

Strategies to Minimize Adhesions to Intraperitoneally Placed Mesh in Laparoscopic Ventral Hernia Repair

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ABSTRACT

Introduction: Adhesions to mesh/tacks in laparoscopic ventral hernia repair are often cited as reasons not to adopt its evidence-based superiority over conventional open methods. This pilot study assessed the occurrence of adhesions to full-sized Polypropylene and Gore-tex DualMesh Plus meshes and the possibility for adhesion prevention using fibrin sealant.

Methods: Two 10-cm to 15-cm pieces of mesh were placed and fixed laparoscopically in pigs (25kg to 55kg). Group I: 2 animals with Polypropylene mesh on one side and DualMesh on other side. Group II: 2 animals with DualMesh on each side with fibrin sealant applied to the periphery of mesh and staples to one side. Group III: 1 animal with 2 pieces of Polypropylene mesh with fibrin sealant applied to the entire mesh. All animals underwent laparoscopy 3 months later to assess the extent of adhesions, and full-thickness specimens were removed for histological evaluation.

Results: More Polypropylene mesh was involved in adhesions than DualMesh. However, with the DualMesh involved in adhesions, more of the surface area was involved in forming adhesions than with Polypropylene mesh. None of the implanted DualMesh had visceral adhesions, while 2 out of 3 Polypropylene meshes had adhesions to both the liver and spleen but none to the bowel. Implanted Polypropylene mesh with fibrin sealant had no adhesions. DualMesh had shrunk more significantly than Polypropylene mesh. Histological evaluation showed absence of acute inflammatory response, significantly more chronic inflammatory response to DualMesh compared to Polypropylene and complete mesothelializa-

tion with both meshes. There was extensive collagen deposition between Polypropylene mesh fibers, while fibrosis occurred on both sides of DualMesh with synovial metaplasia over its peritoneal surface akin to encapsulation.

Conclusions: DualMesh caused fewer omental and visceral adhesions than Polypropylene mesh did. Fibrin sealant eliminated adhesions to DualMesh and prevented adhesions to Polypropylene mesh when applied over the entire surface. These results support our current use of DualMesh and fibrin sealant in LVHR.

Key Words: Laparoscopy, Ventral hernia, Fibrin sealant, Adhesion prevention.

INTRODUCTION

Since laparoscopic ventral hernia repair (LVHR) was introduced in 1989, numerous studies have demonstrated its superiority over conventional open repair, most noticeable with the significant reduction in wound complications.¹⁻³ Although recurrence rates of LVHR have been shown to be <5%, it has not been possible, for ethical reasons, to relaparoscope these patients routinely to assess adhesion formation. It is known that all adhesions have the potential for deleterious effects including bowel obstruction, sometimes even decades after the original surgical intervention. Staples are usually used in LVHR, which have been shown to act as the nidus for adhesion formation⁴ at best and a site of fistula formation at worst.⁵ While efforts are being made to use alternative absorbable fixation devices as well as reducing the number of permanent staples being used,⁶ it may take many years before a solution, if any, is found. Yet there is current evidence available to suggest that, paradoxically, fibrin sealant itself has been shown to reduce adhesions in animal models.⁷⁻⁹

This is a feasibility study that aims to assess whether fibrin sealant has any adhesion prevention effects on commonly used meshes in a large animal model with clinical size dimensions.

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MATERIALS AND METHODS

This study was approved by the Animal Ethics Committee of the Sydney West Area Health Service. Permission was given to use (only) 5 pigs for the purpose of studying adhesion prevention of fibrin sealant during laparoscopic intraperitoneal onlay mesh placement.

