8]. This allows the body to cope with severe infectious or traumatic injuries of the abdominal cavity. On the other hand, the adhesion process is one of the main causes of acute intestinal obstruction, chronic abdominal pain, infertility and other complications. In recent years, the volume and nature of operations performed on the abdominal organs is growing worldwide. This inevitably leads to an increase in the incidence of peritoneal adhesions [1,9-16]. The incidence of intra-abdominal adhesions varies from 67 to 93% after general abdominal surgery and is almost 97% after open gynecological procedures [9,11,17-23].

Currently, the prevention of adhesions can be divided into four ways:

- reduction of peritoneal injury;
- reduction of the inflammatory reaction in the area of operation;
- the effect of the drug on the process of formation and destruction of fibrin;
- delimitation of damaged serous membranes by the formation of protective films on the mesothelium [2, 24-26].

Barrier drugs have become popular in recent years, and their effectiveness has been proven in many studies [12,24,27,28]. The most useful anti-adhesive drugs are compounds based on carboxymethylcellulose and hyaluronic acid, polysaccharides, which form a barrier between the organs of the abdominal cavity, preventing the deposition of fibrin on them and bonding [2,5,19,29,30].

Therefore, the purpose of our study was to determine the effectiveness of the use of the barrier drug, Defensal, in the prevention of the adhesion process under experimental conditions. Defensal is an anti-adhesion solution that affects the main links in the formation of adhesions through:

- separation of traumatized peritoneum surfaces during the critical period of adhesion formation (the first 5 days);
- reduction of the local inflammatory response in the area of operative treatment (anti-inflammatory and anti-exudative effect);
- antihypoxic and antioxidant effect.

Material and methods

Applying a set of morphological methods (macroscopy, histology, morphometry), we investigated abdominal adhesion in 84 laboratory mature white male rats of the Sprague Dawley type, weighing 172-180 g each, which were divided into 8 groups (Table 1). We also used Defensal, which was acquired at a local pharmacy.

Table 1. Groups of experimental animals

Number of the group of researched animals	The name of the group of experimental animals	Number of animals	Duration of the experiment, days	Using Defensal
1	Experimental animals in normal vivarium conditions (control)	6	30	-
2	Experimental animals that underwent laparotomy	6	30	-
3	Exerimental animals treated with a simulation of adhesion disease	12	4	-
4	Experimental animals treated with a simulation of adhesion disease	12	10	-
5	Experimental animals treated with a simulation of adhesion disease	12	30	-
6	Experimental animals treated with a simulation of adhesion disease	12	4	+
7	Experimental animals treated with a simulation of adhesion disease	12	10	+
8	Experimental animals treated with a simulation of adhesion disease	12	30	+

All manipulations and euthanasia of laboratory sexually mature white male rats were performed in accordance with the basic principles of working with experimental animals. The commission on bioethics of the Ternopil National Medical University named after I. Horbachevsky of the Ministry of Health of Ukraine (protocol No. 14 of October 18, 2017) did not reveal any violations of moral and ethical norms during the conduct of research work.

Simulation of the adhesion process in the abdominal cavity was performed according to a certain scheme [31]. After 4, 10 and 30 days from the beginning of the experiment, euthanasia of experimental animals was

performed, the abdominal cavity was opened, the visceral and parietal peritoneum were macroscopically examined, the number of adhesions between these peritoneums and the number of interstitial adhesions were counted and their thickness was measured. The excised pieces of the small intestine were fixed in 10% neutral formalin solution, passed through increasing ethyl alcohols and placed in paraffin. Microtome sections 4-7 μm thick after dewaxing were stained with hematoxylin eosin, according to Van Gizon. Morphometrically measured thicknesses of mucous, muscle, serous membranes and submucosal layer, width and depth of crypts, determined the relationship between them.

