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Original Article

A novel biodegradable esophageal stent: results from mechanical and animal experiments

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Abstract: Biodegradable esophageal stents eliminate stent retrieval, but usually induce hyperplasia. This study investigated the properties of a novel biodegradable stent *in vitro* and *in vivo*. The degradation of the novel stent was observed in phosphate buffered saline (PBS) for 8 weeks. The radial forces, pH values, morphology, and retention rate of the intrinsic viscosity ($R_{[\eta]}$) of the new biodegradable stent were all evaluated. *In vitro*, the pH values remained constant for 4 weeks and declined from weeks 4 to 8. The biodegradable threads degraded and ruptured at 6 weeks. Consequently, the radial force of the stent decreased to zero at that time. The curve of $R_{[\eta]}$ decreased with time linearly in PBS. To study the stents *in vivo*, we used a stricture model in which the middle esophagus of rabbits was damaged by alkali burn. Stents were inserted 2 weeks after injury and observed for 8 weeks. We assessed complications related to stent insertion, degradation of the stent, and survival of the rabbits. Two stents migrated, and one rabbit died. In the other rabbits, two stents degraded and moved into the stomach during the sixth week, five during the seventh week and one during the eighth week, respectively. One stent remained in position until the end of the study. In conclusion, our newly designed stent retained the strong radial force of self-expandable metal stents (SEMSs) and maintained the biodegradable properties of biodegradable (BD) stents.

Keywords: Animal experimentation, biodegradable stent, mechanical experimentation, endoscopic procedure, esophageal strictures

Introduction

Stents are widely used for many types of strictures, especially esophageal strictures. Stents that provide longer periods of dilation are regarded as reasonable alternative treatments for patients with refractory benign esophageal strictures (RBES), when compared to other treatment options [1-5]. Self-expandable metal stents (SEMSs), made of titanium-nickel or stainless steel, are thought to possess the strongest radial force and maintain patency better than stents made of other materials. However, the rigid tubular configuration of SEMSs makes the retrieval of these stents difficult and complicated. Biodegradable (BD) stents were invented to solve this problem [6-8]. However, one disadvantage of BD stents is that tissue grows on the uncovered surfaces of these stents. Furthermore, many clinicians report that the radial force of BD stents is not sufficient when compared with that of metallic stents. Therefore, future studies should aim to develop a fully-covered BD stent to reduce hyperplasia [9].

Recently, we designed a fully-covered biodegradable stent, which combined the advantages of SEMSs and BD stents. The aim of this study was to investigate the qualities of our new stent *in vitro* and *in vivo*.

Materials and methods

Synthesis of the new biodegradable esophageal stent

The novel biodegradable stent for rabbits was 30 mm in length and 10 mm in diameter. It was composed of three curved pieces of covered metallic mesh connected by poly(lactic-co-glycolic acid) (PLGA) biodegradable threads (0.5

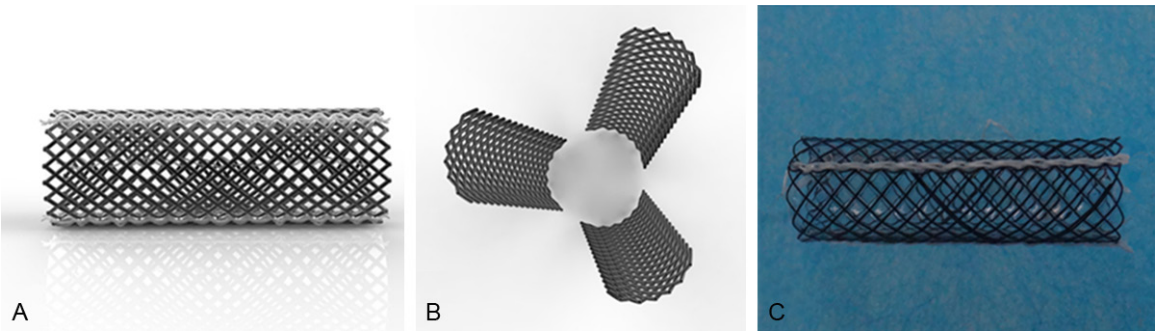

Figure 1. Images of the new biodegradable esophageal stent. Schematic drawings of the new stent (A, B) show that it was composed of three nickel-titanium pieces connected by PLGA threads. The stent disassembles when the connecting threads are degraded. A picture of the new biodegradable stent (C), in which the metallic mesh pieces and the biodegradable threads are fully-covered.

