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ORIGINAL ARTICLES

Poly-ε-caprolactone scaffold for the reinforcement of stapled small intestinal anastomoses: a randomized experimental study

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Abstract

Background Anastomotic leakage is a severe complication in gastrointestinal surgery. Different methods have been evaluated for anastomotic reinforcement to prevent anastomotic leakage. The aim of this study was to investigate the effect of a poly-ε-caprolactone (PCL) scaffold incorporated in the staple-line, on the anastomotic strength and histological wound healing, of small intestinal anastomoses in piglets.

Method This randomized experimental trial included 17 piglets. In each piglet, three end-to-end anastomoses were performed in the small intestine with a circular stapler, i.e. one control and two interventional anastomoses. On postoperative day 5, the anastomoses were resected and subjected to tension stretch test and histological examination.

Results No anastomotic leakage occurred. In the interventional anastomoses, the mean value for maximal tensile strength was 15.7 N, which was significantly higher than control anastomoses 12.7 N ($p = 0.01$). No statistically significant differences were found between the two groups in the histopathological parameters.

Conclusion To conclude, this study has shown that the incorporation of a PCL scaffold in the staple-line was feasible and significantly increased the maximal tensile strength of small intestine anastomoses in piglets on postoperative day 5. The difference in histological parameters was not significantly distinct.

Keywords Poly-ε-caprolactone · Scaffold · Intestinal anastomosis · Reinforcement · Colorectal surgery

Introduction

Anastomotic leakage (AL) is a severe complication in gastrointestinal surgery and associated with increased risk of morbidity and mortality, higher local recurrence rate and lower 5-year survival in cancer patients [1, 2]. Despite improvements in perioperative treatment and technological advances in surgical procedures, the incidence of AL has remained unchanged [3, 4]. The aetiology of AL is multifactorial, but the most important factors are insufficient blood supply, anastomosis under tension, infection and inflammation causing impaired wound healing [5, 6]. A strategy to reduce the incidence of AL is reinforcement of the anastomotic line. Numerous attempts have been made to strengthen gastrointestinal anastomoses and reduce AL. Several materials have been developed for staple-line reinforcement, e.g. sealant materials or the incorporation of biological or synthetic materials into the staple-line [7, 8].

Synthetic scaffolds, made of biodegradable polymeric materials, provide the structural support for cell attachment and subsequent tissue ingrowth, which may facilitate and promote anastomotic healing [9]. Poly-ε-caprolactone (PCL) possesses mechanical strength and a slow degradation profile, which makes it able to maintain long-term resistance and patency, even in the harsh gastrointestinal environment [10]. Furthermore, PCL scaffolds are inexpensive and easy to manufacture.

To our knowledge, no previous studies have been performed on the incorporation of a PCL scaffold in circular stapled intestinal anastomoses.

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The aim of this study was to investigate the effect of a poly-ε-caprolactone scaffold incorporated in the staple-line, on the anastomotic strength and histological wound healing, of small intestinal anastomoses in piglets.

Materials and methods

Ethical considerations

The present study followed the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines and was approved by the Danish Animal Experiments Inspectorate.

Animals

Seventeen weaned female piglets, with a mean weight of 22.7 kg (range 19–31.2), were included in the study. The animals were acclimatised for at least 1 week prior to the trial and housed in a conventional large animal housing facility at a constant temperature of 20–21 °C. The piglets had access to food twice a day (0.9 kg/20 kg body weight) and free access to water.

A medical record for each animal, including all observations, administered medicine, anaesthesia, and pre- and postoperative monitoring was obtained to ensure that no animals would suffer during the trial period. One pig was excluded from final analyses due to euthanasia before study completion because of an ileus due to stenosis, leaving a total sample of 16 piglets. The stenosis was a result of a malfunctioning stapler, which jammed after firing; in the attempt to release the stapler, transmural lesions occurred around the staples; the anastomosis was then oversewn, which led to the obstruction we found in the autopsy.

