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Histologic evaluation of absorbable and non-absorbable barrier coated mesh secured to the peritoneum with fibrin sealant in a New Zealand white rabbit model

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Abstract

Purpose—The purpose of this study is to evaluate the histologic response to fibrin sealant (FS) as an alternative fixation method for laparoscopic ventral hernia repair.

Methods—One non-absorbable barrier mesh (Composix™) and three absorbable barrier meshes (Sepramesh™, Proceed™, and Parietex™ Composite) were used for the study, with uncoated macroporous polypropylene mesh (ProLite Ultra™) as the control. Three methods of fixation were used: #0-polypropylene suture? FS (ARTISS™, Baxter Healthcare Corp.), FS alone (ARTISS™), or tacks alone ($n = 10$ for each group). Two pieces of mesh (of dimensions 4×4 -cm) were secured intraperitoneally in 75 New Zealand white rabbits. After 8 weeks, hematoxylin and eosin (H&E)-stained specimens were evaluated for host tissue response. Statistical significance ($P < 0.05$) was

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determined using a one-way analysis of variance (ANOVA) with Fisher's least significant difference (LSD) post hoc test.

Results—Composix™ with FS only showed significantly greater cellular infiltration than with suture? FS ($P = 0.0007$), Proceed™ with FS only had significantly greater neovascularization than with suture? FS ($P = 0.0172$), and ProLite Ultra™ with suture? FS had significantly greater neovascularization than with tacks only ($P = 0.046$). Differences due to mesh type showed that Composix™ exhibited less extensive cellular infiltration ($P = 0.0032$), extracellular matrix (ECM) deposition, and neovascularization, and demonstrated less inflammatory cells and more fibroblasts compared to the other meshes ($P < 0.05$).

Conclusions—FS did not have a significant histologic effect compared to tacks when utilized for the fixation of mesh to the peritoneum of New Zealand White rabbits. However, the mesh type did have a significant histologic effect. The permanent barrier mesh (Composix™) was associated with less histologic incorporation than absorbable barrier and macroporous meshes, as evidenced by lower levels of cellular infiltration, ECM deposition, and neovascularization, independent of the fixation method used.

Keywords

Fibrin sealant; Fixation strength; TEP and TAPP; Laparoscopic ventral hernia repair, LVHR; Tisseel, Tissucol, ARTISS; Alternative fixation; Postoperative complication; Absorbable, non-absorbable barrier coated mesh

Introduction

Laparoscopic surgery techniques have revolutionized general surgery. Since its introduction less than three decades ago, laparoscopic surgery has become the standard for cholecystectomy and adrenalectomy [1, 2], and has shown major advantages in splenectomy and laparoscopic ventral hernia repair (LVHR) [3, 4]. Decreases in morbidity, complications, recovery time, and length of hospital stay have all been demonstrated. Furthermore, lower recurrence rates after hernia repair have been observed when comparing laparoscopic (4.3%) to open techniques (12.1%) [5]. In order to achieve these lower recurrence rates for LVHR [5], it is assumed that mesh fixation is performed with permanent mechanical fixation and sutures. However, significant acute postoperative pain, chronic pain syndromes, intestinal adhesions, and, rarely, fistulization may result from this fixation technique [6-10].

Fibrin sealant (FS) is being evaluated as a possible alternative to either replace or minimize permanent mechanical fixation devices, as FS can function as a biodegradable adhesive. Polymerized fibrin chains are formed when thrombin is combined with human-derived fibrinogen [9]. Similar to clots formed in vivo, the strength of FS is derived from the polymerized fibrin [11]. It should be noted that the in vivo clot strength is further enhanced by Factor XIII, which causes covalent cross-linking between fibrin polymers [12], and it has been demonstrated that FS products do not have equivalent Factor XIII levels [12]. In vivo, the FS is broken down through fibrinolysis and replaced by a fibrotic layer, while the FS simultaneously acts as a scaffold for fibroblast ingrowth [9]. In the extraperitoneal location, the use of FS has been shown to cause a significantly stronger fibrous reaction and inflammatory response when compared to mesh placed with staples and no fixation [9].