Results

A comprehensive analysis of the obtained data revealed that on the 4th day after modeling the pathological process, adhesions formed in the abdominal cavity of the experimental animals (Figure 1). The number of viscero-visceral adhesions in the abdominal cavity of white laboratory rats was 6.00±0.15, the number of intra-parietal adhesions was much smaller and reached 4.25±0.09 (Table 2).

Table 2. Quantitative characteristics of adhesions of the abdominal cavity of experimental animals without correction Defensal

Indicator	Observation group		
	3rd (4th day)	4th (10 days)	5th (30 days)
Internal-internal adhesions, number	6.00±0.15	3.75±0.12***	4.10±0.12***
Intra-parietal adhesions, number	4.25±0.09	2.66±0.04***	3.15±0.09***
The total number of adhesions, number	10.25±0.24	6.41±0.15***	7.25±0.18***
Adhesion thickness, mm	2.99±0.06	4.80±0.12***	5.60±0.12***

Notes: ***p<0.001 compared with the 3rd group of observations.

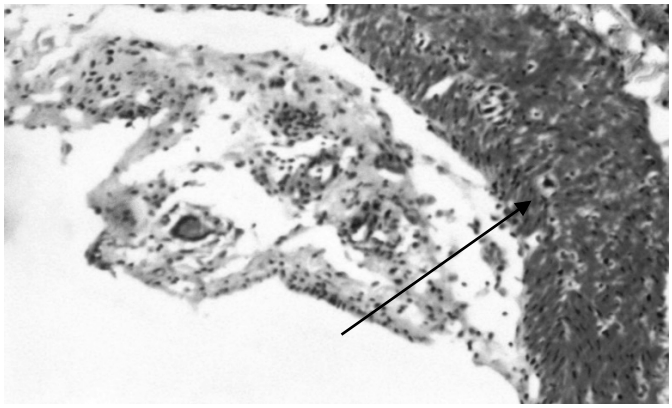


Figure 1. Intra-visceral adhesion in the abdominal cavity of a white rat 4 days after the start of the experiment

Notes: Hematoxylin-eosin staining. Coll.: x 140.

Using morphometric measurements of the duodenal wall, it was found that the quantitative characteristics of its membranes on the 4th day of the simulated pathological process changed significantly. Thus, the thickness of the mucous membrane in these experimental conditions statistically significantly increased by 12.7% (p<0.001), and the submucosal base by 18.7% (Table 3). In addtion, the thickness of the muscular membrane was increased by 8.9%, and that of the serous membrane by 7.6%.

Table 3. Morphometric characteristics of the duodenum

Indicator	Observation group			
	1st (control)	3rd (4th day)	4th (10th day)	5th (30th day)
Thicknesses of mucous, microns	402.5±2.8	453.6±3.3***	435.1±3.0***	416.2±3.0*
Thicknesses of submucosal, microns	28.30±0.28	33.60±0.30***	31.50±0.30***	30.10±0.30**
Thicknesses of muscle, microns	94.70±0.75	103.10±0.81***	99.60±0.72**	97.40±0.72*
Thicknesses of serous membranes, microns	14.40±0.12	15.50±0.18**	15.10±0.18**	14.70±0.09*
The size of the crypt, microns	31.30±0.22	36.20±0.24***	34.10±0.21***	32.80±0.18**
Depth of crypt size, microns	130.20±0.92	160.80±1.20***	149.60±0.96 ***	138.50±0.90***

Notes: *p<0.05; **p<0.01; ***p<0.001.

We found that the quantitative characteristics of adhesions on the 10th day of the experiment changed significantly. The number of visceral-visceral adhesions decreased significantly and reached 3.75±0.12. It should be noted that this macrometric indicator was statistically significant (p<0.001) from that on the 4th day of the experiment and was lower by 37.5%, compared to indicators of the previous group (Table 3).

The total number of adhesions in the abdominal cavity of experimental animals on the 10th day of the experiment decreased by 37.5%.

