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BIOTECHNOLOGY IN SURGERY: POLYPROPYLENE MESHES INCORPORATED WITH CHITOSAN AND ANTIBIOTICS IN THE TREATMENT OF PERITONEOTOMY IN RATS - PRELIMINARY STUDY

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ABSTRACT

Introduction: Surgical meshes are common in peritoneostomies to control damage and reduce mortality in critically ill patients. The use of chitosan provides anti-adherence to the polypropylene mesh and the addition of antibiotics reduces the rate of infections. ***Objective:*** To create and test biocompatible film involving chitosan associated or not with antibiotics, by nanotechnology, and to identify adhesions when in direct contact with the abdominal viscera. ***Methods:*** In vivo experimentation in Wistar rats, with random division, according to the Reduce, Refine and Replace principles. In two of the four groups, there was an association of antimicrobial on the mesh. One animal from each group had the greater omentum removed. In the end, the animals were killed without suffering. **Results:** There was no adhesion between the polypropylene mesh and the viscera. Granulation tissue and total incorporation of the material under test were observed, indicative of biocompatibility. Two animals in the group without antibiotics developed ulceration. ***Discussion:*** The sustainable and low-cost experiment represents an advance in Biotechnology and an alternative in the care of patients undergoing peritoniostomy, after industrial refinement. ***Conclusion:*** Polypropylene meshes with chitosan proved to be effective in terms of non-visceral adherence. Even without the great omentum, there was no rejection, demonstrating the biocompatibility of the nanotechnology used.

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INTRODUCTION

Peritoneotomy consists of leaving the abdominal cavity open, in which there is no complete approximation between the edges of the abdominal wall [1-3]. This communication between the peritoneum and the external environment facilitates access to the abdominal cavity and works as a temporary measure that prioritizes hemodynamic, hydroelectrolytic and metabolic control in critically ill patients, before reconstructive surgery [1]. Through peritoneotomy, it is possible to perform recurrent assessment of the abdominal cavity, spontaneous drainage of collections, aspiration and removal of purulent stores, residual abscesses and debridement of necrotic tissues [4,5]. Thus, the main indications for this procedure are the treatment or prevention of intra-abdominal hypertension, abdominal compartment syndrome, severe peritonitis and damage control surgery [2,4-6]. Although peritoneotomy reduces morbidity and mortality associated with critically ill surgical patients, there is a risk of evisceration, incisional hernia, adhesion formation and spontaneous fistulas 1,2. Thus, in order to avoid the occurrence of these adverse events, early abdominal closure is recommended, without additional harm to the patient's integrity [1,2]. One of the most used techniques for post-peritoneotomy reconstruction is the use

of meshes, which provide support for the abdominal wall, protect the intra-abdominal contents from contact with the external environment and accelerate the healing process by second intention [1]. However, the screens currently used, for the most part, are composed of high-cost, synthetic and non-biodegradable materials. Therefore, they do not have a socioeconomic sustainability profile and make it difficult for patients who need reconstructive surgery to have access to individualized care, especially in the context of the Unified Health System (SUS)[1]. The polypropylene mesh, initially described by Usher in 1959, is the most used in abdominal wall repair [7]. Polypropylene is a synthetic material, has long-lasting tensile strength and lower cost compared to other meshes [7-9]. It is responsible for triggering a foreign body granulomatous reaction, chronic inflammatory reaction and fibrosis, leading to incorporation of the mesh by adjacent structures [10,11]. Faced with a peritonectomy, as it is not possible to bring the edges of the abdominal wall together in some cases, it is necessary to place the mesh in intraperitoneal topography, in order to promote visceral protection and maintain cavity integrity [8]. In this sense, the risk of formation of omental and visceral adhesions is high, and can cause erosion of intestinais loops as well as digestive fistulas due to the erosive effect of the mesh on the intestinal loops, a situation that is difficult to control and resolve [12,13]. Adhesions are part of the usual healing process, affecting almost 100% of patients after abdominal surgeries14. The rate of adhesion formation is determined in the immediate postoperative period, so strategies to prevent or reduce the rate of adhesions are more effective when performed intraoperatively [15]. Thus, barrier systems have been used in studies to avoid contact between intra-abdominal organs and the mesh surface and, therefore, reduce adhesions, fistulas and intra-abdominal infections [14-16].

According to this principle, chitosan is relevant for this purpose due to its biochemical properties. It is a compound derived from chitin, a polysaccharide extracted from crustaceans, and has characteristics such as biocompatibility, biodegradability, non-toxicity and low immunogenicity, in addition to not promoting cell adhesion [13,16-18]. Therefore, the use of incorporated chitosan can confer anti-adherent property to the polypropylene mesh, which helps to prevent the formation of adhesions of organic structures on its internal surface [19-21]. In addition, chitosan has antimicrobial activity and induces the healing process, accelerating the inflammatory phase of healing and reducing the time for incorporation of the mesh into the body [10-13,22]. Perioperative infection promotes the development of adhesions. The coating of the polypropylene mesh with chitosan, in addition to the antimicrobial effect, allows a different route of drug administration, through slow and gradual release, allowing the impregnation of antibiotics and enhancing the prophylaxis and treatment of infections that may occur in the post -operative of reconstructive surgery of the abdominal wall [18,23]. The present study seeks technological innovation in this area of surgery, by proposing a new strategy for the management of peritoneostomy, based on the use of Biotechnology, especially Nanotechnology, since it intends to enable the use of propylene mesh coated with the aggregating agent chitosan, impregnated with antibiotics in a conjugated form. This is an initial study, interrupted abruptly by the emergence of the COVID-19 pandemic. However, previous scientific knowledge of the high rate of adhesions related to the isolated intraperitoneal polypropylene mesh, motivated the authors of the study to share these preliminary results with the scientific community, due to the social relevance that the topic has.