Study design

Three stapled anastomoses were performed on the small intestine of each piglet, 1 control and 2 interventional anastomoses, leaving 16 interventional anastomoses for the maximal tensile strength test and another16 interventional anastomoses for the histological examination. The 16 control anastomoses underwent both the maximal tensile strength test and the histological examination. The predefined location of each anastomosis was randomised and allocated to a position at 160, 180 or 200 cm proximally from the ileocecal ligament, in order to prevent the location of the anastomosis as a confounder. Randomization was performed using Research Randomizer® 4.0 and carried out in permuted blocks of 3 with each block representing one anastomosis.

Scaffold material

The scaffolds were made from PCL with a molecular weight of 80 kDa (Sigma-Aldrich, Denmark).

The novel design of the scaffolds takes into account the existing working principle of the circular stapler: Endoscopic Curved Intraluminal Stapler 21 mm, Ethicon Endo-Surgery GmbH, Germany.

Consequently, the scaffold was shaped as an undulating ring with a centring loop and an outer diameter of 22.7 mm shaped to match the placement of the staples in the stapler cartridge (Fig. 1a). Upon firing the stapler, the inner centring loops were cut from the outer loops by the stapler trocar. The centring loop is thus removed from the anastomosis along with stapler anvil. The outer undulating loop, which now is much less restrained, was incorporated into the anastomosis. The undulations were shaped and spaced in a manner so that each staple could only clamp down on one section of a bend – thereby ensuring reinforcement but not constriction of the anastomosis. Again, the low flexural stiffness of the PCL polymer allows for ample flexibility of the scaffold. It is important to note that the toughness of PCL allows the centring ring to be smoothly cut without generating fracture fragments, which could otherwise trigger inflammation

The total height of the incorporated scaffold is 0.40 mm with a strand width of 0.25 mm. The scaffolds were designed in Autodesk Inventor® and fabricated with the FDM method using a 3D printer (nScrypt 3D300TE 3D printer, nScrypt Inc., USA). The design process omitted design input from Finite Element Analysis with higher priority put on tactile handling, integration with the stapling sequence design simplicity and printability on an FDM printer.

Prior to implantation, the scaffolds were sterilised in 10% hydrogen peroxide for 30 minutes and washed in sterile water. Alkaline hydrolysis of the PCL surface was omitted to preserve the smoothness of the scaffold and improve biocompatibility [11].

Anaesthesia and medication

All animals received preanaesthetic sedation with a combination of midazolam (Midazolam Hameln®, Hameln Pharmaceuticals GmbH, Hameln, Germany) 0.2 mg/kg, medetomidine (Sedator®, Novartis, Copenhagen, Denmark) 0.04 mg/kg, buprenorphine (Temgesic®, Indivior, Berkshire, England) 0.03 mg/kg and atropine (ATROpin®, AMgros I/S, Copenhagen, Denmark) 0.05 mg/kg administered intramuscularly.

For the induction of anaesthesia, propofol (B. Braun Medical A/S, Copenhagen, Denmark) 5 mg/kg was administered through an ear vein, and the piglets were intubated with a cuffed tube, size 4.0. Anaesthesia was maintained with 2.1% isoflurane (Isofluran Baxter®, Baxter A/S, Hillerød,

