Am J Transl Res 2016;8(12):5706-5714
www.ajtr.org /ISSN:1943-8141/AJTR0033508

Original Article

Treatment of de-peritonealized intestine with 4DryField® PH prevents adhesions between non-resorbable intra-peritoneal hernia mesh and bowel

Markus Winny[1], Lavinia Maegel[2], Leonie Victoria Grethe[1], Danny Jonigk[2], Paul Borchert[2], Alexander Kaltenborn[3,4], Harald Schrem[1,3], Juergen Klempnauer[1], Daniel Poehnert[1]

[1]*Department of General, Visceral and Transplant Surgery, Hannover Medical School, Germany;* [2]*Institute for Pathology, Hannover Medical School, Germany;* [3]*Core Facility Quality Management and Health Technology Assessment in Transplantation, Integrated Research and Treatment Centre-Transplantation (IFB-Tx), Hannover Medical School, Germany;* [4]*Department of Trauma and Orthopaedic Surgery, Federal Armed Forces Hospital Westerstede, Westerstede, Germany*

Received June 9, 2016; Accepted August 16, 2016; Epub December 15, 2016; Published December 30, 2016

Abstract: Background: Intraperitoneal onlay meshes (IPOM) can be associated with intestine-to-mesh adhesion formation, implementing risks like pain, enterocutaneous fistula, infection, and female infertility. This study investigates, whether a treatment of impaired intestinum with the anti-adhesive and hemostyptic agent 4DryField® PH prevents adhesion formation. Methods: In 20 male LEWIS rats uncoated polypropylene meshes were sewn to the inner abdominal wall and the cecum of the respective animal was de-peritonealized by peritoneal abrasion by a gauze swap, and meso-sutures ensured a constant contact of injured areas. Rats were treated with 4DryField® PH gel either premixed or applied as a powder with in-situ transformation (100 mg powder plus 0.4 ml 0.9% saline solution). One week postoperatively, the extent of intestine-to-mesh adhesions and the quality of mesh ingrowth were evaluated macroscopically by two independent investigators using two scoring systems. Furthermore, specimens were analysed microscopically. All data were compared with control animals without 4DryField® PH treatment and analysed statistically using student's t-test. Results: Treatment of de-peritonealised cecum with 4DryField® PH significantly reduced intestine-to-mesh adhesions in both treatment groups as compared to controls without 4DryField® PH treatment (68% reduction with premixed gel, $P<0.0001$; 80% reduction with in-situ gel, $P<0.0001$). There was no impact on the quality of mesh ingrowth, confirmed histologically by a single-layer mesothelial coverage. Conclusion: These experiments mimick clinical IPOM implantation scenarios with adjacent bowel depleted from peritoneum. 4DryField® PH gel treatment resulted in intestinal mesothelial surface recovering without development of bowel-to-mesh adhesions. Concurrently, integration of mesh into the abdominal wall is undisturbed by 4DryField® PH treatment.

Keywords: Hernia mesh rat model, adhesion prevention, adhesion barrier, IPOM, 4DryField® PH, polysaccharide

Introduction

The use of intraperitoneal onlay meshes (IPOM) gains increasing interest and acceptance as technique for hernia repair [1, 2]. However, this technique might be associated with adhesion formation between intestine and mesh, which constitutes a serious problem, and which is reported to occur in up to 65% of patients monitored by cine magnetic resonance imaging 67 months after mesh implantation [3]. As reviewed by Chelala et al. [4], such adhesions can induce severe health problems like chronic abdominal pain [5-7], bowel obstruction [8-11], enterocutaneous fistulas and infection [8, 12, 13], as well as secondary female infertility [10, 14, 15]. One major attempt to reduce those adhesions is the improvement of materials, manufacturing or coating of IPOM meshes to reduce causative factors provoking adhesions. Studies showed that missing peritoneal coverage, as it is frequently unavoidable when adjacent hernia sac content needs to be dissected, is an important co-decisive factor for adhesion formation [16-18].

