

Assessment of Adhesion Formation to Intra-Abdominal Polypropylene Mesh and Polytetrafluoroethylene Mesh

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Background. The development of intra-abdominal adhesions, bowel obstruction, and enterocutaneous fistulas are potentially severe complications related to the intraperitoneal placement of prosthetic biomaterials. The purpose of this study was to determine the natural history of adhesion formation to polypropylene mesh and two types of polytetrafluoroethylene (ePTFE) mesh when placed intraperitoneally in a rabbit model that simulates laparoscopic ventral hernia repair.

Materials and methods. Thirty New Zealand white rabbits were used for this study. A 10-cm midline incision was performed for intra-abdominal access and a 2 cm x 2 cm piece of mesh ($n = 60$) was sewn to an intact peritoneum on each side of the midline. Two types of ePTFE mesh (Dual Mesh and modified Dual Mesh, W.L. Gore & Assoc., Flagstaff, AZ) and polypropylene mesh were compared. The rate of adhesion formation was evaluated by direct visualization using microlaparoscopy (2-mm endoscope/trocar) at 7 days, 3 weeks, 9 weeks, and 16 weeks after mesh implantation. Adhesions to the prosthetic mesh were scored for extent (%) using the Modified Diamond Scale (0 = 0%, 1 \leq 25%, 2 = 25–50%, 3 > 50%). At necropsy the mesh was excised en bloc with the anterior abdominal wall for histological evaluation of mesothelial layer growth.

Results. The mean adhesion score for the polypropylene mesh was significantly greater ($P < 0.05$) than Dual Mesh at 9 weeks and 16 weeks and modified Dual Mesh at 7 days, 9 weeks, and 16 weeks. Fifty-five percent ($n = 11$) of the polypropylene mesh had adhesions to small intestine or omentum at necropsy compared to 30% ($n = 6$) of the Dual Mesh and 20% ($n = 4$) of the

modified Dual Mesh. There was a significantly greater percentage ($P < 0.003$) of ePTFE mesh mesothelialized at explant (modified Dual Mesh 44.2%; Dual Mesh 55.8%) compared to the polypropylene mesh (12.9%).

Conclusions. Serial microlaparoscopic evaluation of intraperitoneally implanted polypropylene mesh and ePTFE mesh in a rabbit model revealed a progression of adhesions to polypropylene mesh over a 16 week period. The pore size of mesh is critical in the development and maintenance of abdominal adhesions and tissue ingrowth. The macroporous polypropylene mesh promoted adhesion formation, while the microporous nature of the visceral side of the ePTFE served as a barrier to adhesions. © 2003 Elsevier Inc. All rights reserved.

Key Words: mini-laparoscopy; adhesions; ePTFE; polypropylene; biomaterial; ventral hernia repair; New Zealand white rabbit; laparoscopic surgery; hernia.

INTRODUCTION

Ventral hernia repair has been the topic of great debate for the past two decades. Fascial defects necessitate approximately 100,000 surgical procedures per year in the United States [1]. Incisional hernias occur in 11–20% of patients who have undergone laparotomy [2]. They most commonly occur in the first 3 to 5 years following surgery, but may appear long after the primary operation. These abdominal wall defects tend to cause the local problems of pain and bulging, but can become surgical emergencies if they incarcerate or strangulate.

The use of prosthetic biomaterial (mesh) to buttress the defect of incisional hernias, creating a tension-free repair, has been shown to be superior to primary repair alone [3]. Hernia recurrence rates have been reported to be 4–24% when mesh is used compared with 24–

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50% with primary repair [3, 4]. During the evolution of ventral hernia repair, Rives and Stoppa demonstrated the importance of placing prosthetic mesh posterior to the rectus muscle in a preperitoneal location [5–8]. A large piece of mesh in this anatomical position allowed for dissipation of abdominal wall forces as well as protection of the prosthetic material from the peritoneal cavity. Despite the decreased recurrence rates associated with this technique, it has a significant risk of morbidity. The extensive dissection required for the creation of subcutaneous tissue flaps has a 20% wound complication rate and often requires reoperation [5]. This type of surgical repair often necessitates drain placement and a lengthy hospital stay [6].

