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NEW TECHNOLOGY

Mesh fixation using novel bio-adhesive coating compared to tack fixation for IPOM hernia repair: in vivo evaluation in a porcine model

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Abstract

Background Mesh fixation in hernia repair is currently based on penetrating sutures or anchors, with proven early and late complications such as pain, adhesions, erosions, and anchor migration. In an attempt to reduce these complications, a bio-adhesive-based self-fixation system was developed. The purpose of this study was to assess the performance and safety of this novel self-adhesive mesh (LifeMesh™) by comparing it with standard tack fixation.

Methods A full-thickness abdominal wall defect was created bilaterally in 24 pigs. The defects were measured 14 days later, and laparoscopic intraperitoneal onlay mesh (IPOM) repairs were performed. In each animal, both LifeMesh and a titanium tack-fixed control, either uncoated polypropylene mesh (PP) or composite mesh (Symbotex™), were used. After 28 and 90 days, we performed macroscopic evaluation and analyzed the fixation strength, shrinkage, adhesion scores, and histopathology in all samples.

Results Measurements at both time points revealed that LifeMesh had fully conformed to the abdominal wall, and that its fixation strength was superior to that of the tack-fixated Symbotex and comparable to that of the tack-fixated PP. Shrinkage in all groups was similar. Adhesion scores with LifeMesh were lower than with PP and comparable with Symbotex at both time points. Histology demonstrated similar tissue responses in LifeMesh and Symbotex. Lack of necrosis, mineralization, or exuberant inflammatory reaction in all three groups pointed to their good progressive integration of the mesh to the abdominal wall. By 28 days the bio-adhesive layer in LifeMesh was substantially degraded, allowing a gradual tissue ingrowth that became the main fixation mode of this mesh to the abdominal wall.

Conclusions The excellent incorporation of LifeMesh to the abdominal wall and its superior fixation strength, together with its low adhesion score, suggest that LifeMesh may become a preferred alternative for abdominal wall repair.

Keywords Self-fixating mesh · Hernia repair · Non-traumatic

Hernia repair is one of the commonest surgical procedures performed, with an estimated 20 million surgeries carried out worldwide annually [1]. Hernia repair techniques currently employ synthetic, composite, or biological materials (mesh prostheses) to hold the herniated organs in place and provide a matrix for the ingrowth of new tissue [2]. Utilization of mesh necessitates the use of fixating materials such as tacks and sutures, alone or in combination. The use of these fixating materials is reportedly associated with both early and late postoperative complications including pain [3–5], adhesions [6, 7], injury to internal organs [8–18], nerve injury [19–22], and dislodgement/migration of tacks [23, 24].

Chronic pain following laparoscopic hernia repair has been reported to occur in as many as 25% of patients [25]. In 1–3% of patients, pain due to nerve entrapment can persist for longer than 6 months [26]. Clinical evidence over recent years supports the use of atraumatic methods of mesh fixation as a favorable option compared to tissue-penetrating techniques for open and endoscopic repair of inguinal and incisional hernia. These newer methods include self-adhering meshes and the use of adhesive materials (bio-glues) [27]. Ideally, adhesive materials

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should be biocompatible, strong enough to withstand physiological stresses over a long period, provide adequate fixation strength, conform to the abdominal wall, promote strong host-tissue ingrowth, and easy to use in the operating room [28].

Biosynthetic adhesives consisting of either N-butyl-2-cyanoacrylate or 2-octyl-cyanoacrylate have been used in surgery [29, 30]. However, severe cytotoxicity and potential carcinogenic effects remain a concern [31, 32]. It was also reported that tissue integration of the implant was inhibited, and that this was combined with pronounced inflammatory response [33]. Fibrin sealant, when used as an alternative material for fixation of meshes in open and laparoscopic hernia surgery was found to successfully reduce early postoperative pain [34]. Moreover, when fibrin sealant was used in the repair of incisional hernias rather than employing traditional, tissue-penetrating techniques, postoperative morbidity and the duration of hospital stay were significantly decreased [35, 36]. In some studies, however, despite the promising short-term outcome, hernia recurrence was significantly increased in the fibrin glue groups [37–39]. In addition, some animal studies demonstrated that fibrin glue is not adequate as a sole fixation method in laparoscopic ventral hernia repair owing to its low acute and chronic fixation strength [40–42].

LifeMesh™ is a novel self-fixating adhesive technology in which a hernia mesh is embedded in a coating of dry adhesive matrix composed primarily of porcine gelatin and microbial transglutaminase (mTG). When the coating comes into contact with moisture, the gelatin undergoes enzyme-catalyzed cross-linking to form a flexible hydrogel, providing uniform fixation across the entire mesh/abdominal wall tissue interface, while separating the mesh from the visceral organs. The hydrogel is then gradually degraded and is replaced by the body's natural tissue. In a recent animal study, LifeMesh demonstrated significantly increased acute mesh fixation strength compared to ProGrip™ (Medtronic, Minneapolis, MN) and to a mesh fixed with TISSEEL (Baxter International, Deerfield, IL) [43]. Also, when compared to tissue-penetrating mesh fixation by sutures, LifeMesh showed significantly less shrinkage of mesh at 3 days and 7 days after implantation [44].

The present study was designed to assess the performance and safety of LifeMesh in comparison with tack fixation of two meshes currently utilized in clinical practice: Symbotex™ (Medtronic, Minneapolis, MN, USA), a composite mesh with a biodegradable barrier, and a bare, condensed polypropylene (PP) mesh (Aran, Galway, Ireland). Each of these was used as a control in this study of simulated hernia in a swine model. Special attention was paid to differences in chronic fixation strength, recurrence, adhesions formation, mesh shrinkage, and host-tissue response between LifeMesh and each of the two controls.

Materials and methods

Animals and general procedures

The study was approved by the Ethics Committee of a GLP-approved animal facility at Assaf Harofeh Medical Center, Zerifin, Israel. Animals were provided with a commercial swine diet (Denkapig Battery Pellets, DenkaVit) twice a day, each receiving 400 g of food per meal until the night before surgery. Each animal was sedated by intramuscular injection of xylazine (1–2 mg/kg) and ketamine (10–20 mg/kg) and anesthetized by intravenous injection of midazolam (15 mg).

