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Infection prevention using affinity polymer-coated, synthetic meshes in a pig hernia model

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ABSTRACT

Background: Given concern for hernia mesh infection, surgeons often use biologic mesh which may provide reduced risk of infection but at the cost of decreased repair durability. We evaluated mesh coating to provide sustained release of antibiotics to prevent prosthetic mesh infection and also allow a durable repair.

Materials and methods: Cyclodextrin-based polymer was crosslinked onto multifilament polyester mesh and loaded with vancomycin (1.75 mg/cm^2). Pigs received modified meshes ($n = 6$) or normal, untreated meshes ($n = 4$), which were implanted into acute 10 × 5 cm ventral hernia, then directly inoculated with 10^6 colony-forming unit (CFU) of methicillin-resistant *Staphylococcus aureus* (MRSA). These were compared to animals receiving normal, uninfected mesh. All mesh was secured in an underlay bridge manner, and after 30 d, the abdominal wall was removed for quantitative bacterial culture and biomechanical analysis.

Results: All animals survived 30 d. All six animals with coated mesh cleared MRSA infection. The four control animals did not clear MRSA ($P = 0.005$). Quantitative bacterial load was higher in standard mesh *versus* drug-delivery mesh group (2.34×10^4 *versus* 80.9 CFU/gm). These data were $\log_{10}$-transformed and analyzed by Welch's *t*-test ($P = 0.001$). Minimum number of CFUs detectable by assay (300) was used instead of zero. Biomechanical analysis of controls (1.82 N/mm infected; 1.71 N/mm uninfected) showed no difference to the modified meshes (1.31 N/mm) in tissue integration ($P = 0.15$).

Conclusions: We successfully prevented synthetic mesh infection in a pig model using a cyclodextrin-based polymer to locally deliver vancomycin to the hernia repair site and clearing antibiotic-resistant bacteria. Polymer coating did not impact the strength of the hernia repair.

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Introduction

The advent of prosthetic materials has revolutionized hernia surgery by significantly reducing hernia recurrence rates. The ideal properties of prosthetic mesh have changed little since it was first introduced providing a durable repair while reducing the risk of potential complications including infection, chronic inflammation, and intra-abdominal adhesions. Despite advances in some of these areas, we lack adequate options for the prevention of prosthetic mesh infection.[1,2]

Mesh infections can present up to a year following implantation, yet are often thought to be the result of contamination at the time of implantation.[2] Current options available for treating such an infection rely on high doses of systemic antibiotics, which provide varied penetration into the local tissue.[3] In addition, such therapies put patients at risk for associated complications including Clostridium difficile and the development of resistant organisms.[4] Despite the most aggressive treatment, prosthetic device infections frequently require the removal of the device.

Therefore, instead of treating infections, many surgeons have turned to prevention of infections. Current mainline therapy includes perioperative antibiotics with the goal of obtaining sufficient local tissue levels to prevent bacterial growth. As an adjunct, some investigators are evaluating the potential for drug-delivery polymers which can be used to coat prosthetic devices in an attempt to provide sustained local drug levels. Initial studies have shown varied success[5,6] due to the fact that these polymers often rely on diffusion alone for drug release, resulting in a highly nonlinear profile with a rapid burst of the majority of drug on the order of hours to days, leaving very little behind to be delivered on later dates. This diffusion-based, biphasic release has the potential consequence of too much drug at the initial time points and too little drug at later time points, a perfect storm for generating drug-resistant bacteria. Given the nearly year-long window for hernia mesh infection, we hypothesize that a longer, more sustained delivery profile is necessary to kill bacteria and prevent infections.

Our group has shown success in developing an affinity-based polymer that provides controllable and sustained release of antibiotics from weeks to months. This work utilizing both *in vitro* and *in vivo* models demonstrated our ability to coat a sample (~0.7 × 0.7 cm) of prosthetic mesh and prevent a subcutaneous *Staphylococcus aureus* infection in rodents.[7-9] The aim of the current study was to expand upon our previous work and evaluate the ability of a polymer-coated mesh loaded with vancomycin (VM) to prevent methicillin-resistant *S aureus* (MRSA) infection while providing a durable ventral hernia repair.

Methods

Creation of modified meshes

A 30% (wt/wt) cyclodextrin prepolymer (CD) solution in 0.2 M potassium hydroxide was mixed with ethylene glycol diglycidyl ether (EGDGE) at a molar ratio of 1:0.7 CD: EGDGE. A 15 cm × 10 cm piece of polyester mesh (Parietex TET, Covidien, Mansfield, MA) was uniformly coated with 20 mL of the CD-EGDGE solution; the polymer was allowed to crosslink via base-catalyzed epoxide ring opening on the polyester mesh for 5 d at room temperature in a sealed stainless steel tray. The polymerized CD (pCD)–coated meshes were removed and washed extensively in distilled water for 3 d replacing the water periodically to wash out excess reagents. After washing, each mesh was partially dried and VM was loaded by incubating polymer-coated mesh in a 5% (wt/vol) aqueous VM solution for 2 d. After 2 d, the mesh was briefly rinsed to remove excess, unbound drug; exposed to UV light 20 min on each side to sterilize; and then kept in a sealed plastic container until used. Extensive chemical and physical characterization of these and similar meshes were previously reported.[7,8]

Bacteria

A clinical strain of MRSA (Xen30, Caliper LifeSciences, Hopkinton, MA) was cultured overnight, diluted 1:50 and then placed in a 37°C shaker allowing the bacterial to reach a concentration of 10^8 colony-forming unit (CFU)/mL based on optical density. This solution was diluted utilizing serial dilutions in sterile 0.9% normal saline (NS) to obtain a concentration of 10^6 CFU/mL. One cubic centimeters of fluid was then used to inoculate the mesh after it has been secured in place and prior to closing the wound as described below.

Animals—surgical repair

Female Yorkshire pigs (30-35 kg; Pineview Farms, Valley City, OH) were acclimated to our facility for 7 d prior to surgery. Due to large differences between abdominal tissue composition between males and females, in this preliminary study, only female animals were used. All animal care and operative procedures were performed in accordance with the US Public Health Service Guide for the Care of Laboratory Animals (NIH Publication 85-23, 1985) and were performed with the prior approval of the Case Western Reserve University Institutional Animal Care and Use Committee. Induction of surgical anesthesia consisted of intramuscular injection of Telazol (6-8 mg/kg), followed by endotracheal intubation, and maintenance of anesthesia with inhaled isoflurane (2%-5%). Postoperative pain control was obtained using local injection of Marcaine (5% diluted 1:10) followed by a fentanyl patch (25 μg) for the first 72 h. Prior to any surgery and at the time of necropsy, the abdominal wall was clipped and prepped with 70% chlorhexidine solution. Animals received a single, preoperative dose of systemic antibiotics (Baytril 7.5 mg/kg).

Surgical repair began by creating a 10-cm midline laparotomy centered over the umbilicus. The platysma muscle was then freed from the rectus and external oblique muscle. Rectus muscle (~2.5 cm) was removed from both the left and right sides utilizing electrocautery to create a 10 cm × 5 cm final defect. Animals were then randomly assigned to repair using either pCD-coated mesh loaded with VM or control polyester mesh (Parietex TET, Covidien, Mansfield, MA). The