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Zinc-Impregnated Mesh for Abdominal Wall Repair Reduces Infection in a Rat Model of Peritonitis

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ABSTRACT

Background: The objective of this study was to assess whether a zinc-impregnated polypropylene mesh (ZnMesh) has better antibacterial properties in a contaminated environment compared with a regular polypropylene mesh.

Materials and methods: Thirty-eight Wistar Han rats underwent cecal ligation and puncture to induce peritonitis 24 h before implantation of an intraperitoneal ZnMesh or a regular polypropylene mesh. Primary outcome was the number of colony forming units (CFU) per sample (mesh and abdominal wall). Secondary outcomes were macroscopic (incorporation of mesh, abscesses, and adhesions on mesh surface) and histological (inflammatory cell reaction, mesh-specific parameters, and collagen deposition) parameters. All outcomes were evaluated after 30 and 90 d.

Results: After 30 d, no significant difference in CFU per sample was present between the ZnMesh and control groups. After 90 d, a lower number of CFU per sample was present in the ZnMesh group compared with the control group (trypticase soy agar with 5% sheep blood: 0 $\log_{10}$ CFU/sample IQR: 0-1.40 *versus* 1.58 $\log_{10}$ CFU/sample IQR: 0-4.30, $P = 0.012$; MacConkey: 0 $\log_{10}$ CFU/sample IQR: 0-2.65 *versus* 1.18 $\log_{10}$ CFU/sample IQR: 0-4.04, $P = 0.438$). After 90 d, the percentage of adhesions on mesh surface was significantly higher in the ZnMesh group (95% IQR: 60%-100% *versus* 50% IQR: 23%-75%, $P = 0.029$). No differences were seen in other macroscopic outcomes or histology.

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Conclusions: A significantly lower number of CFU per sample was found in the ZnMesh group after 90 d. After 30 d, no statistically significant differences in CFU per sample were seen. This result suggests that the ZnMesh group has better antibacterial properties in a contaminated environment. However, this is at the cost of a significantly higher percentage of adhesions.

Introduction

Prosthetic implants are used for the repair of abdominal wall hernias, and their application results in significantly lower recurrence rates.[1] However, the use of a nonabsorbable synthetic mesh for hernia repair in a contaminated field remains controversial given the higher risk of postoperative infection.[2] Mesh infection is one of the most severe and disastrous complications after hernia repair and may require surgical removal of the implanted scaffold.[3] Mesh explantation may lead to patient morbidity, prolonged hospital admission, and increasing healthcare costs.[4] Biologic implants have been promoted for contaminated fields for a long time without presenting high-level evidence.[5] In a study performed by Rosen *et al.*,[6] the overall hernia recurrence was 31% using a biological mesh in a contaminated abdominal wall defect, after a follow-up of 21.7 mo (range 1-74 mo). In addition, higher cost of biologic meshes compared with synthetic meshes is a drawback.[7] Despite the wide selection of available meshes, the search for the ideal mesh to use in contaminated fields is still ongoing.

To reduce the incidence of infection, several antibacterial mesh coatings have previously been investigated.[8,9] Bacterial attachment and proliferation are necessary steps in the development of an infection depending on several factors, such as the type of polymer and its structure.[10] Recently, it was found that zinc ions are able to inhibit multiple activities of bacteria, for instance transmembrane proton translocation, glycolysis, and acid tolerance.[11] In addition, zinc oxide may disturb metabolic pathways and exhibit an antibacterial effect on both *Escherichia coli* and *Staphylococcus aureus*.[11] Until now, the polypropylene mesh incorporated with zinc ions (ZnMesh) has only been examined in *in vitro* models.

The primary objective of this animal study was to determine whether a polypropylene mesh incorporated with zinc ions has better antibacterial properties when placed in a contaminated environment compared with a regular polypropylene mesh. The secondary objectives were to assess ingrowth of the mesh, abscess formation, and adhesion. Furthermore, histological parameters were assessed, such as inflammatory cell response, mesh-specific parameters, and collagen deposition.

