Efficacy of Biodegradable Polydioxanone and Polylactic Acid Braided Biodegradable Biliary Stents for the Management of Benign Biliary Strictures

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ABSTRACT

Background: *Benign biliary strictures (BBS) are widely treated by endoscopic procedures involving temporary stent placement. Occasionally, stents are required to be removed, making the treatment process very painful as well as expensive. Until now, no effective biodegradable biliary stents (BDBS) have been available for clinical applications. This study aims to investigate the safety and efficacy of biodegradable polydioxanone (PDO) and polylactic acid (PLA) braided BDBS both in vitro and in vivo.*

Methods: *Monofilaments of 3 different diameters, of PDO (0.30, 0.35, and 0.40 mm) and PLA (0.10, 0.15, and 0.20 mm) were braided to biliary stents and their mechanical properties were studied. The stents were placed in an ex vivo bile duct model perfused with porcine bile, taken out, and observed every week until they were completely degraded. After the bile duct stenosis model was established successfully in piglet, stents with appropriate mechanical properties were further examined under endoscopy; the changes in hematology, patency time, and pathology of the stents were observed for 8 months.*

Results: *A total of 10 pigs were included (2 groups; 5 PDO, 5 PLA) in the study. The patency time of the stents in the PLA group was significantly longer than that in the PDO group (25.7 ± 5.6 weeks vs 11.3 ± 3.4 weeks, respectively).*

Conclusion: *Our results project that biodegradable PLA and PDO braided biliary stents could be a better choice to treat BBS, with different rates of degradation.*

Keywords: *Polydioxanone, polylactic acid, biliary stents, benign biliary stricture, ERCP*

INTRODUCTION

Benign biliary strictures (BBS) can be attributed to a variety of etiologies, most commonly postoperative injury (post-cholecystectomy, post-liver transplantation, etc.) and chronic pancreatitis,[1,2] resulting in local inflammation or ischemia with secondary fibrosis and scarring.[3] Clinical presentation depends on the severity of the biliary obstruction and varies from subclinical mild hepatic dysfunction to a complete cholestatic syndrome with or without cholangitis.[4] Over the past 2 decades, BBS management has changed from surgical to endoscopic treatment.[5] Recently, endoscopic retrograde cholangiopancreatography (ERCP) has been established as the mainstay for a definite diagnosis and relief of biliary obstruction due to its efficacy, safety, and minimally invasive nature.[1,4]

ERCP involves the endoscopic placement of stents to manage BBS.[6] Multiple plastic stents (MPS) and self-expandable metal stents (SEMS) are usually employed to treat BBS.[7] Plastic biliary stents or MPS are considered the stents of choice for most benign strictures, possibly with endoscopic dilatation; however, patency time is relatively short, requiring multiple ERCPs for stent exchange.[8,9] Although different types of SEMS are also increasingly used for the treatment of BBS,[10,11] the metallic stent-related complications, such as stent migration or embedment caused by reactive tissue hyperplasia, pose a significant obstacle toward successful treatment of BBS.[12] This is the reason why MPS are endorsed by the European Society of Gastrointestinal Endoscopy (ESGE) as a treatment of choice.[7]

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Biodegradable biliary stents (BDBS) can be another option to treat BBS because they do not require removal and have better biocompatibility, thereby avoiding multiple ERCPs, long-term severe complications, and additional surgeries.[13-16] Previously, the use of BDBS was found to show a better healing response than with SEMS, with a rapid reversal in local protein expression levels for annexin-A4, galectin-2, transgelin, and MLP-6, and without hyperplasia and hypersensitivity reactions.[17,18] In the continuous development of research toward biodegradable polymer materials, aliphatic polyesters play an important role in the medical field due to their unique biodegradability, biocompatibility, and absorbability. Polymer-based biodegradable stents can be degraded through a hydrolytic reaction and may attenuate local drug delivery. The most frequently used biodegradable polymers for stents include poly-L-lactic acid (PLA), polycaprolactone (PCL), polyglycolide (PLG), and polydioxanone (PDO).[13,16,19-23] Compared to other materials, PDO and PLA possess special advantages such as better flexibility, appropriate absorption rate, proper biocompatibility, and minimal inflammatory response.[24,25]

The use of PDO and PLA biodegradable stents has been applied in several experimental and clinical studies to treat carotid, esophageal, or colorectal strictures,[26-30] but relatively few studies have been reported for the management of BBS.[17,31,32] The main objective of this study is to develop PDO- and PLA-based biodegradable stents using knitting technology and to investigate their mechanical properties and degradation mechanism, following the validation of the expansion effect and biosecurity through animal experiments.