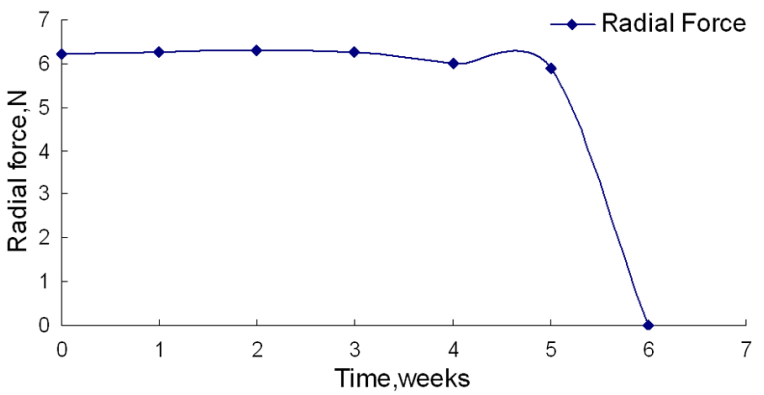

Figure 2. The radial force of the new biodegradable stent after incubation in PBS. The radial force of the new biodegradable stent was 6.2 N initially. This force was essentially unchanged for 5 weeks. The radial force was 0 at week 6.

mm in diameter) (**Figure 1A-C**). When PLGA threads degrade, the stent disassembles and drops into the stomach. The stent and delivery system were made by a manufacturer (Institute of Shandong Provincial Medical Instruments, Jinan, China) according to our specifications.

In vitro mechanical experiments

To measure degradation of the stents, samples of the new stents were immersed in beakers containing phosphate buffer saline (PBS) at 37°C. The radial force was defined as the pressure needed to reduce the diameter of the stent by one-half. The radial force of the new stent was measured using a universal material machine (AGS-H, Shimadzu Corporation, Kyoto, Japan). Comparisons of the new stent with other commercially available stents were previously published [8].

To assess degradation, samples of the PLGA threads were immersed in test tubes using the same conditions as those described for the stents. Morphological changes were observed for 8 weeks. The appearance and morphology of the biodegradable threads were observed using a scanning electron microscope (SEM) (SUPRA 55, Carl Zeiss, Jena, Germany). The pH values of the media were measured with a pH meter (Jingke Scientific Corporation, Shanghai, China). The intrinsic viscosity (η) of the PLGA threads was examined using an Ubbelohde viscometer and phenol/carbon dichloride (1:1) as a solvent. The retention rate of the intrinsic viscosity ($R_{[\eta]}$) was recorded as a percentage. The data of radial force, pH value and intrinsic viscosity were obtained by means of the average number of three repeating measurements.

Animals and stent placement

This study was approved by the Ethics Committee of Shandong Provincial Hospital, which is affiliated to Shandong University. Seventeen New Zealand white rabbits weighing 2.0 to 2.9 kg were utilized. Rabbits were fasted for 24 hrs, and then a corrosive was applied to the middle esophagus to induce stricture formation. Briefly, rabbits were anesthetized with 3% sodium pentobarbital (30 mg/kg) and posed in left lateral decubitus. A modified #10 Foley catheter with a sealed tip and an adjacent

Table 1. Comparison of the new biodegradable stent with other commercially available esophageal stents

	Diameter, mm	Length, mm	Radial force, N
Biodegradable stent in this study	10	30	6.2
Wall stent	8	60	10.3
ZA stent	10	60	5.7
Accucflex stent	8	60	3.9
SMART stent	10	60	5.6
Spiral Z stent	10	60	6.7
NT stent	10	70	3.6

The radial forces of other commercially available stents were compared according to a previously published article [8].