Optical examination of adhesive micropreparations on the 10th day of the experiment revealed that they were significantly compacted due to increased collagen, formation of connective tissue structures, and the appearance of vascular adhesions, nerve endings, cell infiltrates and fibrosis (Figures 2, 3, 4).

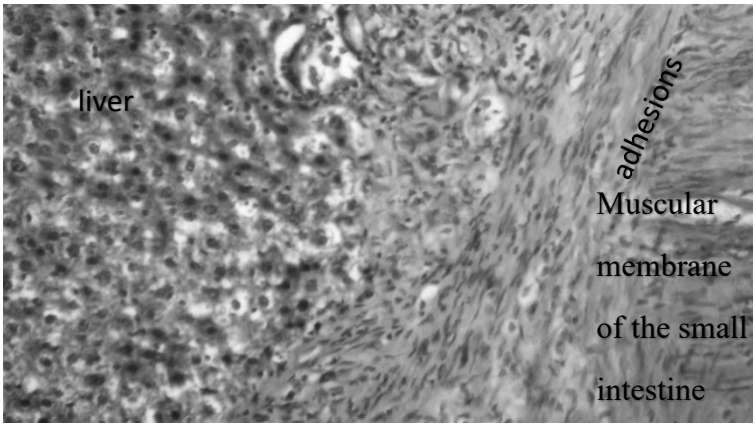


Figure 2. Intra-visceral adhesion between the small intestine and liver in the abdominal cavity of a white rat on the 10th day of the experiment

Notes: Hematoxylin-eosin staining. Coll.: x 140.

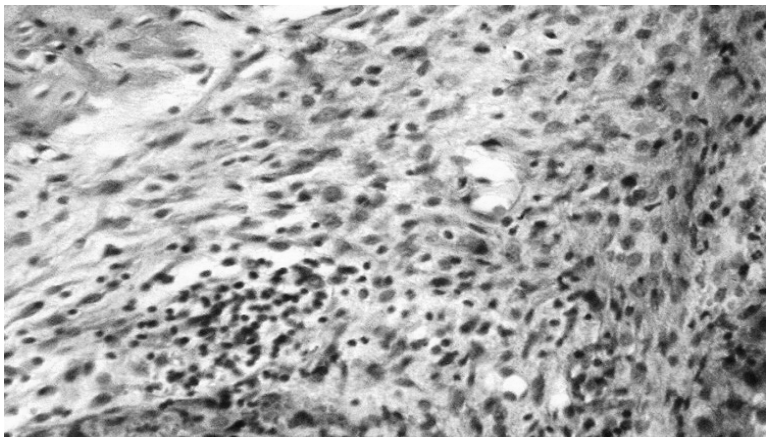


Figure 3. The area of visceral-parietal adhesion in the abdominal cavity of the experimental animal on the 10th day of the experiment

Notes: Hematoxylin-eosin staining. Coll.: x 160.

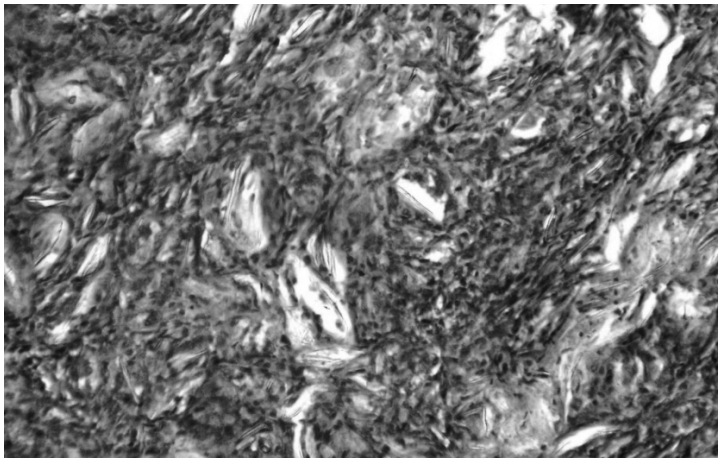


Figure 4. Intra-visceral adhesion in the abdominal cavity of a white rat on the 10th day of the simulated pathology

Notes: Hematoxylin-eosin staining. Coll.: x 160.