Animal and Mesh Placement

Five male Westran pigs of 25kg to 50kg (mean, 35.6) were used (**Table 1**). Procedures were performed with the pigs under general anaesthetic following premedication with intramuscular 1mg/kg Ilium Xylazil (Xylazine, Troy Laboratories Pty. Ltd., Sydney, Australia), 25mg/kg Tiletamine combined with 25mg/kg Zolazepam (Zoletil 100 Virbac, Australia Pty. Ltd., Sydney, Australia) and 1mg/kg Azaperone (Stresnil, Boehringer Ingelheim Pty. Ltd., Sydney, Australia). General anaesthesia was maintained with 1% to 2% Isoflourane (Aerane, Baxter Healthcare Pty Ltd, Sydney, Australia) in oxygen after intubation. The abdomen was prepped with alcohol and Betadine skin prep, and the animals underwent laparoscopic intraperitoneal onlay mesh placement. Briefly, a 2-cm incision is made in the right upper quadrant, and the muscle layers are split until the peritoneum is entered. A 10-mm port (Covidien, Norwalk, Connecticut USA) is inserted under direct vision. The peritoneal cavity was then insufflated with CO₂ to 12mm Hg. Two 5-mm ports are then placed laterally under direct vision, and laparoscopy is then performed to ensure no prior intraperitoneal adhesions are present. A 10-cm to 15-cm piece of mesh, either Polypropylene (PROLENE Mesh, Ethicon, Inc, USA) and/or Gore-tex DualMesh Plus (WL Gore & Associates Inc, Elkton, MD, USA) was placed on each side of the abdomen, and these were fixed with transfascial sutures in 4 quadrants: 1 Gore-tex suture and a double layer of titanium staples (Protacks, Covidien, Norwalk, Connecticut USA) were then applied with the staples being 1cm apart on the “outer crown” and 2cm apart on the “inner crown.” The mesh on one side of the abdomen was then sprayed with 2mL of fibrin sealant (Tis-

seal, Baxter, Vienna). The abdomen was kept insufflated for 5 minutes after fibrin sealant application before deflation and closure of the upper quadrant wound in layers with nylon sutures and the skin wounds with staples. The animals were recovered, and analgesia 0.01mg/kg Buprenorphine (Temgesic, Reckitt & Colman Products Ltd., Hull, UK) was given every 6 hours to 8 hours for at least 48 hours then as necessary. They were kept and fed ad libitum for the next 3 months without any animals experiencing distress or complications.

Laparoscopic Evaluation

Three months later, the animals underwent relaparoscopy where the number of adhesions were assessed. Omentum or visceral (bowel/organ) adhesions to the mesh were recorded, and adhesion tenacity was graded (0–4) intraoperatively. The surface area (cm²) of the mesh was calculated by measuring the cranial-caudal and transverse dimensions (cm) of the intraperitoneal mesh. The surface area of adhesions covering the mesh was estimated in tenth percentiles (0=0%, 10=100%).⁶

Necropsy and Histological Analysis

The animals were then euthanized before full-thickness excision of the meshes with their attached (if any) adhesions. These were placed in 10% Formalin, sectioned, and stained for hematoxylin and eosin and collagen stains. Two random samples (1cm to 2cm) were excised from each piece of mesh and evaluated histologically by 2 observers, blind to the mesh type implanted. The samples were evaluated for acute and chronic inflammation (polymorphonuclear leukocytes=PMNs and chronic inflammatory cells=CICs per high-powered field (HPF; magnification=40): 0–4 CICs/HPF=1, 5–9 CICs/HPF=2, 10–15 CICs/HPF=3 and >15 CICs/HPF=4, tissue ingrowth and mesothelialization as previously described.¹⁰ The predominant inflammatory response comparing acute, as exhibited by polymorphonuclear cell infiltra-

Table 1.
Experimental Design with the Number of Pigs and the Different Meshes with or Without Fibrin Sealant

Group	Pig #	Mesh	Left Side	Right Side
1	1	Polypropylene/Dualmesh	Polypropylene	Dualmesh
	2	Dualmesh/Polypropylene	Dualmesh	Polypropylene
2	3	Dualmesh	Dualmesh	Dualmesh+Fibrin Sealant
	4	Dualmesh	Dualmesh+Fibrin Sealant	Dualmesh
3	5	Polypropylene	Polypropylene	Polypropylene+Fibrin Sealant

