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К ВОПРОСУ О ВЫБОРЕ ОБЛАСТИ РАЗМЕЩЕНИЯ ТЕСТИРУЕМЫХ ОБРАЗЦОВ ПОЛИМЕРНЫХ ИМПЛАНТОВ ПРИ ИЗУЧЕНИИ РЕАКЦИИ ТКАНЕЙ МАКРООРГАНИЗМА

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Цель. Оценка особенностей различных методик имплантации и аутопсии участков тканей в местах размещения полимерных эндопротезов.

Материалы и методы. В подкожную клетчатку брюшной стенки и паравертебральной области 30 крысам имплантировали образцы новых сосудистых эндопротезов (ООО «Линтекс», г. Санкт-Петербург). Оценивали морфологические изменения в местах размещения имплантов, а также вариативность значений разработанных авторами критериев. Результаты, полученные в ходе исследования, оценивались экспертами по выраженности артефактов на микрофотографиях, предполагаемой вероятности повреждения ложа импланта в процессе эксперимента и аутопсии, предположительной технической сложности получения образца импланта и перипротезной капсулы при аутопсии.

Результаты. Сумма баллов достигает наиболее высоких значений (59) в группе исследования реакции тканей лабораторных животных, которым имплантировали тестируемые образцы в подкожно-жировую клетчатку спины, что определяет ее как менее предпочтительную. Вариабельность и погрешность методики подкожной имплантации выше в группе, в которой применяли способ имплантации образцов в паравертебральную область, так как значения стандартного отклонения (m) при гистологическом исследовании в данной группе эксперимента (от 0,89 до 3,64) превышают значения стандартного отклонения животных, подверженных имплантации тестируемых эндопротезов в брюшную стенку (от 0,25 до 2,54).

Выводы. Имплантация в области брюшной стенки отличается меньшей вариабельностью стандартного отклонения (m) морфометрических показателей, малым числом артефактов и практически полным отсутствием технических затруднений проведения аутопсии исследуемого материала, что, по мнению авторов, делает этот метод предпочтительным при проведении экспериментальных исследований.

Ключевые слова: *имплантат; биосовместимость; имплантация; капсула; операция; тканевая реакция; доклинические исследования.*

MORE ON CHOICE OF PLACES FOR INSERTION OF TESTED SAMPLES OF POLYMER IMPLANTS IN STUDY OF REACTION OF TISSUES OF MACROORGANISM

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Aim. Assessment of different methods of implantation and autopsy of portions of tissue at the sites of insertion of polymer implants.

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Materials and Methods. Samples of new vessel prostheses (OOO Lintex, Saint Petersburg) were implanted into the subcutaneous layer of the abdominal wall and paravertebral area of 30 rats. Morphological changes at the sites of insertion of implants, and also variation of the values of criteria developed by the authors were evaluated. The results obtained in studies, were evaluated by experts on the basis of the evidence of artefacts in microphotographs, of expected probability for damage to the implant bed in the experiment and in autopsy, of expected technical complexity of getting a sample of the implant and of the periprosthetic capsule in autopsy.

Results. The total score of evaluated tissue reactions reached the highest meanings (59) in the group of laboratory animals where the tested samples were implanted into the subcutaneous tissue of the back, which determines this method as least preferable. Variability and error of the method of subcutaneous implantation was higher in the group with implantation of samples into the paravertebral area, since the values of standard deviation (m) in histological examination of this group (from 0.89 to 3.64) exceeded deviations in animals with implantation of the tested prosthetic implants into the abdominal wall (from 0.25 to 2.54).

Conclusion. Implantation in the area of the abdominal wall is characterized by lower variability of standard deviation (m) of the morphometric parameters, by lower number of artefacts and by almost complete absence of technical complications in autopsy of the studied material, which, in the opinion of the authors, gives preference to this method in experimental research.

Keywords: *implant; biological compatibility, implantation; capsule; operation; tissue reaction; preclinical trial.*

Reconstructive surgical interventions, mostly conducted on hollow and tubular organs, and also on the abdominal wall, often require use of plastic material for recovery of the damaged area. A promising trend of modern surgery of implants is development of new prosthetic implants that can adequately replace the structure lost by the organ, and even its function [1,2]. This demand stimulated search for actual technologies and materials for production of inert implants of the latest generation possessing most positive physical, mechanical and structural properties [3,4].