This research was justified by the creation and testing of an experimental model containing biofilm for coating polypropylene meshes involving isolated chitosan and/or associated with the incorporation of synthetic antibiotics of different bacterial spectra, with the main objective of evaluating the formation of adhesions to the biofilm when in direct contact with the abdominal viscera, in order to make it biocompatible and low-cost, capable of being used in the future in SUS patients. Therefore, the hypotheses tested included the interference of the incorporation of antimicrobial agents in the absence of adhesions between the biofilm and the abdominal viscera, rejection or not of the biotransformed mesh and whether, even in the absence of the greater omentum, adhesions formed between the mesh and exposed abdominal viscera.

METHODS

Experimental design: The experimental protocol was approved by the Ethics Committee on the Use of Animals, Potiguar University, number 2146/2018, Brazil. Animals were handled in accordance with the Guide for the Care and Use of Laboratory Animals, US National Research Council, 1996. The Institutional Committee on Ethics in the Use of Animals approved the research project under the protocol. Brazilian College of Animal Experimentation (Law 11.794/2008 - CONCEA – Brazilian College of Animal Experimentation). Eight male Wistar rats, two months old, weighing between 220g-320g, from the vivarium of Universidade Potiguar (UnP) were used. The surgeries were performed in the experimentation sector of the Animal House at UnP, where the animals were randomly separated and placed in individual cages, lined with wood shavings. The rats were placed in ventilated racks (Model ALE02; Brand ALESCO/BRASIL-2007®) for adaptation, remaining one week in the acclimatization period, under a standard controlled temperature of 20°C ± 2°C, humidity around 45% ± 15% and ambient lighting, with an inverted 12-hour light-dark cycle. In addition, the environment remained under noise below 60dB and the diet offered was standardized with commercial food from Purina® and filtered water ad libitum. The animals were evaluated daily, being weighed on a Filizola MF-3/1 Brasil 2009® scale. There was a random division into 4 groups with 2 animals each, following the principles of the 3R's - Reduce, Refine and Replace - in order to guarantee the bioethical principles of the study. The experimental groups underwent the same surgical procedure for making a peritonectomy and applying the respective biofilms impregnated with chitosan with and without antibiotics. In the GIV, the polypropylene meshes were implanted in their original form. One animal in each group had the greater omentum resected, in order to further sensitize the study and verify if, even without the large omentum, there would be a greater tendency to adherence after implantation of the orthosis. The number of animals per group is based on Normative Resolution CONCEA No. 25, of September 29, 2015. Only two animals were used in the control group, since the invasive and adherent behavior of the polypropylene mesh was already known since a previous study. when in direct and uncoated contact with the abdominal viscera. Then, the groups of animals were identified as follows:

Group I: Biofilm containing Chitosan on both sides of the polypropylene mesh / with and without large omentum;
Group II: Biofilm containing chitosan associated with ciprofloxacin and metronidazole/polypropylene mesh/with and without large omentum;
Group III: Biofilm containing chitosan associated with ceftriaxone and metronidazole/propylene mesh/ with and without large omentum;
Group IV: Polypropylene mesh without external or internal coating.

After dividing the groups, a daily follow-up form was created for each animal. The observation period adopted was 21 days. The animals were marked with inert paint in the syrup, receiving ordinary numbering, and their cages were identified according to the experimental group to which they belonged, as well as all stages of the experiment. After the observation period, a surgical procedure was performed to verify whether or not there were adhesions in the animals of the different observational groups.

Preparation of Biofilms/Polypropylene Mesh

Group I - *Polypropylene mesh with both sides coated with Chitosan.*

For the preparation of biofilms, 2% chitosan solutions were prepared by solubilizing adequate amounts of this polymer in a 2% acetic acid solution. After dissolution of chitosan, glycerin was added to this solution at a concentration between 5-20% in relation to the mass of

chitosan. The solution obtained was filtered with the aid of sterile gauze and placed in an appropriate container. Prefixed volumes of chitosan solution (25-100mL) were first poured into Petri dishes, whose diameter can vary between 5-15cm. Subsequently, circles of polypropylene meshes were cut with scissors to the same diameters as the inside of the Petri dishes (5-15cm of internal diameter) and carefully placed over the chitosan solution, previously distributed in the dish, in order to coat both sides of the dish. screen with chitosan.