Material and methods

The study protocol was approved by the Ethical Committee on Animal Experimentation of the Erasmus University Medical Center (Rotterdam, the Netherlands, license number: AVD101002015179) and was performed in accordance with the ARRIVE guidelines on the use of laboratory animals.[12]

Animals

Thirty-eight male Wister Han rats, weighing 280-325 g, were purchased from Charles River Laboratories ('s-Hertogenbosch, the Netherlands). The animals were bred under specific pathogen-free conditions. All rats were housed in pairs in individually ventilated cages under 12 h dark/light cycles. The temperature was kept between 20°C and 24°C, and relative humidity was 50% to 60% in the laboratory. Standard rat chow and water was provided *ad libitum*. The rats were accustomed to laboratory conditions 1 wk before the start of the experiment.

Meshes

Regular polypropylene meshes and ZnMesh were provided by the producer (Parx Plastics, Rotterdam, the Netherlands). An existing polypropylene mesh was chemically and physically treated with dietary zinc (Zn 2+). This treatment resulted in positive ionic surface of the polymer. Zinc ions do not migrate during time, and the ZnMesh remains biologically inert. It was hypothesized that the positive ionic surface makes the surface hostile to bacteria, reduces the capability to form biofilm, and interferes with the bacteria proliferation without releasing ions.

Surgical procedure

Preoperatively, 38 rats were randomly divided into two groups to receive either the ZnMesh ($n = 20$) or regular polypropylene mesh ($n = 18$). These two groups were again randomly divided into two groups for a follow-up of 30 or 90 d. Experiments were done under aseptic conditions in an operation room for small animals. All rats were anesthetized with a combination of isoflurane and oxygen inhalation. Preoperatively, a single dose of 0.05 mg/kg buprenorphine was administered subcutaneously. After anesthesia, the abdominal skin was shaved, disinfected with alcohol 70%, and subsequently a 3-cm midline incision was performed, to enter the abdominal cavity.

Cecal ligation puncture model

The cecal ligation puncture model was used for the induction of peritonitis.[13] On day 0, ligation of the cecum was performed just distal to the ileocecal valve with a nonabsorbable polyamide suture (5-0 Ethilon; Ethicon, Inc., Sommerville, NJ), without interrupting the bowel continuity. Subsequently, a puncture with an 18-gauge needle was performed distally in the cecum. The fascia and skin were closed in two layers with running absorbable polyglycolic acid sutures (5-0 Safil; B. Braun, Melsungen, Germany). Postoperatively, all animals received 5 mL sodium chloride 0.9 per cent subcutaneously and were placed under a heating lamp to prevent

hypothermia. After 24 h (day 1), all rats were anesthetized with the same inhalation mixture as on day 0 and the abdominal cavity was disinfected and reopened. The necrotic or ischemic section of the cecum was resected and the abdominal cavity was rinsed with warmed phosphate buffer at 37°C. Aminoglycoside antibiotics (gentamicin) were administered with a dosage of 6 mg per kilogram intramuscularly. A sterile mesh of 2.5 × 3 cm (7.5 cm^2) was placed intraperitoneally and was fixated with six transmuscular nonabsorbable sutures (5-0 Ethilon, Ethicon, Inc). Again, the fascia and skin were closed in two layers with a running absorbable suture (5-0 Safil; B. Braun). Subsequently, the rats received 5 mL sodium chloride 0.9 per cent and were placed under a heating lamp to prevent hypothermia immediately after surgery.

Survival and wellness

All rats were weighed daily during the first 4 d postoperatively. Animals were inspected for signs of pain or surgical site occurrences. In addition, all animals were checked daily by an animal care taker. A 12-point wellness and behavior scoring system was used to assess wellness and behavior (Supplementary Materials,Table 1).[14] Rats were removed from the experiment when they reached the humane endpoint (a wellness score of <5 points or weight loss of more than 20%).

Sacrifice

After 30 and 90 d, euthanasia was performed under anesthesia (combination of isoflurane and oxygen inhalation) by subsequent cardiac cut.[15]

Microbiology

The abdominal skin was shaved and disinfected with alcohol 70%. The ventral abdominal wall was opened via a U-shaped incision, and a picture of the mesh was taken (Figure). Full-thickness abdominal wall samples including mesh were sampled aseptically. The samples measured 1.0 × 1.0 cm and were stored on ice in a tube with 2 mL sterile phosphate buffered saline. Subsequently, samples were homogenized for 30 s (IKA T25 ULTRA-TURRAX). Samples were plated in serial dilutions onto MacConkey Agar (Becton Dickinson, Etten-Leur, the Netherlands) to select for gram-negative bacteria. The samples were also plated on trypticase soy agar with 5% sheep blood (Becton Dickinson) to select for a wide variety of microorganisms. A maximum of three bacteria were identified using the matrix-assisted laser desorption or ionization time-of-flight analyzer (MALDI Biotyper; Bruker Daltonics, Bremen, Germany). The plates were incubated at 37°C for 24 h, and the amount of colony forming units (CFU) per full-thickness abdominal wall and mesh sample (CFU/sample) was counted. Second, a qualitative analysis was performed using 30 μL inoculation loop. For confirmation of the microbiological flora of healthy Wistar Han rats, additional analyses were performed. Feces from five different healthy Wistar Han rats from the same strain and area (Charles River Laboratories) were collected directly from the cecum and analyzed with the same methods as described previously.