There is experimental evidence that a gel basing on 4DryField® PH (PlantTec Medical GmbH, Germany) is highly effective as a barrier preventing intraabdominal adhesions even in case

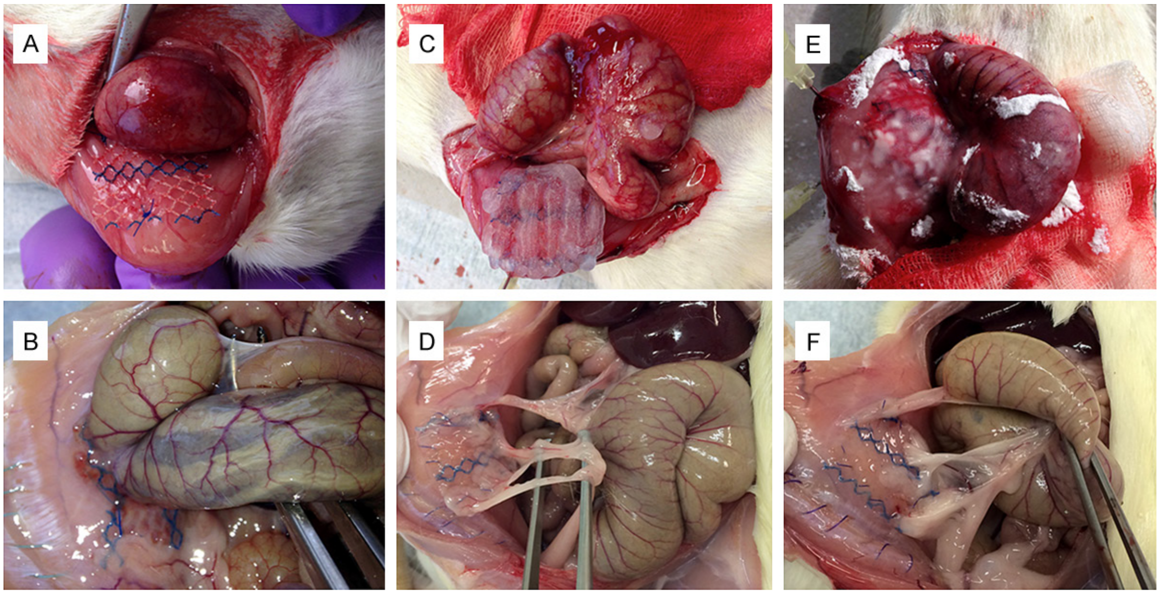

Figure 1. Representative pictures of mesh implantation day 0 (A, C, E) and on postoperative day 7 (B, D, F). (A, B) Control animal with no anti-adhesive treatment; (A) Implanted mesh and abraded cecum, (B) Autopsy reveals severe agglutination of cecum to abdominal wall with the mesh in between. (C, D) Anti-adhesive treatment with 4DryField® PH as premixed gel; (C) Gel applied on mesh and injured cecum; (D) Day 7, adequate integration of mesh into the abdominal wall, no adhesions between cecum and mesh, some adhesions of intra-abdominal fat to edges of mesh. (E, F) Animal treated with 4DryField® PH applied as powder and subsequently transformed into gel in situ; (E) After application of 4DryField® PH on mesh and injured cecum the powder was transformed by subsequent dripping with saline solution to form a gel; (F) Day 7, showing adequate integration of mesh into the abdominal wall, no adhesions between cecum and mesh, some adhesions of intraabdominal fat to edges of the mesh.

of bilateral injury, i.e. lesion of visceral and parietal peritoneum [19-21].

The present study analyses whether treatment with 4DryField® PH in our hernia rat model with de-peritonealised intestine adjacent to mesh [16] is efficient in reducing the incidence of intestine-to-mesh adhesions. 4DryField® PH was applied in two alternate application modes: as a premixed gel or applied as a powder that was subsequently transformed into gel in situ.

Since integration of mesh into the abdominal wall is crucial, a device preventing adhesions should not impede the biological processes of fibrous tissue formation, those are necessary for fixation of the foreign material. Thus, the study also evaluates if adhesion prevention with 4DryField® PH has an impact on the quality of the integration of the mesh into the abdominal wall.

Materials and methods

Animals

This study was approved by The Lower Saxony State Office for Consumer Protection and Food Safety (LAVES, Hannover, Germany; approval code 13/1095). All experiments were performed at the Zentrales Tierlabor of Hanover Medical School (MHH, Hanover, Germany). In order to provide and assure adequate life quality of the laboratory animals all protocols were conducted in accordance with national and European animal protection laws.

