

# Clinical-experimental justification of the method of prevention and treatment of appendicular pylephlebitis

I.V. Kolosovych, I.V. Hanol, Halil Uzun

*Bogomolets National Medical University, Department of Surgery No. 2, Kyiv:  
e-mail: kolosovich\_igor@ukr.net*

*Taking into account the pathogenesis peculiarities of appendicular pylephlebitis, the risk group includes patients with a retrocecal location of the appendix, gangrenous and perforating appendicitis, the course of which was complicated by peritonitis or abscess. The purpose of our clinical-experimental study was to justify the method of pathogenetic treatment of acute appendicular pylephlebitis based on an experimental model of portal hypertension. Acute experiments were performed on male Wistar rats and outbred dogs. Clinical studies were prospectively-retrospective. In addition to traditional methods of treatment, we used the developed technique of draining the retroperitoneal space and introducing antibacterial compositions in a complex with a 10% dimethylsulfoxide (DMSO) solution was used. On the basis of experimental data, it was established that a 10% solution of DMSO complexed with a dye, when injected transperitoneally in the ileocecal angle area, preferentially penetrates the lymphatic and portal systems, even in conditions of portal hypertension. This is explained by the peculiarities of the anatomical structure. The use of the method of intraperitoneal administration of antibiotics in combination with DMSO is pathogenetically justified in patients with appendicular pylephlebitis, as it achieves local sanitation of the immediate source and primary ways of spreading the infection. Implementation of the developed method of prevention and treatment of acute pylephlebitis of appendicular genesis as part of improved treatment tactics allows to improve treatment results by likely reducing the frequency of postoperative complications from 18.7% to 2.7% ( $\chi^2 = 20.02$ , 95% CI 9.25-23.8) and the duration of hospitalization from 22.8 days to 8.5 days. Key words: portal vein; acute appendicitis; portal hypertension; septic thrombosis; dimethylsulfoxide; prevention.*

## INTRODUCTION

Acute pylephlebitis is a pathology characterized by purulent thrombophlebitis of the portal vein system with liver damage and a mortality rate of 47.5% on average, and almost 100% in fulminant forms [1]. The most frequent cause of this complication is destructive appendicitis (70-75%). Simultaneously cases of purulent inflammation of the branches of the portal vein can occur during the use of the umbilical vein for exchange transfusions and in the severe course of several other diseases of the abdominal cavity (such as stomach and pancreas pathology) and retroperitoneal tissue [2]. It should be noted that thrombosis is often preceded by changes in blood coagulation potential, slowing of blood

flow, and contact of the affected vessel with purulent exudate [3]. Under these conditions, the risk group includes patients with a retrocecal location of the appendix, gangrenous and perforating appendicitis, the course of which was complicated by peritonitis or abscess [4].

Although the frequency of development of acute pylephlebitis in acute appendicitis is 0.03-0.15%, it is noted that the real frequency of this complication is much higher due to chronic forms, the diagnosis of which is extremely difficult [5]. Cases with the most vivid clinical picture (fulminant (momentary) or acute forms) are detected mainly, while in the initial stages and with an atypical clinical picture, especially against the background of intensive therapy, certain difficulties arise in the interpretation

of the existing clinical signs [6]. Under these circumstances, the true diagnosis is usually established a week or much later (often patients are unsuccessfully treated for hepatitis of unclear origin). Ultrasound examination with Doppler, computed tomography of the abdominal organs and angiography help clarify the diagnosis.

At the same time, the treatment of acute pylephlebitis is complex and aimed at combating the infectious factor and thrombosis of the portal vein. In the presence of numerous liver abscesses, the goal of surgical intervention is the opening of abscesses [7]. However, some authors point out that liver abscesses in acute pylephlebitis do not require surgical treatment and often undergo a reverse development under the condition of appropriate intensive therapy [8]. Therefore, if a laparotomy becomes necessary during treatment, it is recommended to drain the portal system for antibiotic therapy. Thus, there is a well-known method of administering drugs (for 20 days) into a pre-stimulated umbilical vein, which involves the installation of two polyvinyl chloride catheters, one of which is inserted into the portal vein to a depth of 15 cm for the purpose of injecting medicinal substances, the second into the umbilical vein to a depth of 5 cm for the removal of these drugs by the type of liver dialysis [9]. However, this technique has significant drawbacks, namely, it does not affect the center of infection and the primary ways of its spread. In the case of the spread of the process to the portal vein itself and the vessels of the liver, the technique is effective only in 11% of cases when the umbilical vein flows directly into the trunk of the portal vein, in the variant of its entry into the left branch of the portal vein (89% of cases), the main right lobe of the liver remains without the influence of drugs [10].