Morphometric studies showed that on the 10th day of the experiment, there was a pronounced structural rearrangement of the duodenum. Thus, the thickness of the mucous membrane of this organ was increased by 8.1%, and that of the submucosal base by 11.3%. The thickness of the muscle membrane in the experimental conditions was slightly increased to a lesser extent. The investigated difference was 5.2%. A similar morphometric parameter of the serous membrane in these experimental conditions was revealed that demonstrated statistically significant increase by 4.8%, compared with the same control value (p<0.001). The width and depth of the duodenal crypts remained markedly changed in the simulated pathological conditions. Thus, the width of the crypts of the studied organ on the 10th day of the experiment was 34.10±0.21 μm, and in intact animals 31.30±0.22 μm (Table 2).

On the 30th day of the experiment, the number of visceral-visceral adhesions in the abdominal cavity of experimental rats was equal to 4.10±0.12. The thickness of the adhesions in these experimental conditions (30th day of the experiment) with a high degree of reliability, increased from 2.99±0.06 mm to 5.60±0.12 mm (p<0.001) – almost 1.9 times (Table 1).

On day 30 of the experiment, the studied morphometric parameters of the duodenal wall were still changed. Accordingly, the thickness of the mucous membrane in these experimental conditions statistically significantly exceeded the same control value by 3.4%, and that of the thickness of the submucosal base by 6.3% (p<0.05). The thickness of the muscular membrane differed by 2.8%, compared with the same control morphometric parameter (p<0.05), and the thickness of the serous membrane did so by 2.1% (Table 2).

By means of light-optical research of micropreparations on the 30th day of experimental evoked adhesive disease, it was established that the formed joints were significantly compacted, in comparison with previous observations. In the connections formed on the 30th day of the experiment, in addition to connective tissue elements, vascular structures, muscle cells, nerve formations were found (Figure 5). Sites of cellular infiltration were also observed in the studied compounds. It is worth noting that there were also adhesions with diffuse cellular infiltration.

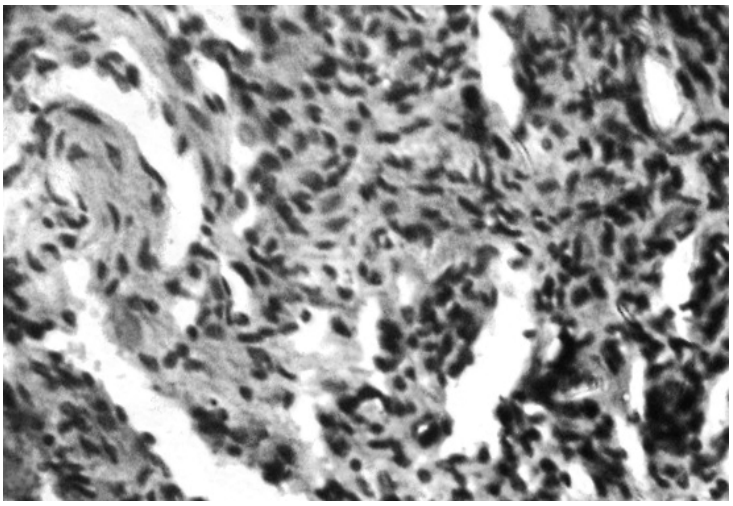


Figure 5. Intra-parietal adhesion in the abdominal cavity of a white rat on the 30th day of the experiment
Notes: Hematoxylin-eosin staining. Coll.: x 200.

Correction of this pathological process was performed using the anti-adhesive drug Defensal. Components of this drug have the ability to affect the main links in the pathogenesis of adhesions [7,24].