A total of 20 male Lewis rats, weighing 300-404 g (mean 330 g ± 30 g) were included in this study. Rats had continuous access to fresh water and food. Animals' welfare was assessed by monitoring of weight and behavioural changes using a standard observation chart (body condition scoring, GV-SOLAS, Charité-Universitätsmedizin Berlin, Berlin, Germany).

Surgical intervention and adhesion prevention measures

Rats were randomly separated into two groups prior to the surgical interventions: Ten rats were treated with 4DryField® PH (4DF) premixed gel (4DF premixed gel) and 10 rats received 4DryField® PH powder which was transformed into a gel in situ (4DF in-situ gel) by dripping sterile saline solution. Recently published data of 10 rats using the same testing conditions [16] were used as a control group (CT).

General anaesthesia was achieved by intraperitoneal injection of 80 mg/kg body weight ketamine and 5 mg/kg xylazine. The required level of narcosis for surgery was achieved as soon as flexor reflexes failed to appear. For laparotomic access to the abdominal cavity the abdomen was shaved and sanitised before a three cm long median laparotomy was performed.

In accordance with our recently introduced rat model [16], the cecum was abraded with dry gauze until the visceral peritoneum was removed and petechial hemorrhages over a 1 × 2 cm area were visible. In both test groups a 1.5 × 2 cm sized patch of Ultrapro® mesh was fixed at the corresponding lateral abdominal wall (**Figure 1**) followed by the 4DryField® PH application on the mesh surface and the abraded cecum. In the 4DF premixed gel group 1.2 ml of premixed 4DryField® PH gel (made from 4 ml saline solution per 1 g 4DryField® PH) was applied (see **Figure 1C**). In the 4DF in-situ gel group 300 mg 4DryField® PH powder were given on the mesh surface and the abraded cecum and transformed into a gel in situ by dripping 1.2 ml of saline solution (see **Figure 1E**). Subsequently, the cecum was replaced intraabdominally and approximated to the mesh with a 4/0 Prolene® suture in both groups. The abdomen was closed using a two-layer closure technique by consecutive sutures.

To minimise possible postoperative pain animals received 200 mg/kg body weight novalminsulfone subcutaneously after surgery and subsequently by mixing 40 droplets into 500 mL drinking water. In case of complications, such as infection or inflammation, the animals would have been sacrificed promptly. All animals were sacrificed on day 7 after mesh implantation. At the end of experiment, the peritoneal cavity was reentered via an incision left-handed and remote to the former laparotomy scar for evaluation of adhesions. Additionally, samples for histological assessments were collected, which were excised en bloc, rinsed, and immersed in 4% buffered formalin. After paraffin embedding, serial sections were stained with haematoxylin and eosin or with a PAS staining kit and evaluated by light microscopy in a blinded fashion.

Evaluation parameters

Animals' constitution was subjected to daily routine observations. The body weight of animals was determined at trial day 0 (before surgical procedure) and at trial day 7. Upon autopsy on postoperative day 7 two independent observers evaluated the mesh surface for adhesion formation according to scoring schemes by Lauder et al. [22] and Hoffmann et al. [23] as well as the quality of mesh ingrowth into the abdominal wall.

The Lauder scoring scheme takes into account number, strength, and distribution of adhesions with the following adhesion scoring: 0; no adhesions, 1; thin filmy adhesions, 2; more than one thin adhesion, 3; thick adhesions with focal point, 4; thick adhesions with planar attachment, 5; very thick vascularised adhesions or more than one planar adhesion. With the Hoffmann scoring scheme and grading scale gross adhesions were measured and expressed as a percentage of the total de-peritonealised surface area. This was further translated into grades 0 to 4 (0; no adhesions, 1; cecum to bowel adhesion, 2; cecum to sidewall adhesion over less than 25% of the abraded surface area, 3; cecum to sidewall adhesion between 25% and 50% of the abraded surface area, 4; cecum to sidewall adhesion over 50% of the abraded surface area). Each animal was additionally evaluated for strength of adhesion formation and graded 0 to 3 (0; no adhesion, 1; gentle traction required to break adhesion, 2; blunt dissection required to break adhesion, 3; sharp dissection required to break adhesion). The extent of adhesion formation was also graded 0 to 3 (0; no adhesion, 1; filmy adhesion, 2; vascularized adhesion, 3; opaque or cohesive adhesion). These three subscores were summed for a total Hoffmann adhesion score. Photographs of the affected areas were taken from each animal for documentation purposes (20.0 megapixel digital camera, Cybershot DSC-RX100, Sony, Germany).

