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Comparability of histological outcomes in rats and humans in a hernia model

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ABSTRACT

Background: Hernia repair is one of the most frequently performed operations. In search of the ideal mesh for hernia repair, animal research is required. Although rats are most often used in experimental mesh experiments, no correlation with clinical findings in humans has ever been shown. Therefore, the aim of our study was to investigate whether adhesion formation and foreign body reactions to meshes in rats are comparable with the reactions in humans.

Materials and methods: A fixed type of mesh was implanted intraperitoneally in a group of 10 rats and 10 patients undergoing elective, temporary stoma formation. In case of the latter, meshes were placed around the stoma. After a follow-up period of 12 wk in rats and after a median follow-up of 6 mo in humans, samples of the mesh were collected. Adhesion assessments were performed, and (immuno-) histochemical evaluation was performed by a specialized experimental pathologist and an experienced clinical pathologist.

Results: After the follow-up period, adhesion formation did not differ significantly between rats and humans. Moreover, general inflammation scores were comparable, although granulocytes and giant cells were more present in rats, compared with humans. On the other hand, the presence of fibrosis was more evident in humans compared with rats.

Conclusions: To our knowledge, this is the first study, which showed that a specific animal model, namely a rat model, correlates with adhesion formation and the foreign body reaction to meshes in humans. It can be recommended to use rats in future experimental mesh for incisional hernia research.

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Introduction

Laparoscopic hernia surgery is commonly performed and frequently has been associated with less wound infections and shorter hospital stay.[1,2] With the increase of laparoscopic hernia repair, the number of intraperitoneally placed meshes has also been increased.[3] However, some possible disadvantages of intraperitoneally placed meshes have to be considered. One limitation is the formation of adhesions to the mesh due to the body's inflammatory response to the foreign body.[4,5] Adhesions are related to chronic pain, bowel obstruction, infertility, and inadvertent enterotomies at the time of reoperations.[6,7] Furthermore, adhesions may complicate future surgery.[7] To reduce those adhesions, several types of meshes with different coatings have been developed in the last decades. However, none of these meshes seem to be able to prevent adhesion formation completely and therefore the development of new antiadhesive meshes still continues.[8]

To assess safety, functionality, and biocompatibility of new medical devices, such as surgical meshes, the use of an animal model is generally the first step. Although there is a large variation in the type and species of animals used, most frequently rats are used as test subjects.[9-11] The rat is a small and easy-to-handle animal but still large enough for mesh implantation. Furthermore, it is relatively inexpensive.

Unfortunately, little is known about the implications of results in a rat model in a human situation. To date no translational research has been performed to assess the degree of similarity of the foreign body response to meshes between human and rats.

The aim of this study is to compare the macroscopic and microscopic outcomes in rats and humans after intraperitoneal mesh implantation, using identical meshes. As such, the translatability of mesh research in a rat model toward the human situation can be proved.

Materials and methods

The experimental animal protocol was approved by the local Animal Ethics Committee of Maastricht University, the Netherlands, according to the Dutch Animal Experimentation Act.

The protocol regarding the human part of this study was approved by the Medical Ethical Committee of Maastricht University Medical Centre, Maastricht, the Netherlands. Informed consent was given by all participants.

Parietex Composite meshes (Covidien, Mansfield, MA, USA), monofilament, polyester meshes of which one side is coated with an absorbable collagen layer to prevent adhesions were used in both the rat model and human situation. The meshes were placed intraperitoneally with the coated side in direct contact with the viscera.

Animals

Ten male Wistar rats weighing 356 g (standard deviation 9 g) were housed and cared for at the Central Animal Facilities of Maastricht University, according to the local standards. Male rats were chosen because it is unclear whether progesterone and estrogen in females influence adhesion formation.[12] Rats had free access to water and food and a day-night cycle of 12-12 h was maintained.

Surgery was performed as described earlier, using a rat model.[13] Briefly, after administration of 0.05 mg/kg of buprenorphine subcutaneously as analgesics, all animals were anesthetized with 5% isoflurane, and anesthesia was maintained with 2.5% isoflurane.

Subsequently, the abdomen was shaved and skin was disinfected with 2% iodine. A 4-cm midline incision was created to enter the abdomen, and a sterile mesh of 20 × 30 mm (Parietex Composite Parastomal; Covidien, Mansfield, MA, USA) was placed and sutured to the intraperitoneal part of the abdominal wall with four sutures of polypropylene 4/0 (PROLENE, Ethicon, Johnson & Johnson, Somerville, New Jersey, USA) in each corner of the mesh. Hereafter, the abdominal wall was closed using a running suture of polyglactin 4/0 (VICRYL, Ethicon, Johnson & Johnson), and the skin was closed intracutaneously with polyglecaprone 4/0 (MONOCRYL, Ethicon, Johnson & Johnson).

After 12 wk, rats were euthanized with an overdose of carbon dioxide. A U-shaped incision was created, and adhesions were scored macroscopically. Subsequently, the mesh was explanted for microscopic evaluation as described previously by Schreinemacher *et al*.[13]

Patients

Ten consecutive patients who underwent elective open low anterior resection of the rectum with temporary stoma placement were invited for participation in a pilot study to assess safety and feasibility of prophylactic mesh placement to prevent incisional hernias after stoma reversal as well as parastomal hernias as long as the stoma is in place. The favorable results of this study were published earlier and are referred to for further detailed information.[14] In brief, after marking the preferred stoma site, inducing anesthesia and administering antibiotics (cefazolin-metronidazole), the abdomen was entered via a midline laparotomy, and a bowel resection with anastomosis was performed. At the marked site, a small circular piece of skin with underlying layers of the abdominal wall was excised to create a passage.

Subsequently, after creating an opening in the center of a mesh with 20 cm diameter (Parietex Composite Parastomal, Covidien, Mansfield, MA, USA), the bowel was passed through the mesh, and the mesh was placed intraperitoneally, with the coated site facing the viscera, and fixed with absorbable tackers (AbsorbaTack, Covidien) at the outer margin of the mesh. Finally, the abdomen was closed, and the stoma was sutured in place.

After a median of 6 (range 2-15 mo), the stoma was reversed. Again, anesthesia was induced and antibiotics (cefazolin-metronidazole) were administered. Before stoma reversal, laparoscopy was performed to assess adhesion formation. Subsequently, the stoma was dissected free from the subcutaneous tissue, abdominal wall and mesh. An anastomosis was created, and a piece of the mesh was excised *en bloc* and fixed in 4% formaldehyde, for later analysis. Next, the fascia and mesh defect were closed with a running suture followed by skin closure.[14]