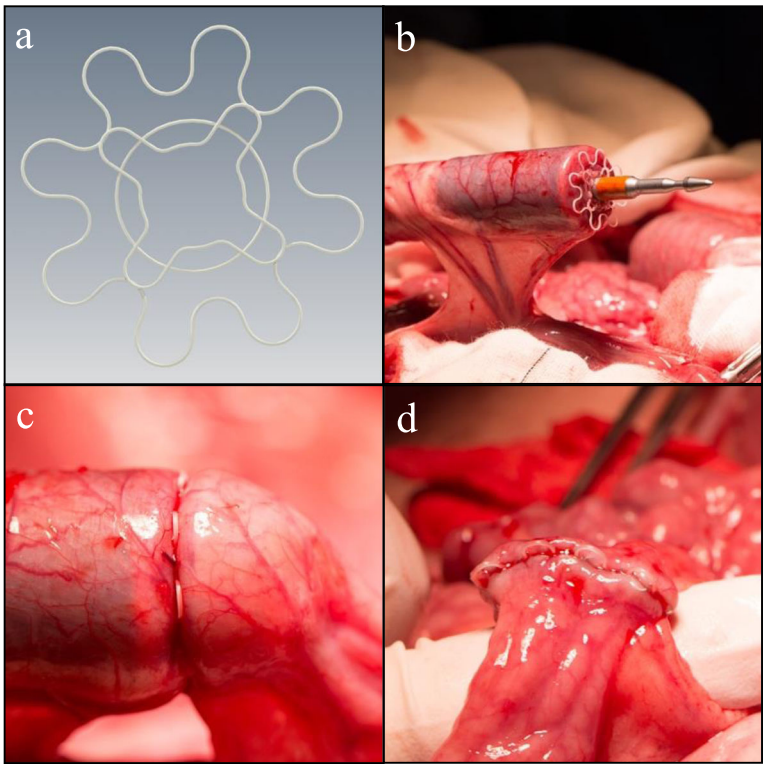

Fig. 1 **(a)** Circular distribution of flexible loops matching the placement of staples; **(b)** scaffold applied to the spear of the stapler cartridge; **(c)** incorporation of the PCL scaffold before firing; **(d)** complete anastomosis

Denmark), 1.8% in oxygen/air (1:1) on an MCM 801 ventilator (Dameca, Rødovre, Denmark). The animals were mechanically ventilated at a respiratory frequency of 16 breaths per minute with a tidal volume of 10 ml/kg. Blood pressure, electrocardiogram, heart rate and oxygen saturation were monitored continuously. The piglets received prophylactic antibiotics preoperatively with amoxicillin (Curamox Prolongatum Vet®. Boehringer Ingelheim Danmark A/S, Copenhagen, Denmark) 15 mg/kg and metronidazole (B. Braun AG, Melsungen, Germany) 20 mg/kg. Postoperatively, amoxicillin (Clamoxyl®, Zoetis, Helsinki, Finland) 30 mg/kg was added to the food once daily until study completion. Postoperative analgesia comprised of a fentanyl transdermal patch (Matrifen®, Takeda Pharma, Taastrup, Denmark) 50 μg per hour, and paracetamol (Pracetam Vet®, Ceva Animal Health A/S, Vejle, Denmark) 30 mg/kg were added to the food once daily.

Surgical procedure

The small intestine was exposed through a 10-cm lower midline laparotomy. Three transections of the ileum and adjacent mesentery were performed, at 160, 180 and 200 cm proximally from the ileocecal ligament. A seromuscular purse suture (monocryl® 4-0, Ethicon, Diegem, Belgium) was placed at both ends and tied over the anvil and cartridge, respectively, of the stapler (Endoscopic Curved Intraluminal Stapler 21 mm, Ethicon Endo-Surgery GmbH, Germany). Three stapled end-to-end anastomoses were made. The two distal anastomoses were performed by introducing the stapler through the proximal transection, which was the nearest. The stapler for the last anastomosis was introduced via an ileotomy 10 cm proximal to the anastomosis and was closed with a running seromuscular suture (Monocryl® 4-0, Ethicon, Diegem, Belgium). For the two interventional anastomoses, the PCL scaffold was mounted onto the spear of the stapler before closing and firing the stapler (Fig. 1b). The integrity of the resected tissue donuts was controlled.

The abdominal fascia was closed with a running suture (PDS*II® 0, Ethicon, Diegem, Belgium). The skin was closed intracutaneously with a running suture (Monocryl® 3-0, Ethicon, Diegem, Belgium) and sealed with a liquid bandage (Wound Plast®, KRUUSE, Langeskov, Denmark).