So, the problem of the diagnosis and treatment of pylephlebitis of appendicular origin has not yet been sufficiently resolved. At the same time, there is no information about preventive measures in the event of the threat of this formidable complication, which would

allow stopping the process directly in the center of its development - the veins of the mesentery of the appendix and the ileocecal angle.

The aim of the study was to justify the method of pathogenetic treatment of acute appendicular pylephlebitis based on the study of the transport properties of DMSO in a complex with a dye to penetrate into the lymphatic and venous systems when they are locally injected into the retroperitoneal area of the ileocecal angle and into the portal system under the conditions of the portal hypertension model.

## METHODS

The study is of a clinical and experimental nature and was conducted in compliance with the existing international principles of the «European Convention on the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes» (Strasbourg, 1986), Article 26 of the Law of Ukraine «On the Protection of Animals from Cruelty» (No. 3447-IV, 21.02.2006), «The Helsinki Declaration of the World Medical Association on the Ethical Principles of Scientific Medical Research with Human Participation» (1964-2008), «Council of Europe Convention on Human Rights and Biomedicine» (1997), and the current «Order of the Ministry of Health of Ukraine No. 960» dated September 23, 2009. The nature of the research was reviewed and approved by the Commission on Bioethics of Bogomolets National Medical University (protocol No. 3 dated March 15, 2005).

The experiments were performed according to the original protocol and consisted of two series. The first series of acute experiments was carried out on 10 male Wistar rats weighing 180-250 g. The animals were kept in a separate room at an air temperature of 21-22°C, a 12-hour light-dark cycle, with free access to water and standard laboratory food. Peculiarities of the penetration of a mixture of 10% DMSO with indigo carmine dye through biological membranes were studied when they were introduced into the

retroperitoneal space of the ileocecal area by visual assessment of the color of the lymphatic vessels of the mesentery of the ileocecal angle. Male rats were divided into main (n = 5) and control (n = 5) groups. Preparation for surgery included premedication (atropine 0.1% 0.001 mg/kg, analgin 50% 0.2 ml, diphenhydramine 0.1 mg/kg) and general anesthesia (1% sodium thiopental solution 0.005-0.01ml/1g of weight). Next, an internal laparotomy was performed, the ileocecal angle was brought out into the wound, and the following substances were injected into the retroperitoneal space of the ileocecal area: in the main group - 1 ml of a 10% solution of DMSO with indigo carmine dye (5 drops), in the control group - 1 ml of isotonic sodium chloride solution with indigo carmine dye (5 drops).

In the second series of acute experiments on four outbred dogs weighing 16-20 kg, the rate of penetration of DMSO in a complex with indigo carmine was studied when they were injected transperitoneally in the area of the ileocecal angle into the lymphatic, general venous and portal systems in conditions of portal hypertension (model of pylephlebitis). Preparation for surgery included: premedication (droperidol 0.5 mg/kg, diphenhydramine 1.5 mg/kg, analgin 50% 50-70 mg/kg); after 20 min, under local anesthesia with a 2% solution of novocaine, a small subcutaneous vein was isolated and a catheter was passed through it into the posterior vena cava; introductory anesthesia with intravenous administration of 3-5 ml of 2% hexenal solution; intubation anesthesia with an ether-oxygen mixture. Next, an internal laparotomy was performed, the thoracic lymphatic duct, inferior cava and portal veins were cannulated, and the portal pressure was measured, after which the lumen of the vessel was ligated by 50% until the pressure in the portal system increased above 250 mm H<sub>2</sub>O (model of pylephlebitis). Control studies of blood and lymph from the three indicated systems were carried out. 5 ml of 10% solution of DMSO in a complex with 1 ml of 0.4% indigo carmine solution (5:1) was injected into

the retroperitoneal space of the ileocecal area. In dynamics (within an hour), blood and lymph tests were performed. The obtained material was centrifuged immediately after taking for 10 min and evaluated photoelectrocolorimetric method (photocolorimeter "KFK-3») at a wavelength of 610 nm.