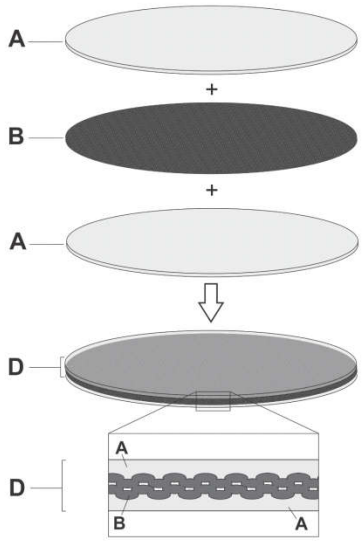

Figure 1. Polypropylene mesh coated with chitosan on both sides. A – Chitosan Biofilm; B – Polypropylene mesh; D – Coated mesh ready to be implanted.
Illustration: Prof. Irochima

Then, pre-set volumes of chitosan solution (25-100mL) were poured onto the surface of the screen, and then taken to the oven for drying at a temperature of 50ºC for 24h. The screens with both sides coated with chitosan were immersed in a solution of NaOH-1N for 1h to neutralize the chitosan. The chitosan-coated screens were washed with distilled water until neutral pH, dried at room temperature and placed in a container free of moisture.

Group II - ***Polypropylene mesh with the outer side coated with Chitosan and the inner side coated with Chitosan impregnated with an association of Ciprofloxacin/Metronidazole.***

After having followed the same preparation steps as in the previous group, 2% chitosan solutions containing ciprofloxacin and metronidazole were prepared by dispersing adequate amounts of ciprofloxacin and metronidazole in a 2% acetic acid solution, generating concentrations of ciprofloxacin and metronidazole of 0 .5% and 5%, respectively. Then, appropriate amounts of chitosan were weighed and dissolved in a 2% acetic acid solution with ciprofloxacin and metronidazole (0.5 and 5%, respectively). After dissolution of chitosan (final concentration of 2%), glycerin was added to this solution at a concentration between 5-20% in relation to the chitosan mass. The solution obtained was placed in an appropriate container. Chitosan-coated polypropylene screens were cut with scissors to the same diameters as the inside of the Petri dishes (5-15 cm inside diameter) and placed on the bottom of the dish with the uncoated side facing the outside. Then, pre-set volumes of chitosan solution (25-100mL) containing ciprofloxacin and metronidazole were carefully poured onto the surface of the screen, and then taken to the oven for drying at a temperature of 50oC for 24h. The meshes with one side coated with chitosan and the other side coated with chitosan impregnated with ciprofloxacin and metronidazole were immersed in a solution of NaOH-1N for 1h to neutralize chitosan. The screens coated with chitosan on one side and chitosan impregnated with ciprofloxacin and metronidazole on the other side were washed with distilled water until neutral pH, where they were dried at room temperature and placed in a container free of moisture.

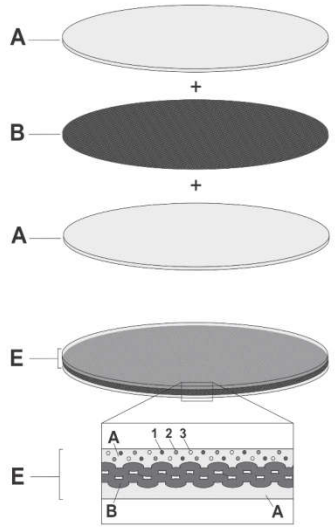

Figure 2. Polypropylene mesh with the outer side coated with Chitosan and the inner side covered with Chitosan and an association of Ciprofloxacin/Metronidazole. A – Chitosan Biofilm; B – Polypropylene mesh; E – Coated mesh ready to be implanted.
Illustration: Prof. Irochima.

Group III - ***Polypropylene mesh with the outer side coated with Chitosan and the inner side coated with Chitosan impregnated with Ceftriaxone/Metronidazole association***

The polypropylene mesh with one side coated with Chitosan and the other coated with Chitosan impregnated with an association of Ceftriaxone and Metronidazole had its preparation following the same parameters of the polypropylene mesh with one side coated with Chitosan and the other coated with Chitosan impregnated with association of Ciprofloxacin and Metronidazole, with the only difference being the replacement of the antibiotic Ciprofloxacin with Ceftriaxone. Group III - Polypropylene mesh with the outer side coated with Chitosan and the inner side coated with Chitosan impregnated with Ceftriaxone/Metronidazole association. The polypropylene mesh with one side coated with Chitosan and the other coated with Chitosan impregnated with an association of Ceftriaxone and Metronidazole had its preparation following the same parameters of the polypropylene mesh with one side coated with Chitosan and the other coated with Chitosan impregnated with association of Ciprofloxacin and Metronidazole, with the only difference being the replacement of the antibiotic Ciprofloxacin with Ceftriaxone.