MATERIALS AND METHODS

Preparation of PDO and PLA Biliary Stents

We used PDO and PLA monofilaments (with diameters of 0.30, 0.35, and 0.40 mm vs 0.10, 0.15, and 0.20 mm, Shanghai Tianqing Medical Industry Co. Ltd, Shanghai, China) which were twisted along a helical trajectory around a cylindrical mold with dowels on both ends and woven 1/1 up–down alternately, and finally knitted into a tubular stent with a lozenge net-like structure after thermoforming (PDO, 75-80°C, 15 min; PLA, 105°C, 5 min) and demolding. The stent system consisted of 2 parts: a degradable braided stent and a braided stent push system. The stent consisted of a single wire woven into a tubular mesh shape, and when expanded, the stent was 10 mm in diameter and 45 mm in length (Figure 1A and B). The push system was mainly composed of coaxial pipe fittings. The inner pipe

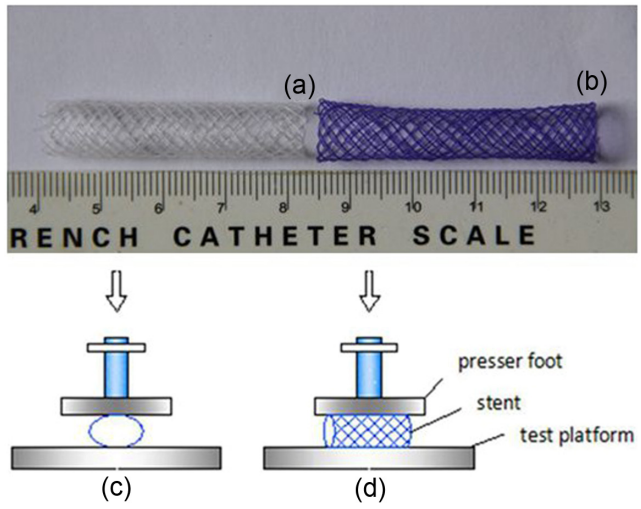

Figure 1. PDO and PLA braided biliary duct stent and principle of radial compression testing (A) PDO, (B) PLA, (C) and (D) radial compressor.

cavity of the coaxial system could pass a guidewire with the specification of 0.89 mm, and the working length of the inserter was 22 cm. The stent could be inserted through the duodenoscopic working channel (the minimum diameter of the channel was 3.7 mm) for treatment or diagnosis.

Stent Test in an Ex Vivo Bile Duct Model Perfused with Porcine Bile

The PDO and PLA groups were divided into 3 subgroups (with monofilament diameters of 0.30, 0.35, and 0.40 mm vs 0.10, 0.15, and 0.20 mm, respectively). Each subgroup included 10 sample stents for testing. All sample stents were placed into the ex vivo bile duct model perfused with porcine bile, developed as previously described.[33] The porcine bile was sterilized with ultraviolet light in a liquid box. Then the bile flowed through the valve and entered the sample experimental area for the bile perfusion test. The stents were taken out and observed every week until they were completely degraded.

Establishment of the Porcine Biliary Stenosis Model and the Stent Placement

All experimental procedures were approved by the Animal Care and Use Committee of Shanghai General Hospital affiliated to Shanghai JiaoTong University, China. A total of 15 pigs aged 3-4 months and weighing 18.7-26.3 kg were included in the study. The pigs were randomly divided into 2 stent groups: 8 pigs for PDO stents and 7 pigs for PLA stents (with monofilament diameters of 0.40 mm vs 0.15 mm, respectively). The porcine biliary

stenosis model was established as previously described.[34] Each stent braided into a lead wire (which had no surface tension) as a marker that could be observed under x-ray was placed into the porcine biliary stenosis model under ERCP.

Characterization and Mechanical Property Changes in the Two Groups

The appearance and color of the stents and the numbers of longitudinal and latitudinal filament breakages of each stent's diamond mesh were observed every week. The changes of single filaments were observed with magnification of 2000, 10000, and 50000 times by electron microscopy (SU8010, high-resolution cold-field emission scanning electron microscope, Hitachi, Japan). The stents were washed (3 times with normal saline solution), dried at 37°C, and measured for quality. Each subgroup was weighed, and the average weight for each group was obtained. The time-varying curve of the quality of each subgroup was then analyzed. The YG061 radial compressor (invented by Dong Hua University, Shanghai, China) was used to evaluate the radial support force of the bile duct stent. The stents were placed between the upper and lower planes. The average support force of each subgroup was obtained, and the time-varying curve of the support force for each subgroup of stents was also analyzed.