After the end of the experiment, animals were deduced from the experiment by intravenous administration of sodium thiopental at a dose of 60 mg per 1 kg of body weight [11]. In view of the obtained results of the experimental study, we have developed a method of prevention and treatment of appendicular pylephlebitis. This method is based on intraoperative drainage of the source and primary routes of spread of infection (retroperitoneal space of the ileocecal region) followed by the administration of antibiotics in combination with DMSO. The method is carried out as follows. Laparotomy according to McBurney and revision of the ileocecal angle are performed. In the presence of macroscopic signs of pylephlebitis (gangrenous or perforating appendicitis, retrocecal location of the vermiform appendix on the background of peritonitis or periappendiceal abscess, detection of enlarged, greenish veins of the peritoneum of the appendix) in addition to clinical and laboratory ones (hyperthermia, chills, progressive deterioration of the patient's condition, pain in the right hypochondria, enlargement of the liver and spleen, ascites, reactive pleurisy, jaundice, hyperbilirubinemia, hyperfibrinogenemia, etc.) a typical appendectomy was performed. After lavage of the abdominal cavity, a blunt tunnel was made in the retroperitoneal tissue of the ileocecal area and catheterised with a microirrigator. The abdominal cavity was drained with a tubular drain and sutured. In the postoperative period, in addition to the generally accepted methods of treatment of pylephlebitis (infusion therapy), local administration of drugs through a microirrigator was additionally used. We used the following combination of drugs: antibiotics, mainly  $\beta$ -lactam antibiotics, in combination with a 10% solution of DMSO

twice a day (the course is continued until the disappearance of clinical and instrumental manifestations of the disease). In the case when the complication occurred a few days after the appendectomy, drainage of the retroperitoneal space of the ileocecal region was performed under local anesthesia with the help of a trocar along the crest of the pubic bone, pushing the latter to a depth of 7-10 cm, followed by a polyvinyl microirrigator along the conductor.

The clinical part of the work was prospective-retrospective. The study included 300 patients with acute appendicitis, who belonged to the risk group for the development of appendicular pylephlebitis, namely patients with a retrocecal location of the appendix, gangrenous or perforating acute appendicitis, complicated by abscess or purulent peritonitis. Exclusion criteria were: pregnancy; severe concomitant diseases of the lungs, liver, and kidneys; use of anticoagulants, and antiplatelet agents within three months before inclusion in the study; aggravated allergic history; mental illness; refusal of the patient to participate in the study. By analyzing archival material (period 1990-2005), a comparison group (n = 150)

was formed, which used traditional methods of treatment (including anticoagulants and antibacterial drugs). The main group (n = 150) included patients who were treated in the clinic of the Department of Surgery No. 2 Bogomolets National Medical University in the period 2005-2020 and which, in addition to traditional methods of treatment, used the developed technique of draining the retroperitoneal space and introducing antibacterial compositions in a complex with a 10% solution of DMSO. The general characteristics of the patients are presented in the Table. 1.

To assess the effectiveness of surgical techniques in the studied groups, a comparative analysis of the frequency of complications, mortality, and duration of hospitalization was conducted.

**Statistical analysis.** Statistical analysis was performed using the programs Statistica 12 (Serial Number: STA999K347150-W) and MEDCALC® (Internet resource with open access, <https://www.medcalc.org/calc/>). Differences between groups were determined using the Student's t-test for independent samples and the Mann-Whitney U-test. Differences in

**Table 1. General characteristics of patients in the studied groups (M ± m, n = 150)**

Indexes	Main group	Comparison group	P
Age (years)	52.7±4.1	51.3±4.1	0.003
Sex:			
- male	79 (52.7%)	77 (51.3%)	0.8
- female	71 (47.3%)	73 (48.7%)	0.8
Duration of illness before hospitalization (hours)	30.1 ±14.7	32.2±15.6	0.23
Frequency of concomitant pathology	60 (40%)	47 (31.3%)	0.11
Clinical forms of acute appendicitis:			
- Gangrenous	87 (58%)	85 (56.7%)	0.82
- Perforative	63 (42%)	65 (43.3%)	0.82
Complications of acute appendicitis:			
- Periappendicular abscess	26 (17.3%)	25 (16.7%)	0.89
- Purulent peritonitis	142 (94.7%)	141 (94%)	0.79
- Pylephlebitis	2 (1.3%)	1 (0.7%)	0.6

indicators between groups were determined using the t-test in the case of linear indicators and with the help of the  $\chi^2$ -test in the case of categorical indicators.