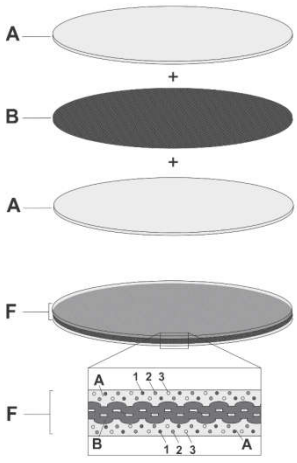

Figure 3. Polypropylene mesh with the outer side coated with Chitosan and the inner side covered with Chitosan and Ceftriaxone/Metronidazole association. A – Chitosan Biofilm; B – Polypropylene mesh; F – Coated mesh ready to be implanted.
Illustration: Prof. Irochima

Group IV - *Polypropylene mesh without internal or external coatings*

Surgical procedure: All animals underwent the same operative procedure for making the peritonectomy and apposition of biofilms according to the experimental group to which they belonged. For anesthetic induction, Zoletil50® was used at a dose of 50mg/Kg, an injectable anesthetic composed of tiletamine hydrochloride and zolazepam hydrochloride in a 1:1 ratio. The anesthetic was administered intramuscularly, in the region of the right quadriceps, with 1mL disposable syringes and a 0.45 x 13 - 26G ½ needle - Descarpack®. After verifying total anesthesia of the rat through the caudal pressure test, the animal's abdomen was shaved and antisepsis with 2% chlorhexidine digluconate spray branded NEBA-SEPT® and the operative area was protected with a sterile surgical drape. All surgical instruments were previously sterilized in an autoclave (BRASMED 21Lts, 2014/Brasil®). Initially, a median laparotomy was performed in an extension of 4cm and exposure of the abdominal muscles. Then, a 3cm2 area of a musculoaponeurotic flap of the abdominal wall was excised, simulating a peritonectomy, by separating the edges of the abdominal wall. To make the peritonectomy, a digital caliper (brand "ZAAS precision" - 8/200mm/2015/Brasil®) was used to standardize the size of the lesion. The next step followed the same technical principle in all groups. A polypropylene mesh impregnated with the respective biofilms was implanted, depending on the group to which the animal belonged, fixing the orthosis with 4.0 polypropylene threads (Ethicon®) at separate points on the abdominal wall, placing the mesh in direct contact with the the abdominal viscera.

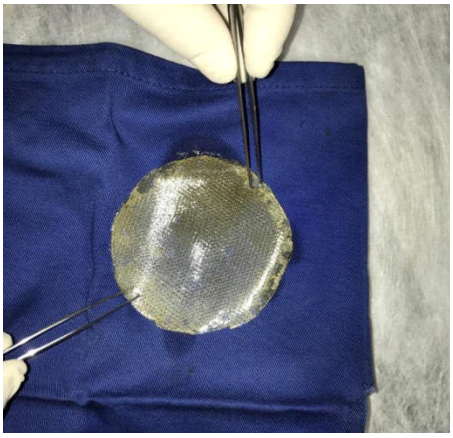

Figure 4. A - Impregnated Polypropylene Mesh; B - Fragment implanted in the animal

Figure 5. Implantation of a Polypropylene Mesh containing Chitosan and antibiotics in direct contact with the abdominal viscera

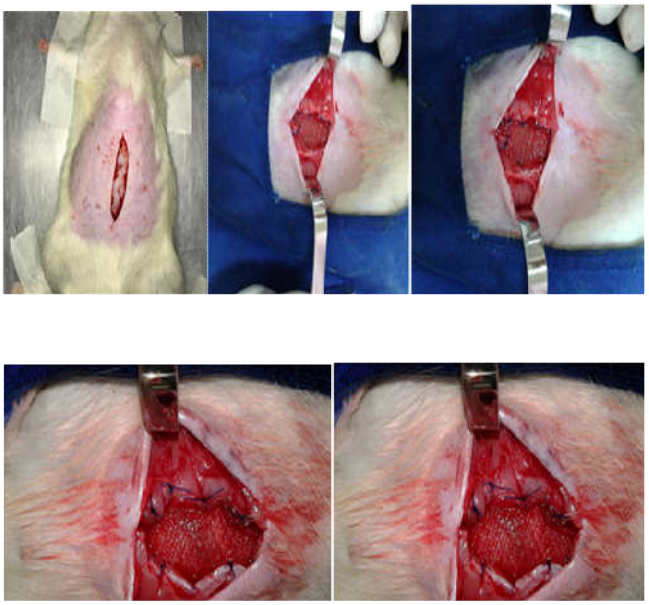

Figure 6. Implantation of a Polypropylene Mesh containing Chitosan and antibiotics in direct contact with the abdominal viscera.

In animals where the greater omentum was removed, the mesh impregnated with biofilm was only implanted after omentectomy. In prolene screens containing chitosan biofilm and antibiotics, the side of the screen containing the antibiotics was placed in direct contact with the abdominal viscera. After reviewing hemostasis, the skin incision was closed with 3.0 nylon thread. (Ethicon®). Then, the animals were placed in individual cages with their registration number and on the ventilated shelves (Model ALE02; Brand ALESCO, 2007/Brasil®), with ad libitum supply of water and food. Postoperative pain control was through meperidine (Roche®Farma-Brasil) - 10mg/Kg, injected subcutaneously once a day, for five days. The observation period was 21 days, a period stipulated as the total time required for tissue healing. On the 21st day, new anesthesia and antisepsis were performed, following the methodology above and exeresis of a rectangular-shaped abdominal wall flap to verify the presence or absence of adhesions between the propylene mesh impregnated by different types of biofilms and the abdominal viscera. Finally, after the analysis macroscopic examinations, the animals, still under anesthetic effect, were killed with an intracardiac injection of 1mL of sodium thiopental, painlessly.