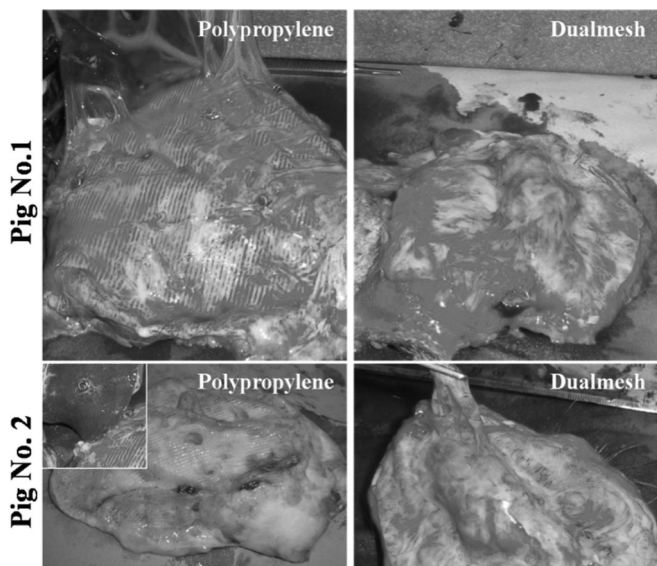


Figure 1. Group 1 animals with Polypropylene animals showing omental and liver adhesions with inset showing displaced staples in liver while Dualmesh Plus animals showing segmental omental or no adhesions.

tion, versus chronic, as exhibited by histiocytic/lymphocytic/foreign body reaction, was assessed.

RESULTS

Combining the adhesion results of all 3 groups without fibrin sealant revealed that a larger amount of Polypropylene mesh was involved in adhesions than DualMesh (2 SD=0 vs 1 SD=0). However, of the DualMesh involved in adhesions, more of the surface area was involved in adhesions than Polypropylene mesh (2.33 SD±1.15 vs 1.67 SD±0.58) (**Figure 1 & 2**). However, there were a large number of staples (35% of total) “pulled” off the Polypropylene mesh and embedded in adhesions to omentum, liver, and spleen (**Figure 1**). None of the DualMesh implanted showed visceral adhesions (**Figure 2**), while 2 out of 3 Polypropylene meshes had adhesions to both liver and spleen but none to bowel. Implanted Polypropylene mesh with fibrin sealant had no adhesions whatsoever (**Figure 3**).

Implanted Polypropylene meshes showed negligible shrinkage with all explanted meshes measuring 9.25cm to 14.4cm (SD ±0.29 and ±0.25, respectively) from 10cm to 15cm at implantation, while explanted DualMesh showed significant shrinkage to 5.3cm to 10.4cm (SD ±0.27 and ±0.42, respectively). Histological evaluation showed complete mesothelialization over the peritoneal surface of

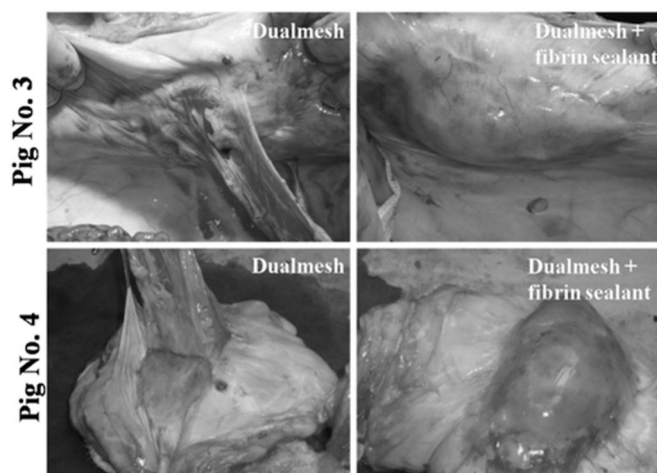


Figure 2. Group 2 animals showing segmental omental adhesions with Dualmesh Plus and no adhesions with Dualmesh Plus and fibrin sealant.