To overcome the inherent complications associated with the Stoppa operation, minimally invasive techniques have been developed to repair ventral hernias. Laparoscopic ventral hernia repair is an intraperitoneal technique that uses a prosthetic biomaterial to repair abdominal wall defects without the need for wide fascial dissection and flap creation [1]. This technique has evolved over the past decade to be feasible and safe. It has been shown in short-term follow-up to be as effective as open repair [1]. There is evidence to support lower recurrence rates when incisional hernias are repaired laparoscopically [9, 10].

Despite the excellent results and low recurrence rates obtained with the laparoscopic repair of ventral hernias, the placement of prosthetic biomaterials in the peritoneal cavity does have potential complications and has intensified the debate concerning prosthetic biomaterial physiology and bioreactivity [11]. The development of intra-abdominal adhesions, bowel obstruction, and enterocutaneous fistulas are among the potentially severe complications related to the intraperitoneal placement of prosthetic mesh.

Laparoscopic ventral hernia repair and novel biomaterials have evolved together over the past decade, with each entity lending some facet to the other to propel its development. The two biomaterials most commonly used for laparoscopic ventral hernia repair are polypropylene mesh and expanded polytetrafluoroethylene (ePTFE) mesh. Retrospective, clinical studies have examined the inflammatory response induced when these prosthetic materials are placed within the peritoneal cavity in open surgery [12, 13]. Leber *et al.* showed that compared with ePTFE, polypropylene had a statistically significant increased rate of infection, adhesion formation, small bowel obstruction, fistula formation, and recurrence [12]. An evaluation of the tissue reaction of these prosthetic biomaterials, when placed intraperitoneally is important to determine their safety and efficacy for laparoscopic ventral hernia repair.

The purpose of this study was to determine the natural history of adhesion formation to polypro-

pylene mesh and two types of polytetrafluoroethylene mesh placed intraperitoneally in a rabbit model that simulated laparoscopic ventral hernia repair (intact peritoneal surface). Interval microlaparoscopy (2-mm endoscope/trocar) was performed in each rabbit over a 16-week period to assess adhesion formation, and histological evaluation was conducted to assess the tissue response to the mesh.

MATERIALS AND METHODS

Animals and Mesh Placement

Thirty New Zealand white rabbits weighing 3 to 4 kg (Robinson Service, Inc., Clemmons, NC) were used for this study and maintained in accordance with National Research Council Guidelines [14]. Experimental protocols were approved by the Institutional Animal Care and Use Committee at the Carolinas Medical Center, Charlotte, NC. All animals were housed individually and given rabbit chow and water ad lib during a 2-week acclimation period before mesh implantation. Each rabbit was induced by an intramuscular injection of Acetylpromazine (0.5 mg/kg) and Ketamine (20 mg/kg). Intraoperative general endotracheal anesthesia was maintained with 3.0% Isoflurane. Under sterile conditions, a 10-cm midline incision was made for intra-abdominal access. A 2-cm × 2-cm piece of mesh ($n = 60$) was sewn to an intact peritoneum using interrupted, non-absorbable, monofilament sutures on each side of the midline. Three different prosthetic biomaterials were implanted, macroporous (620 μm) polypropylene mesh (Marlex, C.R. Bard, Murray Hill, NJ) and two types of microporous (3–22 μm) expanded polytetrafluoroethylene mesh (Dual Mesh and modified Dual Mesh, W.L. Gore & Associates, Flagstaff, AZ). All three prosthetic biomaterials are commercially available for open and laparoscopic ventral hernia repair.

Placement of the mesh was determined by a balanced split-plot design to compensate for being unable to include all types of mesh in each rabbit. After mesh implantation, the abdominal wall fascia and subcutaneous tissue were closed separately with absorbable, monofilament suture material. The animals were recovered, returned to their cages, and given intramuscular Nubain (1 mg/kg, IM prn) for analgesia.