General Conditions, Serum Laboratory Samples, and X-ray Examination

After the endoscope guided-stent placement, every weekend (from month 1) and each day of the first and second weeks after the model operation to month 8, the appetite, color of stool and urine, and spirit of the pigs were observed to check for any signs of depression and agitation. Furthermore, the color of the sclera and the amount of activity were also observed. All pigs resumed their usual diet after 24 hours of stent placement. Serum samples were collected at week 0 (pre-operation), 1, 2, and 4, and at the end of weeks 8, 16, 24, and 32. The levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transpeptidase, amylase, creatinine, and leukocytes were determined. At the end of month 0 (before) and the end of weeks 8, 16, 24, and 32 after stent placement, the piglets were observed for the stent position through x-ray examination under anesthesia. The general condition of the piglets was observed as normal or abnormal, total bilirubin levels were continuously monitored, and any deformation or disorder in the lead wire structure was also observed by x-ray. Additional hematological and x-ray examinations were conducted fortnightly.

Execution of Pigs and Specimen Collection

When the total bilirubin levels of the piglets were more than or equal to 171.2 μmol/L, the piglets were sacrificed, and the pathological changes of the stent and common bile duct were observed; the final follow-up time was 32 weeks, and all piglets were sacrificed in 32 weeks.

Histological Analysis

Hematoxylin and eosin (HE) staining was performed[35] to observe any local tissue inflammatory response against stent placement. For this purpose, stents were obtained from the sacrificed animals, embedded in poly (methyl methacrylate), and sectioned and stained for observation under the microscope.

Evaluation of Stent Degradation Time

It is difficult to evaluate a completely degraded stent. Thus, a new evaluation system was established, as follows: (1) Timepoint of stent degraded in vitro: when a single filament was broken, the stent was in the critical degradation timepoint, from loss of molecular weight to structural collapse. When more than 25% of the longitudinal and latitudinal filaments were broken down, it was considered as partial degradation; and when more than 50% of the filaments were broken down, this was considered as complete degradation. The last point was considered as the final degradation timepoint. (2) The timepoint of stent degradation in piglets: under x-ray observation, when the lead wire structure was normal, it meant that the stent had been incompletely degraded; when it showed a partial structural deformation, the stent was only in loss of molecular weight. The point at which complete structural deformation or chaotic stent was observed was considered the critical degradation timepoint; when the stent had been completely degraded, it was considered the final degradation timepoint. Cases in which the stent disappeared suddenly without any morphological change or in which the pig died due to the operation, postoperative infection, or anesthesia, were excluded as a "0" group.

Statistical Analyses

All statistical analyses were performed using SPSS version 13.0 for Windows (SAS Institute, Cary, NC).[36] Data were presented as the mean and standard deviation. Student's *t*-tests were used to compare continuous quantitative data of the decrease in weight of stents before and after the experiment. A 2-tailed Wilcoxon signed-rank test was used to compare discrete variables. Because multiple

comparisons were performed on some data, it is noted wherever any false positive with statistical significance of >0.05 was observed in some methods, it was removed by using the Bonferroni correction method. *P* values < .05 were considered statistically significant.

RESULTS

Comparison of Mechanical Properties of PDO and PLA Stents

The radial support forces of the PDO and PLA stents were augmented with the increase of the monofilament diameter of the subgroups. The results revealed that the PDO and PLA material is flexible, easy to bend, suitable for a braided structure conducive to compression. The diameters of PLA monofilament (with same elastic recovery rate and weight) were smaller than that of PDO in gaining the same levels of radial support force. (Table 1).

Changes in Quality and Radial Support Forces

The qualities and the radial support forces of the 3 PDO and PLA subgroups decreased gradually with time and varied slightly (before week 11 vs week 23), which might only show a loss of molecular weight. The curves were relatively smooth, and the qualities and forces decreased very slowly. However, these were decreased obviously (after week 11 vs week 23), which could be identified as the critical collapse point of the stents (Figure 2).

Appearance and Microscopic Changes

Gross Observation:

During the establishment of the ex vivo biliary model, the color of the PDO stents did not change significantly by the end of weeks 1 and 2. Later on, stent color began to fade in weeks 3 and 4, became pale in weeks 5 and 6, and colorless in week 8, indicating that the color was completely degraded. The monofilaments broke down in week 11, about 25% of the latitude or longitude of the stents had broken down at weeks 12-13, and complete degradation occurred in week 15. The color of the PLA stents did not change significantly before week 23. The monofilaments broke down in week 25, about 25% of the latitude or longitude of the stents had broken down at weeks 28-30, and a complete degradation was observed in weeks 32-33 (Figure 3B and C).

