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Experimental Evaluation of the Anti-Adhesion Activity of Sodium Carboxymethylcellulose-Based Hydrogel

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Abstract: Purpose of the study. To evaluate the ant proliferative effect of a Na-CMC (carboxymethylcellullose) hydrogel in modulating the adhesion process in the abdominal cavity using experimental models with white rats.

Materials and methods. The experiment was conducted on 100 mature outbred female rats weighing 160-180 grams. The adhesion process in white rats was induced using a standard method: under general anesthesia, a midline laparotomy was performed, the cecum was brought out into the wound, and the adhesion process was modeled by deserosalizing the cecum with a gauze pad.

Results: The study demonstrated that the use of Na-CMC-based hydrogels significantly reduces the severity of the adhesion process in the abdominal cavity. The 3.5% hydrogel, in particular, was found to be especially effective, showing the least severity of adhesions on both the 7th and 10th days.

Conclusion: This study confirmed that Na-CMC-based hydrogels effectively reduce the severity of the adhesion process in the abdominal cavity.

Keywords: abdominal adhesions, hydrogel, carboxymethylcellullose.

Introduction. Understanding the processes of scarring plays a crucial role in developing management strategies for wound healing after glaucoma surgeries, as it allows for the optimization of surgical outcomes and the prevention of potential complications. Targeted intervention at various stages of the scarring process is a key approach in correcting surgical wound healing not only in glaucoma surgery but also in other areas of medicine [1,4,7].

Developing methods aimed at regulating inflammation, stimulating tissue regeneration, and controlling scar formation will improve surgical outcomes and accelerate the healing process [3,5]. Research [1,6,11] in the fields of molecular biology, polymer chemistry and physics, as well as pharmacology, allows the identification of new target molecules and pathways that can be used to optimize the healing process. This opens new opportunities for creating innovative treatment methods and preventing complications after surgeries. Therefore, molecularly targeted intervention at various stages of the scarring process is a promising strategy that can significantly improve surgical outcomes and enhance the quality of life for patients [8,9,10].

One of the ways to prevent adhesion formation is to create a temporary "barrier" by covering the damaged tissue areas with a hydrogel that degrades and absorbs over time during mesothelial recovery.

Currently known "barriers" such as Seprafilm (Genzyme), Interceed, and Oxiplex (FzioMed) are not widely used in Uzbekistan due to their high cost [3,6,12].

At present, researchers at the Institute of Polymer Chemistry and Physics of the Academy of Sciences of Uzbekistan have developed an inexpensive biodegradable bio-gel based on Na-carboxymethylcellulose (CMC) using local raw materials derived from polysaccharides, which are of interest as anti-adhesion agents. The hydrogel based on Na-CMC, a polymer included in clinically used preparations (Seprafilm, Oxiplex), has great potential for practical medical applications, including glaucoma surgery.

Objective of the study. To investigate the antiproliferative effect of the Na-CMC-based hydrogel in modulating the adhesion process in the abdominal cavity in experiments on white rats.

Materials and Methods of the Study.

The Ethics Committee of Tashkent Medical Academy granted permission (protocol No. 10 dated May 25, 2023) for conducting experimental studies on laboratory animals using the Na-CMC-based hydrogel. Measures to limit pain and suffering in the experimental animals, which did not contradict the study design, were implemented. The work with animals was carried out by qualified personnel who had received appropriate training.

The study of the antiproliferative effect of the Na-CMC-based hydrogel in modulating the adhesion process in the abdominal cavity was conducted on 100 adult female outbred rats with a body weight of 160-180 grams. The body weight of the animals selected for the study did not differ from the average body weight of rats by more than 20% (±10%).

The animals were kept under standard laboratory animal housing and care conditions. They were maintained in a controlled environment (18-22°C and relative humidity of 50-70%) under a natural light cycle. The rats were housed in standard plastic cages, 10 per cage, and fed a standard diet according to their age-related nutritional needs. All laboratory animals were active and appeared healthy.

Characteristics of the Na-CMC-based Hydrogel. The preparation was developed at the Institute of Polymer Chemistry and Physics of the Academy of Sciences of Uzbekistan by Professor A.A. Sarimsakov. The development is protected by a patent of the Republic of Uzbekistan (Patent Priority IAP No. 20110496 dated 28.11.2011).

Description of the Medical Product. The anti-adhesion, resorbable, sterile hydrogel appears as a homogeneous, transparent, colorless, odorless gel with high viscosity. The molecular weight (according to international atomic masses 242 g) is 46,000-138,000 daltons. The degree of substitution by carboxymethyl groups (DS) is 0.86. Composition: Active ingredient: purified carboxymethylcellulose; Excipients: water.