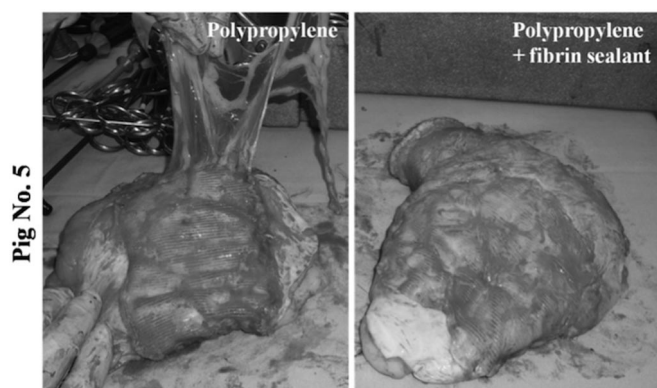


Figure 3. Polypropylene animal showing segmental omental adhesions while Polypropylene and fibrin sealant animal showing no adhesions.

all samples. Implanted Polypropylene meshes (with or without fibrin sealant) showed extensive collagen deposition between the mesh fibers (**Figure 4**), whereas there was only superficial collagen infiltration into the peritoneal surface of implanted DualMesh (**Figure 5**). More importantly, there was a thick layer of fibrous tissue covering the peritoneal surface of the DualMesh with a thick layer of histiocytes (known as synovial metaplasia) at the mesh-fibrous tissue interface (**Figure 5**).

At 3 months, there was a complete absence of polymorphonuclear cells in all the samples, Polypropylene and DualMesh, with or without fibrin sealant. The mean histological score for chronic inflammation was 1.8 SD±1.23 for Polypropylene mesh and 3.0 SD±1.33 for DualMesh. The intense chronic inflammatory cellular infiltration, represented by his-

tiocytic/lymphocytic/foreign body giant cellular infiltration, was present on both surfaces of DualMesh (Figure 5). In addition, there were occasional clusters of eosinophils in 2 of 3 DualMesh samples (Figure 5) but none in the Polypropylene samples.

DISCUSSION

The advent of laparoscopy in general surgery in the late 1980s has seen a large number of procedures, including

cholecystectomy, being treated almost exclusively by laparoscopic means. Apart from reducing wound complications, laparoscopy has also significantly reduced, though not abolished, intraabdominal adhesions.¹¹ In the field of hernia surgery, an increasing number of abdominal wall hernias are being treated with intraperitoneal onlay mesh placement. Currently, there are some 270 different meshes available with the industry concentrating on producing meshes with fewer adhesiogenic properties yet retaining their strength. Although animal models, small and large, have shown potential benefits, in terms of reducing adhesions, extrapolation to humans cannot be assumed. Despite the expense of these meshes, compared to Polypropylene mesh, almost all have shown significant adhesions in humans. In a study of relaparoscopy in patients who had undergone laparoscopic ventral hernia repair, Jenkins et al⁶ demonstrated adhesions to 60% to 100% of mesh surface. Of much concern was that intestinal adhesions occurred in 64% of ePTFE mesh and up to 100% of macroporous meshes. Apart from the periphery of the so-called anti-adhesive meshes being devoid of anti-adhesion barrier, the protruding fixation devices also provide a nidus for adhesions. Although the use of absorbable fixation devices is becoming more common in hernia surgery, it remains to be determined whether they are superior to nonabsorbable fixation devices in humans in preventing intraabdominal adhesions. Furthermore, their use with meshes such as ePTFE, known to cause much less fibrosis and integration into the abdominal wall, is highly questionable.

On one hand, efforts have been concentrated on using fibrin sealant to supplement fixation devices in ventral