Abdominal wall hernia model

The experimental model consisted of surgically created hernia defects with subsequent mesh repair and evaluation of mechanical and histological characteristics at two time periods after mesh implantation. Meshes were implanted after the defect had been allowed to mature for 2 weeks, by which time it had reached a chronic pre-implantation state mimicking the environment encountered in a clinical setting [45]. The porcine abdomen is comparable in size to the human abdomen and their intra-abdominal pressures are similar [46, 47]. Thus, use of this model makes it possible to assess clinically relevant hernia defects and mesh sizes.

Surgery was performed 14 days prior to mesh implantation in 24 female Large-White/Landrace cross-bred swine weighing 60 ± 10 kg on the day of defect formation. In each animal, electrocautery and surgical tools were used to create two full-thickness excisional defects on each side of the abdominal wall midline by removing the muscle and fascia without disrupting the peritoneum. Centers of the defects were positioned at least 8 cm lateral to the animal's midline to allow mesh implantations, and the excision was approximately 5 cm in diameter. The skin and subcutaneous tissue were closed using 2-0/3-0 synthetic suture. Animals were allowed to heal and were monitored for 14 (± 2) days until they underwent hernia repair by implantation of a mesh.

Hernia repair: mesh-fixation arms

Three mesh-fixation combinations were used (Fig. 1). For the study arm we used the self-adhesive LifeMesh™ containing a lightweight (aerial density 28.3 g/m^2), macroporous, condensed polypropylene (PP) surgical mesh (Aran Biomedical, Galway, Ireland). The PP mesh was coated with gelatin–mTG dry adhesive foam. This foam, when activated by the moisture of the tissue, fixates the mesh to the abdominal wall and separates the PP mesh from the visceral organs. In addition, on the side facing the abdominal content, the

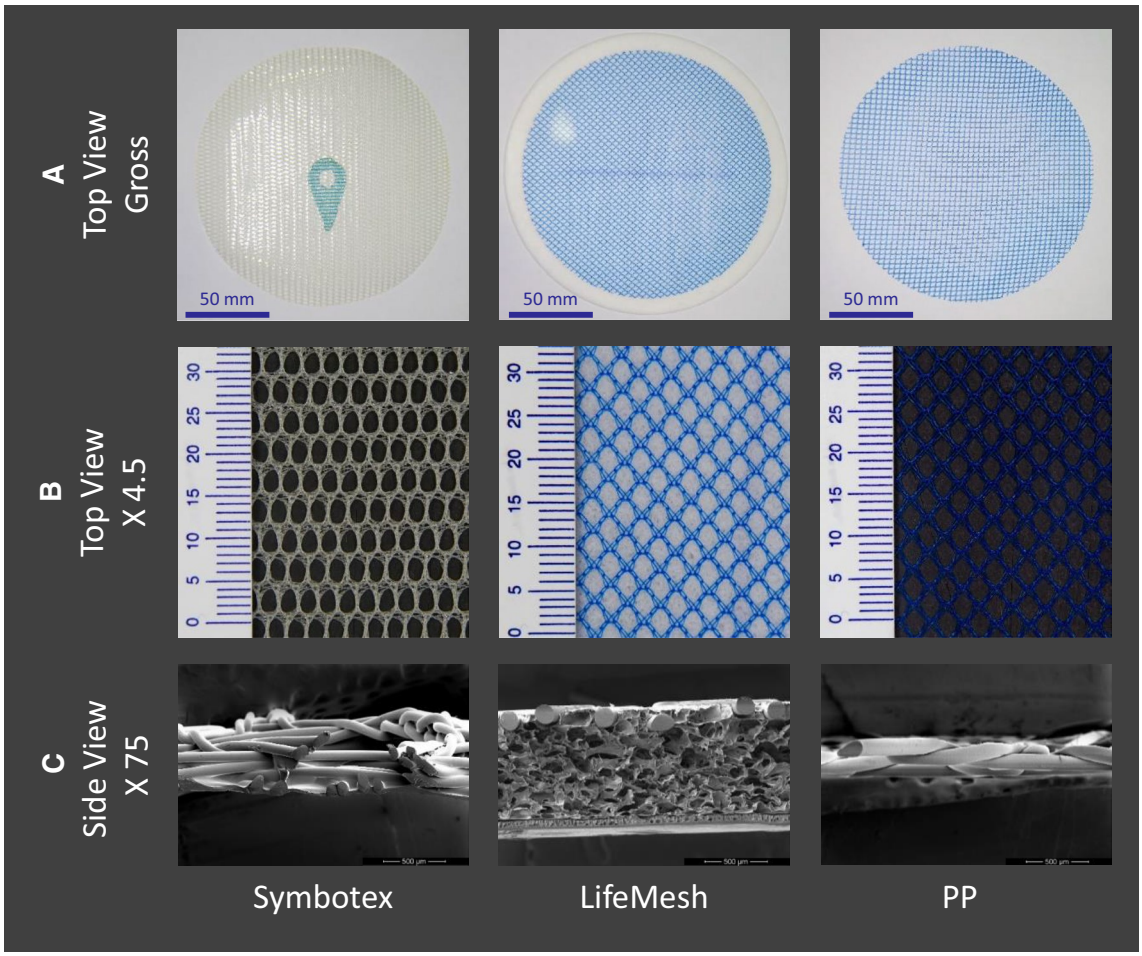

Fig. 1 Gross view images of the implanted meshes (**A**). Macroscopic images takes at ×4.5 magnification (**B**). Scanning electron microscopy (SEM) images taken at ×75 magnification (**C**) of Symbotex: Polyester mesh with collagen backing (bottom layer); LifeMesh: polypropylene mesh coated with bio-adhesive foam (middle layer) and with cellulose backing (bottom layer); PP polypropylene bare mesh

mesh is coated with a cellulose-based backing that prevents intra-operative adhesivity and assists in its handling (LifeBond, Caesarea, Israel). The two control arms were Symbotex™—Polyester mesh consisting of a 3D monofilament macroporous textile (aerial density 66 g/m^2) with a bioabsorbable collagen film (Medtronic), and a bare PP mesh (similar to the one utilized in the study arm). Both control meshes were fixated with ProTack™ titanium spiral tacks (Medtronic) in a single-crown configuration. All meshes were circular, 15 cm in diameter.