As it was noted by researchers, these parameters play the main role in the response of an organism to implantation of polymer mesh implants [5,6]. At present there exist numerous methods of modeling and of evaluation of the evidence of inflammatory and regenerative processes at the site of implantation of new samples of polymer conduits (including methods of placement of implants in an organism of laboratory animals, techniques of surgical intervention, use of different cell indices, descriptive classifications, etc.) [7-9]. We think it necessary to conduct a comparative study of different methods of placement of the tested samples of vascular patches in laboratory animals [10-12], since this permits to optimize planning, conduction of scientific research and preclinical trial of implant samples.

The *aim of study* was a comparative analysis of different methods of subcutaneous implantation of tissue endoprostheses and of complicacy of evaluation of the obtained results.

Materials and Methods

The materials tested in the given study were warp-knitted samples of vascular patches of polyethylene-terephthalate (OOO Lintex, Saint-Petersburg). The study was conducted on 30 rats of Wistar line of 200-

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250 g mass (15 animals in each experimental group). The animals were kept in the conditions of the experimental biological clinic of Kursk State Medical University.

The study was conducted with approval and under observation of the regional ethical committee at Kursk State Medical University. All procedures on animals were performed under general inhalation anesthesia (anesthesia apparatus R340 Isoflurane, RWD Life Science of Hi Tech North Rd, Nanshan Dist, People's Republic of China); with concentration of isoflurane (Baxter, USA) in the inhaled mixture 2.5%, air flow 0.6 L/min, with observance of the international and Russian norms of laboratory animals welfare: Directive 2010/63/EU of the European Parliament and European Union of September 22, 2010 on Protection of animals used for scientific purposes, Order of Healthcare Ministry of Russia №199н of April 01, 2016 «On Approval of Rules of Good Laboratory Practice», Order of Healthcare Ministry of Russia №755 on August 12, 1977 «On Measures of Further Improvement of Organization Forms of Work with Use of Experimental Animals», etc. [13,14].

The study was conducted in two stages. The 1st stage consisted in experimental modeling of two different variants of subcutaneous implantation of samples (on the ventral and dorsal body surface) in all laboratory animals, and in micro- and macromorphological evaluation of the local alterations. In the 2nd stage the studied methods and results of their use were analyzed by experts.

The two kinds of surgical interventions were made on animals in the surgery unit of the laboratory of experimental surgery and oncology of Research Institute of Experimental Medicine.

The technique of the 1st kind of surgery (1st group) was as follows: in the rats, the skin and subcutaneous layer were dissected along the abdominal midline (length of cut 4 cm), using a blunt method two pockets were formed in the subcutaneous layer (between muscle layer and skin) on both sides of the cut of 3.5 m depth along the entire length of the cut. Into each pocket a sample of vascular patch was placed (2x2 cm). The surgical wound was hermetically sutured with capture of the muscle layer for insulation of pockets with the experimental sample (Figure 1).

A peculiarity of the second type of surgery (2nd group) was a choice of a place for subcutaneous insulation of patches. Here, the implant was placed in the subcutaneous layer of the paravertebral zone of a rat, using the same technique and sequence as in the first kind of the operation.

The animals were withdrawn from the experiment on the 14th day after the implantation. In each case autopsy was conducted with excision of a portion of tissue on the right and on left of the postoperative scar with extraction of the implant sample (in a complex with periprosthetic capsule). The obtained biological material was fixed in 10% neutral formalin solution. Histologic preparations made according to standard methods, were stained by Mallory method and with hematoxylin and eosin.

The preparations were microscoped in Livenhuk 320 microscope (Levenhuk Ltd., USA) with x100 and x400 magnification power. For morphometric evaluation photos were taken with use of Livenhuk c310 digital attachment (Levenhuk, Ltd., USA) and Scope Tek ScopePhoto program (version x86, 3.1.268, Scope Tek, USA).