Positive effect of Defensal on adhesion processes in the abdominal cavity of experimental animals was indicated on the 4th day of the experiment. We saw that the quantitative morphological characteristics of adhesions significantly changed under the influence of the named drug medium, and, on the 4th day of the experiment, under the influence of Defensal, the number of intracranial adhesions in the abdominal cavity decreased from 6.00±0.15 to 3.41±0.09 (Table 4).

Table 4. Influence of Defensal on the processes of adhesion formation in the abdominal cavity of experimental animals on the 4th day of the experiment

Indicator	Observation group	
	3rd	6th
Internal-internal adhesions, number	6.00±0.15	3.41±0.09***
Intra-parietal adhesions, number	4.25±0.09	3.50±0.09**
Total number of adhesions, number	10.25±0.24	6.91±0.15***
Adhesion thickness, mm	2.99±0.06	1.90±0.05***

Notes: **p<0.01; ***p<0.001 compared with the 2nd group of observations.

Intra-parietal adhesions in the abdominal cavity under the influence of Defensal tended to decrease. Thus, in the 2nd group of observations, the number of these adhesions in the abdominal cavity of experimental animals was equal to 4.25±0.09, and in the group of animals injected with this drug 3.50±0.09. A statistically significant difference was found between the given morphometric parameters (p<0.01). The last figure was 17.6% lower than the previous one. The total number of adhesions in the abdominal cavity of experimental animals in these experimental conditions, with a high degree of reliability (p<0.001), decreased from 10.25±0.24 to 6.91±0.15 – i.e. almost 1.5 times.

The studied drug medium had a positive effect on the thickness of adhesions. The last morphometric parameter in the simulated experimental conditions (5th group of observations) was 1.90±0.05 mm. The given morphometric parameter was statistically significantly lower (p<0.05) by 36.4% for the same control value.

During the correction of adhesive disease with the drug Defensal on the 4th day of the experiment, it was morphometrically found that the structure of the duodenum was still changed. Thus, the thickness of the mucous membrane of the intact duodenum was equal to 402.5±2.8 μm, and in the conditions of the experiment 432.4±3.0 μm (Table 4). The last morphometric parameter exceeded the previous by 7.4%.

Under these experimental conditions, the thickness of the submucosal base of the studied organ was statistically significantly (p<0.01) higher than the same console rate by 8.1%, the thickness of the muscular membrane – by 2.9%, serous membrane – by 3.4%. The width of the crypt of the duodenal mucosa on the 4th day of adhesive disease corrected with the drug Defensal was 33.70±0.18 μm (Table 5).

Table 5. The effect of the drug Defensal on the morphometric characteristics of the duodenum (M±m)

Indicator	Observation group			
	1st (control)	6th (4th day)	7th (10th day)	8th (30th day)
Thicknesses of mucous, microns	**402.5±2.8**	**432.4±3.0***	**414.3±2.7***	**404.5±2.7**
Thicknesses of submucosal, microns	28.30±0.28	30.60±0.30**	29.50±0.24**	28.40±0.24
Thicknesses of muscle, microns	94.70±0.75	97.50±0.72*	96.10±0.66	95.20±0.66
Thicknesses of serous membranes, microns	14.40±0.12	4.90±0.15*	14.60±0.07	14.45±0.07
The size of the crypt, microns	31.30±0.22	33.70±0.18***	31.90±0.15*	31.40±0.18
Depth of crypt size, microns	130.20±0.92	144.30±0.84 ***	136.30±0.81**	131.35±0.84

Notes: *p<0.05; **p<0.01; ***p<0.001.

Light optical research revealed that the structure of adhesions under the influence of Defensal differed significantly from similar ones without correction. Adjusted adhesions with this drug were loose, moreover, fibrin on the surface of the peritoneum was with different numbers of different sizes and shapes of cells. There was also a small number of undifferentiated cells and fibroblasts, as well as vascular formations (Figure 6).