Microlaparoscopic Evaluations and Adhesiolysis

The rate of adhesion formation was evaluated by direct visualization using microlaparoscopy (2-mm endoscope/trocar) at 7 days, 3 weeks, 9 weeks, and 16 weeks after mesh implantation. For the microlaparoscopic visualizations, the rabbits were anesthetized with Ketamine (35 mg/kg, IM) and Xylazine (5 mg/kg, IM). A 2-mm trocar was inserted in the subxyphoid region, and carbon dioxide pneumoperitoneum established to 5 mm Hg pressure. A 2-mm laparoscope was inserted through the trocar and adhesions to the prosthetic mesh (Figs. 1 and 2) were scored for extent (%) using the Modified Diamond Scale (0 = 0%, 1 = 1–25%, 2 = 25–50%, 3 = >50%) [15]. All microlaparoscopic evaluations were recorded for blinded evaluation by three attending surgeons.

Necropsy and Histological Evaluation

The final adhesion score was determined by microlaparoscopy at 16 weeks, immediately preceding necropsy. The animals were sacrificed by intravenous sodium pentobarbital (300 mg/kg) overdose. The prosthetic biomaterial sites were excised en bloc with the anterior abdominal wall fascia and peritoneum. The specimens were fixed in 10% formalin for histological evaluation of mesothelial layer

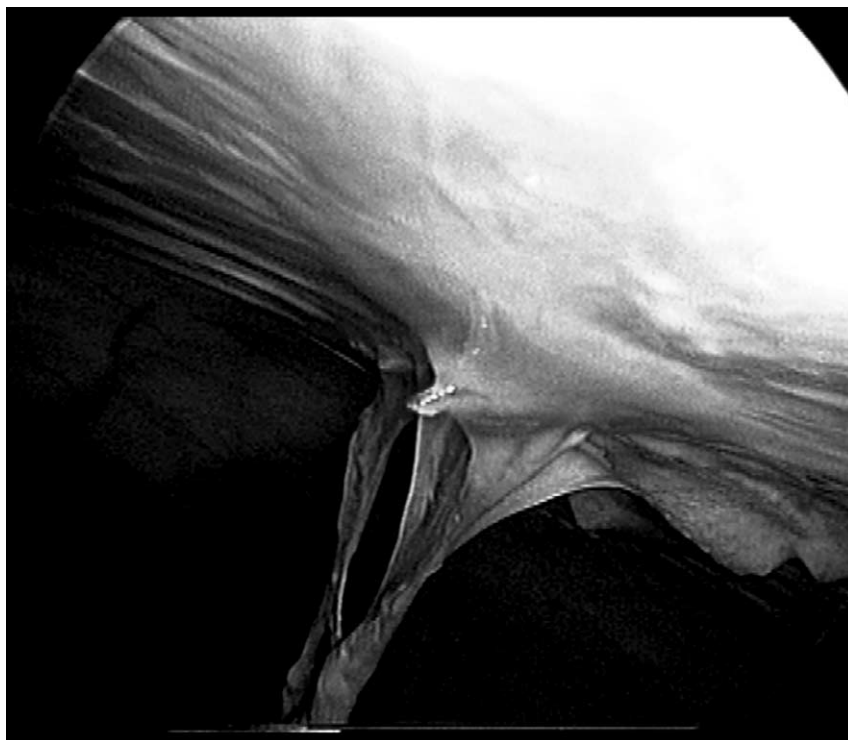


FIG. 1. Laparoscopic view of adhesions to polypropylene.

growth. Thin sections were stained with hematoxylin and eosin, Milligan's trichrome, and fibrin stains. A histologist, blind to the type of mesh used, reviewed all of the specimens for mesothelial layer growth on the visceral surface of the mesh. Mesothelial layer growth was calculated as a percentage of the mesh covered by mesothelium on the visceral surface.

Statistical Analysis

Statistical significance was determined by a two-tailed Student's *t* test. Significance was accepted at a *P* value less than 0.05.