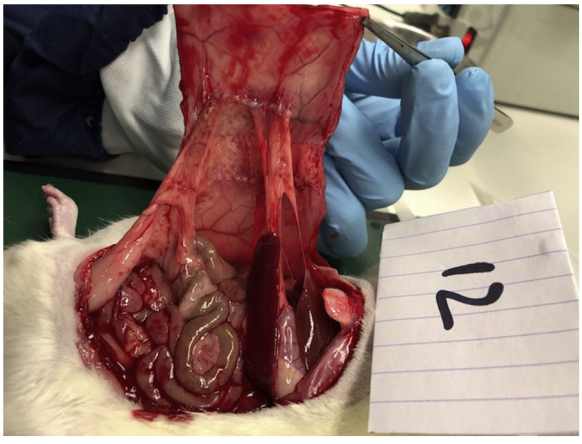

Fig – Photograph (color) taken during the macroscopic assessment. Photo taken during sacrifice showing the inner abdominal wall and a polypropylene mesh without zinc coating. (Color version of figure is available online.)

Macroscopy

All parameters were determined by two blinded, independent observers. In case of disagreement, the results were discussed between the two blinded observers and consensus was reached.

Ingrowth of the mesh

All edges of the mesh were lifted from the abdominal wall and inspected for ingrowth. Ingrowth was computed by using a caliper to examine adhering tissue between abdominal wall and mesh presented as a percentage.[15-17]

Adhesions

Adhesions were determined in a qualitative manner by using the Zühlke score (Supplementary Materials,Table 2) and in a quantitative manner by two independent observers until consensus was reached and expressed in percentages on the mesh surface.[18]

Abscesses

The amount and size of abscesses at the abdominal wall and in the abdominal cavity were assessed visually by using a scoring system (Supplementary Materials,Table 3).[19]

Table 1 – Distribution of survival and follow-up per group.

Mesh type	Start, *n* (%)	Death, *n* (%)	Total FU, *n* (%)	30-day FU, *n*	90-day FU, *n*
ZnMesh	20 (33)	9 (45)	11 (42)	6	5
Control	18 (47)	3 (17)	15 (58)	6	9
Total	38 (100)	12 (32)	26 (100)	12	14

FU = follow-up.

Table 2 – Cecal ligation puncture model—cecum.

Cecum	*n* (%)
Necrotic	16 (42.1)
Ischemic	15 (39.5)
Ischemic and necrotic (combination)	1 (2.6)
No changes (normal cecum)	2 (5.3)
No second operation	2 (5.3)
Missing	2 (5.3)
Total	38 (100)

Histology

Full-thickness (mesh and abdominal wall muscle) samples of 1.0 × 0.5 cm were collected in-between sutures. All samples were fixated in 4% formalin for 24 h. Next, the fixated samples were embedded in paraffin. Sections of 4 μm were cut (Leica RM2255 microtome; Leica Biosystems, Wetzlar, Germany) and stained with Sirius Red (Ventana Benchmark Special Stains system; Hoffmann-La Roche, Bazel, Switzerland) or hematoxylin and eosin staining (Ventana Symphony automated staining instrument; Hoffman-La Roche, Bazel, Switserland). All histological evaluations were performed by a pathologist (MCvG) who was blinded for the type of mesh. The inflammatory cell reaction was evaluated by counting the amount of cells per high-power field (40× magnification), using a scoring system described by Peeters *et al.* (Supplementary Materials,Table 4).[20] Mesh-specific parameters were evaluated using a modified scoring system assessing scaffold degradation, fibrous encapsulation, cellular infiltration, and neovascularization (Supplementary Materials,Table 5).[20] Collagen deposition, as visualized by Sirius Red staining, around the mesh and abdominal wall were evaluated using a scoring system described by Deeken *et al.* (Supplementary Materials,Table 6).[21]

Statistical analysis

A power calculation was not performed because no earlier comparison in the number of CFU between meshes was performed. Outcomes are presented as median (interquartile range). Survival, macroscopy, histology, and microbiological results were compared performing a χ^2 test and a nonparametric Mann-Whitney *U* test for independent samples. Reported *P*-values are two-sided, and *P*-values < 0.05 were considered statistically significant. IBM SPSS Statistics for Windows, version 24.0.0.1, Armonk, NY, was used.