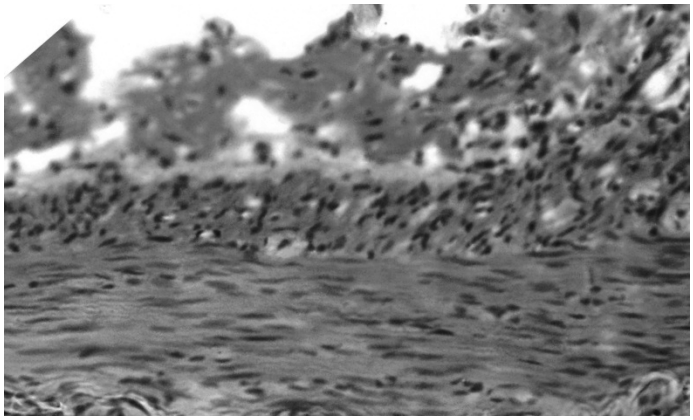


Figure 6. Intra-visceral adhesion in the abdominal cavity of a white rat on the 4th day of the experiment when correcting the adhesion process with Defensal

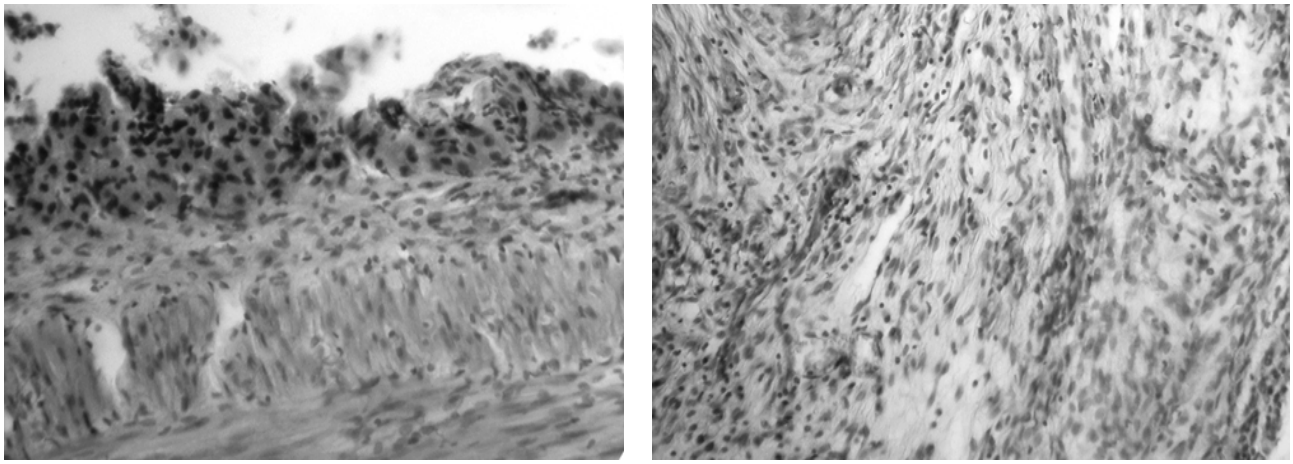
Notes: Hematoxylin-eosin staining. Coll .: x 160.

On the 10th day of the experiment, a positive effect of the studied drug medium on the processes of adhesions in the abdominal cavity of experimental animals was revealed. The number of visceral-visceral adhesions with a high degree of reliability (p<0.001) decreased by 9.1%, and intra-parietal adhesions – by 2.25% (Table 6). The number of total adhesions also decreased by 6.2%, and the thickness of adhesions – by 2.6 times.

Table 6. The effect of the drug Defensal on the processes of adhesions in the abdominal cavity of experimental animals on the 10th day of the experiment

Indicator	Observation group	
	4th	7th
Internal-internal adhesions, number	3.75±0.12	3.41±0.09***
Intra-parietal adhesions, number	2.6±0.04	2.60±0.06
Total number of adhesions, number	6.41±0.15	6.01±0.12*
Adhesion thickness, mm	4.80±0.12	1.85±0.05***

Notees: *p<0.05; ***p<0.001 compared with the 4th group of observations.