Surgical procedure and follow-up

In order to compare LifeMesh to a bare mesh and a commercially available collagen-coated mesh at two time points, the animals were divided randomly into four groups (6 per group). Each animal in group A was implanted bilaterally with LifeMesh and Symbotex and was euthanized 28 days after mesh implantation; in group B, LifeMesh and PP were implanted bilaterally and the animals were euthanized 28 days after mesh implantation; in group C, LifeMesh and Symbotex were implanted bilaterally and the animals were euthanized 90 days after mesh implantation; and in group D, animals were implanted bilaterally with LifeMesh and PP and were euthanized 90 days after mesh implantation. The location of the meshes with respect to the midline (right or left) was randomized between the study arm and control groups.

Pneumoperitoneum was achieved by insufflation of CO_2 through a veress needle (14–15 mmHg). Three laparoscopic ports were then introduced under direct vision along the animal's midline (5–12 mm), according to the surgeon's decision. After placing of the trocars, the appearance of the defect (hernia) site was examined and the defect dimensions were measured along the craniocaudal and mediolateral axes with a measuring tape introduced into the abdominal cavity. In cases where the defect diameter was more than 6 cm an attempt was made to close it with intracorporeal sutures,

and the mesh was then positioned on a closed defect. Where applicable, and at the discretion of the surgeon, seromas were drained prior to mesh application.

In each animal, LifeMesh and control meshes were implanted laparoscopically on the peritoneum over the defect (Fig. 2). The meshes were rolled, held in this configuration using a grasper, and inserted through a 12-mm trocar. A central suture was utilized for guidance and positioning of each implanted mesh at the center of the defect. Following its delivery to the target the mesh was unrolled, spread, and fixated to the target tissue. Control meshes were fixated using 20–25 single-crown titanium tacks, which were evenly distributed at the mesh perimeter. LifeMesh was fixated by pressing it gently with a standard surgical gauze pad to facilitate adhesive activation over the entire surface area. The adhesive was left to cure for 4 min before the pneumoperitoneum was deflated. Following fixation, the central suture was excised and removed from the abdominal cavity.

All meshes were evaluated at 28 days and at 90 days after implantation. These two time points represent different phases of wound healing: 28 days after implantation represents the end of the proliferative phase and the beginning of the remodeling phase [48]. The 90-day time point was selected as the time to assess hernia recurrence and performance parameters such as shrinkage.

After reaching the assigned time point (either 28 ± 3 or 90 ± 5 days post implantation), the animals were sedated and euthanized for necropsy by intravenous injection of KCl.