ARTISS (Baxter Healthcare Corp., Deerfield, IL) is an FS product with a thrombin concentration of 4 IU/ml. TISSEEL (Baxter Healthcare Corp., Deerfield, IL), a previously developed FS product, has a thrombin concentration of 500 IU/ml. The lower thrombin concentration found in ARTISS allows 60 s for graft manipulation prior to FS

polymerization, compared to Tisseel, which allows only 10 s for graft manipulation. The longer polymerization time may offer a unique advantage in laparoscopic settings to allow the correct placement of mesh or graft materials. In 2008, ARTISS received Food and Drug Administration (FDA) approval for the purpose of skin graft fixation to burn wound beds [13]. ARTISS is not currently approved for the fixation of prosthetic mesh and has not yet been histologically evaluated in a model of either preperitoneal or intraperitoneal mesh fixation.

Our laboratory has previously reported our experience with ARTISS as a method for alternative fixation in LVHR [14, 15]. The data presented therein demonstrated similar ($P > 0.05$) acute fixation strengths between ARTISS and TISSEEL with selected meshes [14]. We also showed that chronic intraperitoneal mesh fixation with suture? FS was superior ($P < 0.05$) or similar ($P > 0.05$) to fixation with tacks only [15]. The purpose of this study is to evaluate the histologic response to intraperitoneal FS as an alternative fixation method for LVHR.

Methods

Seventy-five New Zealand white rabbits, weighing 3–4 kg, were utilized for this study, under a protocol approved by the Washington University School of Medicine Animal Studies Committee. Current guidelines established at our institution for the humane treatment of animals were followed at all times. Prior to tissue harvest, euthanasia was achieved with a pentobarbital overdose (>300 mg/kg) after sedation with intramuscular ketamine (35 mg/kg) and xylazine (6 mg/kg).

Meshes utilized

Meshes were chosen to represent three categories of mesh types: (1) non-barrier macroporous polypropylene mesh—ProLite Ultra™ (Atrium Medical Corp., Hudson, NH), (2) absorbable barrier meshes—Sepramesh™ (Genzyme Corp., Cambridge, MA), Proceed™ (Ethicon Inc., Somerville, NJ), and Parietex™ Composite Mesh (Covidien, Mansfield, MA), and (3) non-absorbable barrier mesh—Composix™ (C. R. Bard Inc., Murray Hill, NJ). ProLite Ultra™ is a non-barrier macroporous polypropylene mesh and was selected as a control mesh for maximum possible incorporation and adhesions due to its non-barrier properties. The absorbable and non-absorbable barrier meshes chosen were selected as representative mesh types utilized in LVHR.

Sepramesh™ is a two-sided mesh with a polypropylene surface and polyglycolic acid (PGA) surface which is coated with a bioresorbable, chemically modified hyaluronate, carboxymethylcellulose, and polyethylene glycol (PEG)-based hydrogel. Proceed™ is comprised of an oxidized regenerated cellulose fabric, and PROLENE™ Soft Mesh, a non-absorbable polypropylene mesh, which is encapsulated by a polydioxanone polymer. Parietex™ Composite Mesh is dual-sided mesh with a resorbable porcine collagen barrier on one side and a three-dimensional polyester mesh on the other. Composix™ is a dual-layer mesh comprised of Bard polypropylene mesh and expanded polytetrafluoroethylene (ePTFE). DualMesh® (W. L. Gore & Associates, Flagstaff, AZ) and C-QUR™ (Atrium Medical Corp., Hudson, NH) were evaluated for inclusion in the study but were excluded when preliminary data showed insufficient fixation with FS only [14]. In the case of Composix™, specially manufactured mesh (of dimensions 4×4 cm) was obtained to maintain normal construct composition at the borders of the mesh. All other meshes utilized in this study also measured 4×4 cm.

Mesh fixation

Anesthetic induction was achieved with intramuscular ketamine (35 mg/kg) and xylazine (6 mg/kg) in 75 New Zealand White rabbits. Animals were orotracheally intubated and maintained under anesthesia with 3% isoflurane. Preoperative antibiotic prophylaxis was given as intramuscular Baytril (enrofloxacin) (2.5–5 mg/kg) and perioperative pain relief was dosed as subcutaneous Buprenorphine (0.02–0.05 mg/kg). Intravenous saline was given as needed during the operative procedure. After being placed in the supine position, animals were prepped and draped using standard sterile technique, and all operative procedures were performed under strict sterile conditions.