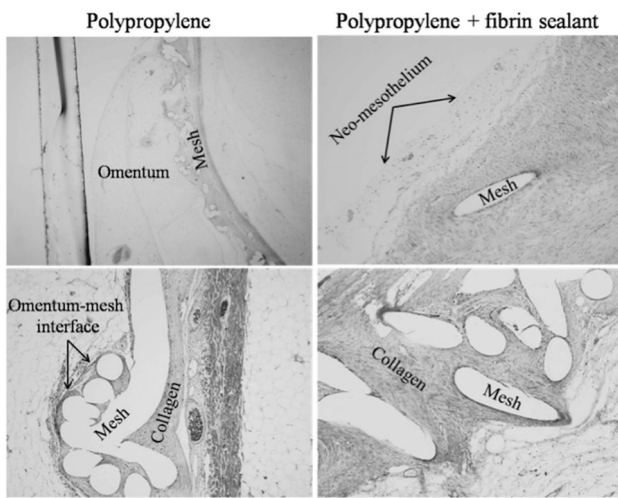


Figure 4. Top pictures showing H&E stain of Polypropylene mesh with adherent omentum (left) while fibrin sealant treated Polypropylene mesh (right) with no adhesions with a neo-mesothelial layer on top of the mesh. Bottom pictures showing collagen stain showing collagen infiltration within the mesh fibers which had been dissolved during preparation.

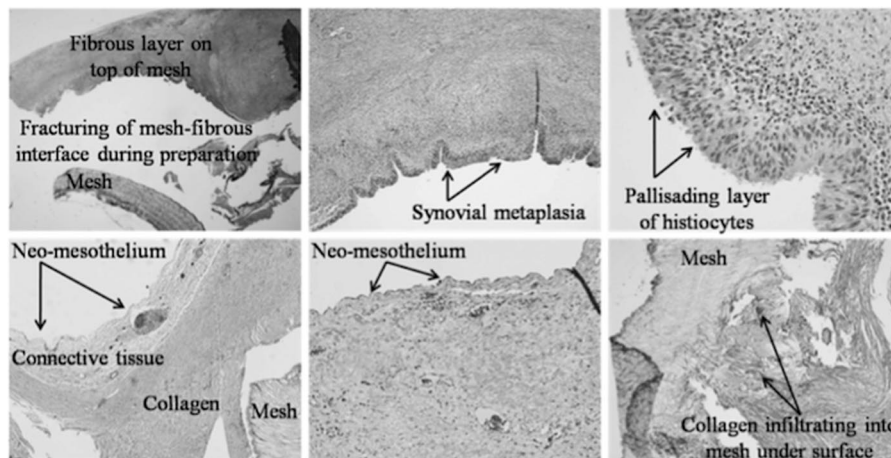


Figure 5. Top pictures showing a thick layer of fibrous tissue overlying Gortex Dualmesh Plus (left) which had been fractured off the mesh during preparation, with the external mesh-fibrous tissue interface showing synovial metaplasia (middle) with pallisading layer of histiocytes (right). Bottom pictures showing neo-mesothelium covering the fibrin treated Gortex Dualmesh (left and middle) while the rough under surface of the mesh is infiltrated with collagen.

hernia repair; on the other, there is both experimental and clinical evidence for beneficial effects of fibrin sealant in minimizing adhesions. Sikkink et al⁷ demonstrated in a study on rats in which abdominal wall defects were created and covered with Polypropylene mesh that application of fibrinogen glue significantly reduced the severity of adhesions compared with Polypropylene mesh alone. Pether-Purchner et al⁸ demonstrated in a rat model that fibrin sealant not only reduced adhesions to implanted condensed polytetrafluoroethylene mesh but also enhanced tissue integration into the mesh. In large animal models, some encouraging results, on the anti-adhesion properties of fibrin sealant, have also been reported. Martin-Cartes et al⁹ demonstrated in a swine model that, both ePTFE and Polypropylene, meshes placed intraabdominally, via laparotomy, reduced both quantity and consistency of adhesions following application with fibrin sealant. Our pilot study in a swine model replicates more closely the human model in that the operation was performed exactly as in humans with clinical size (large) meshes being used. We demonstrated that while Polypropylene mesh produced quantitatively more adhesions than DualMesh with the former causing adhesions to the liver/spleen, fibrin sealant abolished adhesions, to not only DualMesh, but surprisingly to Polypropylene mesh. Admittedly, 6mL of fibrin sealant was used on the Polypropylene implanted animal, compared to DualMesh groups, where only 2mL was used. This was to ensure that the entire Polypropylene mesh including the staples were completely covered with fibrin sealant, compared to the DualMesh group, where only the exposed periphery of the mesh and staples were sprayed with fibrin sealant. It is unfortunate that only one pig was used in this comparison, but permission

was only given for 5 animals to be used. However, this study was designed only to identify potential anti-adhesion properties of fibrin sealant in a qualitative manner.