For a better comparison an 'adhesion reduction rate' (AR) was calculated. Hoffmann total and Lauder scores were set against the corresponding score of controls expressed in percentages. Values were averaged and then subtracted from 100 to allow expression as reduction rate. This means if there was no

Table 1. Mean Lauder and total Hoffmann scores, combined mean of both scores, adhesion reduction rate and *p*-value as compared to control (CT)

	Mean Lauder score	Mean total Hoffmann score	Combined mean of both scores	Adhesion reduction rate	*p*-value to CT
Control*	92%	90%	91%	0%	-
4DF premixed gel	30%	29%	30%	68%	<0.0001
4DF in-situ mixed gel	16%	21%	19%	80%	<0.0001

*Original data published in [16].

adhesion formation, the adhesion reduction rate was 100%.

The quality of the ingrowth of the mesh into the abdominal wall was evaluated and ranked from 1 to 4, with 1 = no/minor integration of the mesh, 2 = partially (25-50% of mesh area), 3 = mostly integrated (50-75% of mesh area) and 4 = 100% integration of the mesh.

Histology

Histological analyses were performed for further evaluation of the impact of 4DryField® PH treatment on adhesion formation and mesh ingrowth. Formalin-fixed samples were paraffin embedded and serial sections were stained with haematoxylin and eosin or with a PAS staining kit and evaluated by light microscopy in a blinded fashion.

Statistical analysis

Adhesion scores are presented in mean values with standard deviations (SD). Scores and weight data were compared using unpaired student's t-test and reported *p* values and were considered significant with $p<0.05$. Statistical analyses were performed with GraphPad PRISM (Version 6 for Mac OS, GraphPad Software, Inc., La Jolly, USA).

Results

A total of 20 animals completed the study, none of the animals had to be sacrificed during the course of investigations. All animals showed equitable viability and course of body weight (body weight loss on day 7: 23.2 ± 11.7 g). **Table 1** shows the adhesion scores for all groups according to Lauder and Hoffmann scoring schemes expressed as a percentage. **Table 2** shows absolute and mean adhesion scores for all animals included in this study. As there were no significant differences between both scoring systems, a mean Lauder-Hoffmann score and based thereon an adhesion reduction rate, were calculated to simplify further comparisons.

Both groups with 4DryField® PH treatment had significantly lower adhesion scores than the control group and revealed only minor adhesions, mainly consisting of adhesions of the intra-abdominal fat to the mesh (**Figure 1D**, **1F**). Animals of the 4DF premixed gel group showed a significantly lower overall mean adhesion score of 30% as compared to controls ($P<0.0001$), equivalent to an adhesion reduction rate of 68%. None of the animals of the 4DryField® PH premixed gel group showed severe agglutinations, 4 revealed medium (50%; 55%, 60%, 65%), 3 had minor (20%; 20%; 25%) and 3 animals had no adhesions at all (0% each). Rats of the 4DF in-situ mixed gel group, in which 4DryField® PH was applied as a powder and subsequently transformed into a gel in situ, showed even lower adhesion scores with an overall mean score of 19% ($P \leq 0.0001$ as compared to controls), equivalent to an adhesion reduction rate of 80%. In this group 6 animals had minor to medium adhesions (3 × 25%; 1 × 30%; 2 × 40%) and 4 animals revealed no adhesions. There were no significant differences in the effectiveness of adhesion prevention between both 4DryField® PH treated groups (**Figure 2**).

To evaluate any impact of the anti-adhesion treatment on the quality of mesh ingrowth into the abdominal wall, mesh ingrowth was rated from grades 1 to 4. As shown in **Figure 3**, no differences in the quality of mesh integration as compared to controls (3.3 ± 0.8) could be observed in 4DryField® PH treated animals on day 7 after surgery (4DF premixed gel = 3.2 ± 0.9, 4DF in-situ gel = 3 ± 0.9).