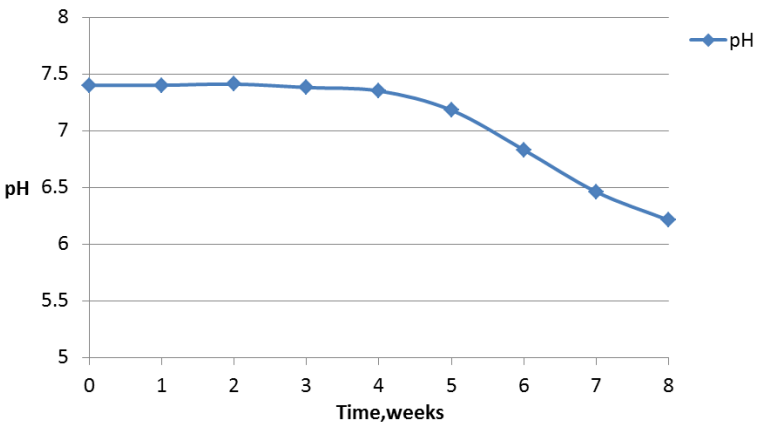

Figure 3. The pH of the medium containing the PLGA threads. The pH changed little from the initial time point to 4 weeks post-incubation in PBS and significantly declined after 4 weeks in PBS.

aperture was inserted into the middle esophagus, approximately 12.5 cm from the maxillary incisors, and 1 ml 4% sodium hydroxide solution was injected through the catheter to create the corrosive injury. Two weeks after the corrosive injury, the stricture was assessed using a digital fluoroscopy system (Prestige II, General Electric Company, Fairfield, CT, USA), and the rabbits were considered injured if the minor diameter of stricture was <1/2 the maximal diameter of the uninjured esophagus. This procedure was discussed fully in a previous study [10].

Stents were inserted 2 weeks after corrosive injury. An ultraslim endoscope (GIF-XP260N, Olympus Optical Co. Ltd., Tokyo, Japan) was used to inspect the stricture and to insert a guidewire into the esophagus. The stent delivery system with the new stent was inserted through the guidewire using the fluoroscope, and the stent was placed in the stricture. The rabbits were observed with the ultraslim endoscope and an X-ray machine weekly until the 4th week. After week 4, they were examined with the endoscope weekly and with the fluoroscope at daily. Stents were evaluated to assess degradation. Complications related to stent insertion included migration of the stent, aspiration, fistula, hemorrhage, perforation, and death.

Results

In vitro mechanical experiments

The radial force of our stent was 6.2 N initially; the radial force was essentially unchanged for 5 weeks of incubation in PBS; at week 6, the force was 0 (**Figure 2**). The characteristics and radial forces of different commercially available stents assessed in previous studies were compared with our novel stent (**Table 1**). The diameter of our stent was 10 mm and the comparable stents were 8 to 10 mm in diameter. Because our new stent was designed for use in rabbits, the length was shorter than that of other stents. The radial forces of the previously used stents ranged from 3.6 N to 11.5 N, and the radial force of our stent was comparable to most of them (**Table 1**). Although the changes in the pH values were insignificant until 4 weeks, there was a sharp decline in pH from 4 to 8 weeks (**Figure 3**). The morphological changes were observed for 8 weeks using SEM. We observed that the PLGA threads maintained their integrity for up to 4 weeks post-incubation in PBS (**Figure 4A**, **4B**). The surface of the PLGA threads became rough and loose after 5 weeks of incubation. Transverse rupture occurred after 6 weeks in PBS (**Figure 4C**). The PLGA threads fragmented into smaller pieces and lost their fibrous structure at 8 weeks. The