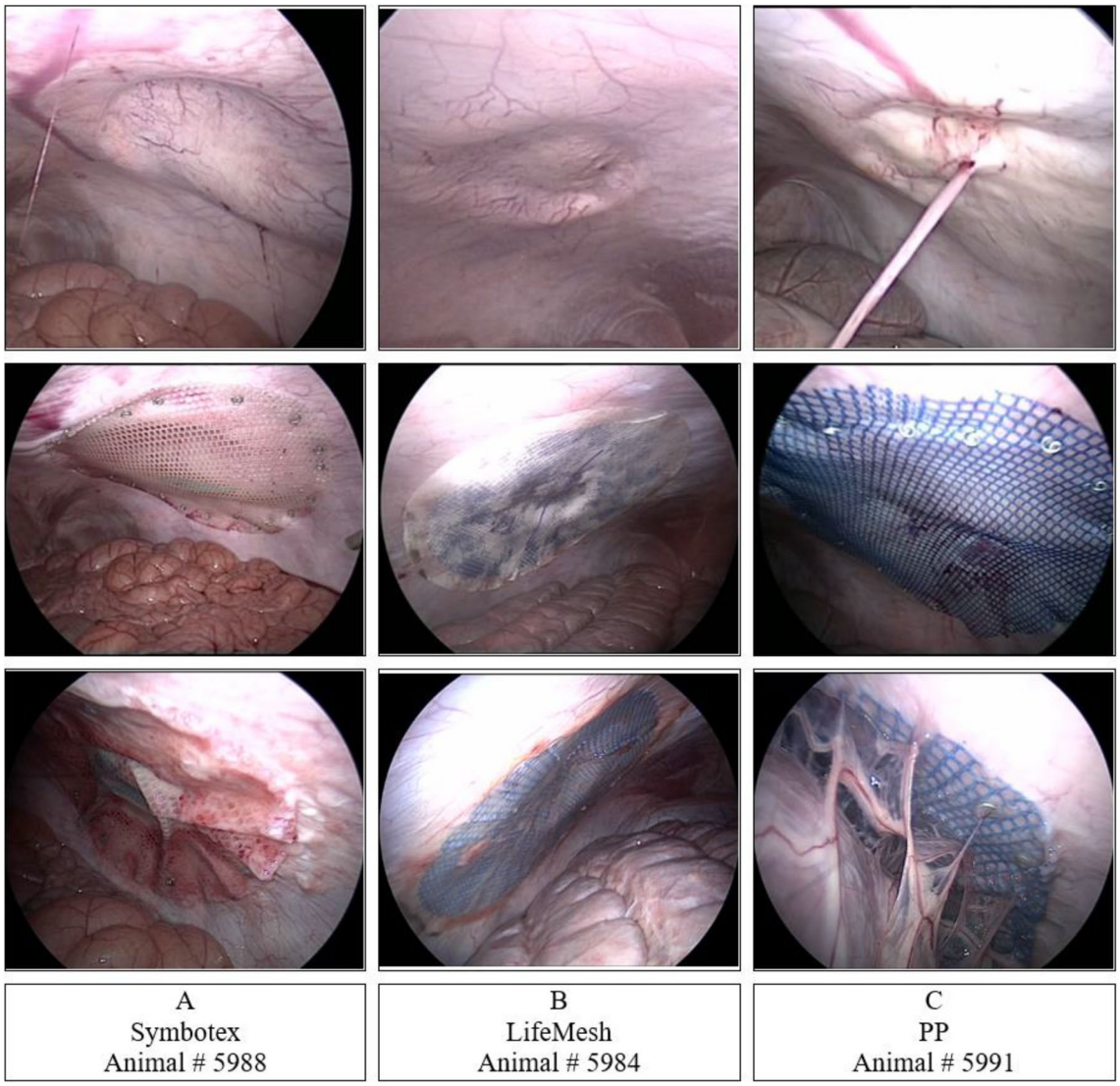

Fig. 2 Representative images from the laparoscopic procedures. Upper row: defects on day of hernia repair (14 days after defect creation). Middle row: meshes placed on the defects immediately after hernia repair. Bottom row: meshes 28 days after implantation. **Column A** Symbotex fixated with tacks, **B** LifeMesh, **C** Bare polypropylene fixated with tacks (PP). Overall, on macroscopic evaluations LifeMesh showed smaller wrinkles (no medium or major wrinkles) and minor, less substantive folds than the other meshes

Prior to euthanasia, laparoscopy was performed in each animal, allowing a macroscopic view of the abdominal cavity. Meshes were evaluated for folds, wrinkles, and conformity to the abdominal wall, their craniocaudal and mediolateral axes were measured, and migration, adhesions, and hernia recurrence were recorded. Recurrence was defined as the presence of intra-abdominal organs within the hernia defect, extending distally to the anatomical plane of the mesh. Migration was defined as the presence of exposed defect area not covered with mesh.

Adhesion score

Implants were observed by laparoscopy and the extent, type, and tenacity of adhesions were then evaluated ex vivo using a scale adapted from previous studies [49]. Adhesion was scored by the degree to which the adhesion tissue covered the mesh (0, no adhesions; 1, involvement of 1–25% of the mesh surface; 2, 26–50% involvement; 3, 51–75% involvement; 4, 76–100% involvement). Adhesion type refers to form and vascularization level (0, no adhesions; 1, filmy adhesions; 2, dense adhesions; 3, capillaries present; 4, larger vessels present). Adhesion tenacity was scored on the basis of resistance of the tissue to separation (0, no adhesions; 1, adhesions fall apart easily; 2, traction force required; 3, sharp dissection required). The total adhesion score was then calculated by summing the three subscores (range 0–11).

Shrinkage

Mesh shrinkage was defined as the percentage of area loss in relation to the original size of the mesh. Shrinkage was originally assessed ex vivo using a grid, but the method was prone to deviation since the peritoneum continues to shrink once excised from the abdomen. Therefore, shrinkage at the 90-day time point was assessed laparoscopically by means of a measuring tape introduced into the abdominal cavity. Each mesh was measured along the two axes (craniocaudal and mediolateral). The change in each dimension relative to baseline was divided by the baseline value to yield the percentage of mesh surface area.

Histology

Following laparoscopy, the animals were euthanized according to the animal facility procedure. All animals were necropsied and gross pathology samples were obtained. The following organs and tissues were sampled and preserved in containers filled with 4% formalin: tested sites (defects and mesh application areas); inguinal lymph nodes; gross abnormalities if found. Tissue sections (≈5–6 microns thick) were stained with both hematoxylin & eosin (H&E) and Masson's trichrome (tested sites only). Toxicity was assessed by histopathological examinations carried out by a Board-certified toxicologic pathologist (A.N.), and included evaluation of regional device-contacting and downstream tissues. It also included (but was not limited to) the following parameters and grading scales (adopted from the internationally accepted Guideline: ISO 10993-6, 'Biological evaluation of medical devices—Part 6: Tests for local effects after implantation'; 2nd ed., April, 2007). Particular attention was given to confirm the presence or absence of necrosis, mineralization, or exuberant inflammatory reaction, which would ultimately affect integration of the mesh to the abdominal wall.

Fixation strength

The strength of mesh fixation to the underlying tissue was evaluated by using the lap-shear method on freshly harvested samples immediately after necropsy. Tissue samples were cut into strips, each 5 cm long and 4 cm wide. One short edge of the mesh was freed from the fascia for a length of 1 cm, leaving 3 cm adhered to the tissue (fixation testing area). Tacks were not removed before testing. The sample was loaded into a tensile testing device (Instron Model 3343 equipped with a 1000 N load cell). The freed tissue was clamped to the upper grip and the free mesh edge to the lower grip (Fig. 3). The grips were displaced at a rate of 0.4 mm/s until the load dropped back to zero. Fixation strength was evaluated by normalizing the maximal force at failure to the original mesh width (N/cm). For each tested specimen, the failure mode (detachment of the mesh from the tissue) was recorded as well. The failure mode refers to the part of the specimen (mesh, tissue or interface) that failed first.