Table 2. Original Lauder and Hoffmann, mean Lauder-Hoffmann, and mesh ingrowth scores of all animals. Numbering of animals adopted and continued from [16]

Animal	Lauder score		Total Hoffmann score		Mean Lauder-Hoffmann score	Mesh ingrowth
	Score	Percentage	Score	Percentage	Percentage	Score
Control*						
B1	5	100%	10	100%	100%	3
B2	5	100%	10	100%	100%	2
B3	5	100%	10	100%	100%	4
B4	5	100%	9	90%	95%	2
B5	5	100%	10	100%	100%	4
B6	5	100%	10	100%	100%	4
B7	5	100%	10	100%	100%	4
B8	1	20%	1	10%	15%	3
B9	5	100%	10	100%	100%	4
B10	5	100%	10	100%	100%	3
4DF premixed gel						
C1	3	60%	4	40%	50%	3
C2	3	60%	5	50%	55%	3
C3	4	80%	5	50%	65%	3
C4	0	0%	0	0%	0%	4
C5	0	0%	0	0%	0%	4
C6	0	0%	0	0%	0%	4
C7	1	20%	2	20%	20%	3
C8	0	0%	4	40%	20%	3
C9	3	60%	6	60%	60%	1
C10	1	20%	3	30%	25%	4
4DF in-situ gel						
D1	0	0%	0	0%	0%	1
D2	1	20%	3	30%	25%	3
D3	0	0%	0	0%	0%	3
D4	1	20%	3	30%	25%	3
D5	0	0%	0	0%	0%	2
D6	1	20%	4	40%	30%	3
D7	2	40%	4	40%	40%	3
D8	1	20%	3	30%	25%	4
D9	2	40%	4	40%	40%	4
D10	0	0%	0	0%	0%	4

*Data originally published in [16].

Representative histological findings of the control group without 4DryField® PH treatment showed that the abdominal wall and the cecum were agglutinated with the mesh in between (**Figure 4A**). In contrast, representative histological findings in rats treated with 4DryField® PH prepared as a premixed gel (**Figure 4B**, **4C**) and treated with 4DryField® PH applied as powder and transformed into a gel in-situ showed that the mesh was integrated well into the abdominal wall in both treatment groups without signs of adhesion formation. Mesh fibers were embedded in granulating tissue of the abdominal wall. Some remnants of 4DryField® PH were visible in these areas, which are covered by a neo-mesothelial mono-layer cell coverage.

Discussion

Intestinal adhesions due to implantation of intraperitoneal onlay meshes (IPOM) are a

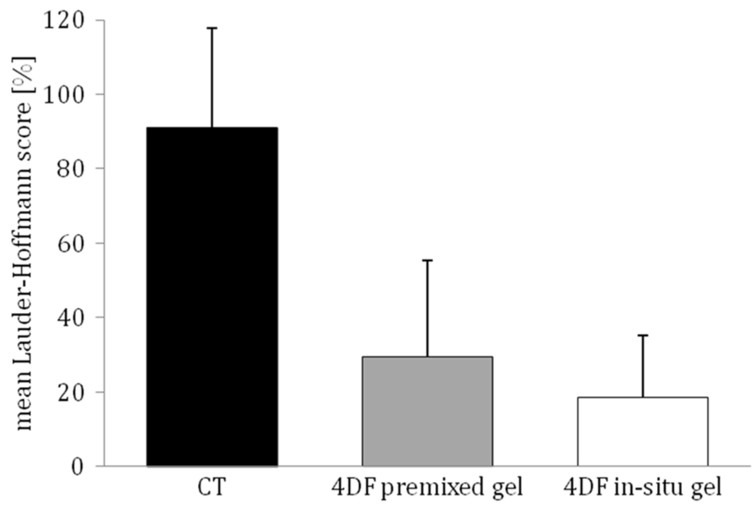

Figure 2. Mean combined Lauder and Hoffmann adhesion scores of the control (CT), 4DryField® PH (4DF) premixed gel and 4DryField® PH (4DF) in-situ gel groups.