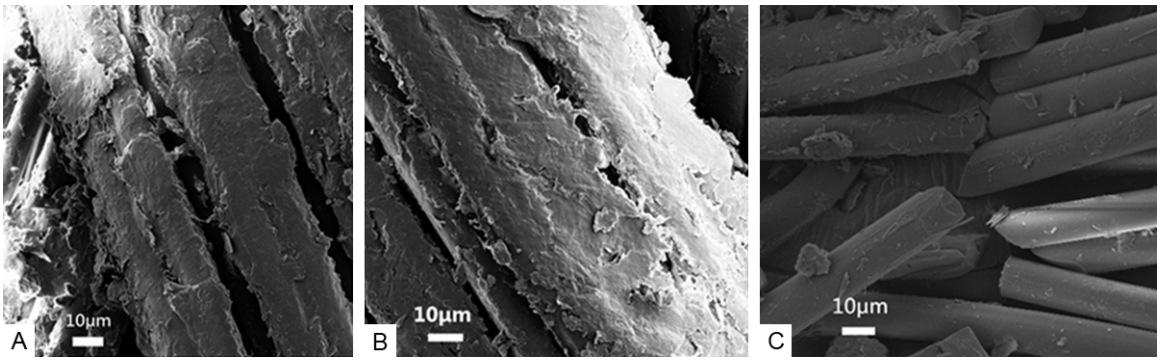

Figure 4. Scanning electron micrographs to show the structural changes to the PLGA threads. The PLGA threads remained intact from the start of incubation (A) to 4 weeks post-incubation (B). Transverse ruptures occurred after 6 weeks in PBS (C).

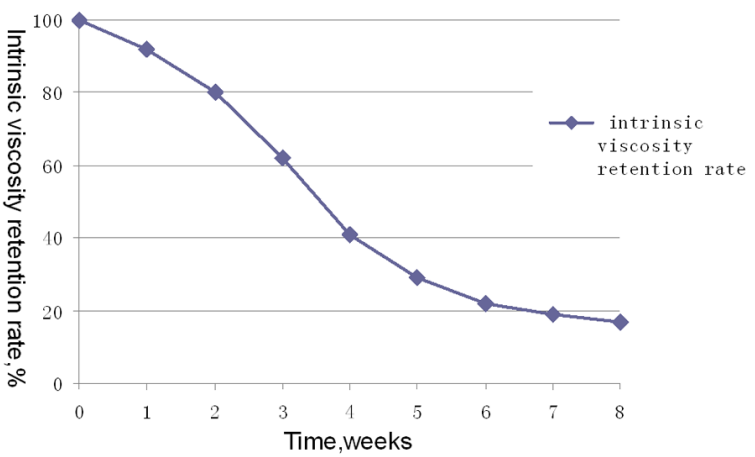

Figure 5. The curve of intrinsic viscosity retention rate ($R_{[\eta]}$). The $R_{[\eta]}$ decreased significantly from 0 to 6 weeks and became stable after 8 weeks in PBS.

curve of $R_{[\eta]}$ decreased with time linearly in PBS (**Figure 5**). The curve of $R_{[\eta]}$ declined significantly from week 0 to week 6 and only minor changes were observed from week 6 to week 8.

Assessment of the stents in an animal model

The strictures in 12 rabbits satisfied the criteria for injury. To successfully implant the stent, we used the fluoroscope to ensure that the stent was placed in the middle of the esophagus and overlapped the stenosis. Migration of the stent occurred in two cases, and one rabbit died of malnutrition during observation period. No severe complications related to stent implantation occurred. Two stents degraded and moved into the stomach during the sixth week, five during the seventh week and one during the eighth week, respectively (**Figure 6**). One stent was not completely detached at the end of the study, but the stent collapsed when pulled with biopsy forceps (FB-19K-1; Olympus Optical Co. Ltd., Tokyo, Japan).