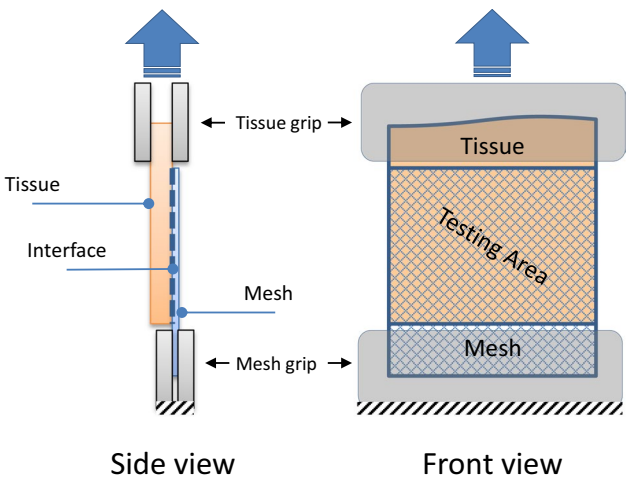

Fig. 3 Schematic drawing of the fixation strength biomechanical testing

Usability

For each mesh the ease of handling, deployment, and delivery to the target tissue were assessed and recorded in a dedicated questionnaire filled out by each of the two implanting surgeons (A.B.Y. and A.S.). Seven specific questions were provided for the evaluation and the surgeons were required to rate their opinion regarding each statement on a scale ranging from 'totally disagree' to 'totally agree': (1) The backing side of the mesh was detectable; (2) mesh was easily prepared; (3) mesh was easily delivered; (4) mesh stuck to gloves/visceral organs before its application; (5) mesh fixation to peritoneum was easily performed; (6) mesh covered the defect with sufficient margins; (7) mesh fully conformed to the target tissue.

Statistical analysis

Based on the fact that two meshes were implanted in each animal and that different numbers of specimens were taken in each group, it was decided to use a mixed model for analysis of the results. It was assumed that in this model, measurements within the animal are dependent, and that the correlation between the multiple measurements is the same (compound symmetry covariance structure). Prior to analysis, the results for each group were evaluated for normality.

Results

A total of 48 meshes were implanted on simulated hernia sites: 24 Lifemesh, 12 Symbotex, and 12 PP. Defect dimensions on the day of mesh implantation ranged from 8×6 cm to 3×2 cm (mean, 5.0 ± 1.3 cm $\times 4.5 \pm 1.2$ cm). Defects larger than 6 cm in diameter were sutured prior to mesh implantation (7 out of 46 defects). One animal had defects larger than 6 cm that could not be sutured, and was therefore excluded from the study. At both time points, laparoscopic examination prior to necropsy revealed no events of hernia recurrence and no seroma formation.

POD 28 re-laparoscopy revealed one event of LifeMesh migration, with evidence of the mesh capsuled and not attached to the abdominal wall. Retrospective evaluation of the application recorded on camera revealed failure to properly center the LifeMesh, resulting in a margin of only 2 cm from one side of the defect, with primary partial detachment on that side. It was therefore concluded that this was an intra-operative application failure that could have been avoided.

Mesh adhesions were present in 40% and 50% of LifeMesh implants, in 67% and 100% of PP implants, and in 40% and 33% of Symbotex implants, at the 28-day and 90-day time points, respectively. Assessment of the overall occurrence of adhesions in all groups (day 28 + day 90 results combined) revealed that LifeMesh was superior to PP in this respect ($p = 0.03$; Fig. 4), whereas the difference between LifeMesh and Symbotex in this regard was not significant ($p = 0.7$). In most cases the adhesions involved omentum, but in some animals visceral adhesions involved

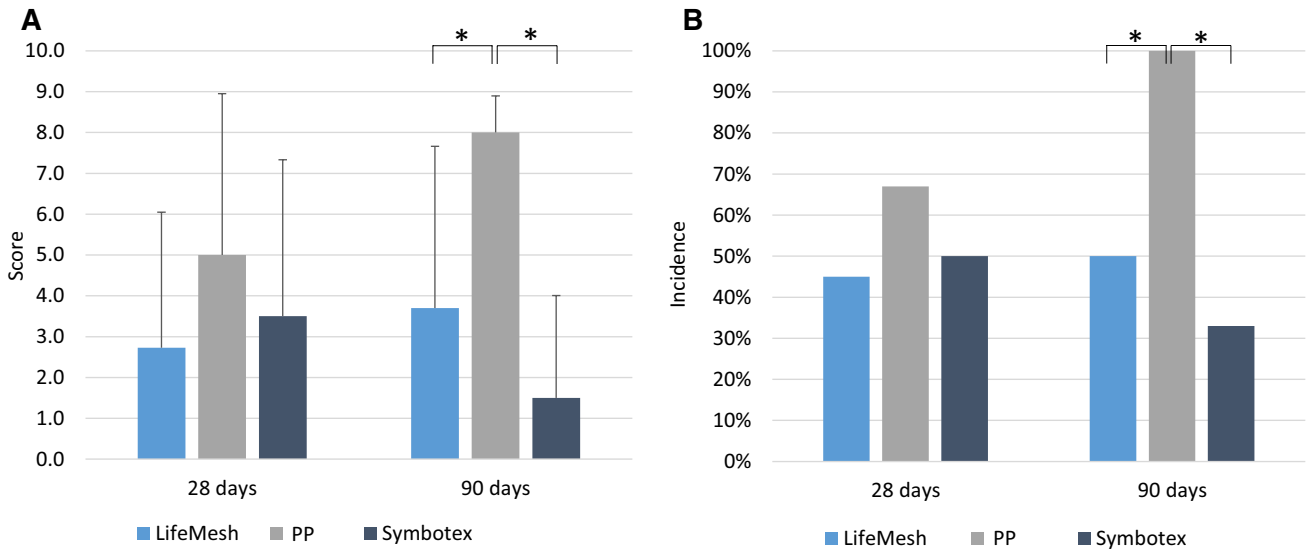

Fig. 4 Adhesion score (**A**) and incidence (**B**) of LifeMesh™ (light blue), Symbotex fixated with tacks (dark blue), and Bare polypropylene (PP; gray) fixated with tacks on days 28 and 90 post surgery. *Statistically significant difference ($p < 0.05$)

the colon or spleen (in 1 of 22 Lifemesh, 1 of 11 Symbotex, and 4 of 12 PP implants). In the 28-day groups, both LifeMesh and Symbotex showed a trend towards lower adhesion scores than PP (2.3 ± 3.2 and 2.8 ± 3.8 vs. 5.0 ± 3.9, respectively), but the differences were not significant. In the 90-day groups, both LifeMesh and Symbotex showed significantly lower scores than PP (3.7 ± 4.0 and 1.5 ± 2.5 vs. 8.0 ± 0.9, respectively, $p < 0.05$), but differences in scores between LifeMesh and Symbotex were not significant. Comparison of overall adhesion scores between groups (mixed model, day 28 + day 90 combined) revealed that both LifeMesh and Symbotex were superior to PP ($p = 0.008$ and $p = 0.004$, respectively).