Relaparotomy

On postoperative day 5, the piglets were anaesthetised as previously described, and a relaparotomy was performed. Pathological observations were noted, and care was taken not to detach adhesions from the anastomoses. The anastomoses were examined for macroscopical abnormalities including abscess, leakage, pseudo-diverticulosis and signs of ileus or stenosis. The external diameter was measured before resection, with a 15-cm sterile ruler (Securline®, Aspen Surgical, Worcestershire, UK), on anastomotic level, 5 cm proximal and distal to the anastomotic site. The anastomoses were resected

with a 5-cm margin proximally and distally and subjected to maximal tensile strength test (MATS).

Upon study completion, the piglets were euthanised with pentobarbital (Euthanimal, ScanVet®, Animal Health A/S, Fredensborg, Denmark) 120 mg/kg administered through the ear vein.

Anastomotic strength test

The strength of the anastomoses was assessed using the maximal tensile strength test [12]. The resected intestinal segments, including the anastomoses, were mounted in the testing machine (LF Plus; Lloyds Instruments, Fareham, UK) equipped with an XLC 100 N loadcell (Lloyds Instruments, Fareham, UK). In order to prevent cold ischemia as a confounder, the MATS test was evaluated exactly 5 min after resection. With a distance of 60 mm between the clamps, the anastomotic segments were stretched at a constant deformation rate of 15 mm/min. The applied force was measured at two points:

- When a tear became visible in the serosa (MATS-1).
- When a transmural rupture appeared (MATS-2). MATS-2 is equivalent to the maximal tensile strength also known as breaking strength. The ultimate load was confirmed by a simultaneous drop in the load-strain curve calculated by the software NEXYGEN Plus® (version 3.0; Lillerød, Denmark).

Finally, it was noted whether the rupture was located within or outside the anastomosis. The manufacturer calibrated the equipment before initiating the trial.

Histological analysis

Tissue samples were fixed in a 10% formaldehyde solution for 5 days. In the preparation for histological analysis, staples and residues of the PCL scaffold were removed, and the samples were subsequently embedded in paraffin. The samples were then sliced, 3 μm thick, and stained with haematoxylin and eosin (HE), alpha smooth muscle actin (α-SMA), desmin and picrosirius red. HE was used to identify epithelial coverage and to identify an immune response represented by macrophages and foreign body giant cells (FBGCs). α-SMA and desmin were used to identify the growth of smooth muscle cells and fibroblast. Picrosirius red was used to estimate the amount of collagen. All tissue samples were examined under a light microscope at 10× to 400× magnification. Quantification of tissue healing was estimated by visual evaluation by an independent pathologist, blinded to the randomisation.

Histologic parameters were graded 0–3 according to the Verhofstad Score [13], evaluating necrosis, the accumulation of polymorphonuclear cells, lymphocytes and macrophages, the degree of oedema, the state of the epithelial layer and the bridging of the submucosal muscular layer. Furthermore, amount of collagen formation and fibroblasts at the anastomotic line was estimated as decreased deposition, 0; normal deposition, 1; and increased deposition, 2.

Three tissue samples did not contain an anastomotic site and could not be evaluated, leading to the exclusion of three piglets from the analysis.

Statistical analysis

Data are presented as mean (±SD) unless indicated otherwise. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using Stata/IC (version 14; Texas, USA).

Prior to the study, a power calculation was performed. An increase in anastomotic strength of at least 20% was considered clinically relevant by the authors. A standard deviation of 2.4, a significance level of 0.05 and a power of 80% required 12 piglets. With an expected mortality of 20%, a total of at least 15 piglets were required in the study. Two additional piglets were included from a successful pilot study, with the exact same design and set-up. One piglet died before study completion; hence a total of 16 piglets were included in the final statistical analysis.

MATS and external diameter were compared using paired Student's t-test. Each piglet served as its own control. Histological parameters were compared using the Wilcoxon signed-rank test.