## RESULTS

In the first series of experiments, blue staining of the lymphatic vessels of the ileocecal angle was observed in male rats of the main group at  $15.2 \pm 0.5$  min after transperitoneal injection of dye with DMSO. In the animals of the control group, no staining of the lymphatic vessels was recorded during the first hour after the dye injection. However, an hour after the administration of the mixture of drugs, due to the lymphotropic nature of indigo carmine, a weak blue coloration of the lymph nodes and venous vessels of the ileocecal area was noted.

Taking into account the results of the first series of experiments (the appearance of the dye also in the venous system), a second series of experiments was performed on dogs that have a greater similarity in the anatomical structure of the ileocecal area, including the syntopy of the vessels of the lymphatic and venous systems (thoracic lymphatic duct, portal vein and inferior cava vein) to human anatomy. The dye's appearance rate in the lymphatic and venous systems in the second series of experiments is shown in Table 2.

The presence of the dye in the lymph was detected at  $5 \pm 0.2$  min after transperitoneal

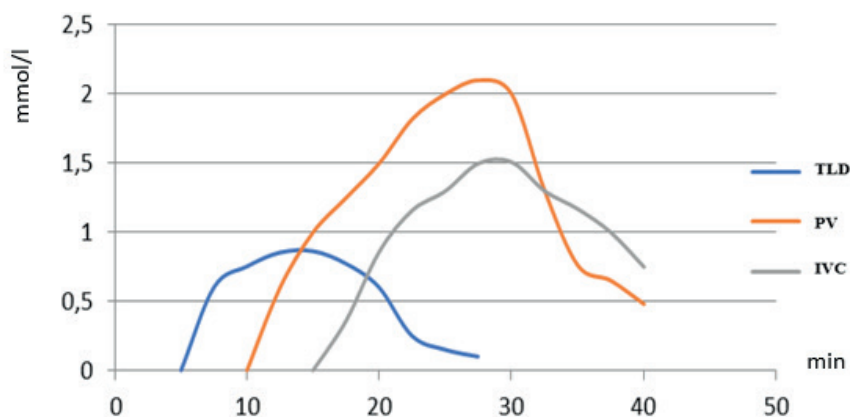
administration of the drugs, and the maximum concentration of indigo carmine in the lymphatic system was recorded at  $15 \pm 0.8$  min (Figure).

At the same time, the appearance of the dye in the general venous system was detected at  $15.3 \pm 0.8$  min after administration, the maximum concentration was registered at  $30 \pm 1.2$  min. Also, an earlier appearance of indigo carmine dye in the portal system was established even in conditions of portal hypertension ( $14.5 \pm 1.0$  min) than in the general venous system. When analyzing the results of the study, it was found that the frequency of complications in the immediate postoperative period in patients of the comparison group was 18.7% (28/150), in the main group was 2.7% (4/150) ( $\chi^2 = 20.02$ , 95% CI 9.25-23.8,  $P < 0.0001$ ). The characteristics of complications are presented in Table 3.

It should be noted that 4% (6/150) patients of the comparison group needed repeated surgical interventions, in the main group repeated interventions were not performed ( $\chi^2 = 6.1$ , 95% CI 0.70-8.45,  $P = 0.01$ ). At the same time, no deaths were observed among patients in the main group, whereas in the comparison group, the mortality was 1.3% (2/150) ( $\chi^2 = 1.95$ , 95% CI -1.37-4.68,  $P = 0.16$ ). Specifically, two patients aged 38 and 64 died after appendectomy due to destructive forms of acute appendicitis, complicated by putrefactive phlegmon of the anterior abdominal wall, diffuse purulent-fibrinous peritonitis and pylephlebitis. The duration of hospitalization of patients in the main group was  $8.5 \pm 1.2$  days,

**Table 2. Levels of indigo carmine concentration in the lymphatic and venous systems**

Dye concentration (mmol/l)	Time (min)							
	5	10	15	20	25	30	35	40
Thoracic lymphatic duct	0.05±0.004	0.75±0.02	0.75±0.02	0.74±0.01	0.14±0.02	0.05±0.002	–	–
Portal vein	–	–	0.85±0.02	1.4±0.2	1.82±0.08	2.0±0.04	0.8±0.01	0.4±0.02
Inferior vena cava	–	–	0.05±0.004	0.7±0.02	1.2±0.03	1.5±0.04	1.2±0.03	0.6±0.03



Distribution of the dye with dimethylsulfoxide in the lymphatic, general venous and portal systems (portal hypertension) during their transperitoneal administration (TLD - thoracic lymphatic duct; PV - portal vein; IVC - inferior vena cava)

while in the comparison group was  $22.8 \pm 6.1$  days ( $P < 0.0001$ ).