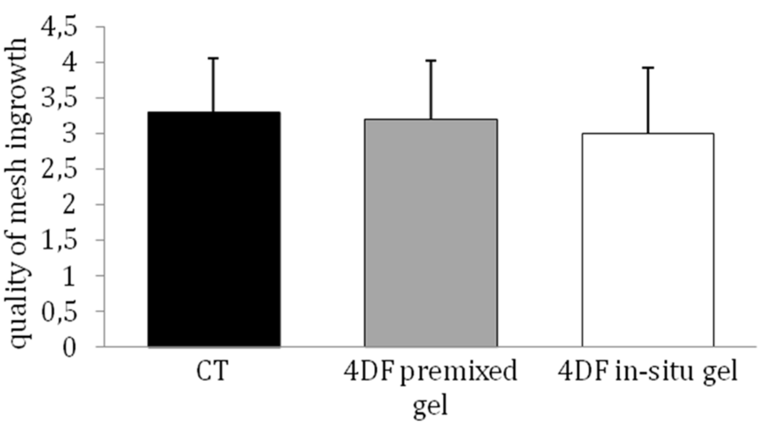

Figure 3. Comparable quality of mesh ingrowth into the abdominal wall in all tested groups.

problem in hernia surgery [2, 24]. The triggers of these adhesions are not yet fully understood. Conventionally, the mesh itself, as a foreign body, is thought to be the responsible stimulus for adhesion formation. Furthermore, polypropylene is supposed to induce adhesions more frequently than other materials [25]. However, recent experiments provide evidence that the impairment of the intestinal peritoneum is an important factor for the development of adhesions [16-18]. Areas depleted from peritoneum typically are present in the center of large hernias where the hernia sack content is agglutinated to the hernia sack itself. Here will be zones of intestine and omentum without peritoneal coverage, unpreventable even with meticulous dissection techniques.

For the present study we chose an ambitious model, combining the factors material (polypropylene) and peritoneal injury (fresh abrasion of cecum). Additionally a meso-suture ensured that both structures at risk for adhesion formation remained approximated. Such a model induces adhesions with high probability [16].

Due to the promising adhesion prevention results achieved with 4DryField® PH [21], the current study investigated, whether 4DryField® PH was also capable to effectively prevent intestine-to-mesh adhesions. Taking in consideration the severity of trauma induced in this model, the results achieved with 4DryField® PH need to be rated as excellent. They compete with data from the literature obtained with coated meshes, whereby most of these models only implemented traumata induced by the mesh itself without taking account the factors of missing or injured intestinal peritoneum or an approximation of areas at risk by a suture [26-29]. The less challenging character of these models is also expressed in the fewer adhesions of their controls as compared to our results.

In the present study with 4DryField® PH gel an intact single-layer mesothelium is found on the healed cecum as well as on the surface of the integrated mesh. This is in accordance with literature indicating that even in large peritoneal injuries a neo-mesothelium reconstitutes within days [30, 31]. Furthermore, the presence of a mono-layer coverage of parietal and visceral peritoneum is important as it allows the presumption that the adhesion prevention effect is sustainable [30, 31].

