ACUTE AND CHRONIC TOXICITY STUDY OF MESH IMPLANT WITH NEW COMPOSITE COATING

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Abstract. *Based on the results of a study of the acute toxicity of a mesh implant with a composite coating, the authors came to the conclusion that a mesh implant with a new composite coating can be classified as a low-toxic drug with a single injection. Based on the fact that a single injection of a mesh implant into the abdominal cavity didn`t cause death in animals, according to the currently accepted WHO classification, the toxicity of this composite coating can be classified as mild.*

Keywords: *hernia, mesh implant, toxicity, composite coating, experimental research.*

Introduction. More than 20 million abdominal hernia surgeries are performed worldwide every year, several million of which are combined with synthetic implants. Of these synthetic implants, polypropylene resin surgical kits are most commonly used. The method of implantation is commonly used to study the systemic toxicity of implantable devices and is described in ISO10993 Part 11. However, there is no standard for the amount of material to be implanted for a proper and acceptable assessment of the risk of systemic toxicity. It should be understood that if small amounts of material are implanted, systemic toxicity will not be detected and a false sense of security will be created. For a proper risk assessment, systemic toxicity should be investigated after implantation of an appropriate amount of material. The appropriate amount of material should be calculated based on clinical application, device surface area, and scaled allometrically to test species used for implantation.

Aim of the research is to study the acute and chronic toxicological properties of mesh implant with a new composite coating in experimental animals.

Materials and methods. The implant is a woven polypropylene mesh. Polypropylene has the ability to stimulate the growth of connective tissue, thereby strengthening the connective tissue frame at the site of the hernial defect. A negative property of the mesh made of propylene is an increased tissue reaction to propylene, as well as the presence of micro-slits in the places where the nodes of the mesh are formed, which contributes to the penetration of microbes and their long-term persistence with the development of chronic inflammation.

We have developed a composite coating of the stack, a state of three layers: the side of the mesh that is in contact with the tissues is a 200 micron thick film of a biocompatible absorbable material that has increased adhesiveness and antimicrobial action: Sodium-Carboxymethylcellulose, which is mixed with a 1% solution of methylene blue in the proportion of 1 g of crystalline powder and 0.5 ml of 1% methylene blue solution.

The second layer of a natural biocompatible polymer from cellulose derivatives is a woven polypropylene mesh impregnated with the composition: Sodium-Carboxymethylcellulose + calcium chloride + oxidized viscose in a ratio of 60:25:15. The upper - outer layer of the mesh is a film of cellulose derivatives and glycerin in the ratio of Sodium-Carboxymethylcellulose - 1 g, glycerin 20% 0.5 ml.

The experiments were carried out on 25 white outbred rats with an initial weight of 250-300 g. In accordance with the requirements of ISO 10993-2, under general anesthesia with isoflurane vapor, a median laparotomy 2-3 cm long was performed and a 1x1 cm mesh implant was placed on the diaphragmatic surface of the liver.

The laparotomic wound was sutured in layers. To study acute toxicity, the condition of the operated animals was observed for a week, in the specified order according to GOST ISO 10993-11-2011. Animals were withdrawn from the experiment 1 week after implantation by an overdose of anesthesia. Blood and biopsy material was examined according to the standard method.

To study chronic toxicity, a 1x1cm implant was placed in the abdominal cavity on the diaphragmatic surface of the liver and observed for 1-3 months. After 1, 2, 3 months after implantation, the animals were taken out of the experiment, blood was taken for general and biochemical analyzes. A biopsy of organs and tissues was sent for histological studies.

Results. During the entire observation period, no significant signs of changes in the clinical condition and behavior of the experimental animals were observed. No delayed death of animals was noted during the observation period. In our study group, there were no significant changes in the amount of food and water consumed compared to the rats in the control group. Throughout the experiment, the dynamics of body weight growth of animals was positive.

The rates of body weight gain in groups with a mesh implant with a composite coating compared with the control group (intact animals) did not differ significantly and were not statistically significant (Table 1).

To assess the state of the internal organs, an integral indicator used in toxicology was determined, the mass coefficient (MC) - the percentage ratio of the mass of the organ to the body mass.

The analysis of this indicator in toxicological studies makes it possible to detect a toxicant in the organs, to identify signs of endocrine-related effects. The mass coefficient determines the state of the internal organs.

Table 1

Dynamics of body weight in rats after implantation of a mesh with a composite coating into the abdominal cavity.