On the obtained microphotos the structure of the connective-tissue capsule, distinctness of its layers and the degree of maturation of collagen fibers were evaluated. Besides, composition of cell layer immediately surrounding the fibers of prosthesis was examined. In each experimental group cell index (CI) was evaluated – ratio of cells of fibroblastic group (residents) to cells of inflammatory infiltrate (non-residents).

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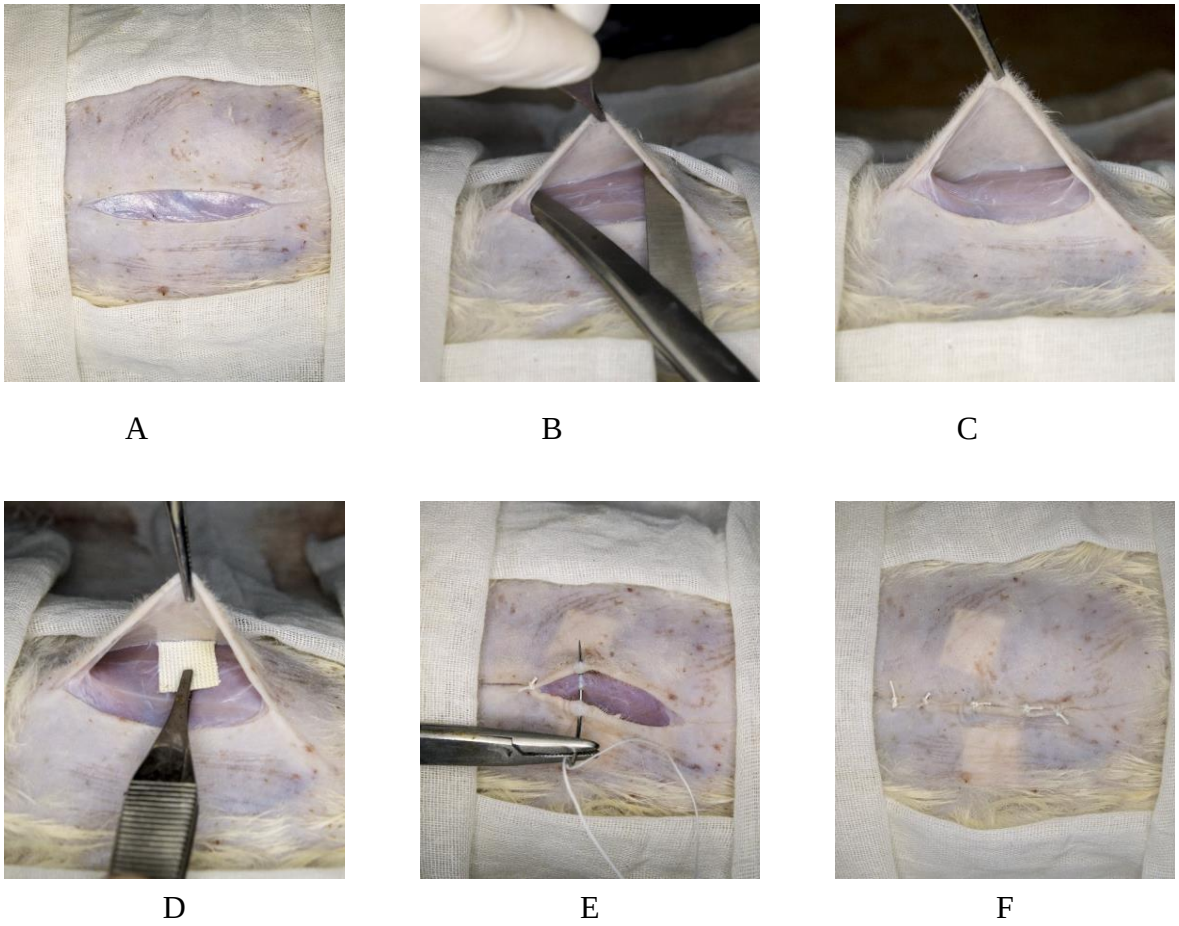