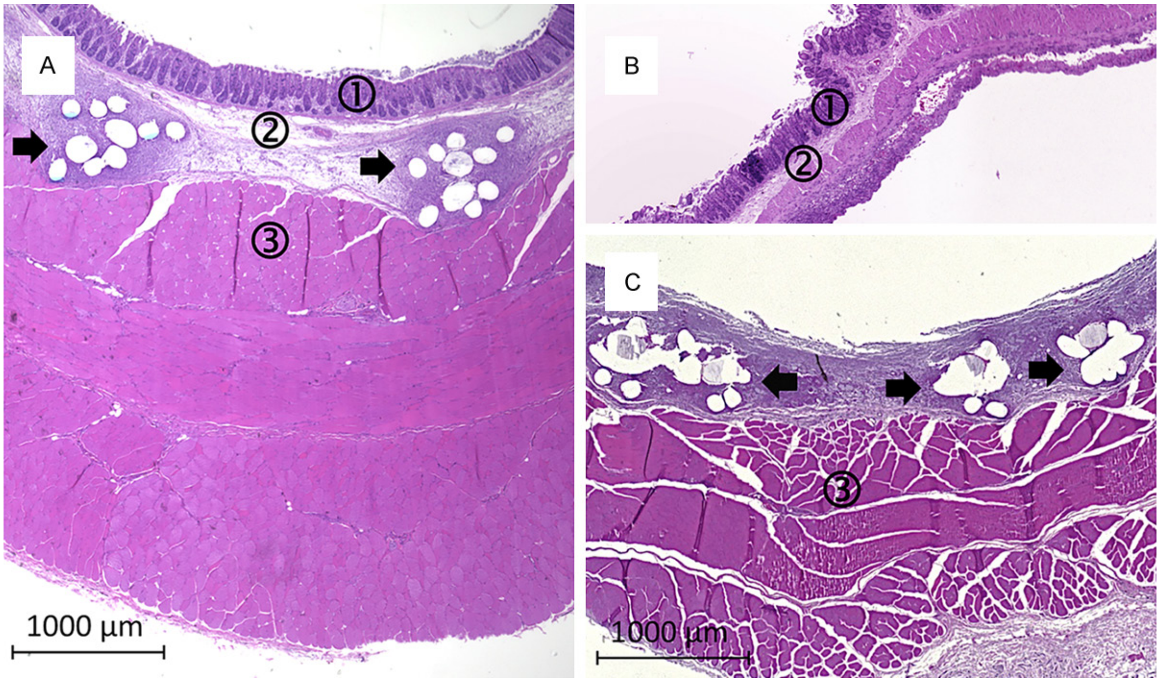

Figure 4. Representative photos of HE-stained tissues of rats with mesh implantation one week after implantation. A: Control animal with agglutinated abdominal wall and cecum and the mesh in between. The mesh is positioned in the granulating tissue between abdominal wall and cecum. B: Cecum of a rat treated with 4DryField® PH gel, with normal cecal mucosa and tunica muscularis, peritoneal coverage with thickened sub-mesothelial tissue. C: Abdominal wall of a rat treated with 4DryField® PH gel showing skeletal muscle, mesh fibers surrounded by granulating tissue with minor remnants of 4DryField® PH, peritoneal coverage without adhesion formation. ① = mucosa, ② = tunica muscularis caeci, ③ = skeletal muscle, arrows = granulation tissue around mesh fibers.

The use of adhesion prevention devices in IPOM surgery must be assessed carefully because a device should not hinder ingrowth of the mesh into the abdominal wall. To solve this dilemma various composite hernia meshes have been developed. Such meshes typically are coated on one side to reduce formation of intestine-to-mesh adhesions, while the other side is uncoated to prevent impairment of abdominal wall ingrowth. However, the effectiveness of this attempt seems to be limited [32-34] and side effects such as infections have been observed [10, 29].

If considering an uncoated mesh with the application of 4DryField® PH as a clinical alternative to coated meshes, it is important to evaluate the impact on mesh ingrowth into the abdominal wall. Macroscopically, the mesh integration into the abdominal wall was unimpaired by 4DryField® PH application. This was confirmed by histological work-up indicating that controls as well as 4DryField® PH-treated animals showed equal incorporation of mesh fibers with granulating tissue. On the one hand, the 4DryField® PH gel layer provides an effective barrier for the formation of adhesions, therefore healing and reconstitution of a neo-mesothelial coverage can occur simultaneously. Furthermore, 4DryField® PH particles are degraded rapidly by macrophages, which are also involved in the process of mesh integration. Accordingly, the stimulation of macrophage proliferation and invasion induced by 4DryField® PH particles might even be considered a support rather than a suppression for mesh ingrowth, since no disadvantages of 4DryField® PH in matters of ingrowth could be proven.

Conclusion

In an IPOM model with high probability to induce severe adhesion formations, application of 4DryField® PH gel significantly reduced intestine-to-mesh adhesions. Concurrently, the integration of mesh into the abdominal wall was not affected. The placement of a 4DryField® PH gel layer between mesh and intestine should therefore be considered as a tool to reduce adhesion formation in clinical IPOM surgery.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Daniel Poehnert, Department of General, Visceral and Transplantation Surgery, Hannover Medical School, Carl-Neuberg-Str. 1, Hannover 30625, Germany. Tel: +495115-326534; Fax: +495115324010; E-mail: poehnert.daniel@mh-hannover.de

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