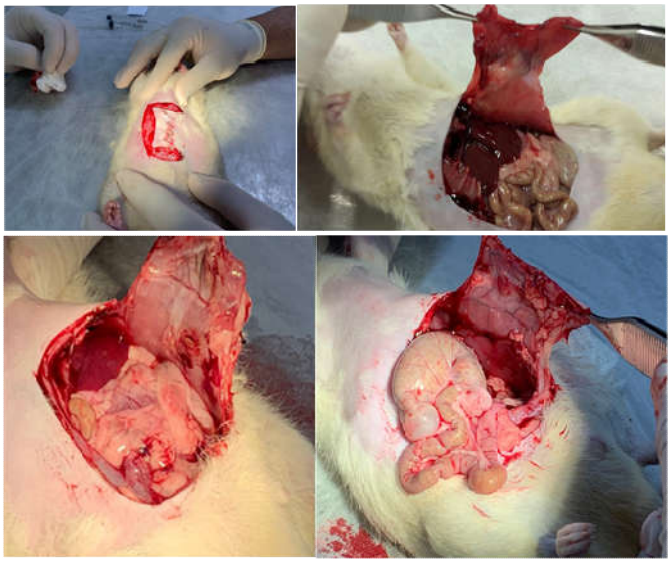

Figure 7. Abdominal wall flap excision demonstrating full incorporation of the mesh and absence of adhesions between the implanted mesh and the exposed abdominal viscera (With and without greater omentum).

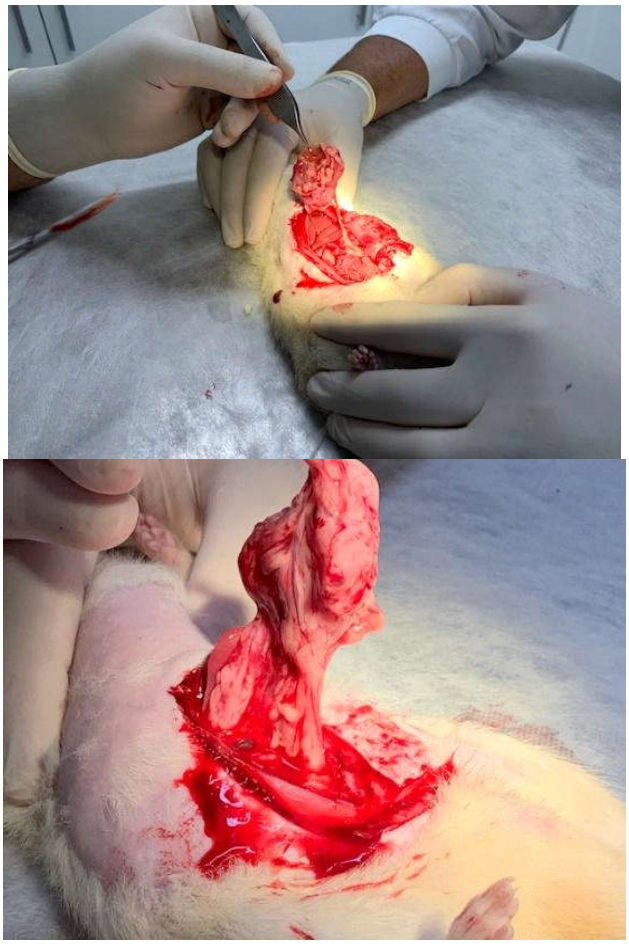

Figure 8. Polypropylene mesh without internal or external coatings

Analysis

Macroscopic evaluation: The macroscopic analysis evaluated the formation of adhesions in the postoperative period between the abdominal viscera and the implanted orthosis, in the groups with and without greater omentum. The analysis was carried out blindly, through a researcher who was unaware of the randomization of the animals. In this phase, the Adherence Score was used, a parameter used in previous experimental studies [12]. This graduation is verified through the force necessary to overcome the resistance and remove the adhesion (Table 1).

Table 1. Adherence Score

Punctuation	Characteristics
0	No adhesions
1	Fragile adhesions: easily removed by dissecting with blunt forceps and limited bleeding
2	Intermediate adhesions: removed with more intense blunt dissection or little sharp-edge dissection, presence of good dissection plane and moderate bleeding
3	Firm adhesions: removed only by dissecting with a sharp tip, bleeding profusely and no dissection plane present.

Microscopic Evaluation: After 21 days, the tissue samples containing the mesh were removed along with the adjacent structures and sent for analysis by a pathologist, who was unaware of which group the respective samples belonged to. The material was fixed with 10% formaldehyde, processed and, after that, the fragments were sectioned 5 mm thick and stained with eosin and hematoxylin. The parameters analyzed microscopically by the pathologist were the presence of the inflammatory response and its intensity, acute inflammation (polymorphonuclear cells), chronic inflammation (lymphocytes, plasma cells, histiocytes), foreign body granuloma, granulation tissue, fibrosis and its intensity, fibrin and leukocytes. The analysis was performed in a semi-quantitative manner, being negative (-), or positive (+), (++), (+++) [12].

