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Substantiation of Effectiveness of Photodynamic Therapy in Multiple Peritonitis

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Abstract

This article presents the experience of using photodynamic sanitation of the abdominal cavity using methylene blue as a photosensitizer at a concentration of 0.05% in generalized peritonitis. For patients in the control group of patients, 0.02% aqueous solution of chlorhexidine was used to sanitize the abdominal cavity. It was found that when using the "FDU-1" apparatus with a wavelength of 630 ± 20nm as a radiation source, the following parameters are required: exposure time 3-5 minutes per irradiation area, output radiation power in continuous mode 100mW / cm2, energy density from 25 to 35 J / cm2. On the basis of the data obtained, it was proved that, in terms of bactericidal properties, 0.02% chlorhexidine solution is inferior to the method of photodynamic exposure with methylene blue. The introduction of the developed method of sanitation of the abdominal cavity made it possible to reduce postoperative complications from 23.5% to 13% and to reduce the average length of hospital stay from 9.3 ± 0.32 to 6.5 ± 0.21 bed-days.
Keywords: widespread peritonitis; complications; photodynamic therapy; methylene blue; abdominal sepsis; methylene blue.

INTRODUCTION

Peritonitis remains an urgent problem in modern abdominal surgery. This is due not only to the persistence of a high level of morbidity and economic costs of treatment, but also to the fact that the mortality rate from this pathology ranges from 11% to 53%, and with the development of multiple organ failure, the mortality rate reaches 80-90% [1,9,10].
One of the most important and critical stages of the operation is the sanitation of the abdominal cavity, which largely determines the dynamics of the development of the pathological process, the quality of its implementation, as well as the need for its subsequent treatments. A positive result in the treatment of peritonitis, according to V. Savelyev (2007), 80% depends on the quality of sanitation during the operation and 20% on subsequent measures [10].
Despite the many proposed methods of sanitation of the abdominal cavity in peritonitis, it is not always possible to completely remove the pathogenic microflora, due to technical difficulties caused by a destructive process or anatomical features [2,9,11], and some methods are laborious or costly.
Recently, antimicrobial and anti-inflammatory photodynamic therapy - PDT [3, 4, 5] with the use of photosensitizers has been widely used to combat surgical infections.
Many authors note that the bactericidal effect of PDT does not disappear with long-term treatment of surgical infections, while pathogenic microorganisms do not develop resistance to PDT [5,8]. A number of authors believe that the effectiveness of the method does not depend on the spectrum of sensitivity of pathogenic microorganisms to antibiotics [6,7].
Photodynamic damage is local in nature, and the bactericidal effect is limited to the zone of laser irradiation and is not accompanied by the side effects observed with antibiotic therapy

[8]. As photosensitizers used: photoditazine, brilliant green, dimegin, radachlorin, methylene blue (MS), etc. Among photosensitizers, MS is the most accessible and less toxic. The substance was synthesized in 1877 and was originally used in medicine and industry as a dye and pigment. But later it turned out that MS has a wide range of therapeutic properties. MS is known to be an active photosensitizer. This is a group of light-sensitive substances, the effect of which is enhanced by exposure to light of the appropriate wavelength. The photosensitizer transfers the energy of light to oxygen, due to which it goes into the so-called singlet state. Singlet oxygen is chemically very active: it oxidizes proteins and other biomolecules, destroying the internal structures of pathological cells, bacteria, after which they become nonviable.

The above facts provide grounds for studying the possibility of using PDT with MS as measures for sanitizing the abdominal cavity in the treatment of generalized peritonitis.

Purpose of the study:substantiation of the possibility of application and development of a method of photodynamic therapy using methylene blue for intraoperative sanitation of the abdominal cavity in generalized peritonitis.

MATERIAL AND METHODS

The work was carried out at the Tashkent City Clinical Hospital No. 4, on the clinical base of the Department of Surgical Diseases of TashPMI.

97 patients with widespread peritonitis, divided into 2 groups, were under observation. In group 1 (control; n = 51), patients received intensive therapy according to the protocol for the treatment of abdominal sepsis. Sanitation of the abdominal cavity was carried out by sequential washing, first with 3-4 liters of saline, and then with 2 liters of 0.02% aqueous solution of chlorhexidine. In group 2 (main; n = 46), the intensive care regimen was also the same as in group 1. Sanitation of the abdominal cavity was carried out with 3-4 l of saline followed by the introduction into the abdominal cavity of 0.05% aqueous solution of methylene blue in a volume of 300 ml. The absorption spectrum of methylene blue is characterized by a broad absorption band in the red region (650-700 nm).