Observations Under Fluoroscopy Electron Microscopy:

Monofilament performance differed, as shown by electron microscopy (a magnification of 2000, 10000, and 50000 times was used). For PDO stents: the monofilaments were dense and showed no signs of degradation in week 1. However, in week 11, stents had obvious cracks, breakage, and exfoliation (Figure 4). For PLA stents: obvious cracks, breakage, and exfoliation were observed in week 23.

Follow-up, Changes in Laboratory Parameters, and X-ray Examination After Stent Placement

X-ray angiography performed after modeling shows successful stent placement in piglets (Figure 5). Mild to moderately abnormal levels (<1.5-3.5 times the normal value) of serum ALT (58-83 IU/L), AST (54-92 IU/L), and amylase (98-216 IU/L) were observed. Mild abnormal levels (<1.5 times the normal value) for leukocyte counts while establishing the porcine biliary stenosis model were also observed. The levels for these enzymes returned to normal soon after stent placement. These changes were thought to be related to surgery or biliary stenosis. Five pigs were excluded due to surgery-related biliary obstruction (n = 1), deep anesthesia (n = 1; one in the PDO group at the time of modeling), and stent migration (n = 3; one in the PDO group at week 8, the other 2 in the PLA group at weeks 8 and 16). The remaining 10 pigs were distributed among the groups as follows: 5 in the PDO group and 5 in the PLA group. Moreover, at the end of follow-up, piglets' final weight was found to have increased, from 18.7-26.2 kg to 40.9-54.3 kg.

Table 1. Comparison of Mechanical Properties of PDO and PLA Stents ($\bar{X} \pm s$)

Group	Monofilament Diameter (mm)	Radial Support Force (cN)	Elastic Recovery Rate (%)	Weight (mg)
PDO	0.28±0.02	89.4±8.3	83.8±5.2	139.3±15.2
	0.36±0.01	120.6±10.2	91.6±3.3	173.6±19.8
	0.41±0.02	145.7±13.3	92.1±2.4	201.7±23.4
PLA	0.11±0.01	118.7±17.4	90.0±3.9	52.7±11.6
	0.15±0.01	186.3±25.5	94.4±1.8	71.9±13.0
	0.19±0.02	246.7±31.9	96.2±1.3	92.3±17.2

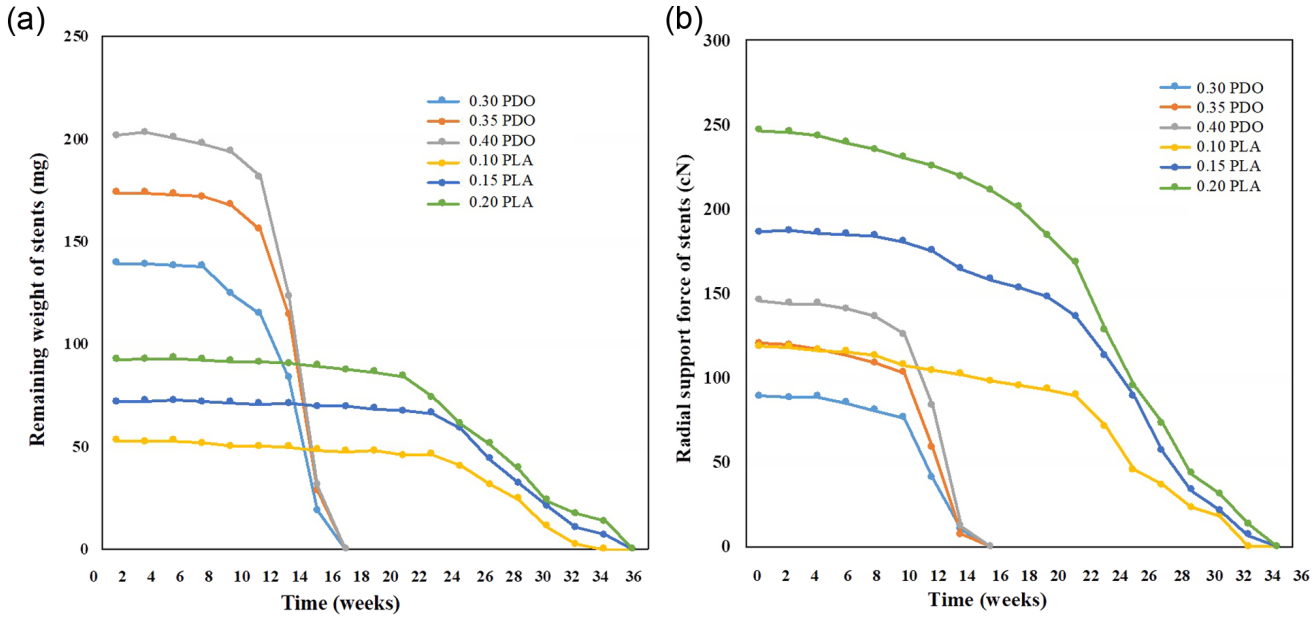

Figure 2. Changes of quality and radial support forces (± s, mg; cN). (A) Remaining weight of stents (mg) over the period (36 weeks). (B) Radial support force of stents (cN) over the period (36 weeks).