Results

Survival

Initially, all rats survived the first operation. In the first 4 d postoperatively, 12 rats (32%) of the 38 rats died of sepsis. Nine of 12 rats belonged to the ZnMesh group, and three of 12 rats belonged to the control group. However, two of nine rats from the ZnMesh group had never received a ZnMesh as they died before the second surgery and subsequent mesh implantation. This difference in two groups was not significantly different ($P = 0.086$). One of 12 rats died at day 15 for an unknown reason. None of the rats reached the humane endpoint. Finally, 26 rats (68.5%) remained for follow-up with 12 rats (46.2%) in the 30-day follow-up group and 14 (53.8%) in the 90-day follow-up group (Table 1).

Cecal ligation puncture model

Sixteen rats (42.1%) had a necrotic cecum and 15 rats (39.5%) had an ischemic cecum (Table 2). All animals showed symptoms of sepsis, including weight loss, abnormal posture, ocular exudates, apathetic behavior, diarrhea, shivering, and piloerection.

Microbiology

At 30 d, no significant difference in CFU/sample was present between the ZnMesh and control groups (Table 3). At 90 d, a significantly lower number of CFU/sample were present in the ZnMesh group compared with the control group (0 $\log_{10}$ CFU/sample, IQR 0-1.40 *versus* 1.58 $\log_{10}$ CFU/sample IQR 0-4.30, $P = 0.012$, Table 3). Mainly, *Enterococcus* and *Staphylococcus*, both gram-positive bacteria, were identified. In an additional experiment, mostly *Escherichia* (a gram-negative bacterium) and *Lactobacillus* (a gram-positive bacterium) were identified in the feces of five Wistar Han rats. Furthermore, *Enterococcus* and *Staphylococcus* were identified.

Macroscopy, ingrowth

There were no significant differences in ingrowth of the mesh in percentages in both groups at both time points (30 d of

Table 3 – Microbiology, 30 and 90 d of follow-up.

30 d of follow-up	ZnMesh ($n = 6$)	Control ($n = 6$)	*P*-value
MacConkey ($\log_{10}$ CFU/sample)	3.75 (1.11-4.72)	2.93 (1.11-5.85)	1.000
TSA-SB ($\log_{10}$ CFU/sample)	3.98 (1.94-6.08)	3.98 (1.94-6.08)	0.818
90 d of follow-up	**ZnMesh ($n = 5$)**	**Control ($n = 9$)**	***P*-value**
MacConkey ($\log_{10}$ CFU/sample)	0 (0-2.65)	1.18 (0-4.04)	0.438
TSA-SB ($\log_{10}$ CFU/sample)	0 (0-1.40)	1.58 (0-4.30)	**0.012**

Statistically significant values ($P < 0.05$) are given in bold.
TSA-SB = trypticase soy agar with 5% sheep blood.

Table 4 – Macroscopy: ingrowth and adhesions (%) 30 and 90 d of follow-up.

30 d of follow-up	ZnMesh ($n = 6$)	Control ($n = 6$)	P-value
Ingrowth (%)	75 (65-88)	78 (70-81)	1.000
Adhesions (%)	85 (74-96)	75 (56-93)	0.394
90 d of follow-up	**ZnMesh ($n = 5$)**	**Control ($n = 9$)**	**P-value**
Ingrowth (%)	66 (49-74)	59 (47-75)	0.797
Adhesions (%)	95 (60-100)	50 (23-75)	**0.029**

Median (interquartile range).
Statistically significant values ($P < 0.05$) are given in bold.

follow-up: 75 [IQR 65-88] percent *versus* 78 [IQR 70-81] percent, $P = 1.000$; 90 d of follow-up: 66 [IQR 49-74] percent *versus* 59 [IQR 47-75] percent, $P = 0.797$, see Table 4).