The abdominal cavity was accessed via a 6-cm midline laparotomy incision, and 4 × 4-cm pieces of mesh were secured to the intact peritoneum on both sides of the laparotomy incision. The aforementioned meshes were utilized (ProLite Ultra™, Sepramesh™, Proceed™, Parietex™ Composite Mesh, and Composix™). Meshes were secured with suture? FS (ARTISS, Baxter Healthcare Corp.), FS alone (ARTISS), or tacks alone (ProTack™, Covidien, Mansfield, MA). Animals were randomly assigned the mesh type and fixation method, for a total of ten pieces of each mesh secured with each fixation method ($n = 150$ total number of mesh pieces). Three constructs of either sutures or tacks were utilized to secure the medial and lateral edges of the mesh for the suture? FS and tacks-only fixation methods, respectively (Fig. 1). Spatial orientation of the fixation constructs as shown in Fig. 1 allowed for separation of the mesh upon harvest for histology and tensiometry testing. The tensiometry data was presented previously [15]. 0-polypropylene sutures were placed transfascially and secured with 8 knots after application of the FS. Knots were later buried in the subcutaneous space. Manufacturer's instructions were followed for reconstitution of the FS product, including use of the Fibrinotherm (Baxter Healthcare Corp., Deerfield, IL) device for warming and stirring of the FS during reconstitution. Prior to application, activated thrombin and the fibrinogen mixed with aprotinin were drawn up into two separate syringes and loaded into the dual-syringe application system. A quantity of 1 ml of FS was applied (approximately 16 cm²/ml) in an even layer to the intact peritoneum (4 × 4 cm area) using a DuploSpray MIS Applicator (Baxter Healthcare Corp., Deerfield, IL). Pieces of mesh secured with either suture? FS or FS only were promptly applied to the FS product and gentle pressure was maintained for 5 min to allow initial polymerization between the mesh, FS, and abdominal wall.

Midline laparotomy incisions were then closed with interrupted 3–0 polypropylene and 4–0 PDS™ II (Ethicon Inc., Somerville, NJ) in the fascial and subcutaneous layers, respectively. The skin was sealed with cyanoacrylate glue. Postoperative pain prophylaxis was administered as subcutaneous Buprenorphine (0.02–0.05 mg/kg) that evening, the following morning, and continued on an as-needed basis.

Histologic evaluation

Animals were euthanized at 8 weeks. Upon sacrifice, the entire abdominal cavity was examined through a wide circumferential excision of the abdominal wall. Mesh samples were examined for adhesions, percent original area, and mesh migration (data presented previously) [15]. Mesh samples were then divided into a 3 × 4-cm piece for tensiometry testing (data presented previously) [15] and a 1 × 4-cm piece fixed in 10% neutral buffered formalin for histologic examination (Fig. 1). From the formalin-fixed samples, 1 × 1-cm pieces of mesh and tissue were then embedded in paraffin and prepared with hematoxylin and eosin (H&E) staining for histologic examination by a veterinary pathologist blinded to the mesh type and fixation method. Samples were examined by light microscopy at high power (40, 100, and 200× magnification), and the mesh tissue interface was scored according to a scoring system adapted from Valentin et al. [16] (Table 1). Scoring categories

included cellular infiltration, cell types, inflammatory response, host extracellular matrix (ECM) deposition, neovascularization, fibrosis, and fibrous encapsulation, with more favorable incorporation outcomes represented as higher scores. Five to ten non-overlapping fields at 100× magnification were scored for each histologic sample. Representative photos of each mesh at 100× magnification are presented in Fig. 2. Fibrous encapsulation was measured utilizing the micrometer feature of the microscope.

Statistical analysis

Statistical significance ($P < 0.05$) was determined using a one-way analysis of variance (ANOVA) with Fisher's least significant difference (LSD) post hoc test.