Results

Anastomotic tensile strength test

In the interventional anastomoses, the mean value of MATS-2 was 15.7 N (± 2.8 N) and 12.7 N (± 4.1 N) in the control anastomoses ($p = 0.01$) (Fig. 2). No statistically significant difference was found in MATS-1 values (Table 1). In 6 out of 32 anastomoses (18.7%), rupture was extra-anastomotic, equally divided between the interventional and control anastomoses. The six extra-anastomotic ruptures were observed in five piglets. By excluding these piglets, the MATS-2 value in the interventional anastomoses was 15.1 N (± 3.3 N) and that of control anastomoses was 11.8 N (± 4.3 N) ($p = 0.03$), corresponding to an increase in anastomotic strength of 22.1%.

Histological findings

No statistically significant differences were found between the interventional and control anastomoses for any of the

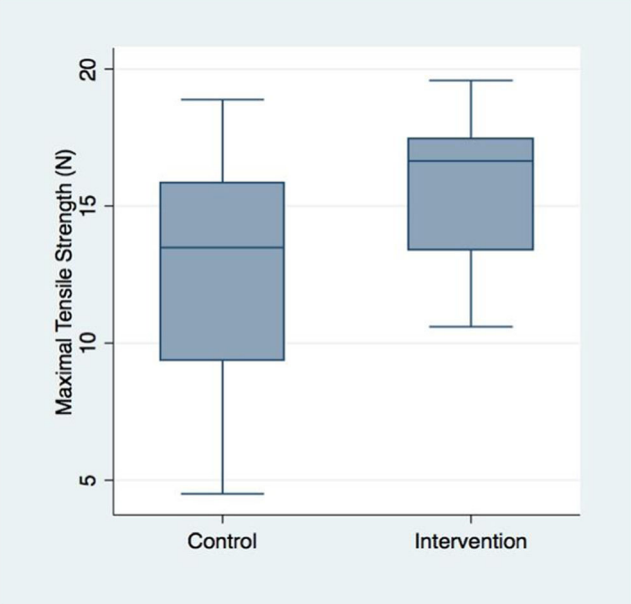

Fig. 2 Box and whisker plot

parameters included in the Verhofstad Score, the total Verhofstad Score or the content of fibroblasts and collagen (Table 1).

Macroscopic findings

A small, sealed leakage from the handsewn ileostomy was found in one piglet. No intraabdominal abscesses, fistulas or anastomotic leakages were observed. Only filmy adhesions were observed. The measurement of the external diameter proximal and distal and at the anastomosis was similar (Table 1).

Discussion

The present study shows that incorporation of a PCL scaffold in stapled small intestine anastomoses in piglets significantly increased the maximal tensile strength (MATS-2) on postoperative day 5. Moreover, incorporation of the scaffold did not significantly affect the histological parameters regarding wound healing, the adhesions grade or the external diameter at anastomotic level.

In a study [14] with a similar design, including 30 pigs, decellularised human cadaveric dermis (AlloDerm®, Biohorizons, Birmingham, USA) was used in end-to-end stapled rectal anastomoses. No significant differences in mechanical strength, measured by bursting pressure, were found between interventional (175.0 ± 52.0 mmHg) and control anastomoses (150.0 ± 45.8 mmHg) on postoperative day 5. Moreover, no improvement in the strength of the anastomoses was observed during different stages of healing (0, 3 and 30 days) [14].

Wrapping of stapled colonic end-to-end anastomoses with a mesh of small intestinal submucosa has been described in another study in pigs [15]. The mechanical strength was evaluated by measuring the bursting pressure on postoperative day 30. In both groups, all anastomoses remained sufficient and leakproof when applying an intraluminal pressure up to 200 mmHg. Moreover, no significant differences were found in the histological and macroscopic parameters. In a similar study [16] using small intestinal submucosa in two pigs with multiple small intestinal anastomoses, a significant difference was found in bursting pressure between interventional (83 ± 28 mmHg) and control (53 ± 17 mmHg) anastomoses, when bursting pressure was assessed immediately after making the anastomosis. Various forms of fibrinogen-thrombin patches have been developed. A single study found that TachoSil™ is feasible on colorectal anastomoses in humans [17], although a systematic review on animal studies [8], as well as a more recent study in rats, has not been able to find a significant effect on the incidence of anastomotic leakage [18].