Macroscopy, adhesions

The highest Zühlke score in the ZnMesh group was Zühlke 3 in six rats (100%) and Zühlke 3 in five rats (100%) after 30 and 90 d, respectively. In the control group, the Zühlke score was 3 in four rats (80%) after 30 d. After 90 d, eight rats (88.9%) had a Zühlke 3 score. The highest Zühlke score in the control group was Zühlke 4 in two rats (20%) after 30 d of follow-up and in one rat (11.1%) after 90 d of follow-up. No significant differences were found after 30 d of follow-up in adhesions expressed in percentage (85 [IQR 74-96] percent *versus* 75 [IQR 56-93] percent, $P = 0.394$, Table 4). The percentage of adhesions on the mesh surface was significantly higher in the ZnMesh group after 90 d (95 [IQR 60-100] *versus* 50 [IQR 23-75], $P = 0.029$, see Table 4).

Macroscopy, abscesses

Macroscopically, only one rat developed one small abscess located on the mesh. This rat had a regular polypropylene mesh and was randomized for the 90-day follow-up group.

Histology

Histological analyses showed no significant differences in inflammatory cell reaction (overall inflammatory cell reaction [$P = 0.781$], eosinophils-neutrophils [$P = 0.274$], macrophages-foreign body giant cells [$P = 0.432$], and mononuclear cells [$P = 0.432$], Table 5) and mesh-specific parameters (scaffold degradation [$P = 0.820$], fibrous encapsulation [$P = 0.193$], cellular infiltration [$P = 0.595$], neovascularization [$P = 0.820$], and extracellular matrix deposition [$P = 0.820$], Table 6). In addition, no significant differences were found in collagen deposition across the four groups ($P = 0.257$, Table 6). Four rats showed microscopically signs of abscess formation, at both time points with one rat implanted with a ZnMesh and one rat in the control group.

Discussion

In this rat study, a polypropylene mesh impregnated with zinc ions was compared with a regular polypropylene mesh in a contaminated environment. After a follow-up of 90 d, a lower CFU per sample was found in favor of the ZnMesh on the trypticase soy agar with 5% sheep blood agar plate. This difference was not seen at the other agar plates after a follow-up of 30 d. In addition, a higher percentage adhesions on the mesh was found in the ZnMesh group after 90 d of follow-up. Adhesion formation is an important parameter for investigating the biocompatibility of meshes. Prolonged exposure to the mesh and/or the addition of zinc ions could result in more extensive reactions and could be an explanation for this finding. The exact reason for this difference in adhesions between groups remains unclear. No differences were found in macroscopically assessed ingrowth and abscesses between meshes. The histological parameters including inflammatory cell reaction, mesh-specific parameters, and collagen deposition were not significantly different between the two groups after 30 and 90 d. However, the power calculation was not based on these secondary outcomes and might therefore lack enough power to detect a difference.

The mortality after peritonitis induction was 32%, which is slightly higher when compared with previous literature using this cecal ligation puncture model (10%-28%)[13,16,17,22,23] A notable high mortality rate was seen in the ZnMesh group (nine ZnMesh animals *versus* three control animals). However, two of these nine rats never received a ZnMesh. These two rats died before implantation due to the implications of the sepsis based on the induced peritonitis. This difference in dead animals between the two groups and mesh types was not significantly different ($P = 0.086$). An explanation for this high mortality could be a less resistant strain of animals for infection or the presence of a more fulminant abdominal infection due to the experimental set-up.

Various meshes are available for the repair of an abdominal wall hernia in the presence of intra-abdominal infection. Still, the introduction of a mesh reduces the amount of bacteria

Table 5 – Histology: inflammatory cell reaction.

Inflammatory cell reaction	ZnMesh ($n = 6$) 30 d	Control ($n = 6$) 30 d	ZnMesh ($n = 5$) 90 d	Control ($n = 9$) 90 d	P-value
Inflammatory cell reaction	3 (2-3)	3 (3-3)	3 (2-3)	3 (2,3)	0.781
Eosinophils-neutrophils	3 (1-3)	3 (3-3)	3 (0-3)	2 (0-3)	0.274
Macrophages-foreign body giant cells	3 (2-3)	3 (2-3)	3 (1-3)	3 (3-3)	0.432
Mononuclear cells	3 (2-3)	3 (2-3)	3 (1-3)	2 (1-3)	0.432

Median (interquartile range).

Table 6 – Histology: mesh-specific parameters.