Group of animals	Initial data (gr)	7 days	1- month	2- month	3- month	Body weight gain, %
Control group	280±0,05	288±0,05	322.5±0,05	344±0,05	355±0,05	+ 26,7
1 group acute toxicity	330±0,05	335.4±0,05	-	-	-	+ 1,5
2 group chronic toxicity	331±0,05	338.4±0,05	370,5±0,05	390±0,05	400±0,05	+ 20,8

P <0.05

From the results presented in Table 2, it follows that the introduction of a mesh implant into the abdominal cavity of rats did not lead to a significant change in the mass coefficients of their internal organs compared to control animals.

At the same time, in rats of the studied groups, a significant increase in the ratio of liver weight to body weight was established, however, the mass coefficients for the kidneys and spleen did not differ from those of intact animals, and quantitative changes were not statistically significant.

Table 2

Mass coefficients of the internal organs of rats after the introduction of a mesh implant into the upper part of the liver sac of the abdominal cavity

Organ	Groups				
	Control	Experience			
		7 days	1 -month	2 -month	3 -month
Kidneys	2,3±0,05	2,5±0,05	2,3±0,05	1,9±0,05	2,6±0,05
Spleen	0.9±0,05	1.16±0,05	1.16±0,05	0,8±0,05	1,3±0,05
Liver	9±0,05	10±0,05	11,4±0,05	9±0,05	12,8±0,05

P <0.05

At the end of the experiment, blood samples were taken from animals from each group for morpho- and biochemical studies. Changes in morphological parameters of blood are shown in Table 3.

Table 3

Morphological parameters of the whole blood of rats after the upper part of the hepatic sac of the abdominal cavity introduced a mesh implant

Indicators	Groups				
	Control	Acute toxicity	Chronic toxicity		
			1- month	2- month	3- month
Hemoglobin	156±31.51	146,4±24.54	136,6±65.9	110±13.9	133±15.5
Erythrocytes	8.2±0.57	7,7±0.61	7,76±0.46	7±0.59	7,8±0.55
Thrombocytes	826±32.1	945,2±27.8	750±30.5	806±35.2	961±32.5
Leukocytes	5.4±0.55	7,8±0.64	9,5±0.49	7,35±0.43	7,2±0.5
Band neutrophils	1±0,2	4,8±0,35	11±0,45	14±0,68	4,6±0,3
Segmented neutrophils	15±0,2	18,2±0,36	19,6±0,4	22,5±0,65	12,3±0,15
Eosinophils	1±0,2	1±0,2	1±0,2	0	1±0,2
Monocytes	3±0,45	6,4±0,66	5,2±0,58	0	4±0,5
Lymphocytes	80±0,69	69,8±0,55	63,4±0,5	63,4±0,5	80±0,69

P>0.05

No significant differences in hematological parameters (erythrocytes, hemoglobin, leukocytes, lymphocytes, monocytes, eosinophils) in comparison with the control group of animals were registered in acute and chronic experiments with implantation of a mesh with a composite coating in laboratory animals. The level of the studied parameters corresponded to the parameters comparable with the physiological parameters in the control group of animals.

Table 4

Biochemical parameters of blood serum of rats

Indicators	Control	Experience			
		Acute toxicity	Chronic toxicity		
ALT, U/l	43.5±2	53.6±2.8	52.8±2.5	71.5±3.3	79±3.6
AST, U/l	70±4.3	61 ± 3.5	24±1.5	24.6±1.56	26.2±1.8
Chol, mM/l	1.4±0.14	1.4±0.14	1.6±0.2	1.5±0.18	1.4±0.14
GLU, mM/l	4.4±0.4	8.6±0.66	6.6±0.5	6.2±0.49	5.9±0.45
TP, gr/l	77.5±1.46	65.9±1.25	70.7±1.34	79±1.49	76.6±1.45

BIL-T, mkM/l	6±0.5	7.3±0.66	6.4±0.52	10±0.85	6.3±0.48
BIL, mkM/l	6±0.5	7.3±0.66	6.4±0.52	10±0.85	6.3±0.48

P>0.05

In the biochemical assessment of blood serum (Table 4), the difference in the animals of the experimental and control groups in the content of total protein, glucose, cholesterol, total bilirubin, as well as the activity of AST, ALT enzymes was insignificant, the level of the studied parameters corresponded to the parameters of the physiological norm for this type of animal.

Conclusion. According to the results of the study of acute toxicity of a mesh implant with a composite coating, toxicometry data, observation of experimental animals in the post-intoxication period of acute poisoning, as well as necropsy results were obtained, which made it possible to attribute the above-mentioned agent to the class of low-toxic drugs with a single injection. Based on the fact that a single introduction of a mesh implant into the abdominal cavity did not cause the death of animals, according to the current WHO classification, the toxicity of this drug can be classified as non-expressed. In accordance with GOST 12.1.007-76, according to the degree of toxicity, the study drug belongs to the IV class of hazard - substances of low hazard.

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