International Journal of Surgery Open 5 (2016) 27–32

Contents lists available at ScienceDirect

International Journal of Surgery Open

journal homepage: www.elsevier.com/locate/ijso

Research Paper

Histological and adhesiogenic characterization of the Zenapro Hybrid Hernia Repair Device

Jason P. Hodde [a,*], Mark D. Suckow [b,1], Chad Johnson [a,2], Eric Rodenberg [a,2], Rae D. Ritchie [a]

[a] Cook Biotech, Incorporated, 1425 Innovation Place, West Lafayette, IN 47906, USA
[b] The University of Notre Dame, 400 Freimann Life Science Center, Notre Dame, IN 46556, USA

ARTICLE INFO

Article history:
Received 13 September 2016
Accepted 24 September 2016
Available online 8 October 2016

Keywords:
Hernia mesh
Ventral hernia
Incisional hernia
Adhesion
Abdominal wall reconstruction

ABSTRACT

Background: A major clinical problem relating to hernia repair is the formation of intra-abdominal, post-surgical adhesions when mesh products are used to reinforce the abdominal wall. To achieve better outcomes, more technologically-advanced products designed to achieve permanence of repair while eliminating serious complications such as adhesion formation are needed. This study was designed to assess the histological remodeling and adhesiogenic properties of the Zenapro™ Hybrid Hernia Repair Device as compared to uncoated and coated polypropylene.

Materials and Methods: Zenapro™, Prolene® and Ventralight® ST Mesh were implanted to repair full-thickness abdominal wall defects in rabbits and rats and were allowed to survive for various lengths of time. Animals were euthanized, the implants were identified, and the extent and tenacity of adhesions were evaluated. Tissue samples were collected and evaluated for inflammation, integration of the mesh with the abdominal wall, and collagen deposition.

Results: A significant difference was found in the extent of adhesions in the Prolene group as compared to the Zenapro group ($p = 0.021$) and the Ventralight ST group ($p = 0.04$) in the rat study. The tenacity of the adhesions in the Prolene mesh group trended higher than in the other groups but failed to reach statistical significance. Histological evaluation demonstrated that collagen accumulation was greatest for the Zenapro implants as compared to either the Ventralight ST or Prolene samples. At the conclusion of 6-months in the rabbit model, the Zenapro sites showed signs of a thicker repair composed of more organized mature collagen than was seen in the Ventralight ST samples. Neither device was found to elicit any sort of detrimental inflammatory tissue reaction.

Conclusion: A combination hernia device composed of a complete extracellular matrix with a synthetic mesh can result in enhanced tissue ingrowth and neovascularization while maintaining high tensile strength and mitigating adhesiogenic effects.

1. Introduction

Over the last 75 years, hernia repair surgery has moved from primary closure with suture alone to the use of mesh to achieve successful, prolonged outcomes. Mesh reinforcement has more recently evolved as complex materials have been developed to include a selection of a wide range of synthetic, biologic, or combination mesh products, each with their own advantages and disadvantages.

Surgical debate continues to precisely define the typical characteristics of the optimal hernia mesh; however it is generally agreed that the ideal prosthetic material should be nontoxic, biocompatible, and effective in minimizing postoperative adhesions. The mesh should allow for repair of the primary fascial defect, integrating into the surrounding tissue while maintaining high tensile strength and low adhesion development. It should also allow for tissue ingrowth, neoperitoneum formation, and neovascularization without interfering with the normal healing process [1]. Currently-available products struggle to meet these needs. To achieve best outcomes for patients, newer and more technologically-advanced products designed to achieve permanence of repair while eliminating serious complications such as erosion, infection, chronic inflammation or adhesion formation are needed.

To prevent adhesions, preservation of the parietal peritoneum during hernia repair has been suggested because it forms a barrier between the viscera and the mesh [2]. However, in daily practice,

* Corresponding author. Cook Biotech, Incorporated, 1425 Innovation Place, West Lafayette, IN 47906, USA. Fax: +1-765-807-7706.
E-mail address: jason.hodde@cookbiotech.com (J.P. Hodde).
[1] Present address: University of Minnesota, Research Animal Resources, 516 Delaware Street S.E., Minneapolis, MN 55455.
[2] Present address: Cook Regentec, LLC., 1102 Indiana Avenue, Indianapolis, IN 46202, USA.

http://dx.doi.org/10.1016/j.ijso.2016.09.005

it is sometimes not feasible to preserve the parietal peritoneum in order to protect the abdominal contents from the direct contact with the mesh. Additionally, the advent of laparoscopic hernia repairs and various intraperitoneal onlay mesh (IPOM) procedures require that mesh come in contact with the bowel.

While commonly used synthetic materials, such as polypropylene, are inexpensive, they can be attributed to many serious adverse events and are still considered relatively contraindicated for use in contaminated and infected settings because surgical removal is often necessary if chronic infection occurs. Synthetic mesh materials are prone to chronic inflammation and erosion, and often cause extensive adhesion formation when placed directly in contact with the bowel and visceral organs [3].

Commonly used biologic materials, such as porcine dermis or small intestinal submucosa, while more expensive than synthetic mesh, are often touted as a template for rapid remodeling and collagen deposition by the patient, leading to a naturally-stable outcome. These materials are susceptible to rapid degradation by some bacterial collagenases in contaminated or dirty fields, but are also less prone to erosion and chronic inflammation than are synthetics, and have been shown to have the added benefit of being relatively less adhesiogenic than their synthetic counterparts [4,5].