Mesh-specific parameters	ZnMesh ($n = 6$) 30 d	Control ($n = 6$) 30 d	ZnMesh ($n = 5$) 90 d	Control ($n = 9$) 90 d	P-value
Scaffold degradation	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.820
Fibrous encapsulation	1.5 (1-2)	1 (1-1)	2 (1-2)	2 (1-2)	0.193
Cellular infiltration	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0.595
Neovascularization	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.820
Extracellular matrix deposition	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.820
Collagen deposition	3.5 (2.75-4)	2.5 (2-3)	3 (2-3.5)	3 (2-4)	0.257

Median (interquartile range).

needed to result in an infection by a factor 10^4.[24] The evidence for using biological mesh in contaminated abdominal wall hernia repair is still limited.[25] The aim of this experimental study was to add knowledge in this search for an ideal mesh to use in a contaminated environment for ventral hernia repair. The occurrence of a clinically relevant infection depends on both patient-related factors as well as the quantity of bacteria.[26] An earlier conducted study by Tubre *et al.* showed that contamination with more than 10^5 CFU per gram may result in wound infections.[26] Pathogens found in humans at surgical site infection were *S. aureus* and *Enterococcus* species.[26] These organisms are the same as found in this study, which is performed in rats. Recently, a study showed that rats represent a good preclinical model in hernia and mesh research.[27] In addition, future studies may consider electron microscopy for the evaluation of biofilm formation because this supports bacterial attachment to the mesh.[26] The results of this present study may encourage us to conduct more research with zinc-impregnated meshes in a contaminated environment, to decrease the risk of surgical site infection or mesh infection after abdominal wall repair. However, a comparison should be made with different types of meshes because the placement of a polypropylene mesh intraperitoneally is certainly not the standard.[28] New *in vitro* and *in vivo* studies could be performed with direct inoculation on the mesh surface with a known quantity and quality of the bacteria, and to compare this with different permanent synthetic, slowly resorbable synthetic and nonsynthetic (biological) meshes.

Limitations

Information regarding the regular microbiological flora was required to differentiate between contamination during surgery or an effect of the ZnMesh on a fewer amount of CFU per sample in favor of the ZnMesh. However, microbiological assessment of preoperative and intraoperative feces was lacking in this study. Nevertheless, Charles River laboratories kindly provided data regarding the microbiological flora of these rats. These data showed that they found comparable microbiological flora as was found in this present study. Besides, feces from rats from the same laboratory, strain and area were analyzed with the same methods as in this experiment to confirm the additional data from Charles River laboratories. With these supplementary tests, an effect of the ZnMesh on CFU per sample was confirmed. Consensus and comparability among animal experiments to study mesh behavior is lacking.[29] Several differences between this experimental study and the human situation were present. Examples are the treatment of abdominal sepsis and the relative dimensions of the mesh.[15] Because this experimental study was performed with animals, these results may not be translated to the human population directly.

Conclusion

A significantly lower number of CFU per sample were found in the ZnMesh group after 90 d. However, no differences in other outcomes were found between the ZnMesh and control groups after 30 d of follow-up. These results suggest that a zinc-impregnated mesh has antibacterial properties when placed in a contaminated environment, compared with a regular polypropylene mesh. However, this is at the cost of a significantly higher percentage of adhesions. In addition, an antiadhesive mesh coating could be added to reduce adhesions. Further experiments are required to confirm this hypothesis.

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Author contributions: Y. Yurtkap Data curation; formal analysis; project administration; writing - review and editing; A.P. Jairam Conceptualization; investigation; methodology; validation; writing - review and editing; R. Kaufmann Conceptualization; funding acquisition; investigation; methodology; validation; writing - review and editing; L.F. Kroese Conceptualization; investigation; methodology; validation; writing - review and editing; M.C. Clahsen-van Groningen

Investigation; supervision; validation; writing - review and editing; J.W. Mouton Investigation; supervision; validation; writing - review and editing; A.G. Menon Conceptualization; supervision; validation; writing - review and editing; G.J. Kleinrensink Conceptualization; supervision; validation; writing - review and editing; J.J. Jeekel Conceptualization; supervision; validation; writing - review and editing; J.F. Lange Data curation; conceptualization; funding acquisition; supervision; writing - review and editing; E.J. Belt Conceptualization; funding acquisition; supervision; writing - review and editing.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Supplementary data

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