After 90 days, the mean mesh surface area was reduced by $37 \pm 14\%$, $33 \pm 12\%$, and $39 \pm 10\%$ for LifeMesh, Symbotex, and PP, respectively. Differences between the groups were not significant.

The results of mesh fixation strength to underlying tissue showed that at 28 days the fixation strength of LifeMesh (19.5 ± 7.7) was significantly higher than that of both Symbotex (8.5 ± 4.5, $p < 0.0001$) and PP (15.3 ± 7.5, $p = 0.03$) (Fig. 5). At 90 days, the fixation strength of LifeMesh (20.7 ± 5.8) was significantly higher than that of Symbotex (11.6 ± 5.0, $p = 0.0001$), but similar to that of PP (19.6 ± 5.8, $p = 0.6$). The increase in fixation strength over time (from 28 to 90 days) was significant ($p = 0.04$) and was similar for all three groups.

Histopathological findings at 28 days post implantation demonstrated similar tissue responses to LifeMesh (Fig. 6B) and Symbotex (Fig. 6C). The response was characterized by mild to moderate granulation tissue with uniform thickness along the entire implantation site. The inner layer, interfacing with the adhesive, consisted of typical minimal to mild foreign body reaction. The absence of necrosis, mineralization, and/or exuberant inflammatory reaction suggested good progressive integration of the mesh to the abdominal wall, ultimately leading to the formation of maturing granulation tissue of uniform thickness. The tissue response to PP (Fig. 6A) was characterized by the presence of mild non-uniform granulation tissue, which was thicker at areas related to the mesh fibers and thinner at the intervals between fibers (mesh fiber locations can be seen as white voids in the histological images).

The fixation and anti-adhesion gelatin layers in LifeMesh, as well as the collagen barrier in Symbotex, showed marked degradation with the presence of several fragments. At the 90-day post-implantation time point, the tissue reactions to both LifeMesh (Fig. 6E) and Symbotex (Fig. 6F) were characterized by mild mature granulation tissue (consisting only of collagen deposition) of uniform thickness along the entire implantation site. In contrast, the tissue reaction to PP (Fig. 6D) was characterized by the presence of minimal, non-uniformly distributed minimal mature granulation tissue. Both the gelatin layer in LifeMesh and the collagen barrier in Symbotex had undergone complete degradation by this time point. Histopathological evaluation of regional (inguinal) lymph nodes for all three meshes was scored as a mild grade of lymphoid hyperplasia. None of the lymph nodes showed any morphological changes reflecting a reactive increase in lymphoid activity (i.e., proliferation), inflammation, and/or abnormal foreign material contents.

LifeMesh obtained similar or better usability scores regarding most items of the questionnaire. The mean overall usability scores were 44.6 for LifeMesh and 42.5 for Symbotex, a difference trending towards statistical significance ($p = 0.096$). Specifically, LifeMesh achieved the highest scores for mesh application and conformity to the target tissue. PP scores were higher only for 'ease of insertion of the mesh through the 12-mm trocar.' For this group (PP), no averaging and statistical analysis was performed as one question was not applicable in the case of the bare mesh.

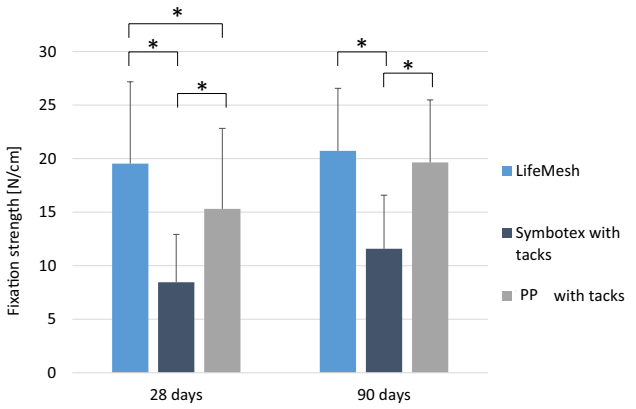

Fig. 5 Fixation strength (N/cm) of LifeMesh™ (light blue), Symbotex fixated with tacks (dark blue), and bare polypropylene (PP; gray) fixated with tacks, on days 28 and 90 post surgery. *Statistically significant difference ($p < 0.05$)

Discussion

Hernia repair by laparoscopy is generally accepted as preferable to open surgery [50]. However, because laparoscopy requires the use of tacks or sutures for mesh fixation, it carries several potential complications such as sensory nerve entrapment with neuralgia, bleeding, hematomas, and chronic pain [51, 52]. These complications have led surgeons to consider alternative methods of mesh fixation. Preclinical [53, 54] and clinical studies [37, 55–60] have reported on the use of glue for prosthetic mesh fixation during laparoscopic ventral hernia repair. Our aim in the present study was to compare the effectiveness of LifeMesh, a novel bio-adhesive coating for fixation of surgical mesh during intraperitoneal