A B

Figure 7. Intra-visceral adhesion (A. Coll.: x160.) and a fragment of intra-parietal adhesion (B. Coll.: x140.) in the abdominal cavity of a white rat on the 10th day of experimental adhesive disease corrected through Defensal

Notes: Hematoxylin-eosin staining.

Connective tissue elements and single vessels appeared mainly in intra-parietal adhesions on the 10th day of experimental adhesive disease corrected by Defensal (Figure 7). In addition, structural changes in the duodenum on the 10th day of the simulated adhesive disease corrected by Defensal were smaller than the previous. Thus, the thickness of the mucous membrane in the studied conditions statistically significantly (p<0.05) exceeded the same morphometric parameter of the 1st group of observations by 2.9%, and the submucosal base – by 4.2% (Table 4).

On the 30th day of the experiment, a positive effect of Defensal on the quantitative characteristics of adhesions in the abdominal cavity of experimental animals was also found (Table 7).

Table 7. Influence of Defensal on the processes of adhesion formation in the abdominal cavity of experimental animals on the 30th day of the experiment (M±m)

Indicator	Observation group	
	5th	8th
Internal-internal adhesions, number	4.10±0.12	2.60±0.09***
Intra-parietal adhesions, number	3.15±0.09	1.80±0.06***
Total number of adhesions, number	7.25±0.18	4.40±0.12**
Adhesion thickness, mm	5.60±0.12	1.60±0.05***

Notes:**p<0.01; ***p<0.001 compared with the 4th group of observations.

During the correction of the simulated pathological process by Defensal, the studied morphometric parameter reached 2.60±0.09, and the last morphometric indicator was lower than the previous by 36.6%. In these experimental conditions (7th group of animals), the number of intramural adhesions, with a pronounced

degree of reliability (p<0.001), decreased by 42.8%. Similar dynamics were observed when studying the total number of adhesions in the abdominal cavity of experimental animals under the influence of the studied drug medium. Under the conditions of the experiment, this morphometric parameter decreased by 39.3%. In addition, the thickness of adhesions on the 30th day of the unadjusted experiment was 5.60±0.12 mm, and under the influence of Defensal, statistically significantly (p<0.001) decreased to 1.60±0.05 mm, ie 3.5 times (Figure 8).