RESULTS

None of the prosthetic biomaterials became infected. The mean adhesion scores for the polypropylene mesh, Dual Mesh, and modified Dual Mesh at 7 days, 3 weeks, 9 weeks, and 16 weeks are summarized in Table 1. The mean adhesion score for the polypropylene mesh was significantly greater ($P < 0.05$) than Dual Mesh at 9 weeks and 16 weeks and modified Dual Mesh at 7 days, 9 weeks, and 16 weeks. There was no difference in the mean adhesion score when comparing Dual Mesh and modified Dual Mesh at any of the interval microlaparoscopic evaluations. The mean adhesion score for Dual Mesh and modified Dual Mesh decreased after 3 weeks, while the mean adhesion score for polypropylene mesh increased between 7 days and 16 weeks. Fifty-five percent ($n = 11$) of the polypropylene mesh implants had adhesions to small intestine or omentum at necropsy compared with 30% ($n = 6$) of the

Dual Mesh and 20% ($n = 4$) of the modified Dual Mesh. There was a significantly greater percentage ($P < 0.003$) of the ePTFE mesh mesothelialized at explant (modified Dual Mesh 44.2%; Dual Mesh 55.8%) compared with the polypropylene mesh (12.9%).

DISCUSSION

Fibrovascular adhesions occur in 50–95% of patients who have undergone open abdominal surgery [13, 16, 17]. Mechanical trauma, thermal injury, infection, tissue ischemia, and foreign materials are the most important factors contributing to adhesion formation [18]. Foreign bodies have been reported to cause 61–69% of postoperative adhesions [19]. The majority of adhesions form in the immediate postoperative period. More than 440,000 procedures for intra-abdominal adhesiolysis are performed each year, and 3% of all laparotomies are performed for intestinal obstruction because of adhesions [20, 21]. This has placed a tremendous burden on the United States health care system with an estimated cost of 1.2 billion dollars annually [22].

Incisional hernias have been repaired over the past 100 years using open, tissue approximation techniques. Unacceptable recurrence rates led surgeons to develop newer methods which incorporated synthetic biomaterials into the repair. This allowed for tension-free repairs, which has resulted in significantly lower

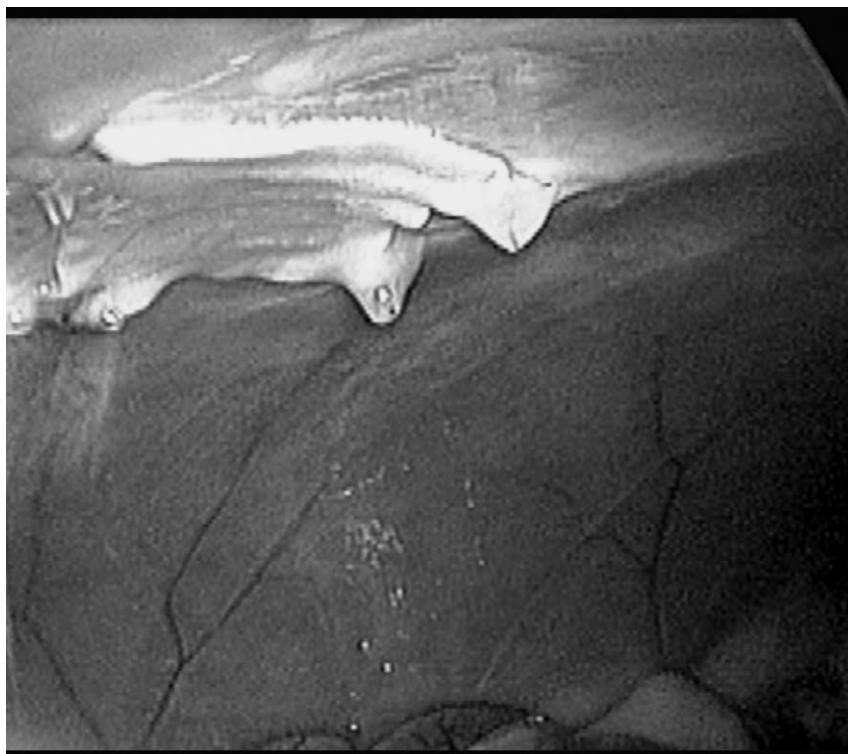


FIG. 2. Laparoscopic view of adhesion-free ePTFE.

recurrence rates [5, 6]. In 1958, Francis Usher introduced the first generation of polyethylene mesh for abdominal wall hernia repair [23]. This synthetic biomaterial had many promising properties (strength, inertness), but it could not be easily sterilized. This limited its clinical application. To overcome this obstacle, polypropylene was introduced in 1962. This biomaterial provided all of the benefits of polyethylene and could be sterilized using an autoclave [24]. This opened the door for the development of several types of prosthetic biomaterials which are in clinical use today.