Methylene blue was delivered to hard-to-reach areas of the abdominal cavity with napkins soaked in solution. The photosensitizer solution was kept for 5-7 minutes (this is the time required to fix the MS on the surface of bacteria), then drainage and photodynamic therapy were performed: all areas of the abdominal cavity were irradiated with an LED light source, wavelength 630 ± 10 nm, a device of domestic production “FDU- 1 ”, exposure time 3-5 minutes for each area of irradiation, output radiation power in continuous mode 100 mW / cm2, energy density from 25 to 35 J / cm2. A block of LEDs was placed above the operating field at a distance of 10-15 cm, the diameter of the light field was 15-20 cm2. Subsequently, the abdominal cavity is drained with four drains through the counter-apertures, the surgical wound is sutured.

The age of the bulk of the patients who applied for help was from 17 to 77 years (the average age was 50.2 ± 1.6 years). The patients were divided by gender: there were 54 men (55.7%), 43 women (44.3%). The main number - 22 (22.7%) patients were aged 41-50 years, the second place was occupied by persons 51-60 years old, there were 19 (19.6%), patients under 30 years old - 18 (18.6%), 31-40 years old in -10 (10.3%), 61-70 years old and over 70 years old in 14 patients (14.4%). The patients were mostly of mature, working age and old age, which reflects the importance of solving the problem under consideration.

The nature of the diseases of the patients of both groups examined by us was practically identical. All patients on admission to the emergency department underwent standard, generally recognized diagnostic tests.

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The presence of RGP in a patient was an absolute indication for the appointment of antibiotic therapy. In the absence of bacteriological research data, antibacterial drugs were used that covered the entire possible spectrum of pathogenic microorganisms. The sampling of peritoneal exudate for the study was performed during the operation before the sanitation of the abdominal cavity, and also after the sanitation. In the absence of data from bacteriological studies, antibacterial drugs were used that covered the entire possible spectrum of pathogenic microorganisms. In addition, antibacterial therapy was carried out taking into account the local microbiological landscape, which we established during the operation.

STATISTICAL PROCESSING METHODS.

The data obtained were processed by the method of variation statistics. As characteristics of samples of quantitative features, the arithmetic mean of the sample values (M) and its standard error (m) were calculated. To assess the statistical significance of differences in quantitative characteristics, Student's t test and Fisher's F test were applied.

RESULTS AND DISCUSSION.

To assess the severity of the process and its development from clinical and laboratory tests selected: body temperature, pulse rate, leukocyte count, neutrophil count, ESR, LII, protein, ALT, AST, urea, creatinine. Table 1 shows the clinical and laboratory parameters of patients with widespread peritonitis in patients in the control group, and in the main group in table 2.

Table1
Clinical and laboratory parameters of patients with generalized peritonitis. Control group (n = 51)

Indicator (norm unit of measure)	Upon enrolment	Postoperative period		
		1 day	3 day	7 day
Body temperature (0C)	38,6±0,22	38,4±0,22	37,9±0,21*	37,5±0,17***
Pulse (bpm)	125,8±2,8	120,2±3,0	114,2±3,1*	92,5±1,3***
Number of leukocytes (4.0-8.8x109 / l)	19,21±0,58	23,7±0,73***	15,9±0,59***	11,8±0,47***
Rod neutrophils (1.0-6.0%)	9,35±0,29	11,7±0,35***	7,9±0,28**	3,93±0,15***
Segmented neutrophils (47.0-72.0%)	64,59±1,9	72,2±2,2*	68,8±2,3	65,8±2,6
Monocytes (3-11%)	4,6±0,15	5,9±0,18***	8,7±0,24***	10,9±0,34***
LII (0.3-1.5 units)	18,8±0,56	10,6±0,38***	6,3±0,26***	4,89±0,19***
ESR (2.5-15 mm / h)	30,8±1,1	38,2±1,2***	26,9±0,94*	23,9±0,87 ***?
Total protein	53,84±1,7	51,1±1,6	59,1±1,9*	58,8±1,8*

Note: *- reliable compared with the indicators on admission (* -P <0.05; ** - P <0.01; *** - P <0.001)

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Table 2
Clinical and laboratory parameters of patients with generalized peritonitis. The main group (n = 46)