Fig. 1. Stages of implantation of samples into the subcutaneous tissue of rats:
A – dissection of skin, B-C – formation of pocket between skin and muscles of the ventral wall,
D – positioning of implant in the formed pocket, E – suturing of skin with capture of muscle layer,
F – interrupted sutures applied on the wound

Below the formula is given used for CI calculation:

$$\text{Cell index (CI)} = \frac{\text{Resident cells}}{\text{Non-resident cells}},$$

where resident cells – the total amount of macrophages, fibroblasts and fibrocytes; non-resident cells – the total amount of leukocytes in the cell layer of capsule

CI <1 evidenced predomination of inflammatory alterations characteristic of I phase of the wound process, CI >1 evidenced predomination of reparative tendencies characteristic of II phase of inflammatory process (according to M.I. Kuzin) [2].

The obtained results were statistically processed using descriptive statistics (calculation of arithmetic means, of standard deviations) and variation statistics methods. Reliability of mean difference was determined using non-parametric Mann-Whitney test. Statically significant were considered differences at $p \leq 0.05$. As software environment, Statistica 6.0 program (Stat Soft Inc., USA) was used for data processing.

In the 2nd stage of study, visual data arrays were formed including a pair of micro- and macrophotographs illustrating a transverse section of implanted sample and the exterior view of the postoperative scar on the 14th day after implantation. Besides, descrip-

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tion of the operative technique of used implantation methods was submitted to the experts. In the study, five experts having experience in conduction of acute and chronic surgical experiments participated. The evaluation was conducted in a competitive comparative aspect between the two experimental groups.

The criteria for evaluation were subjectively evaluated amount of artefacts in microphotographs, expected probability of damage to the implant bed in the course of experiment and autopsy, expected technical difficulty of obtaining a sample of implant and of periprosthetic capsule in autopsy. Each criterion was evaluated by experts on a five-point scale (with 1 being a maximal positive mark, meaning absence of artefacts, minimal complexity of autopsy and of probability for sample damage, and 5 – maximal negative mark). After that the obtained values were summated and tabulated.

Results and Discussion

The parameter «Presence of artefacts» characterized an entire array of events that in complex may influence the result of micromorphological study of periprosthetic tissues surrounding the samples. These criteria may include: location of bone structures in close vicinity to the site of implant (illustrative are artefacts in the preparations of the 2nd experimental group with implantation of the material in the paravertebral region), formation of calcifications, necrosis, defects of periprosthetic capsule in result of ingrowth of its fibrous elements into the bone-muscle basis.

In the 2nd group the values of this parameter were twice as high as in the 1st. The presence of artefacts was shown to be directly dependent on the evidence of postimplantation inflammation (hypervolemia, edema, deformation of cell structures caused by influence of differently directed forces: tight fixation of the implant to the surrounding tissue through connective-tissue fibers of the capsule, and active movements of the animal causing muscle tension and defect of the capsule, Table 1).

Table 1

Comparative Characteristic of Parameters Evaluated by Experts, points

Parameter	Group 1	Group 2
Existence of artefacts	5	21
Probability of damage to implant bed	10	18
Technical difficulties of autopsy of studied material	10	20
In total	**25**	**59**

Note: In the table the average scores are presented given by five experts in evaluation of each separate parameter

Criterion «Probability for damage to the implant bed» is indirectly related to the criterion «Existence of artefacts» and is determined by the extent of involvement of the animal's self tissue into the wall of the periimplantation capsule. This is the result of traumatization of the place of insertion of transplant in the process of its vital activity or in palpation and autopsy. In the 2nd experimental group the experts more negatively evaluated this criterion, than in the 1st group which can be explained by topographo-anatomical peculiarities of the paravertebral zone of rats (comparatively thinner muscular basis, higher amount of bone elements: scapulae, cervical and thoracic sections of the spine, ribs).

«Technical difficulties of autopsy of the studied material» (a higher value was noted in the 2nd group, lower value – in the 1st) is the

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key evaluation criterion, since it is most important for obtaining a good section of the wall of periprosthetic capsule. In evaluation the experts were guided by subjective total influence of the following peculiarities of autopsy at the given site of the implant: the volume of surgical intervention, time of autopsy, access to the implantation site, non-uniformity of tissues (skin, subcutaneous tissue, muscle layer, bone structures) that conditioned the labor intensity and complicacy of the isolation of the sample. Ranking of the methods was based on calculation of the total score for each.

