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Research of a novel biodegradable surgical staple made of high purity magnesium

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A B S T R A C T

Surgical staples made of pure titanium and titanium alloys are widely used in gastrointestinal anastomosis. However the Ti staple cannot be absorbed in human body and produce artifacts on computed tomography (CT) and other imaging examination, and cause the risk of incorrect diagnosis. The bioabsorbable staple made from polymers that can degrade in human body environment, is an alternative. In the present study, biodegradable high purity magnesium staples were developed for gastric anastomosis. U-shape staples with two different interior angles, namely original 90° and modified 100°, were designed. Finite element analysis (FEA) showed that the residual stress concentrated on the arc part when the original staple was closed to B-shape, while it concentrated on the feet for the modified staple after closure. The in vitro tests indicated that the arc part of the original staple ruptured firstly after 7 days immersion, whereas the modified one kept intact, demonstrating residual stress greatly affected the corrosion behavior of the HP-Mg staples. The in vivo implantation showed good biocompatibility of the modified Mg staples, without inflammatory reaction 9 weeks post-operation. The Mg staples kept good closure to the Anastomosis, no leaking and bleeding were found, and the staples exhibited no fracture or severe corrosion cracks during the degradation.

1. Introduction

Titanium and titanium alloys surgical staples are widely used in the reconstruction of the intestinal tract and stomach [1]. The application of staples in gastrointestinal anastomosis shorten the operation time, reduce surgical complication and alleviate the patient's pain. But these served Ti staples cannot be absorbed and retain in human body for a long time. In addition, the Ti staples produce artifacts on Computed Tomography (CT) and other imaging examination which increase the risk of misdiagnosis. On the contrary, the bioabsorbable staple made from polymers that can degrade in human body environment, is an alternative. Currently, polylactic and polyglycolic acid subcuticular absorbable staples are available in skin closure [2]. However, the poor mechanical properties of polymers restrain their applications in gastrointestinal anastomosis which need high closure strength.

Due to the biodegradable property [3], good biocompatibility [4], and significantly higher mechanical stability and ductility than polymers [5], magnesium and its alloys are considered to be candidates as surgical staples. Yan et al. [6] implanted Mg-6Zn pins in Sprague–Dawley rats' cecum and found the Mg alloy exhibited promising applications in gastrointestinal reconstruction because of good biocompatibility and better performance in promoting healing process and reducing inflammation compared to Ti alloy. Chng et al. [7] used Mg based microclip, similar to surgical staple, for pig vocal fold microsurgery. The results showed that the Mg microclip could be absorbed and had good biocompatibility in pig vocal fold after 2 weeks and 3 weeks post-implantation. Another practical Mg based surgical staple was developed by Cao et al. [8]. They implanted Mg alloy surgical staples into beagle dogs by

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performing gastrojejunal and colonic anastomosis. 90 days post-operation, the anastomosis healed well and Mg based staple degraded completely. Histological examination showed that the degradation of Mg based staple didn't harm the important organs. It concluded that Mg based staple was safe and feasible for gastrointestinal anastomosis in beagle dogs.

The closure of staple often induce residual stress on the surface, which will influence the corrosion behavior of Mg in physiological environment. However, few studies considered residual stress in the implantation of the staple. In present study, we aimed to develop a novel biodegradable staple made of high purity Mg (HP-Mg) for gastric anastomosis to reduce the effect of residual stress on the corrosion of Mg. In vitro corrosion behavior of the original right angle and modified 100° staples were investigated. Then the modified staple was implanted in pigs' stomach to assess in vivo corrosion performance.

2. Materials and methods

2.1. Biodegradable surgical staple design

The cold-drawn HP-Mg wire (99.99 wt% Mg; 0.002 wt% Si; 0.0015 wt% Fe; 0.0008 wt% Al; 0.0008 wt% Mn; 0.0002 wt% Ni; 0.0003 wt% Cu) with a diameter of 0.26 mm, supplied by Suzhou Origin Medical Technology Co. Ltd., China was used as raw material in this study. The yield tensile strength of the HP-Mg wire was 147 ± 8 MPa, the ultimate tensile strength was 196 ± 5 MPa and elongation was 14.6 ± 5%. The original HP-Mg staple was designed according to the clinical used U-shape titanium staple. Considering the high stress corrosion sensitivity of magnesium [9–11], the interior angles of the modified staple were designed to 100°. The closure of the staples were performed through the linear cutter stapler (MLC-60, Nanjing Maidixin Medical Device Co., Ltd. China). After closure, the U-shape staples changed to B-shape. The residual stress distribution of two different staples during the deformation was simulated via FEA analysis by using Abaqus software (Abaqus 6.11-PR3, Dassault Systèmes).