When studying the long-term results by analyzing outpatient visits and active calling of certain categories of patients in the comparison group, two (1.3%) cases were found, accompanied by complaints of jaundice, and pain in the right subcostal area with radiation to the back. Later, during the examination, these patients were diagnosed with portal hypertension, and the development of this pathology was associated with the previous thrombosis of the branches of the portal vein. In the patients of the main group, complications were not observed in the remote period ( $\chi^2 = 1.95$ , 95% CI -1.37-4.68,  $P = 0.16$ ).

## DISCUSSION

In the treatment of patients with acute pylephlebitis of appendicular genesis, selective

arteriography is widely used followed by the insertion of a catheter into the abdominal artery for massive antibiotic therapy in combination with a 100% dimethylsulfoxide solution [12]. However, the use of this method seems problematic due to the hepatotoxicity of highly concentrated DMSO. There is also a well-known method of administering drugs (reserve antibiotics, corticosteroids, anticoagulants, vitamins, etc.) into a previously accessed and cannulated umbilical vein [13]. However, these methods have certain drawbacks, namely, there is no direct delivery of drugs to the source of infection (ileocecal angle) and the primary ways of its spread. Under these circumstances, the method of transumbilical drug treatment of pylephlebitis, which is almost the only one among local methods, is effective in only 11% of patients.

In a series of experiments, we found that a 10% solution of DMSO, administered in a

**Table 3. Characteristics of early postoperative complications in the studied groups ( $M \pm m$ ,  $n = 150$ )**

Type of complication	Main group	Comparison group	P
Early adhesive intestinal obstruction	–	3 (2%)	0.08
Peritonitis	–	2 (1.3%)	0.16
Intra-abdominal abscesses	–	4 (2.7%)	0.04
Postoperative wound suppuration	4 (2.7%)	17 (11.3%)	0.003
External intestinal fistula	–	1 (0.7%)	0.3
Pylephlebitis	–	1 (0.7%)	0.3
In total	4 (2.7%)	28 (18.7%)	<0.0001

complex with indigo carmine, improves the penetration of the dye into the lymphatic system of the ileocecal area, which is explained by the ability of DMSO to transport drugs through biological membranes. The early appearance of indigo carmine dye in the portal system was also observed even in conditions of portal hypertension ( $14.5 \pm 1.0$  min) than in the general venous system, although the pressure gradient between them is quite large (150-200 mm H<sub>2</sub>O). In our opinion, this is due to the peculiarities of the anatomical structure of the retroperitoneal space of the ileocecal area. Yes, it is known that v.ileocolica, which flows into v. mesenterica superior, lies retroperitoneally between the parietal peritoneum of the right mesenteric sinus and Toldt's fascia. Next comes the retroperitoneal tissue (textus cellulosis retroperitonealis), which is limited by the retroperitoneal fascia. The last layer of the retroperitoneal space is the intra-abdominal fascia. The inferior vena cava lies on this fascia [14]. The microirrigator, through which DMSO with a dye was injected, was installed in the thickness of the retroperitoneal tissue, that is, between Toldt's fascia and the retroperitoneal fascia. Therefore, in order to penetrate into the system of the inferior vena cava, the dye must overcome the retroperitoneal fascia and a thick layer of retroperitoneal tissue, and to get into the portal system, the drug overcomes only the thin fascia of Toldt.

So, it can be stated that with this method of administration of drugs in a complex with a 10% solution of DMSO, their penetration into the lymphatic, general venous system, and the portal vein system, including in conditions of portal hypertension. It is also known that a 10% solution of DMSO exerts a moderate hypocoagulation effect, which gives reason to count on its prophylactic and therapeutic effect in septic thrombosis of the veins of the portal system of appendicular origin [15]. Under these circumstances, we developed a pathogenetically justified method of prevention and treatment of acute pylephlebitis, which is

based on intra-operative drainage of the primary routes of spread of infection (retroperitoneal space of the ileocecal region) followed by local administration of antibiotics in combination with DMSO.