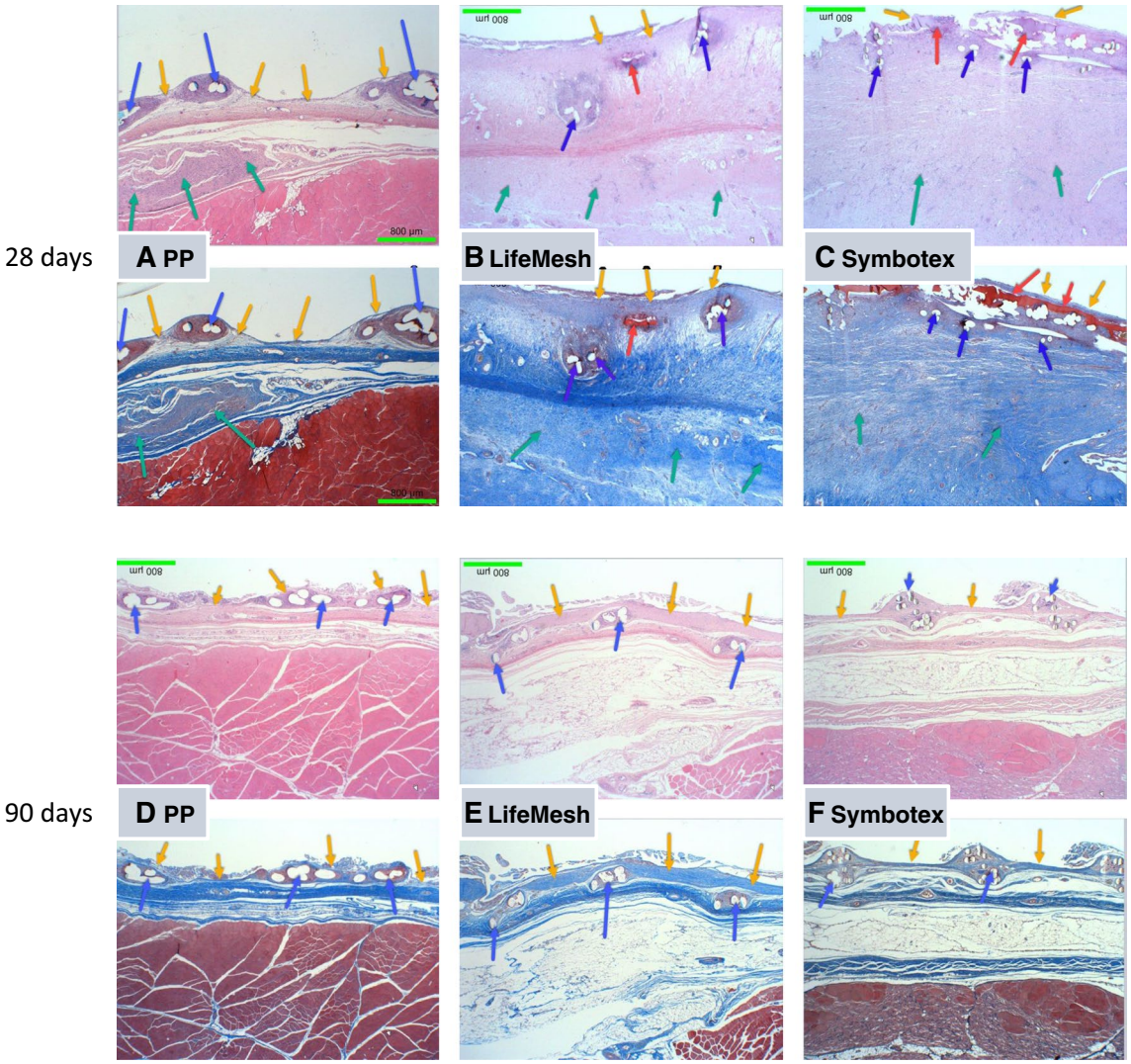

Fig. 6 Histopathological analysis. Upper images, H&E; lower images, Masson's trichrome. Blue arrows: voids related to the mesh; yellow arrows, fibrotic layer bordering the abdominal cavity; green arrows, fibrotic layer (scar formation) at the excision site; red arrows, gelatin adhesive (LifeMesh), collagen coating (Symbotex). No necrosis, mineralization, or exuberant inflammatory reaction were observed in any of the groups, suggesting good progressive integration of the mesh to the abdominal wall. **Panel A, B, C** 28 days post surgery. In particular, note that the fibrotic layer over the mesh and at intervals between the mesh (voids) in the PP sample is very thin relative to those seen in the Symbotex and LifeMesh samples, where the corresponding fibrotic layer is of uniform thickness and is relatively thicker. Note that at this stage the scar tissue related to the excision (green arrows) is still relatively prominent. **Panel D, E, F** 90 days post surgery. At this time point there is already full degradation of adhesive gelatin. Compared to the 28-day post-surgery time point, and consistently with the progress of healing, the overall thickness of the gelatin-related fibrosis and of the excision-related scar tissue are significantly reduced. In particular, note that in the PP sample, the fibrotic layer over the mesh and at the intervals between the mesh (voids) is very thin relative to those seen in the Symbotex and LifeMesh samples, where the fibrotic layer is of uniform thickness and relatively thicker. This particular characteristic is suggested to contribute to more effective adherence of the mesh to the abdominal wall, without the complication of intra-abdominal organ adhesions

mesh repair (IPOM), to that of two control mesh materials fixated with tacks.

Fixation strength using the self-adhesive mechanism was found in this study to be comparable with or higher than that obtained with tacks. This finding was attributed to the fact that the adhesive attaches the entire mesh surface to the underlying tissue in a homogeneous manner, resulting in good conformity to the tissue, and eventually facilitating ingrowth of the tissue surrounding the mesh textile, strengthening the mesh/tissue interface. This finding of comparable chronic tissue attachment of LifeMesh and of tack-fixated PP is of great importance. Several preclinical studies of acute and chronic fixation strengths of fibrin glue, as the potential non-traumatic alternative for penetrating fixation

techniques, have demonstrated the inferiority of their mesh/tissue interfacial strengths to those of other penetrating and non-penetrating fixation methods [40, 41, 61, 62]. These preclinical findings might explain the higher recurrence rate experienced by patients in whom fibrin glue was used [37–39, 63]. However, since distribution of glue on the mesh surface is user-dependent, variability in the resulting tissue ingrowth and fixation strength is to be expected. It was also shown that the mesh selected for use with fibrin glue might significantly affect the fixation strength to an extent that could hamper the outcome of the repair [64]. In the present study, the uniformly strong attachment of LifeMesh to the abdominal wall observed 28 days and 90 days postoperatively can be attributed to a predetermined amount of adhesive that was designed for uniform distribution throughout the mesh, allowing easy handling and application as well as a robust and user-independent outcome.