2.2. In vitro corrosion experiment

In order to evaluate the in vitro corrosion behavior of the HP-Mg staple, the closure formed staples with two different staples were immersed in modified simulated body fluid (m-SBF) for 7 days. The m-SBF was prepared according to Ref. [12]. 10 staples as a group were immersed together in 100 ml m-SBF. After 7 days immersion, the staples were taken out and immersed in 200 g/LCrO_3 and 2 g/L $AgNO_3$ solution for 30s [13] to remove the corrosion products, then rinsed in deionized water and dried in flow air. After sputtered with gold, the corrosion morphologies of the samples were observed using field emission scanning electron microscope (FE-SEM, Quanta 250 FEG, FEI).

2.3. In vivo corrosion experiment

The experimental protocol was approved by the Animal Care and Experiment Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Three pigs with a body weight of ~40 kg were used for gastric anastomosis. After general anaesthesia, the pigs were intubated using a 5 mm endotracheal tube and anaesthesia was maintained with isoflurane (up to 3%). A median incision was made to expose the stomach of pigs in the abdomen. In order to drag the stomach out, a suture line was bound with parts of the stomach, as shown in Fig. 1a. When the stomach was dragged out, parts of the stomach was cut and closed using the linear cutter stapler loaded with the modified HP-Mg staples, as shown in Fig. 1b. Hemostasis was assessed immediately after the closure and again 2 min later, and the integrity and quality of the staple line was evaluated visually. After implantation, all animals received a subcutaneous injection of penicillin.

The pigs were sacrificed after 9 weeks post-implantation. Histological analysis of the stomach tissue around the anastomotic part aimed at assessing the local lesions relating to the HP-Mg staples, such as inflammation and tissue necrosis. The gastric tissue samples surrounding the staples were fixed in 10% buffered formaldehyde. After that, the gastric tissue samples were embedded in methylmethacrylate, according to the manufacturer's instructions, and stained with hematoxylin and eosin (HE), then were observed via an optical microscope (Scope.A1, ZEISS). The remained staples were retrieved and examined by FE-SEM and EDS.

3. Results and discussion

3.1. HP-Mg staple design and in vitro corrosion behavior

The schematic of the original and modified HP-Mg staples were exhibited in Fig. 2. It could be seen a wider distance between the feet of the modified staple in Fig. 2b because of a bigger interior angle of 100° than the original one in Fig. 2a. Accordingly, the residual stress distribution changed greatly after the staple closed to B-shape. FEA analysis showed that the residual stress mainly concentrated on the arc part of the original staple, whereas it concentrated on the staple feet for the modified staple.

The immersion test indicated that the modified staples kept almost complete in shape and the original staples broke apart after 7 days immersion (Fig. 3a, b). The arc part of original staple, which was the residual stress concentration site analyzed by FEA ruptured firstly as shown in Fig. 3a. The corrosion behavior of biodegradable Mg is affected by many factors, including alloy elements [14], the nature of corrosive environment [15], surface characteristics of samples [16] and residual stress as well as applied stress [17], etc.

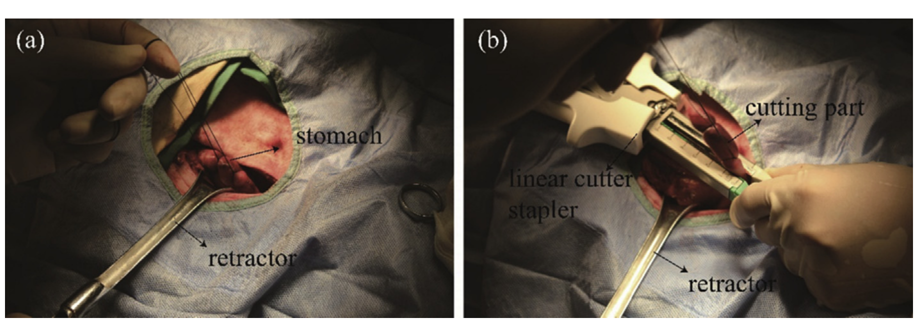

Fig. 1. The surgical procedure of gastric anastomosis. (a) The stomach was dragged out using a suture line, (b) Parts of the stomach was cut and closed using the linear cutter stapler loaded with HP-Mg staples.