Method of Administration and Dosage Selection. The Na-CMC-based hydrogel is applied to the tissue in the surgical area after completing the main stage of the operation. In open surgeries, the hydrogel is squeezed from a syringe directly onto the tissue. In laparoscopic surgeries, it is squeezed from a syringe and applied to the tissue using a polymer tube. The amount of gel administered is determined by the specific situation and application area.

The product is available as sterile hydrogels in polymer tubes of 30 g or syringes of 1.5 g; 2.0 g; 3.0 g; 4.0 g; 5.0 g; 10 g; 20 g; 50 g; 100 g.

Experimental Design. The experiment was conducted on 100 adult female outbred rats with a body weight of 160-180 grams. It was performed under aseptic conditions in the operating room of the Central Research Laboratory of TMA. The adhesion process in white rats was induced by a standard method as follows: under general anesthesia, a midline laparotomy was performed, and the cecum was exteriorized. The adhesion process was modeled by deserosalizing the cecum with a gauze swab.

The animals were divided into 10 groups of 10 rats each:

Group 1 - intact animals;

Group 2 - sham-operated animals;

Group 3 - sham-operated animals + 1 ml of 0.9% NaCl solution;

Group 4 - sham-operated animals + 1 ml of 3.5% Na-CMC-based hydrogel;

Group 5 - adhesion process, no administration in the abdominal cavity;

Group 6 - adhesion process + 1 ml of 3.5% CMC solution;

Group 7 - adhesion process + 1 ml of 3.0% Na-CMC-based hydrogel;

Group 8 - adhesion process + 1 ml of 3.5% Na-CMC-based hydrogel;

Group 9 - sham-operated animals + 1 ml of 3.0% Na-CMC-based hydrogel;

Group 10 - sham-operated animals + 1 ml of 3.5% Na-CMC-based hydrogel.

Various solutions were administered to groups 3, 4, 6, 7, 8, 9, and 10. Surgeries and all manipulations with the animals were performed using general anesthesia in accordance with the "Rules for the Humane Treatment of Laboratory Animals" and the "Rules for Conducting Work with Experimental Animals."

A macroscopic scale was used for the quantitative assessment of the severity of the adhesion process in the abdominal cavity of the laboratory animals [2].

Table 1. Macroscopic Scale for Assessing the Severity of the Adhesion Process in the Abdominal Cavity

Score	Number of Adhesions	Structure of Adhesions	Spread of Adhesions	Deformation of Intestinal Tube
0	No adhesions	None	None	None
1	Single adhesion between organs or between organs and the abdominal wall	Filmy	1 anatomical region (in our case, the cecum)	Mild deformation without lumen narrowing
2	2 adhesions between organs or with the abdominal wall	Loose, avascular	1 level of the abdominal cavity (cecum + other organs)	Moderate deformation without lumen narrowing
3	More than 2 adhesions between organs or with the abdominal wall	Dense, avascular	2 levels of the abdominal cavity	Deformation, narrowing up to 1/2 of the lumen
4	Adhesion conglomerate	Dense, vascularized	More than 2 levels	Severe deformation, narrowing more than 1/2 of the lumen

For statistical processing of research results, the standard MC Office 2016 software package was used.

Results.

On days 7 and 10 from the start of the experiment, visualization of the abdominal cavity of the operated animals was performed. Below is a description of the dynamics of the adhesion process visualization in the abdominal cavity of experimental and control white rats.

Group 1: Day 7: No adhesion process, the scar is in the regeneration stage.

Group 2: Day 7: No inflammatory process, suture material encapsulated.

Group 3: Day 7: No inflammatory process, suture material encapsulated.

Group 4: Day 7: No inflammatory process, suture material encapsulated.

Group 5: Day 7: Pronounced inflammatory process, presence of purulent-serous fluid, hyperemia, fibrin deposits, and loose adhesions between the peritoneum and the omentum. The omentum is loosely adhered to the small and large intestines. Day 10: The omentum is tightly adhered to the peritoneum forming a dense conglomerate, with no signs of inflammation, indicating the formation of a mature adhesion process in the peritoneum.

Group 6: Day 7: Pronounced inflammatory process, presence of purulent-serous fluid, hyperemia, fibrin deposits, and loose adhesions between the peritoneum and the omentum. The omentum is loosely adhered to the small and large intestines. Day 10: The omentum is tightly adhered to the peritoneum, with no signs of inflammation, indicating the formation of a mature adhesion process in the peritoneum.

Group 7: Day 7: The inflammatory process persists, with a small amount of purulent-serous fluid, mild hyperemia. Presence of fibrin deposits in the form of threads between the peritoneum and the omentum. The omentum is loosely adhered to the intestines. Day 10: The omentum is partially adhered to the peritoneum with foot-like structures, no inflammation, only elements of a mature adhesion process in the peritoneum.