Discussion

Benign esophageal stricture is one of the most common digestive diseases and can reduce a patient's quality of life. This condition may also result in severe complications, including anemia, weight loss, malnutrition, and death. To minimize the unwanted complications and to maximize the therapeutic effect of stent implantation for esophageal strictures, especially RBES, numerous studies have examined the properties of different types of stents [8, 11-16]. Short-term stents are considered for palliation of dysphagia and to reduce discomfort caused by sustained dilation. However, the complications related to stent insertion and extraction have prevented the use of conventional stents to treat RBES.

The ideal stent to alleviate benign esophageal stricture would be temporary and easily extracted once luminal patency is accomplished. The main body of our new stent is made of radiopaque wire, which is reported to have good tissue compatibility and memory. The nickel-titanium alloy allows the stent to expand to its largest diameter at body temperature and to com-

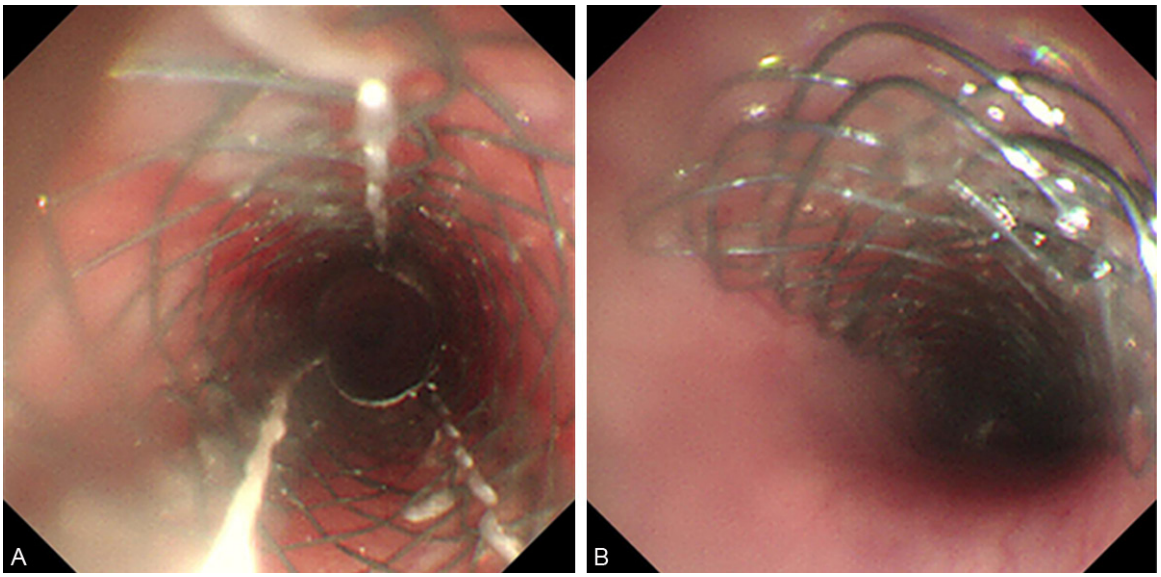

Figure 6. Endoscopic images of stent insertion and extraction. The stent was expanded so that it covered the stricture (A). The debris from the stent was extracted using biopsy forceps after the PLGA threads degraded (B).