Patency Time and Bile Mud Analysis

The stent degradation process was also observed using x-ray examination either as normal structure, partial structural deformation, complete structural deformation, or chaotic structure (Figure 6). The patency time of the PLA stent group was found significantly longer than that of the PDO stent group (25.7 ± 5.6 weeks vs 11.3 weeks ± 3.4 (P = .01), respectively) in the pigs.

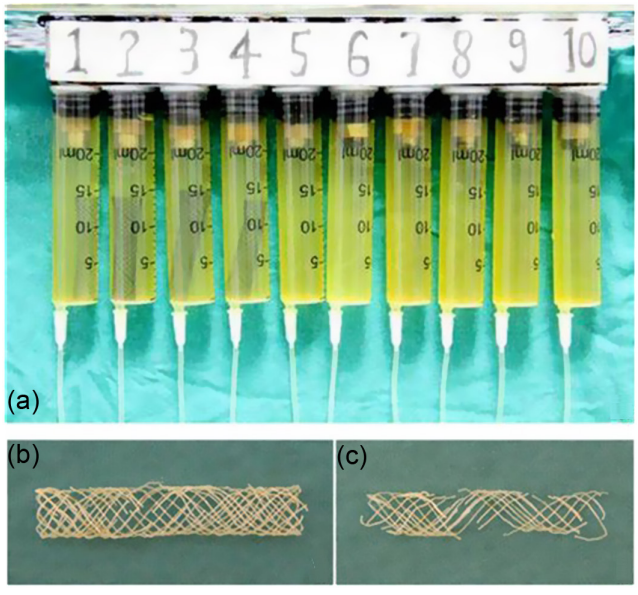

Figure 3. Bile duct stents in the in vitro biliary perfusion system and stents' gross degradation changes (A) stents in experiment; (B) partially degraded; (C) completely degraded.

Gross and Microscopic Findings

Gross Observation: There was no obvious adhesion or exudation around the bile duct anastomosis. The bile ducts dilated well, with diameters of 1.0-1.8 cm. The inner wall of the duct was smooth, there was no adhered sediment, the lumen cavity was dilated, and the inner wall was yellow, with high wall tension (Figure 7A and B). HE staining showed no obvious infiltration of inflammatory cells, ulceration, or necrosis under the mucosae (Figure 7C and D). The mucosal layer near the opening of the common bile duct did not show necrosis, exudation, ulcer formation, wall thickening, etc. There was no exudation or necrosis on the surface or granulation tissue formation.

Additionally, there was no obvious infiltration of neutrophils, monocytes, lymphocytes, or plasma cells in the whole layer, nor was there any proliferation of fibers or nerve fibers. The vascular endothelium of the bile duct was good, and there was no proliferation or thickening of the vascular wall or thrombosis in the blood vessel, which indicates that the litholytic biliary stent caused no obvious pathological damage to the bile duct (Figure 7C and D).