In our opinion, the probability for suppuration in animals was higher in the 1st group with implantation of the tested samples into the subcutaneous layer of the abdominal wall. This is associated with the fact of location of the postoperative scar on the lower surface of the animal's body due to which it was in permanent contact with the contents of the bottom of the cage which resulted in infection of the wound and of the implantation zone. To note, cases of suppuration were also noted among rats with implantation of the studied samples into the subcutaneous tissue of the paravertebral zone which was due to gnawing of sutures by other animals present in the cage. Animals in whom suppuration was noted were rejected on the 14th day of the experiment. This complication was seen in two animals of the 1st group and in three in the 2nd group.

The data obtained in examination of histological reparations are given below (Table 2).

Table 2

Ratio of Different Types of Cells in Cell Layer of Periprosthetic Capsule in Different Method of Implantation, M±m

Parameter	Group 1	Group 2	p
Fibroblasts	32.70±2.54	27.80±3.64	0.0001
Fibrocytes	29.70±2.31	31.40±3.50	0.13
Lymphocytes	10.60±2.27	9.60±1.75	0.0023
Macrophages	5.00±2.16	7.90±2.84	0.008
Neutrophils	9.30±2.00	11.40±2.59	0.41
Eosinophils	3.80±1.62	4.80±1.62	0.17
Monocytes	8.90±2.02	7.10±2.44	0.00002
Cell index	2.11±0.25	2.13±0.89	0.00004

Demonstrative results of morphometric study are the standard deviation values (m), since it is this parameter of dispersion that characterizes spread of the obtained values. This, in turn, permits to make a judgement about the extent of influence of the so called stochastic factors on the course of study. In the 2nd group m values (from 0.89 to 3.64) practically in all cases of counting cell elements exceeded m values of the 1st group (from 0.25 to 2.54), except for the quantity of lymphocytes, standard deviation of which was higher in the 1st group (2.27) than in the 2nd group (1.75). Accordingly, variability and error of the subcutaneous implantation method were higher in the 2nd group. This was confirmed by a low variability and a high spread of standard deviation values (m).

On the basis of the mentioned above data (Table 1), group 1 (implantation of the tested samples into the subcutaneous tissue of the abdominal wall) with the lowest score, in the experts' opinion, had an undoubted advantage. This subjective expert evaluation

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was confirmed by the results of objective morphometric examination (Table 2), which permits to say that implantation of the tested samples into the paravertebral region shows a higher error in calculations due to low variability and high spread of the standard deviation values (m).

However, speaking about the current publications describing methods of evaluation of the evidence of tissue reactions in *in vivo* chronic experiments with indication of the technique of surgical intervention, it should be noted that different scientific schools follow different ways in the experimental surgery (including those described in the given work) [1,4,5,8,9]. In our opinion, this can be attributed to a low amount of freely available works on testing of the materials implanted into a macroorganism.

Besides, this question remains debatable due to the absence of the pool of necessary normative documents regulating evaluation of the properties of the implanted sample. This is associated with a considerable variety of such samples (by shape, material, purpose, etc.). Thus, from such normative legal documents the following should be marked GOST R ISO 25539-2-2012: cardiovascular implants. intravascular implants, which clearly regulate the sequence and method of evaluation of the mentioned medical products.

Conclusions

1. The score of negative evaluation of experts was highest (59) in the experimental group of laboratory animals with implantation of the tested samples into the subcutaneous tissue of the back which determines this method as least preferable.

2. Variability and error of the method of subcutaneous implantation were higher in the group with implantation of the samples into the paravertebral region, since the standard deviation values (m) in histologic examination in this group (from 0.89 to 3.64) exceeded the standard deviation values for animals with implantation of tested endoprostheses into the abdominal wall (from 0.25 to 2.54).

3. In result, in a study of reaction of tissues of laboratory animals the more optimal method was recognized to be implantation of the tested samples into the subcutaneous tissue of the abdominal wall of rats.

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Дополнительная информация [Additional Info]

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