Indicator (norm unit of measure)	Upon enrolment	Postoperative period		
		1 day	3 day	7 day
Body temperature (0C)	38,51±0,23	38,28±0,22	37,51±0,17**	37,1±0,13***
Pulse (bpm)	130,3±2,5	123,7±2,7	96,52±3,02***	84,26±2,5***
Number of leukocytes (4.0-8.8x109 / l)	18,52±0,62	23,32±0,68***	11,92±0,47***	9,42±0,36***
Stab neutrophils (1.0-6.0%)	10,23±0,33	11,07±0,37	5,87±0,24***	1,92±0,08***
Segmented neutrophils (47.0-72.0%)	64,78±2,10	73,35±2,3*	62,28±2,11	56,61±1,9*
Monocytes (3-11%)	5,0±0,17	7,5±0,23***	11,7±0,35***	14,9±0,47***
LII (0.3-1.5 units)	18,37±0,59	7,52±0,27***	3,32±0,11***	2,42±0,09***
ESR (2.5-15 mm / h)	28,34±1,0	35,1±1,2***	23,82±0,93**	18,54±0,68***
Total protein	59,65±2,02	57,39±1,8	61,11±2,1	66,83±2,3*

Note:*- reliable compared with the indicators on admission (* -P <0.05; ** - P <0.01; *** - P <0.001)

As can be seen from Tables 1 and 2, in the control group, the body temperature remained high on the 7th day, while in the main group the temperature dropped to 36.82 ± 0.5. The increased pulse rate up to 92.81 ± 0.75 persisted in the control group on day 7, i.e. endogenous intoxication was maintained, as evidenced by low-grade fever. In the main group, on the 3rd day, the number of stab, segmented neutrophils returned to normal, in the control group - only segmented neutrophils, and stabs only by 7 days. LII in the main group almost returned to normal on day 7, while in the control group this indicator remained above normal. The rest of the indicators remained elevated throughout the observation period. However, the trend towards their normalization was significantly more active in the main group.

ESR in patients of both groups against the background of the existing purulent peritonitis was, naturally, initially high: in the comparison group - 30.8 ± 1.1 mm / h, and in the main group - 28.34 ± 1.0 mm / h. ESR in the main group on the 7th day remained above the norm - 18.88 ± 0.58, and in the control group it was even higher than 23.9 ± 0.87 mm / h. It probably takes a relatively longer period to normalize ESR. Thus, our data allow us to consider the results of treatment of patients in the main group as more favorable. By day 3, the total amount of protein was restored in the main group; in the control group, the protein remained slightly below normal (58.8 ± 1.8).

Analysis of the main biochemical parameters are presented in table 3, namely urea and creatinine in patients of the comparison group and the main group. The initial level of blood urea exceeded the standard values by 1.5 - 2 times, determining the severity of endotoxicosis and organ dysfunction. In the control group, a significant improvement in the indicator was

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noted only by 5 days, but by 7 days it had not yet reached normal values. In the main group, by day 3, a significant positive difference was noted in comparison with the comparison group: by day 5, the urea level became 1.3 times lower than in the control group.
Similar and more significant changes were noted when analyzing the dynamics of creatinine levels. In the control group, a significant decrease in creatinine level occurred only by day 5, which indicated that organ (renal) dysfunction persisted for a long time. In the main group, a more significant effect was achieved - by the 3rd day the creatinine level decreased by 30% from the initial indicator, and by the 5-7th day it was approaching normal values.

Table 3
Dynamics of blood biochemical parameters in patients with different methods of sanitation of the abdominal cavity in the main and control groups

Index	Норма	Groups	Terms (days)			
			1	3	5	7
Urea (mol / L)	2,5-8,3	Control (n = 51)	13,42±0,53	10,43±0,37	9,51±0,34	8,7±0,31
		Main (n = 46)	14,75±0,49*	8,06±0,32***	6,53±0,24***	6,04±0,22***
Creatinine (μmol / L)	44-106	Control (n = 51)	159,8±5,8	154,9±5,3	138,7±4,7	122,6±4,2
		Main (n = 46)	168,3±5,9	118,7±4,7***	108,5±3,8***	105,9±3,6**

Note:*- reliable compared with the indicators of the control group (* -P <0.05; ** - P <0.01; *** - P <0.001)

Changes in the level of total bilirubin in the examined groups, as well as other studied parameters, were within the limits of physiological values. Dynamics of some biochemical parameters in patients in the main and control groups at different times after surgery (Table 4).
The bilirubin level, which was initially elevated in both groups, returned to normal somewhat faster after sanitation of the abdominal cavity using the MS photosensitizer. The above can be attributed to the indicators of AST and ALT, which did not show critical shifts, by the 7th day they were normal.