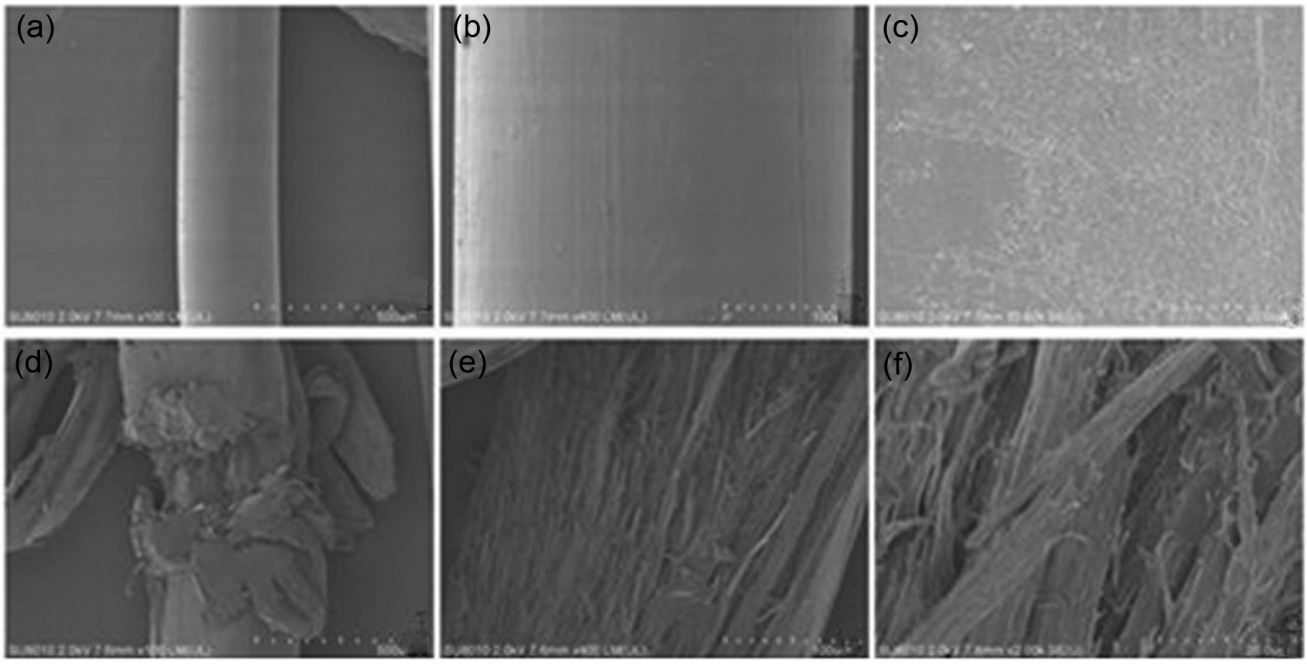

Figure 4. Changes observed by electron microscopy at PDO. Observation at week 1 (A) 2000 times magnification; (B) 10 000 times magnification; (C) 50 000 times magnification. Observation at week 1 week 11 (D) 2000 times magnification; (E) 10 000 times magnification; (F) 50 000 times magnification).

DISCUSSION

Endoscopic therapy provides a minimally invasive but safe and reliable first-line management option for most BBS. Currently, the sequential placement of multiple plastic biliary stents represents the preferred treatment approach. However, this setting's major limitation is clogging of the plastic stent, which requires patients to undergo multiple ERCP procedures for stent exchange.

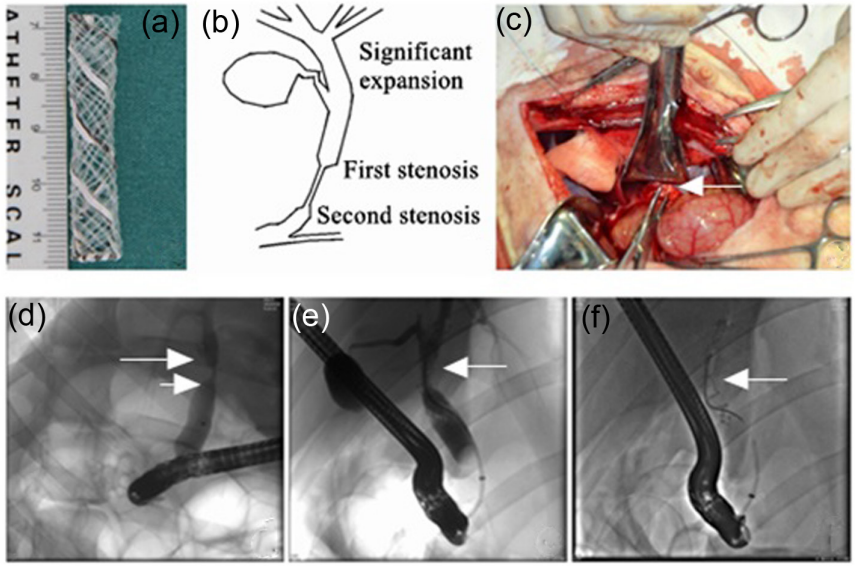

Figure 5. The modeling process of bile duct double stenosis model and ERCP (A) a stent braided into lead wires as a marker; (B) diagram of the modeling process; (C) operation of bile duct double stenosis model in pig; (D) x-ray angiography after successful modeling, short arrow shows the lower stenosis, long arrow shows the upper one; (E) stent placement process in piglet, arrow shows the lead mark; and (F) x-ray examination after stent placement, arrow shows stent lead mark.