Ethical Aspects: The study was carried out at the Vivarium of Universidade Potiguar after analysis and approval by the Ethics Committee for the Use of Animals - CEUA/UnP, under protocol number 2146/2018.

RESULTS

The results presented refer to the eight rats included in the study, a reduced amount related to the context of the new coronavirus pandemic, following the principle of the 3R's (Reduce, Refine and Replace) in experimental surgery. No animal deaths occurred during anesthetic induction, perioperative or postoperatively. Furthermore, the death of the rats occurred under anesthesia (Zoletil® - 50mg/Kg) and without suffering (intracardiac injection - 1mL of sodium thiopental).

Macroscopic Assessment: In the period of 21 days that followed the insertion of the polypropylene mesh in the rats, no presence of incisional hernias was observed on palpation. However, one of the animals in the group without antibiotic incorporation (G1) evolved with central skin ulceration and the other with small ulceration in the epidermis without abscess (G2). Furthermore, there was no significant weight loss among the animals of the evaluated groups. After the prescribed period, a flap was removed from the abdominal wall and non-adherence between the polypropylene mesh and the abdominal viscera was observed. The mesh was fully incorporated into the abdominal wall, indicating the biocompatibility between the material and the organism (Figure 6).

Microscopic Evaluation: Microscopic evaluation of each rat was performed according to the parameters (Table 1): Inflammatory Response, Intensity of Inflammatory Response, Acute Inflammation, Chronic Inflammation, Foreign Body Granuloma, Granulation Tissue, Fibrosis, Fibrosis Intensity, Fibrin and Leukocytes. The acute chronic inflammatory reaction varied with a predominance of mild to moderate in ⅝ of the rats submitted to the study. In addition, rare foreign body granulomas and the presence of fibrin, polymorphonuclear cells and red blood cells were observed covering one of the sides of the fragment. An area of granulation tissue was observed in 50% of the sample and the histological sections revealed skin with crust in the horny layer of the epidermis, completely re-epithelialized in ⅛. However, young fibrous tissue was present in the granulation tissue in a moderate amount in Masson's trichrome stain in all rats and mature tissue in those with ulcers and with crust in the stratum corneum of the epidermis. The RAT1 GI component with implantation of the chitosan-coated prolene mesh after omentectomy was the most distinct animal, as it presented an intense inflammatory response and acute inflammation (polymorphonuclear). In addition, the presence of chronic inflammation (lymphocytes, plasma cells, histiocytes), presence of granuloma, moderate presence of granulation tissue, mild fibrosis and little presence of fibrin and leukocytes were observed.

The GI component RAT2 showed a low inflammatory response and mild acute inflammation with the presence of ulcer. This fact differs from that of their group, as they presented distinctly mild inflammation with a low inflammatory response. Furthermore, the presence of chronic inflammation (lymphocytes, plasma cells, histiocytes) and moderate presence of granulation tissue were observed. Unlike RAT1, it presented moderate fibrosis and intermediate presence of fibrin and leukocytes. The RAT3 component of the GII with implantation of the polypropylene mesh with one side coated with Chitosan and the other coated with Chitosan impregnated with the association of Ciprofloxacin and Metronidazole presented a moderate inflammatory response with low mild acute inflammation without associated lesions different from the GI. The presence of chronic inflammation (lymphocytes, plasma cells, histiocytes), moderate presence of granulation tissue, mild fibrosis and presence of

fibrin and leukocytes were observed. The GII component RAT4 showed an intense inflammatory response with moderate acute inflammation without associated lesions, different from the GI, but with a more exacerbated inflammatory response than the RAT3 of the same group. In addition, he presented with moderate presence of granulation tissue, mild fibrosis and presence of fibrin and leukocytes. The RAT5 component of GIII with implantation of the polypropylene mesh with one side coated with Chitosan and the other coated with Chitosan impregnated with a combination of Ceftriaxone and Metronidazole presented a moderate inflammatory response with mild acute inflammation and the presence of crusts. There was the presence of chronic inflammation (lymphocytes, plasma cells, histiocytes), moderate presence of granulation tissue, mild fibrosis and presence of fibrin and leukocytes. The RAT6 component of GIII showed similar microscopy to RAT5, but without the presence of crusts and with less presence of fibrin and leukocytes.

	IR	IRI	AGUD	CHRON	GC	TG	FIBR	IF	F/L
RAT1	present	+++	+++	+	-/+	++	+	+	-/+
RAT2	present	+	+	+	-	++	+	++	++
RAT3	present	++	+	+	-/+	++	+	++	+
RAT4	present	+++	++	+	-/+	++	+	+	++
RAT5	present	++	+	+	-	++	+	++	++
RAT6	present	++	+	+	-	++	+	++	+

IR: Inflammatory Response; IRI: Intensity of Inflammatory Response; AGUD: Acute Inflammation (polymorphonuclear); CHRON: Chronic Inflammation (lymphocytes, plasma cells, histiocytes); GC: Foreign body granuloma; TG: Granulation tissue; FIBR: Fibrosis; IF: Intensity of fibrosis; F/L: Fibrin and leukocytes.