The biocompatible qualities of prosthetic biomaterial has been well established by Cumberland and Scales [25, 26]. The ideal prosthetic mesh should not be physically altered by tissue fluids or produce foreign-body reactions. It should be chemically inert, non-carcinogenic, non-allergenic, capable of resisting me-

chanical strains, and suitable for sterilization without altering its inherent characteristics. Despite the development and testing of numerous types of mesh prostheses over the past three decades, there is still disagreement about the ideal design for implantation. A critical component in the architecture of a mesh biomaterial is its pore size and shape. Tissue incorporation of the prosthetic material may be proportional to the degree of porosity [27]. Macroporous mesh with pore sizes greater than $100\ \mu\text{m}$ are thought to allow fibrous tissue in-growth, while the surrounding synthetic fibers provide reinforcement of the abdominal wall [28]. Biomaterials that contain pore spaces less than $75\ \mu\text{m}$ may be more prone to be encapsulated rather than infiltrated by the host tissue [29]. It is this phenomenon that may be responsible for the lower rate of adhesion formation to the visceral surface of the

TABLE 1
Mean Adhesion Scores Comparing Three Types of Mesh

Week	Mean adhesion score			<i>P</i> value		
	Polypropylene mesh	Dual mesh	Modified dual mesh	Polypropylene vs dual mesh	Polypropylene vs modified dual mesh	Dual mesh vs modified dual mesh
1	1.23	0.85	0.57	0.23	0.03	0.29
3	1.63	1.10	0.91	0.14	0.06	0.61
9	1.63	0.84	0.91	0.02	0.01	0.78
16	1.79	0.78	0.79	0.02	0.02	0.98

ePTFE when it is placed in the peritoneal cavity. The laminar, microporous structure of ePTFE gives rise to a well structured, homogenous neo-peritoneum with fibers running parallel to the implant surface, which is covered by a layer of mesothelial cells [30]. It is this mesothelial monolayer which is believed to be responsible for attenuating the adhesion response [31].

Polypropylene is a monofilament mesh produced by controlled polymerization of propylene, a derivative of propane gas [24]. It displays the excellent chemical resistance of hydrocarbon polymers and has a remarkable hinge life [32]. It possesses good stress crack resistance, burst strength of more than 25 pounds per square inch, suture retention of 10.7 pounds (warp) and 6.9 pounds (course), and stretchability of 60% (warp) and 20% (course). Long-term studies have shown that the tensile strength of polypropylene implanted in tissue is unchanged over time [23, 33]. The slight roughness of the surface of the individual polypropylene fibers as well as the texture of its weave stimulates fibroplasia and promotes tissue incorporation. The pore size of greater than 100 μm enhances infiltration of the host tissue into the mesh [24].

Expanded polytetrafluoroethylene was first introduced into clinical practice in 1972 as a prosthetic vascular bypass material and further developed as a prosthesis for the repair of abdominal wall defects by Bauer *et al.* [34]. Expanded polytetrafluoroethylene is a negatively charged, soft, smooth microporous biomaterial composed of columns of compact nodules of polytetrafluoroethylene interconnected by fine fibers of the same material [35]. The internode distance is between 17 and 41 μm , with a multidirectional fibrillary arrangement that provides equal strength in all planes [24]. This relatively small internode distance classifies this biomaterial as a microporous material.

To improve the tissue in-growth characteristics of the smooth ePTFE mesh, W.L. Gore has developed Dual Mesh. The peritoneal surface of the Dual Mesh is smooth with micropores less than 3 μm in size, while the parietal surface has shallow geometric depressions, with a macroscopic pore at each apex approximately 2 mm in diameter [24]. The macroporous side of the mesh increases cellular migration, proteinaceous infiltrate and collagen in-growth, while the smooth, microporous surface resists cellular penetration and was designed to reduce adhesion formation on the visceral surface of the mesh [24, 36].