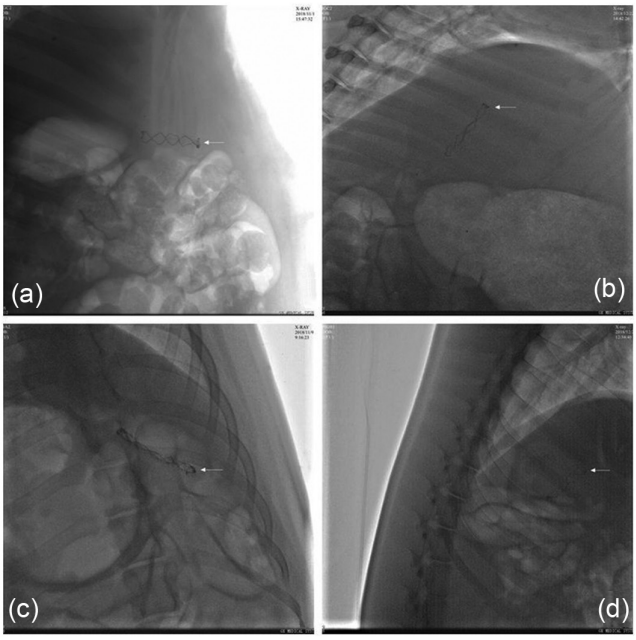

Figure 6. The stent degradation process under x-ray examination ((arrow shows the lead mark) (A) normal structure; (B) partial structural deformation; (C) complete structural deformation; (D) chaotic structure.

Self-expanding metal stents (SEMs) have the advantage of a larger expansion diameter, resulting in a longer duration of patency.[37,38] Uncovered SEMs are not recommended for BBS because of problems with stent occlusion as well as irretrievable embedment caused by the ingrowth of epithelial hyperplasia.[39] Several studies of fully covered SEMs have reported favorable clinical success rates (ranging from 80% to 90%) as well as low recurrence rates.[40,41] However, a significant drawback is the high rate of stent migration, ranging from 20% to 40%.[13,42] Partially-covered SEMs have uncovered proximal and distal ends as anti-migratory modifications, but the potential for tissue hyperplasia involving the bare ends still exists, making stent removal difficult.[13,39,41-43] To date, none of these stents has succeeded in showing superiority for the treatment of BBS. Biodegradable stents may offer advantages for the treatment of BBSs, including enough stent diameter, decreased proliferative changes, and elimination of the need for frequent ERCPs for stent removal.[40,42,43]

The BDBS that were initially developed were unsuccessful due to the low patency and low radial expansion forces.[44,45] To avoid these problems, PDO- and PLA-based biodegradable stents, developed with high patency and mechanical strength, could be considered as a reasonable treatment option for BBS.[20-23] Suitable degradation characteristics are vital for biodegradable stents to achieve the perfect therapeutic effect. Thus, we have used PDO and PLA to produce stents, with biodegradable aliphatic polyesters with good thermoplastic properties.[46] PDO and PLA stand out because their monofilament fibers have the high tensile and mechanical strength to maintain their

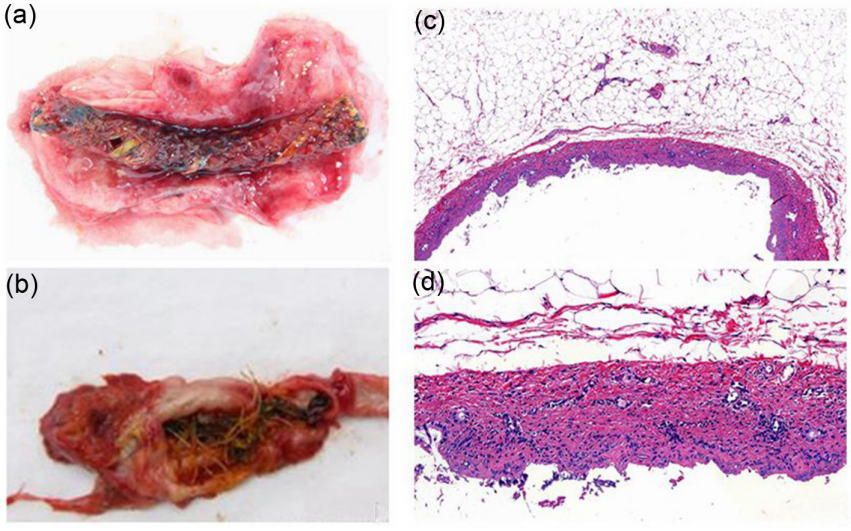

Figure 7. Macroscopic observation and HE staining (A) The PDO stent and the mark of lead line were intact in gross observation on weekend 8 after implantation; (B) The PDO stent was completely degraded, and the residual lead wire was disorderly on weekend 16 after implantation; (C) and (D) microscopic appearance of the stented part of the common bile duct showing smooth mucosa with mild inflammatory cell infiltration. Hematoxylin and eosin stain; × 50 (C), × 200 (D).