Group I - Polypropylene mesh with both sides coated with Chitosan - rats 1 and 2 (Omentectomized).

Group II - Polypropylene mesh with one side coated with Chitosan and the other coated with Chitosan impregnated with an association of Ciprofloxacin and Metronidazole - rats 3 and 4 (Omentectomized).

Group III - Polypropylene mesh with one side coated with Chitosan and the other coated with Chitosan impregnated with a combination of Ceftriaxone and Metronidazole - rats 5 and 6 (Omentectomized).

The animals from the Grupo IV in which there was no impregnation of the polypropylene mesh with Chitosan with or without associated antibiotics showed intense adhesions between the abdominal wall and the viscera, abscesses, rejection of the mesh with its expulsion, in addition to an intense inflammatory reaction around the prosthesis. , as can be seen in Figure 8 below.

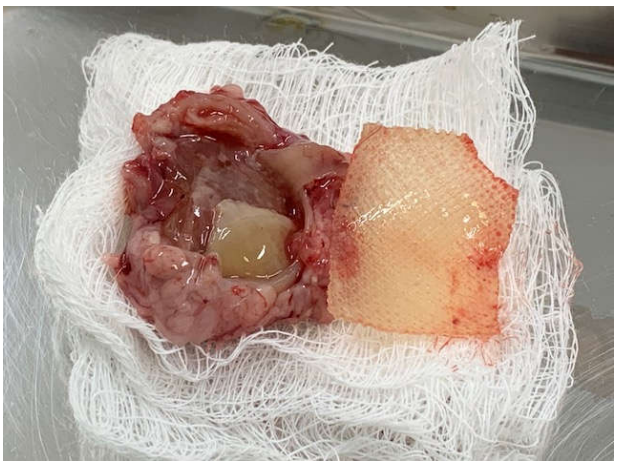

Figure 9. Polypropylene mesh without internal or external coatings and the tissue reactions observed

DISCUSSION

Abdominal reconstruction after peritoneotomy often requires the use of meshes to ensure tensile strength and aggregation with adjacent tissues necessary for good repair [13]. Polypropylene mesh is the synthetic compound most used for this purpose, due to its tensile characteristic and for triggering a foreign body granulomatous reaction, chronic inflammatory reaction and fibrosis, leading to the incorporation of the mesh by adjacent structures [13,24]. However, the intraperitoneal application of such materials is associated with adverse events, such as adhesion formation, erosion of intestinal loops, fistulas and infections [25-27]. Different mechanisms have been used to try to avoid or reduce the formation of intraperitoneal adhesions after surgical procedures [28]. This study sought to reduce adhesions in the short term after peritoneotomy, through the constitution of a new biomaterial associating polypropylene, chitosan and antibiotics (Metronidazole and Ceftriaxone or Ciprofloxacin) through the use of nanotechnology. Chitosan is a natural polysaccharide derived from the deacetylation of chitin. It is the most abundant biopolymer in nature after cellulose, predominantly found in the exoskeleton of crustaceans [29,30]. This compound has attracted the attention of biotechnological studies due to its relevant properties of biocompatibility, biodegradability, non-toxicity and low immunogenicity [16,31]. The seafood industry produces large amounts of waste from the unused parts of crustaceans, especially the shell, which are discarded at sea, burned or left to decompose, even generating environmental pollution [32]. In this sense, the extraction of chitin from the shell of crustaceans for the production of chitosan is a viable possibility in order to reduce waste and damage to the environment, in addition to presenting itself as an opportunity for entrepreneurship, employment and income in fishing communities, frequent in the coast of the Brazilian Northeast, where the study was developed.

It has characteristics such as biocompatibility, biodegradability, non-toxicity and low immunogenicity [16-18,33]. Such factors allow chitosan to be applied in scenarios as an antibacterial agent, which allows a route of drug administration and in the tissue reconstruction process that fits perfectly in the cases of peritoneotomy, analyzed in this study [18,23,34-36]. Regarding the use of chitosan in the tissue remodeling process, the physicochemical properties of the compound allow it to have an excellent performance, as it has good biocompatibility and biodegradability [14-17]. Chitosan has histological similarities with the extracellular matrix, presenting the peculiarity of having pores in its composition, which allows the flow of nutrients and electrolytes between cells, helping to promote better cell adhesion, proliferation and differentiation [27-29]. Such characteristics are especially important in the context of the use of chitosan in the reconstruction of the abdominal wall under peritoneotomy, as they can reduce the occurrence of postoperative adhesions, which makes the use of polypropylene mesh in this scenario possible [24,30]. Another innovative aspect of the present study, which is only possible due to the characteristics of chitosan, is the demonstration of a new route of administration of antibiotics through a propylene mesh impregnated with chitosan and antibiotics [5-8]. Chitosan allows drugs to be released in a controlled manner, remaining constant over a long period of time. Thus, a good and innovative route that works as a vehicle for drug administration [31,32]. It is worth noting that chitosan itself already has antimicrobial properties due to chemical reactions it causes when in contact with tissues. In other words, the alternative proposed by this study works as a protection against infections through two ways: by the antibiotics administered and the actions inherent to chitosan [21-23]. By analyzing the results achieved in the study and the context in which it is immersed, it is possible to affirm that the research represents a great advance achieved through the biotechnology used, since it will positively influence the care of patients undergoing peritoneotomy.