To our knowledge, only two randomised studies on the reinforcement of stapled anastomoses in humans have been reported. In one study, including 258 patients, a synthetic copolymer (polyglycolicacid:trimethylene carbonate, Gore Seamguard®, Goremedicals, Arizona, USA) was incorporated in the staple-line of colorectal anastomoses [19]. No significant difference in the rate of AL was observed compared to the control group. Another study including 202 patients showed no difference in the rate of AL between the interventional and control groups [20], when a poly-ether-ester-urethane intraluminal sheath (C-Seal®, University Medical Centre Groningen, Groningen, Netherlands) was used in stapled colorectal anastomoses.

PCL scaffolds have been used successfully for biliary duct repair [21] and vascular anastomoses [22]. Thus, an experimental study in gastrointestinal anastomoses was considered reasonable. PCL possesses favourable characteristics like slow biodegradability, mild host reactions and tissue regeneration [10]. The degradation of PCL takes between 2 and 4 years, depending on the in vitro or in vivo environment. Several studies have shown a significant reduction in the degradation time when PCL is in the presence of microorganisms, acid and digestive enzymes [10, 23]. A risk may be that the degradation of PCL scaffolds may be too rapid and lead to formation of pseudo-diverticula, as reported in a study with the closure of an oesophageal defect with a PCL scaffold [24]. Biomaterials like lyophilised dura mater, polyethylene terephthalate or polytetrafluoroethylene incurred a long-term risk of stenosis in the repair of oesophageal defects in dogs[22], and small intestinal submucosa has shown a risk of long-term strictures on small intestine anastomoses in rabbits [25, 26]. No studies have reported a risk of long-term stricture

Table 1 Maximal tensile strength, macroscopic findings, results of the histological examination with the parameters (graded 0–3) included in the Verhofstad Score and the content of fibroblasts and collagen (graded 0–2) in the control and intervention anastomoses. Values are mean ± standard deviation (SD)

Parameters	Control anastomosis	Intervention anastomosis	*P* value
Maximal tensile strength (MATS)	(*n* = 16)	(*n* = 16)	
MATS-1	7.9 ± 3.8 N	8.5 ± 3.8 N	0.65
MATS-2	12.7 ± 4.1 N	15.7 ± 2.8 N	0.01
Macroscopic findings			
Diameter 5 cm proximally from anastomosis	2.8 ± 0.6 cm	2.9 ± 0.6 cm	0.33
Diameter at anastomotic line	2.8 ± 0.6 cm	2.9 ± 0.4 cm	0.46
Diameter 5 cm distally from anastomosis	2.8 ± 0.4 cm	2.9 ± 0.5 cm	0.35
Histological parameters (Verhofstad Score)	(*n* = 13)	(*n* = 13)	
Necrosis	0.54 ± 0.66	0.46 ± 0.66	0.93
Polymorphonuclear cells	0.92 ± 0.86	1.00 ± 0.91	0.65
Lymphocytes	0.38 ± 0.65	0.30 ± 0.48	0.56
Macrophages	0.00 ± 0.00	0.00 ± 0.00	.
Oedema	0.69 ± 0.75	0.53 ± 0.52	0.59
Mucosal epithelium	2.69 ± 0.85	2.61 ± 0.87	0.56
Submucosal muscular layer	0.92 ± 0.76	0.69 ± 0.48	0.37
Total score	6.15 ± 3.16	5.62 ± 2.60	0.50
Fibroblasts	1.23 ± 0.73	1.23 ± 0.73	0.63
Collagen	0.92 ± 0.76	0.92 ± 0.64	1

formation with PCL scaffolds, and no short-term stricture formation was observed in our study.