The modified ePTFE mesh is similar to the Dual Mesh configuration (W.L. Gore & Associates, Flagstaff, AZ) with the exception of larger macropores on the parietal surface to induce more tissue ingrowth. This structure enhances early fixation to host tissue and allows for extensive neovascularization.

In the early 1990s, the first prosthetic biomaterials were placed laparoscopically for the repair of incisional

hernias [37]. This was a unique intra-abdominal, intraperitoneal technique which was based on the Stoppa repair. This minimally invasive technique eliminated the need for wide fascial dissection and flap creation required with the open techniques. Laparoscopic ventral hernia repair has been shown to minimize wound complications and morbidity, but introduces potential complications with respect to the intraperitoneal mesh placement [1, 38, 39]. Long-term complications associated with prosthetic repair of incisional hernias and intraperitoneal placement of mesh have been well documented and include adhesions, bowel obstruction, erosion of mesh into viscera, transmigration of mesh, and fistula formation [12].

Adhesion formation is a complicated process involving essentially all of the cellular components and mediators of the inflammatory response. Leukocytes, mesothelial cells, the coagulation cascade, cytokines, growth factors, and cellular metabolites have all been implicated to play a vital role [40, 41]. The formation of adhesions is a physiological process during the restoration and reconstruction of normal tissue surfaces. Research is ongoing to better understand the details of this intricate process. Nonetheless, the final common pathway for the development of intraperitoneal adhesion formation has been identified as the formation of an insoluble fibrin gel matrix [42]. A homeostatic defense mechanism against adhesion formation is intraperitoneal fibrinolysis. Fibrinolysis is activated to lyse fibrinous adhesions formed by the fibrin gel matrix. This is accomplished by the release of tissue plasminogen activator (tPA) from mesothelial cells [42]. The release of tPA leads to a cascade of events which produces the final common pathway enzyme; activated plasmin. Plasmin is postulated to be responsible for adhesiolysis [43, 44]. Factors that inhibit fibrinolysis, such as peritoneal ischemia from sutures and poor mesothelial cell growth and proliferation, promote the formation of fibrinovascular adhesions.

The growing popularity of laparoscopic ventral hernia repair over the past decade has intensified the important debate concerning prosthetic biomaterial physiology and bioreactivity. The intraperitoneal placement of prosthetic material is inherent to laparoscopic ventral hernia repair. Prosthetic biomaterials elicit inflammatory responses which are dependent on the unique properties (porosity, electrical charge, surface chemistry, texture) of each individual mesh [45]. Reticular, macroporous biomaterials such as polypropylene have the tendency to provoke a high incidence of adhesion formation when placed adjacent to intra-abdominal viscera. This is due in part to the structurally disorganized and irregular neoperitoneum formed when the macroporous prostheses is placed within the peritoneal cavity [30]. However, this type of biomaterial integrates within the host tissue and provides good

tensile strength and resistance to traction in the repaired area [29].

In contrast, the laminar, microporous configuration of ePTFE induces a lower number of adhesions by allowing uniform migration of mesothelial cells onto the mesh, creating a complete neoperitoneal surface [29]. The parietal surface of the Dual Mesh has been modified to a macroporous environment similar to that of polypropylene which may allow ePTFE to achieve similar tissue in-growth characteristics.

CONCLUSIONS

Serial microlaparoscopic evaluation of intraperitoneally implanted polypropylene mesh and ePTFE mesh in a rabbit model revealed a progression of adhesions to polypropylene mesh over a 16-week period. After 3 weeks, there was a significantly ($P < 0.02$) greater mean adhesion score for polypropylene mesh compared with the two types of ePTFE mesh combined. The pore size of the visceral side of the mesh is critical in the development and maintenance of abdominal adhesions and tissue in-growth.

The macroporous polypropylene mesh promoted adhesion formation, while the microporous ePTFE served as a barrier to adhesions. Experimental studies have documented that mesothelial cells prevent adhesion formation [31]. Histological evaluation of the explanted prosthetic biomaterials demonstrated a significantly greater degree of mesothelial layer re-epithelialization on the visceral side of the ePTFE mesh compared with the polypropylene mesh. The development of this adhesion-resistant layer may explain the lower adhesion score for Dual Mesh and modified Dual Mesh.

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