Results

Histology results based on fixation method

There were only three significant results out of 90 comparisons based on the fixation method, $P > 0.05$ for all other comparisons (Supplemental Material, Table 2). Composix™ with FS only showed significantly greater cellular infiltration than with suture? FS ($P = 0.0007$). Proceed™ with FS only had significantly greater neovascularization than with suture? FS ($P = 0.0172$). ProLite Ultra™ with suture? FS had significantly greater neovascularization than with tacks only ($P = 0.046$).

Histology results based on mesh type

Possible scores for cellular infiltration range from "0", indicating zero cells in contact with the mesh, up to "3", in which cells have infiltrated into the center of all meshes. All meshes except for Composix™ scored approximately 2.9–3.0 for cellular infiltration, indicating that cells penetrated into the center of all of the other meshes for all three types of fixation. Composix™ meshes exhibited significantly lower cellular infiltration scores of approximately 2.2–2.6 compared to all of the other meshes, regardless of the type of fixation ($P = 0.0032$) (Fig. 3a). Scores in this range indicate that cells infiltrated the Composix™ meshes but did not reach the center in many cases.

Higher inflammation scores represent a more favorable histologic response with the presence of fewer inflammatory cells, while lower scores represent the presence of many inflammatory cells, including both mononuclear and foreign body giant cells. Composix™ secured with FS only exhibited a significantly higher inflammation score of 1.2 ± 0.1 (indicating the presence of mononuclear cells) compared to all of the other meshes secured with FS only, which scored approximately 0.2–0.7, indicating the presence of both mononuclear and foreign body giant cells ($P < 0.05$ for all comparisons). Composix secured with suture? FS exhibited a significantly higher inflammation score of approximately 1.2 ± 0.2 compared to Sepramesh™ and Parietex™ Composite secured with suture? FS, with scores of 0.6 ± 0.2 and 0.03 ± 0.0 , again indicating the presence of both mononuclear and foreign body giant cells ($P < 0.05$ for all comparisons) (Fig. 3b). Similarly, Composix™ secured with tacks exhibited a significantly higher inflammation score of 1.1 ± 0.2 compared to all of the other meshes secured with tacks (scores of approximately 0.1–0.6, indicating the presence of both mononuclear and foreign body giant cells), except for ProLite Ultra™ ($P = 0.0614$), which scored 0.6 ± 0.1 , indicating the presence of primarily mononuclear cells with a few foreign body giant cells. In addition, Parietex™ Composite secured with suture? FS or tacks both resulted in significantly lower inflammation scores (0.03 ± 0.0 and 0.06 ± 0.0 , respectively) compared to all of the other mesh types, which scored approximately 0.6–1.2 ($P < 0.05$) (Fig. 3b).

ECM deposition was scored from 0 to 3, with a score “0” indicating no detectable ECM deposition, up to a score of “3”, indicating ECM deposition within the mesh interstices and bridging between mesh fibers. Composix™ secured with FS scored 2.4 ± 0.1 (indicating some ECM deposition within mesh interstices, but little bridging between mesh fibers), which was significantly less extensive ECM deposition compared to both Proceed™ and Parietex™ Composite with FS only ($P = 0.027$), with scores of 2.8 ± 0.1 and 2.7 ± 0.1 , respectively (Fig. 3c). Composix™ secured with suture? FS or tacks also exhibited significantly less ECM deposition with scores of 2.1 ± 0.2 and 2.2 ± 0.1 , respectively, compared to all of the other meshes secured with suture? FS or tacks ($P < 0.001$), which scored approximately 2.7–3.0 for both types of fixation (Fig. 3c).