Group 8: Day 7: Persistent signs of inflammation, hyperemia with slight accumulation of serous fluid. The omentum is loosely adhered to the intestines. Day 10: Presence of fibrin deposits between the peritoneum and the omentum in the form of loose formations on 2-3 foot-like structures. Only areas of mature adhesion process in the peritoneum are present.

Group 9: Day 7: No inflammatory process, suture material encapsulated. Day 10: Complete scar formation of the surgical wound, suture material organized, easily movable. The scar surface is covered with a dry crust.

Group 10: Day 7: No inflammatory process, suture material encapsulated.

Day 10: Complete scar formation of the surgical wound, suture material organized, easily movable. The scar surface is covered with a dry crust.

Table 2 below shows the results of the analysis of the severity of the adhesion process in the abdominal cavity (total score) in the studied groups 5, 6, 7, and 8.

Table 2. Results of Comparative Analysis of Adhesion Process Severity in the Abdominal Cavity (Total Score) in the Studied Groups

Time Point	Group 5 Adhesion Process, Nothing Introduced into the Abdominal Cavity (n=10)	Group 6 Adhesion Process + 1 ml 3.5% CMC Solution (n=10)	Group 7 Adhesion Process + 1 ml 3.0% Na-CMC Hydrogel (n=10)	Group 8 Adhesion Process + 1 ml 3.5% Na-CMC Hydrogel (n=10)
	M±m	*M±m*	*M±m*	*M±m*
Day 7	11,6±1,71	11±1,33	7,1±1,45 [5,6]	5,9±1,2 [5,6]
Day 10	12,9±0,74	11,3±1,06	6,3±1,77 [5,6]	4,7±2,0 [5,6]

*- *statistically significant compared to the indicators on day 7 at p<0.05*

5 - statistically significant compared to the indicators of group 5 at p<0.05

6 - statistically significant compared to the indicators of group 6 at p<0.05

7 - statistically significant compared to the indicators of group 7 at p<0.05

The data show that the adhesion process was most pronounced in the control group (Group 5). The introduction of a 3.5% CMC solution (Group 6) did not show significant reduction in the adhesion process compared to the control group. However, in Groups 7 and 8, where Na-CMC hydrogels were used, a significant decrease in the severity of the adhesion process was observed. Comparison of the results on day 10 with those on day 7 indicates that in the control group (Group 5), the severity of the adhesion process increased. In Group 6, which received a 3.5% CMC solution, a slight increase in the adhesion process was also observed. The greatest reduction in the adhesion process on day 10 was recorded in Group 8, which used a 3.5% Na-CMC hydrogel. The study results demonstrate that the use of Na-CMC hydrogels significantly reduces the severity of the adhesion process in the abdominal cavity. This is especially noticeable with the use of the 3.5% hydrogel, which showed the lowest severity of the adhesion process on both day 7 and day 10.

Discussion

One of the aims of the study was to identify the anti-adhesive properties of the Na-CMC hydrogel. According to literature data [1,3,4,5], the adhesion process is initiated by inflammation and activation of fibrinogenesis involving amino acid residues. Subsequently, fibrinogenesis culminates in the formation of connective tissue, which ultimately causes adhesion disease.

The Na-CMC-based hydrogel is intended for use in the biological environment of the human body as a preventive measure against adhesion formation during open and laparoscopic surgeries on internal organs and tissues, as well as during anti-glaucoma surgeries in ophthalmology, where there is a risk of postoperative adhesions or excessive scarring of soft tissues. The Na-CMC-based hydrogel creates a temporary artificial "barrier" that prevents the contact of organs and tissues during healing and is then gradually absorbed and completely eliminated from the body within one to three months, depending on the density and amount of gel introduced. It does not have general toxic, allergenic, or locally irritating effects. By creating a "barrier" and a protective hydrophilic film, the Na-CMC-based hydrogel prevents the adhesion of organ and tissue surfaces, thus preserving normal anatomy and preventing the formation of coarse adhesions. The Na-CMC-based hydrogel has regenerative, antiproliferative properties, and its high viscosity ensures prolonged contact with tissues and even distribution over the surface. The product is not mutagenic, teratogenic, carcinogenic, or embryotoxic.

Conclusion

The study confirmed the effectiveness of Na-CMC-based hydrogels in reducing the severity of the adhesion process in the abdominal cavity. Special attention should be given to the 3.5% hydrogel, which showed the highest efficacy. The above findings highlight the high potential of this agent for preventing scarring in glaucoma surgery, necessitating further research in this area.

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