press to the smallest diameter at colder temperatures. Our new stent has a diagonal braiding pattern, which is consistent with the majority of commercially available nitinol esophageal stents, such as Wallflex stents (Boston Scientific Corporation, Natick, MA, USA), Niti-S (Taewoong Medical, Seoul, Korea), Gianturco Z stent (Wilson-Cook Europe, Bjaeverskov, Denmark), and Evolution (Cook Medical, Limerick, Ireland). This braided design allows the stent longitudinal expansion during contractions. This reduces the radial force and maintains elasticity because contractions can abate the angle of the crossover wire. The braided design of these stents allows the radial force to gradually reach 0 [17]. Our new stents are contain PLGA threads, and many studies have demonstrated that the toxicity of this biodegradable material is very low [18-20]. PLGA is the primary biodegradable polymer used in a variety of clinical fields during the past few decades. This copolymer is widely used in surgical sutures, bone nails, and sustained drug release systems because it degrades quickly [21]. In physiological conditions, hydrolysis reactions may fragment PLGA polymers. The products of these reactions include free lactic and glycolic acids, which could be metabolized by the Krebs cycle and converted into carbon dioxide and water [19, 22]. In this study, the PLGA threads were hydrolyzed after 6 weeks in PBS, and the radial force of the new stent was also reduced to 0 at 6 weeks. These results suggested that the new stent maintained patency until the PLGA threads degraded and that radial force diminished rapidly due to this degradation. The SEMs images showed that the PLGA threads had transverse ruptures, which suggested that the stents could be removed easily. Consistent with this idea, a stent was detached from the rabbit esophagus by gently squeezing the stent once these transverse ruptures develop.

In our animal experiments, 9 of 12 rabbits were successfully implanted with the new stent. In these rabbits, we did not observe any stent-related complications, which included severe bleeding, perforation, aspiration, and fistula. Stent migration occurred in two animals and another animal died of malnutrition. Currently, all commercially available BD stents are uncovered. Ella BD stents (Ella-Cs, Hradec Kralove, Czech Republic) are widely used and are made of poly-dioxanone [9, 23, 24]. When this BD stents fail, patients receive SEMSs [9]. A previous study described an Ultraflex-type stent knitting with poly-*l*-lactic acid threads, and the migration rate for these stents was 77% (10/13) within 10 to 21 days after implantation [25]. Eight of nine stents were degraded, and the stent debris had fallen into the stomach within the observation period in our study. Although the PLGA threads were not completely degraded by the end of the study, the stents collapsed by pulling the connecting threads.

An ideal stent would lose the capacity to support the surrounding tissue once dilation is achieved so that the stent will not cause further damage to the esophageal wall. In this study, we report a new biodegradable stent with the following properties: (1) the main body of the stent is made of nickel-titanium, which has great elasticity and is strong enough to maintain patency; (2) the PLGA connecting threads are biodegradable; (3) the fully-covered stent prevents tissue hyperplasia; (4) the stent debris is easily removed; and (5) the devices involved are simple and economical to make.

Currently, all types of stents used in clinical practices exhibit radial force during stent removal. This study characterizing a new biodegradable stent is a continuation of our previous work with a detachable "pieced" stent [10]. Our newly designed stent retained the strong radial force of SEMSs and the ability to degrade *in vivo* like other BD stents. Limitations of this study are that these stents were assessed *in vitro* and that only limited studies were performed using animals. Further studies are needed to assess if the mesh can be safely excreted in the feces. Also, other biodegradable materials should be tested and their degradation kinetics determined, so that these devices can be optimized for use in other tissues.

In conclusion, our new biodegradable stent provides long-lasting tissue support and detaches by itself within a certain timeframe. This design concept could be used anywhere in the digestive tract. We anticipate that human patients could benefit from this new stent in the near future.

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Disclosure of conflict of interest

Dr. Jiyong Liu and Dr. Jin Liu own the patent of the biodegradable stent (Patent NO. ZL2011-10323099.5) Dr. Chengyong Qin and Dr. Liang Shang disclosed no conflict of interest.

Authors' contribution

Dr. Jin Liu have contributed to carry out the study, analyzed the data, and drafted the manuscript; Dr. Liang Shang assisted with the endoscopic operation and analyzed the data; Dr. Chengyong Qin participated in the experimental design and supervised the study; Dr. Jiyong Liu participated in the technical support and endoscopic operation. All authors have read and approved the final manuscript.

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