To combat the complications associated with purely synthetic or biologic materials, products containing synthetic materials coated with biologically-friendly components have been developed. These products typically utilize a synthetic mesh that has been coated with an extracellular matrix component as a means of improving the tissue-compatibility of the synthetic polymer.

Newer devices, however, combine the complete extracellular matrix (ECM) found in a biologic device with a polymer core of synthetic mesh. The currently available device, Zenapro™ Hybrid Hernia Repair Device (Cook® Medical, Bloomington, IN, USA), is composed of a medium-weight polypropylene core embedded in a multilaminate structure of porcine small intestinal submucosa (SIS), a naturally-occurring ECM that has a long and extensive history of use in multiple human clinical applications, including hernia repair.

The main aim of the current animal studies was to demonstrate the histological remodeling and adhesiogenic properties of the Zenapro Hybrid Hernia Repair Device and compare it to uncoated (Prolene®, Ethicon) and coated (Ventralight® ST mesh, C.R. Bard, Inc.) polypropylene.

2. Materials and methods

2.1. Animals

A total of twenty-four (24) Sprague–Dawley rats weighing approximately 200–300 g and six (6) female New Zealand White (NZW) rabbits (Covance, Inc., Indianapolis, IN) weighing 3.5–4.0 kg were used to evaluate the adhesiogenic properties and histological remodeling of the Zenapro and Ventralight ST devices. Additionally, the adhesiogenic properties and histological remodeling of uncoated polypropylene were also studied in the rat model.

The minimum number of animals deemed necessary to evaluate adhesiogenesis and remodeling were utilized. All animals were randomly assigned to treatment groups. They were housed in a light-controlled environment in separate cages maintained at 22 ± 1 °C, were fed a high-fiber diet and water *ad libitum*, and were under veterinary care throughout the study. All procedures were performed following institutional animal care and use committee approval.

2.2. Test samples

Test devices (3 × 3 cm for rabbits, 2 × 2 cm for rats) of the Zenapro Hybrid Hernia Repair Device were manufactured specifically for this study. Briefly, the Zenapro device configuration consisted of 4 layers of SIS, 1 layer polypropylene, and 2 additional layers of SIS, all of which were vacuum press-laminated together in a final stacked configuration. The test devices were sterilized with ethylene oxide and were implanted as underlays such that the surface containing 4 layers of SIS was oriented closest to the abdominal viscera.

Prolene® and Ventralight® ST Mesh were obtained in final package form from a commercial distributor. While Prolene is composed of uncoated knitted polypropylene monofilament, Ventralight ST Mesh consists of knitted polypropylene and polyglycolic acid (PGA). A bioresorbable hydrogel coating comprising sodium hyaluronate (HA), carboxymethylcellulose (CMC), and polyethylene glycol (PEG), collectively known as Sepra® technology, is adhered adjacent to the PGA layer. The Sepra coating is designed to resorb over 30 days and provide a temporary adhesion barrier to the polypropylene layer so as to protect the viscera. Test devices (3 × 3 cm for rabbits, 2 × 2 cm for rats) were cut from larger, sterile mesh sheets just prior to being surgically implanted into the animals.

2.3. Implant surgery

Each rat was anesthetized with an intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg). Following anesthetic induction, a midline incision was created along the abdomen. The abdominal fascia was exposed and a 2 × 2 cm defect was made in the abdominal fascia and muscle tissue planes, exposing the abdominal viscera. A 2 × 2 cm Zenapro device, Ventralight ST mesh, or Prolene mesh, was placed as an underlay beneath the full-thickness defect and secured with nylon suture to the adjacent muscle tissue plane. Silk suture was used to close the subcutaneous tissue plane. The dermal flaps were re-approximated and the midline incision was closed. A total of eight (8) rats were implanted with each device. Animals were recovered from anesthesia and were carefully monitored by the animal care team at the University of Notre Dame for the duration of the study.

Each rabbit was anesthetized with a mixture of 35 mg/kg ketamine and 5 mg/kg xylazine given via intramuscular injection. Isoflurane was administered by mask to maintain a surgical plane of anesthesia. Following anesthetic induction, a midline incision was created along the abdomen. On either side of the midline, an approximately 2 cm wide full-thickness defect was created bilaterally by cutting through the abdominal fascia and muscle tissue planes, exposing the abdominal viscera. A 3 × 3 cm Zenapro device (right-hand side) and Ventralight ST device (left-hand side) were placed as underlays beneath the full-thickness defects and secured with nylon suture to the adjacent muscle tissue plane. Silk suture was used to close the subcutaneous tissue plane. The dermal flaps were re-approximated and the midline incision was closed. A total of six (6) rabbits were implanted with each device. Animals were recovered from anesthesia and were carefully monitored by the animal care team for the duration of the study.

2.4. Explant surgery

Rats were euthanized after 3 weeks and rabbits were euthanized after 6 weeks, 3 months, or 6 months. Rats were euthanized using an overdose inhalation of CO_2, and rabbits were humanely euthanized using a combination of ketamine (25 mg/kg), acepromazine (2.5 mg/kg), and xylazine (5 mg/kg), followed by direct cardiac injection of 3 mL of Euthasol® (pentobarbital sodium and phenytoin sodium). Upon confirmation of cardiac arrest, an incision was created through the abdominal dermis midline. The implants were identified and the extent and tenacity of adhesions were evaluated using a scale adapted from similar studies of adhesiogenesis (Table 1). Adhesion tenacity was regarded as the resistance of the tissue to separation, and adhesion extent was regarded as the degree to which the adhesion tissue covered the explanted device. Tissue samples