Neovascularization scoring criteria were similar to ECM deposition, with a score of “0” indicating zero new blood vessels, up to scores of “3”, in which new blood vessels were evident within the mesh interstices and bridging between mesh fibers, forming an interconnected microvascular network. Composix™ secured with FS only demonstrated significantly less extensive neovascularization than either Proceed™ or Parietex™ Composite secured with FS only ($P < 0.05$), with a score of 2.0 ± 0.1 (indicating new blood vessels present within the mesh, but not bridging across interstices) compared to scores of 2.6 ± 0.1 and 2.4 ± 0.1 , respectively (indicating bridging of vessels across some interstices) (Fig. 3d). Similarly, Composix™ secured with suture? FS revealed less neovascularization than either ProLite Ultra™ or Parietex™ Composite secured with suture? FS ($P = 0.01$) (Fig. 3d), with a score of 1.8 ± 0.1 compared to scores of 2.4 ± 0.2 and 2.3 ± 0.1 , respectively. In addition, Composix™ and Sepramesh™ secured with tacks both demonstrated less neovascularization (scores of 1.8 ± 0.1 and 1.7 ± 0.2 , respectively) compared to either Proceed™ or Parietex™ Composite with tacks only, with scores of 2.4 ± 0.2 and 2.2 ± 0.1 , respectively ($P = 0.034$) (Fig. 3d). Finally, Proceed™ secured with FS only demonstrated significantly more neovascularization than Sepramesh™ or ProLite Ultra™ secured with FS only or compared to Proceed™ secured with suture? FS ($P < 0.05$ in all cases). Proceed™ secured with tacks also demonstrated significantly greater neovascularization compared to ProLite Ultra™ secured with tacks ($P = 0.0383$).

The types of cells present in each mesh specimen were also evaluated, with lower scores indicating the presence of mostly inflammatory cells and higher scores indicating the presence of primarily fibroblasts with little evidence of inflammation. Composix™ secured with FS only exhibited fewer inflammatory cells and more fibroblasts (score of 1.8 ± 0.0) compared to ProLite Ultra™ and Parietex™ Composite with FS only, which both had “cell types” scores of 1.5 ± 0.1 and 1.5 ± 0.0 , respectively ($P = 0.0041$), indicating a mixture of inflammatory cells and fibroblasts (Fig. 3e). Composix™ secured with suture? FS demonstrated fewer inflammatory cells and more fibroblasts (score of 1.7 ± 0.1) than Parietex™ Composite with suture? FS, which had a score of 1.5 ± 0.0 ($P = 0.016$) (Fig. 3e). Composix™ secured with tacks only revealed fewer inflammatory cells and more fibroblasts (score of 1.8 ± 0.1) compared to ProLite Ultra™, Proceed™, and Parietex™ Composite with tacks only, which scored 1.5 ± 0.1 , 1.6 ± 0.1 , and 1.5 ± 0.0 , respectively ($P < 0.05$) (Fig. 3e). In addition, Sepramesh™ secured with tacks only revealed fewer inflammatory cells and more fibroblasts (score of 1.7 ± 0.1) than Parietex™ Composite with tacks only, which scored 1.5 ± 0.0 ($P < 0.05$) (Fig. 3e).

No significant differences were observed for any combinations analyzed for fibrosis or capsule thickness (Fig. 3f, g, respectively). Scores for fibrosis ranged from 1.5 to 2.1, indicating that all meshes exhibited fibrosis surrounding individual mesh fibers, with some bridging across the interstices. Capsule thicknesses ranged from 0.00 to 0.09 mm, with no significant differences between meshes or due to the type of fixation ($P > 0.05$ in all cases).

Refer to the included table for a complete listing of the statistical results for comparisons based on differing mesh types with the same fixation method (Supplemental Material, Table 3).

Discussion

This study demonstrated no significant histologic effect due to fixation with FS. All histologic scoring categories (cellular infiltration, cell types, inflammatory response, host ECM deposition, neovascularization, fibrosis, and fibrous encapsulation) showed non-significant results when comparing fixation with FS? suture, tacks only, or FS only. As hernia repair efficacy and the avoidance of postoperative complications such as seromas, hematomas, and mesh or wound infections may be directly related to the ability of the patient to effectively incorporate the mesh repair, it is important to note that the histologic data of this study did not support either the inhibition or acceleration of healing with the use of FS product for mesh fixation.

Despite findings from a previous study demonstrating significantly stronger fibrous reaction and inflammatory response to FS compared to staples or no fixation of mesh in the preperitoneal space [9], once again, our findings demonstrate that FS did not have a significant histologic effect compared to tacks when utilized for the fixation of mesh to the peritoneum. Differences in tissue reaction between these two studies may be due to preperitoneal versus intraperitoneal use of the FS products. It is also possible that a more aggressive inflammatory response is produced in a porcine model [9] compared to our rabbit model due to species-specific responses to the human thrombin protein in the FS. Another important possible difference between the two studies is the difference in thrombin concentration in the FS utilized in these studies. The preperitoneal, porcine study utilized FS with a thrombin concentration of 500 IU/ml [9], while this intraperitoneal, rabbit study utilized FS with a thrombin concentration of 4 IU/ml. The effect of varying thrombin concentrations on the subsequent inflammatory response has not been evaluated.