Clinical use of cyanoacrylate synthetic glues as an alternative to mesh fixation in laparoscopic hernia repair is not widely accepted because reports have described local toxicity and carcinogenic effects on both patients and medical staff [65, 66]. In addition, the low degradability and the impenetrability of cyanoacrylates inhibit tissue integration of the implant and evoke a pronounced inflammatory response [33], prompting recommendations that their application be restricted to only a few drops at the surface of the mesh. In contrast, the gelatin-mTG bio-adhesive present in LifeMesh and tested in this study showed no toxicity, and a beneficial tissue response resulting in good progressive integration of the mesh to the abdominal wall.

Placing of the mesh in the intraperitoneal cavity can potentially cause the formation of adhesions between visceral organs and the mesh surface, resulting in bowel erosion and fistula formation. Bare PP mesh is known to strongly induce adhesion formation [67]. Multiple modifications of synthetic mesh surfaces designed to reduce adhesion rate and severity are currently available for IPOM hernia repair [68]. Symbotex composite mesh, made from a polyester textile and covered with a bio-absorbable collagen film on the visceral side, was designed to minimize exposure of the synthetic mesh material to intraperitoneal contents. The manufacturers claim that this mesh implant provides long-term reinforcement of abdominal wall soft tissues, while the absorbable film minimizes tissue attachment to the mesh in the event of direct contact with the viscera. Our findings are in agreement with studies [69] clearly indicating a reduction in adhesion incidence and adhesion scores for composite mesh containing collagen film compared to unprotected PP mesh. Interestingly, adhesion incidence and scores in the cross-linked gelatin layer of LifeMesh exhibited improvements similar to those reported with Symbotex. Furthermore, both with LifeMesh and with Symbotex the occurrence of visceral adhesions involving colon or spleen was lower than their occurrence in uncoated PP mesh, possibly reducing the likelihood of adhesion-related complications.

It is well known that the peritoneum re-mesothelializes within 5–8 days post surgery and that the neoperitoneum serves not only as a physical barrier separating the mesh from the abdominal viscera but also potentially promotes fibrinolysis by releasing tissue plasminogen activator and inhibits cell–cell and cell–tissue interaction by releasing hyaluronic acid [70]. Whereas the severity and extent of post-surgical adhesions may change over a period of weeks, the incidence of adhesions is determined during the first 5–8 days after peritoneal trauma [71]. Thus, to prevent or reduce adhesion-related complications, the synthetic mesh material should remain protected at least during this critical period. In LifeMesh, as in Symbotex, the synthetic mesh is protected by a biodegradable layer as the PP mesh is embedded in the gelatin-mTG bio-adhesive. During the first month after implantation, the gelatin matrix undergoes gradual degradation accompanied by cell ingrowth and tissue coating of the PP component, as is evident from the histopathology data. Previous reports indicate that at day 7 post implantation, the gelatin layer is prominent around the PP mesh, ensuring mesh protection during the critical period of adhesion formation [44].

Several studies have shown that after surgical implantation of a mesh, the repair process involving tissue formation at the defect area causes the mesh to shrink [72], an event that might be related to hernia recurrence. Although the mechanism of mesh shrinkage is still a subject of controversy, the most popular theory is that the local inflammatory reaction of the abdominal wall in response to the presence of the mesh leads to fibroblast migration and proliferation, periprosthetic fibrosis, and subsequent mesh shrinkage [73]. Shrinkage was evaluated in our study until the 90-day time point, and we believe that by this time it reflected the chronic state of the mesh. The neoperitoneum had formed and was completely covering the prosthetic material, and no further changes were anticipated. As expected, by this time all meshes used in this study showed size reductions relative to their initial surface areas, with no significant differences in this respect between the groups. These results correlated well with the histological findings; all groups developed comparable levels of fibrotic tissue around and inside the mesh. Previous studies have reported that the amount of fibrotic tissue produced around and within the meshes directly affects the size of the implanted material in the long term: the denser and more rigid the fibrosis, the more significant the shrinkage of the mesh [72]. In a recent study comparing LifeMesh to control mesh fixated by sutures, at early postoperative days 3 and 7, the LifeMesh group was found to display significantly smaller mesh shrinkage than the control group [44]. It should be noted that during those early days, the mesh in LifeMesh was still surrounded by the gelatin matrix that maintained the mesh in its original position,

preventing significant shrinkage. Concomitantly with degradation of the gelatin matrix during the first month, the mesh gradually becomes covered with new tissue ingrowth and the differences in shrinkage levels become less substantial.

Our histological findings demonstrated similar tissue responses in LifeMesh and Symbotex at both time points. Their lack of necrosis, mineralization, or exuberant inflammatory reaction points to good progressive integration of the mesh to the abdominal wall, leading ultimately to the formation of uniformly thick maturing granulation tissue, consistently with a normal course of healing and wound maturation. In the PP mesh, by contrast, the observed lack of uniformity in the thickness of the granulation tissue may indicate a potential non-uniform adherence of the mesh to the abdominal wall. The gelatin layer in LifeMesh was substantially degraded by the 28-day postoperative time point, leading to gradual tissue ingrowth that became the main fixation mode of the mesh to abdominal wall.

Conclusions

To summarize, for many years, considerable effort has been devoted to the challenge of finding, as an alternative to penetrating methods of fixation, a viable method that meets the criteria for laparoscopic ventral hernia repair without compromising the local tissue response and the long-term clinical outcome. Based on strong experimental evidence, as demonstrated in this study, of comparable fixation strength, shrinkage, and adhesion profile, combined with the favorable tissue response observed for the self-adhesive mesh, it seems that the penetrating fixation methods currently used in hernia repair could be replaced by the use of this novel adhesive coating, thereby potentially reduce the occurrence of postoperative complications such as pain, migrating tacks, and others. Validation of these findings will require further research, in human studies as well.

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Compliance with ethical standards

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