Table 4
Dynamics of indicators of enzymes and bilirubin

Indicators	Groups	1 day	3 day	5 day	7 day
AST, mmol / h / l ALT, mol / h / l	Main (n = 46)	0,56±0,018*	0,45±0,016*	0,33±0,013*	0,18±0,007***
	Control (n = 38)	0,63±0,021	0,51±0,018	0,37±0,015	0,28±0,011
Bilirubin, μmol / l AST, mmol /	Main	0,59±0,020	0,48±0,017	0,36±0,014*	0,21±0,007*
	Control	0,61±0,023	0,50±0,019	0,42±0,016	0,24±0,009

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h / l					
ALT, mol / h / l	Main	32,1±1,02**	27,4±0,97**	21,6±0,79***	12,5±0,51***
	Control	37,6±1,23	32,5±1,09	26,4±0,92	22,1±0,83

Note: *- reliable compared with the indicators of the control group (* -P <0.05; ** - P <0.01; *** - P <0.001)

- - the data are statistically reliable (p <0.05)
- - basic: reorganization - PDT + MS
- - sanitation with 0.02% chlorhexidine solution

We also analyzed the complications, hospitalization periods and mortality in the studied groups of patients, depending on the method of sanitation of the abdominal cavity with advanced peritonitis (Table 5).

When analyzing the complications that arose in patients operated on for widespread peritonitis, it was revealed that in 6 cases in the group where PDT was used for sanitation, and in 12 cases where 0.02% chlorhexidine solution was used for sanitation. On the 4th - 5th day in the main group, 2 patients showed suppuration of the median wound within the subcutaneous tissue, and in the control group - 6. In 3 patients in the control group and in 2 in the main group, infiltration of the median wound was observed.

In the control group, an abscess of the abdominal cavity (1), acute early adhesive intestinal obstruction (1), relaparotomy (1) due to anastomotic leakage were still observed, and in the main group in the postoperative period there was an acute myocardial infarction in 1 patient of 70 years.

Table5
The structure of postoperative complications in patients with widespread peritonitis

Complications	Main group (n = 46)		Control group (n = 51)	
	abs.	%	abs.	%
Abdominal infiltration	-	-	1	2,0
Abdominal abscess	-	-	1	2,0
Suppuration of a postoperative wound	2	4,3	6	11,8
Postoperative wound infiltrate	3	6,5	2	3,9
Acute early adhesive intestinal obstruction	-	-	1	2,0
Relaparotomy (anastomotic leak)	-	-	1*	2,0
Acute myocardial infarction	1	2,2	-	-
Total	6	13,0	12	23,5

Note: * - 1 patient died after ralaparotomy against the background of ongoing peritonitis and multiple organ failure (terminal phase of peritonitis).

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The small number of observations in this group of complications does not allow making any convincing conclusions. Probably, the latter complication is not associated with the method of sanitation of the abdominal cavity. To resolve the issue of the effect of such a scheme of abdominal sanitation on mortality in advanced purulent peritonitis, studies involving a larger number of patients are required.

Thus, PDT sanitation of the abdominal cavity in peritonitis made it possible to halve postoperative complications in comparison with the control group, when 0.02% chlorhexidine solution was used for sanitation. Moreover, in the main group, the average length of stay of the patient on the bed was 6.5 ± 0.21, and in the control group, 9.3 ± 0.32, i.e. the duration of stay of patients in the main group was reduced by almost 3 days.

In the control group, the duration of treatment was, on average, 9.6 ± 1.7 bed-days, in the main group 6.7 ± 1.4 bed-days (Table 6)

Table 6
Hospital stay (bed-day) in the compared groups

Patient groups	Number of patients	Bed days
Main	46	6,5±0,21*
Control	51	9,3±0,32

Note: *- reliable compared with the indicators of the control group (* -P <0.001)

Statistically, the differences in the incidence of suppurative complications in the area of the postoperative wound indicate the role of the type of sanation in the development of local suppuration. Moreover, it is important that the volume of the sanitizing solution is sufficient to achieve decontamination, the thoroughness of sanitation, the sparing attitude to the wound tissues, adequate hemostasis, the protection of the wound edges from the ingress of infected contents, i.e. all those preventive measures that are important in elective surgery.

The analysis of the results obtained on the clinical study of the developed method of non-pharmacological potentiation of the traditional treatment of various forms of purulent peritonitis on the basis of the experience gained allows us to assert that the PDT method proposed by us contributed to a more rapid relief of the inflammatory reaction in the abdominal cavity and, accordingly, rapid rehabilitation of patients in the postoperative period. The simplicity of the method and its effectiveness, the availability of methylene blue determines the expediency of using PDT in the complex treatment of peritonitis.

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