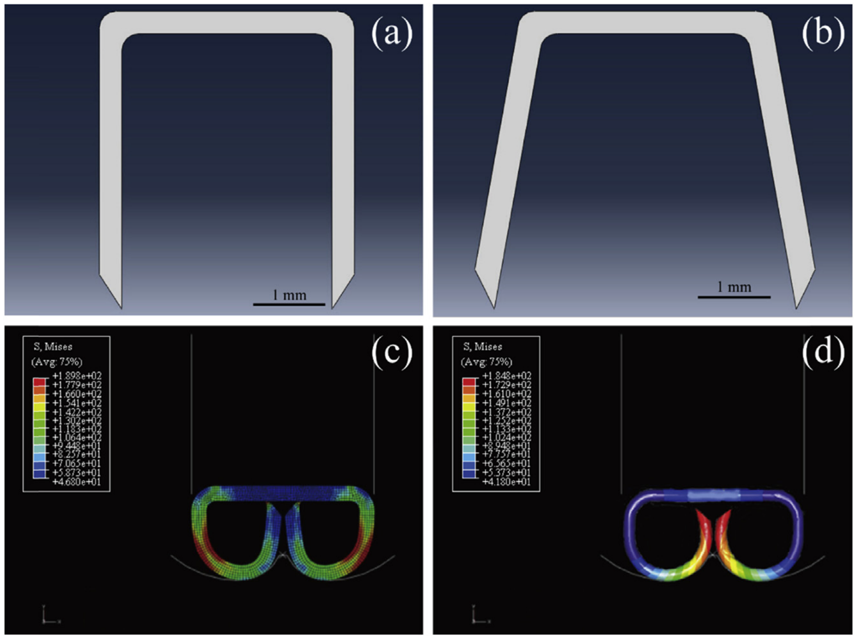

Fig. 2. The skeleton diagrams and residual stress diagrams of biodegradable staple (a)(c) original shape (b)(d) modified shape.

Mg is susceptible to stress corrosion [18–20]. So different residual stress distribution may greatly change the corrosion behavior of Mg devices. The report by Zhang et al. [20] indicated that the residual tensile stress would accelerate corrosion rate of Mg alloy, because it accelerated pre-crack propagation. The outside surface of the arc part in this experiment, suffered high tensile residual stress, therefore, fracture firstly. In contrast, the modified staple showed different corrosion behavior as the residual stress concentration apparently changed. The surface morphology of the whole modified shape staple showed homogeneous corrosion without severe corrosion holes or cracks in the arc part (Fig. 3c, d).

Combined with the applied stress by the gastric tissue during closure, the original staple would not satisfied the requirement of gastric anastomosis. In contrast, the residual stress concentrated at the end of the modified staple feet, which minimized the impact of the stress, leading to a mild corrosion of HP-Mg and an intact remaining structure. In fact, it takes at least 1 week for wound healing and strength recovery of the healing tissue with the necessary inflammation, angiogenesis, new tissue formation, and finally tissue remodeling. In gastric anastomosis, wound healing completely even takes longer because of the aggressive environment and gastric peristalsis. The modified HP-Mg staple with