Our study clearly shows that the histologic response was dependent upon the biomaterial and/or barrier coating of the mesh products utilized. Although the use of FS for intraperitoneal fixation in a rabbit model did not have a significant histologic effect, this study demonstrates that the mesh type does have a significant histologic effect. Composix™ (a composite of polypropylene mesh coupled with a microporous ePTFE permanent barrier layer) is associated with less histologic incorporation than absorbable barrier and macroporous meshes, as evidenced by less extensive cellular infiltration, ECM deposition, and neovascularization, independent of the fixation method used. However, Composix™ meshes also contained more fibroblasts, fewer inflammatory cells, and zero foreign body giant cells compared to the other meshes, indicating that this particular mesh incites a less aggressive inflammatory response compared to the absorbable barrier meshes and the bare macroporous polypropylene mesh. It is possible that the absorption of the barrier layer components leads to a greater inflammatory response at 8 weeks compared to the permanent barrier mesh (Composix™). Many mesh types are available for use in LVHR, in part because no single mesh has been demonstrated as being superior to all others. This study was not undertaken as a hernia repair model, and, as such, the histologic findings cannot be correlated with either superiority or inferiority regarding hernia recurrence.

As this study is the first of its kind to evaluate the histologic response generated by FS as a mesh fixation agent, further evaluation is required in order to compare the responses generated by both available concentrations of FS (4 and 500 IU/ml) and both mesh placement locations (preperitoneal and intraperitoneal). FS may hold promise as a mesh fixation agent in conjunction with permanent mesh fixation, such as transfascial suture.

Although alleviating chronic problems related to permanent fixation devices is the goal of any alternative fixation device, it should be noted that a lasting repair should be the primary goal of each hernia repair. The risk of early hernia recurrence must be weighed against the prospect of a more comfortable hernia repair. Further investigation should be undertaken to evaluate the efficacy of FS? suture for the fixation of mesh in LVHR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1. Depiction of the mesh dimensions and fixation construct locations. The *dotted line* depicts the division point for tensiometry and histology samples

Fig. 2.
Photos of hematoxylin and eosin (H&E)-stained slides at 100× magnification

Fig. 3. Histologic results for: (a) cellular infiltration, (b) inflammation, (c) extracellular matrix (ECM) deposition, (d) neovascularization, (e) cell types, (f) fibrosis, and (g) capsule thickness

Table 1

Histologic scoring system

Histologic scoring system	Score			
	0	1	2	3
Cellular infiltration	Zero cells in contact with mesh	Cells contact periphery, no infiltration into mesh	Cells infiltrate mesh, but none reach the center	Cells penetrate into the center of the mesh
Cell types (inflammatory cells include neutrophils, macrophages, and foreign body giant cells)	Inflammatory cells present, no fibroblasts	Primarily inflammatory cells, few fibroblasts	Primarily fibroblasts, few inflammatory cells	Fibroblasts only, no inflammatory cells
Inflammatory response	Mononuclear and foreign body giant cells	Primarily mononuclear cells	Few mononuclear cells	Zero inflammatory cells present
Host extracellular matrix (ECM) deposition	No host ECM deposition	Host ECM deposited at the periphery of the mesh	Host ECM deposited around individual mesh fibers but not bridging across mesh interstices	Host ECM deposited within mesh interstices and bridging between mesh fibers
Neovascularization	Zero blood vessels present	Vessels present at mesh periphery only, no vessels present within mesh interstices	Vessels present within mesh interstices but not bridging across mesh interstices	Vessels present within mesh interstices and bridging mesh interstices, forming an interconnected microvascular network
Fibrosis	Scar plate fully embedding the entire mesh, including fibers and interstices	Fibrosis surrounding individual mesh fibers and bridging across mesh interstices in some places	Fibrosis surrounding individual mesh fibers but not bridging across mesh interstices	No fibrosis
Fibrous encapsulation	Measurement of thickness rather than a score			