Implementation of the proposed method of prevention and treatment of acute appendicitis pylephlebitis as part of improved surgical tactics in patients of the main group probably reduced the frequency of complications in the postoperative period by 16% ( $\chi^2 = 20.02$ , 95% CI 9.25-23.8,  $P < 0.0001$ ), the duration of hospitalization was 14.3 days ( $P < 0.0001$ ). There was also a trend towards a 1.3% reduction in mortality ( $\chi^2 = 1.95$ , 95% CI-1.37-4.68,  $P = 0.16$ ) and a 2% reduction in the risk of developing pylephlebitis (taking into account the immediate postoperative period and long-term outcomes) ( $\chi^2 = 3.02$ , 95% CI-0.82-5.71,  $P = 0.08$ ). Therefore, the proposed method of prevention and treatment of pylephlebitis is effective. This is caused by taking into account the anatomical features of the retroperitoneal space of the ileocecal area, and the direct effect on the source of infection, the primary ways of its spread, DMSO allows drugs to penetrate directly into the portal system even in conditions of portal hypertension. The creation of a significant concentration of antibiotics at the site of the primary development of thrombosis, and the hypocoagulant effect of DMSO allow to reduce mortality in this category of patients.

## CONCLUSIONS

1. Based on experimental data, it was established that a 10% solution of dimethylsulfoxide in a complex with a dye when administered retroperitoneally into the area of the ileocecal angle preferentially penetrates the lymphatic and portal systems even in conditions of portal hypertension, which is explained by the peculiarities of the anatomical structure.

2. Taking into account the peculiarities of the pathogenesis of appendicular pylephlebitis, we identified a risk group for the development of

this complication, which includes the retrocecal location of the vermiform appendix, gangrenous or perforating appendicitis complicated by abscess or purulent peritonitis.

3. The use of the method of transperitoneal administration of antibiotics in combination with dimethylsulfoxide is pathogenetically justified in patients with appendicular pylephlebitis, as it achieves local sanitation of the immediate source and primary ways of spreading the infection.

4. Implementation of the developed method of prevention and treatment of acute pylephlebitis of appendicular genesis as part of improved treatment tactics allows to improve treatment results by likely reducing the frequency of postoperative complications from 18.7% to 2.7% ( $\chi^2 = 20.02$ , 95% CI 9, 25-23.8,  $P < 0.0001$ ) and the duration of hospitalization from 22.8 days to 8.5 days ( $P < 0.0001$ ).

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**І.В. Колосович, І.В. Ганоль, Халіл Узун**

#### **КЛІНІКО-ЕКСПЕРИМЕНТАЛЬНЕ ОБҐРУНТУВАННЯ МЕТОДУ ПРОФІЛАКТИКИ ТА ЛІКУВАННЯ АПЕНДИКУЛЯРНОГО ПІЛЕФЛЕБІТУ**

*Національний медичний університет імені  
О.О. Богомольця, Київ; e-mail: kolosovich\_igor@ukr.net*  
Враховуючи особливості патогенезу апендикулярного пілефлебіту, до групи ризику розвитку відносяться пацієнти

з ретроцекальним розташуванням червоподібного відростка, гангренозним та перфоративним апендицитом, перебіг якого ускладнився перитонітом або абсцесом. Метою дослідження було обґрунтування способу патогенетичного лікування гострого апендикулярного пілефлебіту на основі експериментальної моделі портальної гіпертензії. Робота носила клініко-експериментальний характер. Була здійснена серія гострих дослідів на щурах-самцях лінії Вістар та безпородних собаках. Клінічна частина роботи носила проспективно-ретроспективний характер. У хворих основної групи додатково до традиційних методів лікування застосовувались розроблена методика дренивання заочеревинного простору та введення антибактеріальних композицій в комплексі з 10%-м розчином диметилсульфоксиду. На основі експериментальних результатів було встановлено, що цей розчин у комплексі з барвником при заочеревинному введенні у ділянку ілеоцекального кута пріоритетно проникає у лімфатичну та портальну системи навіть у умовах портальної гіпертензії, що пояснюється особливостями анатомічної будови. Застосування методики заочеревинного введення антибіотиків у комплексі з диметилсульфоксидом є патогенетично обґрунтованим у хворих на апендикулярний пілефлебіт, так як при цьому досягається місцева санація безпосереднього джерела та первинних шляхів поширення інфекції. Впровадження розробленого способу профілактики та лікування гострого пілефлебіту апендикулярного генезу у складі удосконаленої лікувальної тактики дозволяє покращити результати лікування шляхом вірогідного зниження частоти розвитку післяопераційних ускладнень з 18,7 до 2,7% ( $\chi^2 = 20,02$ , 95% ДІ 9,25-23,8) та тривалості госпіталізації з 22,8 діб до 8,5 діб.

Ключові слова: ворітна вена; гострий апендицит; портальна гіпертензія; септичний тромбоз; диметилсульфоксид; профілактика.

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