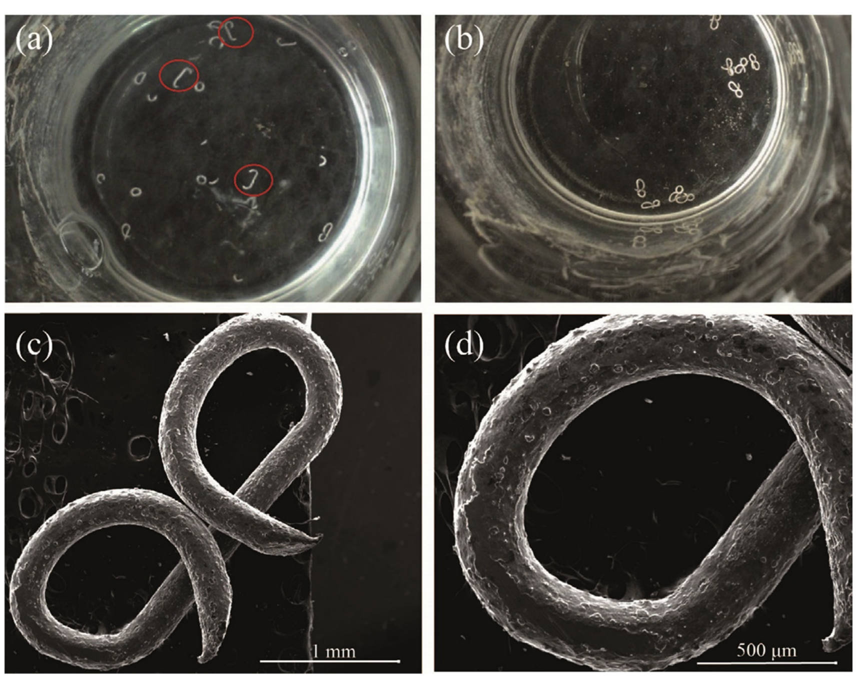

Fig. 3. The macroscopic view of closed biodegradable surgical staples with (a) original staple and (b) modified staple during 7 days immersion in m-SBF, (c) (d) the SEM surface morphology of modified staple.

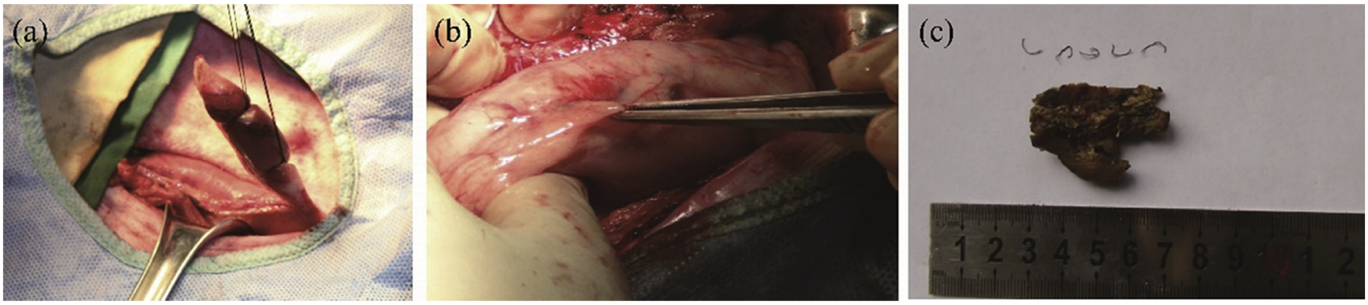

Fig. 4. (a) The anastomosis part during gastric anastomosis, (b) revival of anastomosis part and residual staples and (c) tissue sample around anastomosis part after 9 weeks implantation.

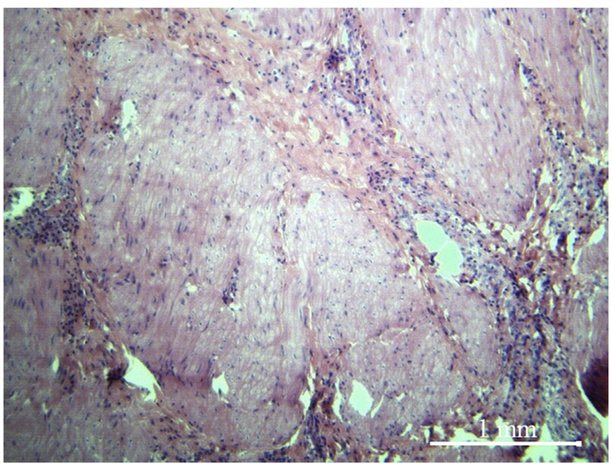

Fig. 5. HE stained stomach tissues of pigs.

suitable stress distribution will delay the arc of staple cracking and help to maintain closure strength for a longer time.

3.2. In vivo corrosion experiment

All the stomachs of the 3 pigs after cutting were successfully closed by the HP-Mg staples. The wound of stomachs were smooth and the modified HP-Mg staples were closed to smooth staple line without failure, as presented in Fig. 4a. No leaking or bleeding of the stomach anastomosis was found immediately and in the later stage after the closure. 9 weeks post-operation, the wound of the stomach anastomosis was completely healed without anastomotic leakage and the staples were embedded in the stomach tissue (Fig. 4b). The staples were not absorbable completely and the remained part kept homogeneous shape without fracture (Fig. 4c). It suggested that the staples provided enough closure strength during the healing process of the stomach anastomosis.