No consensus has been reached on the ideal postoperative day for investigating anastomotic strength [5]. Healing in gastrointestinal anastomoses begins with the inflammation phase on days 0–4, which is followed by the proliferation phase on days 5–14 and the remodelling phase starting on day 16 and continuing for up to 18 months [27]. We chose to examine anastomotic strength on postoperative day 5, at the transition between the inflammatory and proliferative phases, as it is considered the most critical time for AL, because collagen decomposition is superior to collagen synthesis [5]. In addition, anastomotic leakage typically becomes clinically apparent between the 5th and the 8th postoperative day [4].

Concerning the clinical applicability of our findings, we are aware of the fact that the reinforcement with a PCL scaffold is clinically most relevant in low-rectum anastomoses; however porcine large intestine presents an anatomical challenge due to the curled up structure, which favours the small intestine. Nevertheless, we were able to demonstrate the safe use of PCL scaffolds for anastomotic reinforcement in a large animal model.

From a clinical perspective, AL would be the most ideal outcome to evaluate, but this would demand a far larger population of animals. In experimental studies, surrogate measurements such as tensile strength and bursting pressure combined with macro- and microscopic findings are generally accepted to assess anastomotic strength and healing. MATS and bursting pressure are correlated and considered equivalent surrogate outcomes for anastomotic strength [12, 28].

In a recent study, bursting pressure was found to be less suitable after postoperative day 3 due to increased tendency to rupture outside the anastomotic line and high variability compared with MATS [29]. MATS reflects the deposition of new collagen in the anastomosis between days 3 and 7 and thus represents the physiological processes of wound repair [30].

MATS may underestimate the anastomotic strength when extra-anastomotic ruptures occur [12]. A second analysis was therefore performed, excluding five piglets with extra-anastomotic ruptures, leading to an additional increase in the MATS-2 score.

No significant differences were found in serosa ruptures (MATS-1). However transmural ruptures (MATS-2) may be more relevant as it inevitably will lead to AL.

No significant differences were found in the histological parameters. These results suggest only a mild host reaction to PCL, in accordance with other studies [10]. In addition, these findings suggest that adding the PCL scaffold does not significantly change the physiology of the healing process and that the anastomotic strengthening is primarily mechanical. Unorganised epithelial and smooth muscle cell ingrowth, together with the gradual degradation of the PCL scaffold, has previously been shown in a rabbit oesophagus study [24]. Due

to the short observation time in our study, it was not possible to assess tissue ingrowth in the scaffolds. The staples and PCL scaffold had to be removed before histological preparation, which may have distorted healing and led to random error results.

The short observation time and the use of MATS represent limitations of our study. No complications were found in relation to the use of PCL scaffolds, and all PCL scaffolds were intact at assessment. Future in vivo studies should have a longer observation period in order to investigate the safety and possible long-term complications.

To conclude, this study has shown that the incorporation of a PCL scaffold in the staple-line was feasible and significantly increased the maximal tensile strength of small intestine anastomoses in piglets on postoperative day 5. The difference in histological parameters was not significantly distinct.

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The data, methods used in the analysis and materials used to conduct the research will be made available to any researcher for the purposes of reproducing the results of replicating the procedure and can be accessed at https://www.dropbox.com/sh/yxtsd1vok0izn78/AADiu5bO8pimxYqTGK2Cn4P1a?dl = 0

Authors' contributions K.D. Larsen and M. Westerholt conceived and designed the study, collected the data, analysed and interpreted the data, drafted the manuscript and obtained funding. G. Madsen collected the data, provided critical revisions and approved the final version of the manuscript. D.Q.S. Le conceived and designed the study, provided critical revisions and approved the final version of the manuscript. N. Qvist and M.B. Ellebæk conceived and designed the study, provided critical revisions that are important for the intellectual content and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

This article does not contain any studies with human participants performed by any of the authors.

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