integrity for a longer time.[47] Moreover, PDO or PLA monofilament fibers show an excellent knitting feature in the manufacturing process of the stents and other biomaterials.[48] All these characteristics make it possible for PDO and PLA stents to dilate the biliary stricture powerfully and persistently. In this study, the complete degradation time of the PDO and PLA biliary stents was 13.5 ± 2.0 and 31.4 ± 4.6 weeks, respectively, and further analyses show that the degradation process of PDO and PLA stents could be divided into 2 stages: (1) Recessive degradation stage: the PDO or PLA stent retains its structural shape within 11 (vs 23) weeks, both material degradation and weight loss are slow without obvious gross change; during this stage, the weight of the monofilaments lightened at the molecular level. (2) dominant degradation stage: 11 (vs 23) weeks later, the PDO or PLA stent begins to have a visible deformation, both material degradation and weight loss occur faster, and the overall stent structure gradually disintegrates into pieces.

Previously, in porcine carotid arteries, PDO- and PLA-based biodegradable stents showed partial and minimal absorption in 13 weeks, respectively.[49] The stents' degradation speed or behaviors are inconsistent,[19,25,39] due to the markedly varied microenvironment of the bile duct from the gastrointestinal tract, urinary tract, or other hollow body organs or intraluminal space. In the in vivo studies, the stent begins to degrade from 8 weeks, earlier than in vitro, supposedly due to the complexity of the bile duct's actual physical environment. The biochemical action of water, digestive enzymes, and the other components of bile flow, and the contraction and relaxation of the sphincter make it degrade faster than under the conditions in vitro.[50]

The mechanical properties of BDBS materials may also have an important impact on the therapeutic effect. The stent should mainly provide mechanical support, which can dilate bile ducts and improve biliary drainage. Thus, the stent needs proper radial support force against the compression and movement of the bile duct during the degradation process. In in vitro studies, PDO or PLA stents maintained their radial support force for at least 11 weeks (vs 25 weeks) (>103cN), which is comparable to commercially available metallic mesh stents (Figure 2). After 11 weeks (vs 25 weeks), at the dominant degradation stage, the expansibility of the stent dropped significantly, with the degrading fragments eventually excreting into the digestive tract with bile flow. During a follow-up of in vivo studies, imaging examination showed that the PDO stents had retained their tube-shaped configuration after 8 weeks (or PLA, 16 weeks). It can be proposed that the radial support force of this type of stent should be adequate for the treatment of BBS. In vivo analysis has shown the adaptability of all the animals to stent placement, and there were no signs of cholangitis or pancreatitis in the clinical observation (Figure 7). At necropsy, the stent didn't cause a severe inflammatory reaction or epithelial hyperplasia during its effective degradation phase, which speaks for our stent's safety and biocompatibility. Previous studies with PDO-based biliary stent placement have also shown management of intrahepatic biliary strictures without any minor or major complications, while stents were completely degraded within 6 months.[31,32]

Our study shows one of the preliminary reports on BDBS. However, we did not include the control group comparisons, that is, with a plastic stent group and a metal stent group, which can be considered a limitation. This study still features and proposes PLA and PDO braided biliary stents as a better choice for BBS treatment with the least complications. We propose that studying the mechanical friction between the stent and bile duct wall and other similar factors that may affect the degradation process, and the mechanical properties of PDO and PLA stents should be studied in the future. The uncovered stent design may cause long-term stent placement complications, such as granulation tissue hyperplasia, lumen renarrowing, or even stent occlusion; future studies should elaborate these features with a longer observation time and a larger sample size.

CONCLUSION

In conclusion, the novel biodegradable PDO and PLA braided biliary stent seems effective and safe to use in animal bile ducts. Such encouraging results warrant further studies to better define its applications, complications, and cost-effectiveness. Observing safety and efficacy as significant concerns in the future, these stents could be a novel choice for the treatment of benign biliary strictures.

Ethics Committee Approval: The use of piglets for research purposes was approved by the Ethical Committee of Shanghai General Hospital, granted on July 19, 2018.

Informed Consent: (It should be stated from whom the verbal or written consent was obtained.)

Peer Review: Externally peer-reviewed.

Author Contributions: Main Experimental Operations and Drafting and Critical Revision of the Article – W.X.Z., F.K., M.F.R.; Concept, Funding Acquisition, Design, and Final Approval of the Article – X.J.W; Review and Approval of the Final Manuscript – All Authors.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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