Fig. 5 of the HE staining histologic image showed no dynamic inflammatory cell infiltration in the stomach anastomosis and no tissue separation was observed in the implantation site. The gastric tissue exhibited normal morphology. It suggested good biocompatibilities of the HP-Mg staples. It is generally known that the kidney excretes any surplus of Mg in plasma, therefore the serum Mg level usually keep balance [22]. And the no-observed adverse effect level is considered to be 250 mg for supplemental Mg, about 250 staples [21]. Besides that, the previous study by Yan et al. [23] indicated that Mg ions from Mg alloy degradation promoted the secretion of TGF-β1 in intestinal tract and then increased the synthesis of b-FGF and VEGF which promoted angiogenesis and wound healing.

Fig. 6a showed the surface morphology of the remained staple after 9 weeks implantation. The degradation of the staple was slight and cracks or severe corrosion holes were not found on the whole staple. Fig. 6b showed the arc part of staple without fracture. The corrosion product on the surface of the remained staple was consisted of Mg, Ca, P, O and C elements. It suggested that apatite and some protein were deposited in staple surface.

It's well known that anastomotic leakage is a severe complication of gastric anastomosis and a significant cause of post-operative morbidity that may lead to re-operation, prolonged hospital stay, psychological trauma and even death [24]. The closure strength of the surgical staples was one of the vital factors that influence anastomotic leakage. In particular, the HP-Mg staple would lose mechanical integrity during degradation. In order to keep closure effect as long as possible, the shape of the HP-Mg staple was modified through FEA analysis. The in vitro immersion results confirmed the simulation. In the in vivo experiment, the modified HP-Mg staple provided an enough closure strength in pig's gastric anastomosis, and there were absent of anastomotic leakage and no bleeding during the implantation. Moreover, the surface morphology of the modified staple after 9 weeks implantation showed homogeneous corrosion without any fracture. It concluded

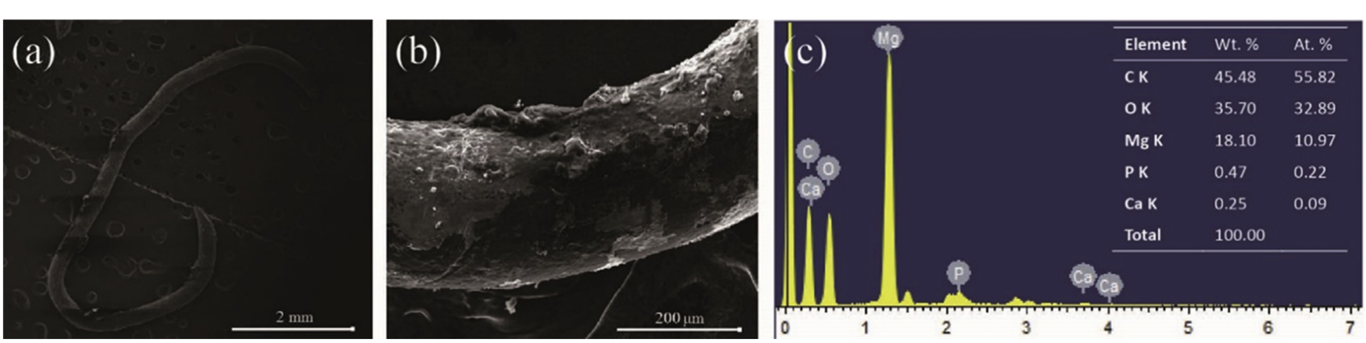

Fig. 6. The surface morphology of the whole staple (a), the arc part of staple (b), the composition element of corrosion product in staple (c).

the modified staple still maintained closure effect after prolonged corrosion in accord with simulation and in vitro results, then decreased the occurrence rate of anastomotic leakage. That would help gastric anastomosis wound healing. However, more setting different end points for each survival study group should be needed to monitor the presence of the modified surgical staple in vivo for future studies.

4. Conclusion

In the present study, a novel biodegradable surgical staple made of HP-Mg for gastric anastomosis were developed by comparing two different shape through FEA. In vitro corrosion behavior and in vivo performance of the modified HP-Mg surgical staple were evaluated.

1 A modified structure with about 100° interior angle of U-shape was selected through two different shapes of the biodegradable surgical staples by using FEA.
2 In vitro immersion experiment showed homogeneous corrosion behavior and good biodegradation of the modified HP-Mg surgical staple.
3 In vivo implantation suggested that the modified HP-Mg surgical staple had enough closure strength and good biocompatibility in gastric anastomotic.

Acknowledgements

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