While Polypropylene mesh in this swine model did not show any significant shrinkage at explantation, DualMesh showed significant shrinkage from 10cm to 15cm on implantation to 5.5cm to 10.5cm at explantation at 3 months. Histological evaluation showed a thick layer of fibrous tissue covering the parietal and peritoneal surfaces of DualMesh with synovial metaplasia, represented by a palisading layer of histiocytes, at the fibrous tissue-mesh (peritoneal) surface, akin to fibrous encapsulation of breast implants.¹² This could therefore be the reason for the significant shrinkage of DualMesh. There was a complete absence of acute cellular infiltration with both mesh types at 3 months. There was only sparse chronic cellular infiltration in Polypropylene mesh samples, predominantly associated with mesh fragments, while this was quite intense around DualMesh. In addition, 2 of 3 DualMesh samples had small clusters of eosinophils signifying a potential allergic reaction.

Because this was a pilot study, permission was given to use only 5 animals, therefore preventing any statistically conclusive statements to be made on the adhesion prevention effects of fibrin sealant. Furthermore, the authors purposefully did not seek any commercial support for the project in order to prevent any bias, perceived or otherwise, or worse prevention of publication of the results of this project should they turn out to be negative. Despite the limitation imposed by the small number of animals, these exciting results permit us, and possibly other research groups, to obtain further approval for a more quan-



Figure 6. Patient with previous LVHR (left) presented with bilateral inguinal hernias and underwent single incision laparoscopic inguinal hernia repair (inset). Intraoperative view (right) of previous implanted Dualmesh which had been sprayed with fibrin sealant along periphery of mesh and staples showing no adhesions.

titative study where a larger number of animals (preferably 4 to 6 animals in each arm of the experiment) will be used with Polypropylene mesh and different volumes of fibrin sealant. It should be acknowledged that large animal experiments, especially those involving larger animals such as pigs, are very expensive and financial support in the form of a grant will be necessary to pursue this further.

Since October 2007, our hernia clinic has routinely been using fibrin sealant for all of our patients undergoing laparoscopic ventral/incisional including parastomal hernia repair. We have routinely sprayed 2mL of fibrin sealant along the periphery of the mesh and on the staples for meshes 15cm to 19cm or less, and 4mL for bigger meshes. The process of mesh spraying is relatively easy using the DuploSpray MIS applicator (Micromedics, St. Paul, MN, USA) and adds only a couple of minutes to the operation time, although the abdomen must remain inflated for an additional 3 minutes to ensure that the fibrin sealant has completely set. From October 2007 to January 2011, we had 57 patients undergoing LVHR including 3 with parastomal hernias. The average mesh size was 460cm² (range, 225 to 884) with an average length of hospital stay of 1.2 days (range, 1.2 to 5). There have been no complications or challenges using the spray intraabdominally on the mesh. In particular, there has been no recurrence or readmission for bowel obstruction with a follow-up of 12 to 48 months. One patient in this study underwent laparoscopic single-incision total extraperitoneal inguinal hernia repair 3 years after his LVHR. It was possible to enter the peritoneal cavity at the end of the procedure, and we demonstrated no adhesions to the previously placed Du-alMesh that had been fixed with a double layer of staples, and fibrin sealant was used along the periphery of the mesh and over the staples (**Figure 6**).

CONCLUSION

This study demonstrates powerful qualitative experimental evidence in the preclinical pig model mimicking LVHR in humans of the anti-adhesive properties of fibrin sealant even to traditionally adhesiogenic Polypropylene mesh in correct volumes. Indeed routine application in humans undergoing LVHR has not demonstrated any deleterious side effects in the short to medium terms. This study is the first to support the use of fibrin sealant as an adhesion preventing substance in a large animal model similar to LVHR with clinical-sized meshes with parallel application in humans.

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