Once the material tested proved to be effective in preventing adhesions of the intestinal loops and the implanted orthosis, it becomes an alternative for the reconstruction of the abdominal wall, added to a low cost from its production to implantation [15-17]. Many patients will benefit from this new biotechnological product, given the multiple clinical scenarios associated with indications for peritoneotomy: severe or large/multiple trauma, damage control

surgeries, acute abdominal laparotomies with diffuse abdominal sepsis, giant tumors with extensive resections and loss of muscle tissue and fascia that were previously part of the anatomical composition in the containment of abdominal viscera, severe acute pancreatitis, abdominal compartment syndrome, among others [1,2,7]. In the abdomen, there are several tumor pathologies of the abdominal wall or organs, inflammatory or not, which, when not treated or treated late, may require the so-called peritonectomies, where the abdominal wall is open and its contents are in contact with the external environment [20,32]. However, the new strategy proposed in this study has the potential to also contribute to the treatment of pathologies of the thoracic and pelvic cavities [14]. This is because voluminous wall tumors can occur in the thoracic cavity, where resection of the rib cage is necessary, in addition to diaphragmatic injuries due to trauma or tumors, which require resections of the aforementioned elements16. A situation similar to the pelvic cavity, where pelvic tumors, whether of gynecological origin or involving soft tissues, require extensive resections [31]. In the aforementioned clinical situations, reconstruction of the cavities is necessary, which can be carried out using a polypropylene mesh impregnated via nanotechnology with chitosan and antibiotics, as it is biocompatible, easy to acquire, cheap, economically sustainable and ecologically viable [12-15].

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It is worth mentioning that the present study may represent an important advance in the treatment of severe peritonitis, due to the possibility of controlling intra-abdominal damage, which is still considered a major challenge for surgeons today [5,6]. As already seen, it is a viable alternative for the reconstruction of the abdominal wall submitted to peritoneotomy, in addition to providing the possibility of administering antibiotics impregnated with polypropylene mesh, which will be more effective in the treatment of the cause of peritonitis and will promote a better prognosis for patients [14,33-36]. From then on, it is possible to establish a route of local administration that makes the effect of the drugs localized, increasing their local bioavailability, effectiveness and without producing unwanted systemic effects. In this way, an alternative is obtained to treat the cause of peritonitis, avoid possible secondary infections and mitigate adverse events [7,12-15,34]. Based on the above, it is believed that through biotechnology/nanotechnology it was possible to create a product capable of promoting an economically viable alternative to the most diverse realities of health services that make up the Unified Health System (SUS), in especially in the area of general surgery and digestive system [8-10]. It is an extremely innovative biocomponent in the surgical area, since most of the non-adherent materials currently used in the treatment of peritoneotomy are expensive, which profoundly hinders the feasibility of these materials in the routine of a public health servisse [33-35]. Therefore, through the new strategy proposed in this study outlined in the Brazilian Northeast, a region with precarious investments in scientific production and health promotion, it was possible to develop, from nanotechnology, a very low cost material, whose main raw material is of easy to obtain [15,17,36]. However, despite being a significantly innovative study in the area and which will bring important contributions to the treatment of peritoneotomy, it also has certain limitations that deserve to be mentioned. It is worth noting that the study was developed in the midst of the COVID-19 pandemic scenario, which only allowed the conclusion of the main part, which aimed at the manufacture of the material and its application in the experimental models to evaluate its non-stick capacity. Therefore, this is just a preliminary stage of the study that will be completed after the pandemic subsides, in a safe, ethical, innovative and scientifically rigorous way. This research is fundamental to support new studies, which are already in progress, from which at least two to three patent registrations are expected to be registered at the INPI - National Institute of Industrial Property. In the near future, the authors intend to go to the conclusion of the study, where microbiological analyzes of surgical specimens will be carried out, measurement of blood bioavailability of incorporated antibiotics, product testing in experimental models of abdominal sepsis, among other analyzes, which due to conflict of interest in keeping the secrecy linked to the research, they will only be revealed in future publications.

CONCLUSION

The chitosan-impregnated polypropylene meshes proved to be effective in terms of non-adherence of the mesh to animal viscera. Even in the groups in which the greater omentum was removed, which would have a greater willingness to adhere and reject the implanted orthosis, the mesh was incorporated without rejection, demonstrating the biocompatibility of the technology used. The association of polypropylene mesh with chitosan and antibiotics showed encouraging results as it enabled the use of biotechnology combined with pharmacology as a cheap and sustainable alternative in the area of general surgery and the like.

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