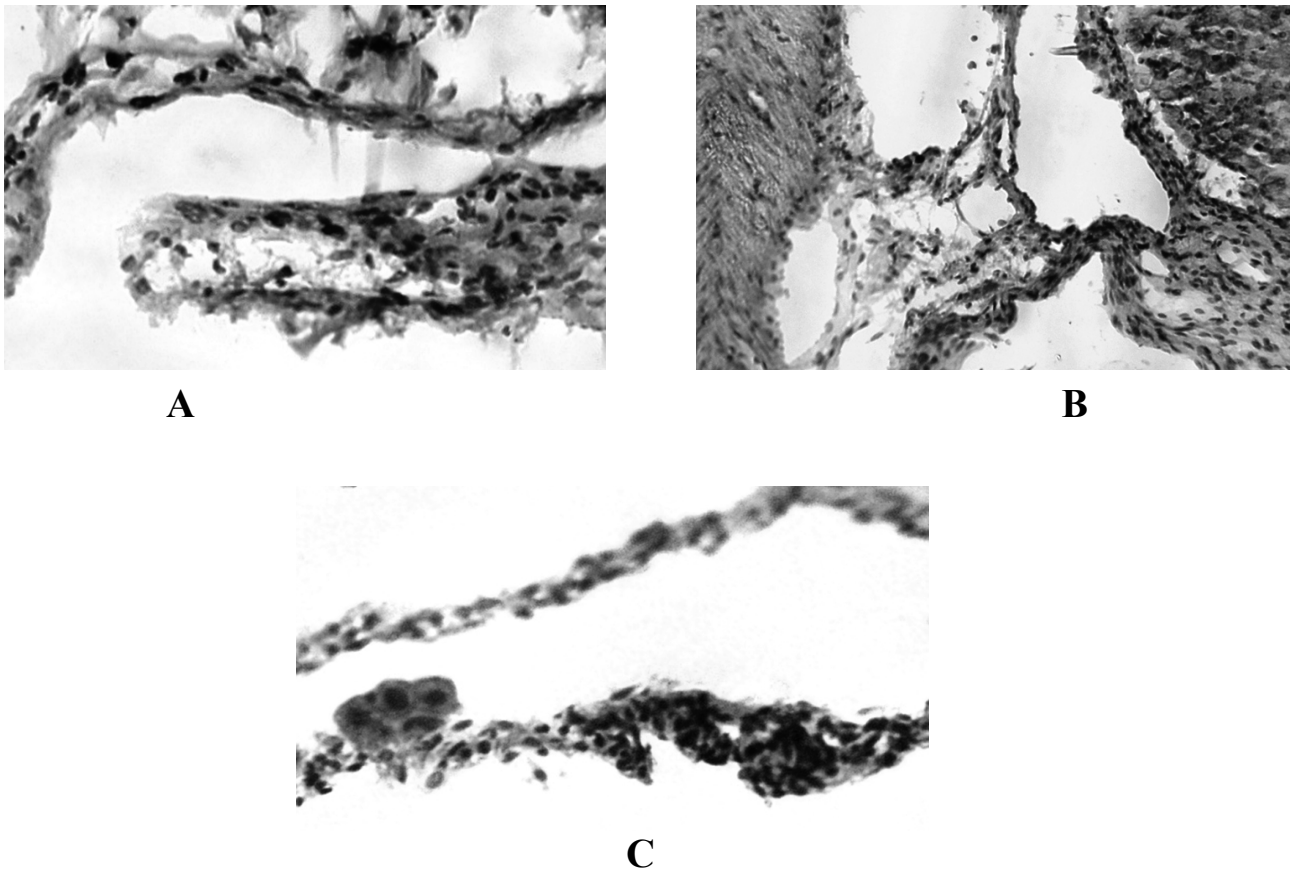


Figure 8. Intra-parietal junctions in the abdominal cavity of white rats (A), intra-visceral adhesions between the small intestine and liver (B) and single filamentous adhesions in the abdomen (C) on the 30th day of experimental adhesive disease corrected through Defensal

Notes: Hematoxylin-eosin staining. Coll .: x 140.

Discussion

It is known that mechanical damage to the peritoneum leads to a pronounced increase in the permeability of blood vessels and the entry into the peritoneal cavity of blood cells, undifferentiated cells, inflammatory cells, and the liquid fraction of blood with fibrinogen. The latter next transforms into fibrin [5-7,9,12,18]. This component is deposited on the surface of the damaged peritoneum in the form of threads, and fibroblasts are formed in undifferentiated cells, which are the source of collagen synthesis (the main substance of connective tissue). Later, nerve endings, blood vessels and even smooth muscle cells migrate into the formed adhesions [32,33].

Studies and results show that the drug Defensal has a positive effect on the course of experimental adhesion disease. In the process of correction of experimental adhesion disease with this drug, the number of adhesions in the abdominal cavity of experimental animals was significantly reduced, the vast majority of them were thread-like, loose, easily separated and did not deform the structure of the lumen and the cavity of the organs of the digestive tract was almost unchanged. Finally, the formed adhesions are loose due to the low content of collagen in them.

Conclusions

The use of Defensal in the experiment led to a decrease in the number of adhesions in the abdominal cavity. The vast majority of these were filamentous, loose, easily separated, did not deform the hollow organs of the digestive system and did not affect their function. Vessels and nerve elements were rarely observed in these adhesions. The effectiveness of barrier methods for the prevention of adhesions in the models of peritoneal adhesions has been experimentally proven.

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