Role of metallic stents in benign esophageal stricture

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ABSTRACT

Simple esophageal strictures, which are focal, straight, and large in diameter, usually require 1 - 3 dilation sessions to relieve symptoms. However, complex strictures, which are long, tortuous, or associated with a severely compromised luminal diameter, are usually more difficult to treat with conventional bougie or balloon dilation techniques, and often have high recurrence rates.

Although the permanent placement of self-expandable metal stents (SEMS) has been used to manage refractory benign esophageal strictures, this procedure is associated with additional problems, such as stricture from tissue hyperplasia, stent migration, and fistula formation. Thus, several new types of stents have been developed, including temporary SEMS, self-expandable plastic stents (SEPS), and biodegradable stents. The use of these new products has produced varied results. Temporary SEMS that have been used to relieve benign esophageal conditions have caused granulation tissue at both ends of the stent because of contact between the mucosa and the exposed metal components of the stent, thus hindering stent removal. We examined the tissue response to two new types of SEMS, a flange-type and a straight-type, each coated with a silicone membrane on the outside of the metal mesh. These two SEMS were evaluated individually and compared with a conventional control stent in animal experiments. Although the newly designed stents resulted in reduced tissue hyperplasia, and were thus more easily separated from the esophageal tissue, some degree of tissue hyperplasia did occur.
We suggest that newly designed DES (drug-eluting stents) may provide an alternative tool to manage refractory benign esophageal stricture.

Key Words: Metallic stent, benign esophageal stricture, tissue hyperplasia, DES

1. INTRODUCTION

An esophageal stricture can be classified as a malignant stricture resulting from cancer, or as a benign stricture caused by peptic injury, Schatzki rings, esophageal webs, radiation injury, caustic ingestion, or anastomotic strictures [1]. Simple esophageal strictures, which are focal, straight, and large in diameter, usually require 1 - 3 dilation sessions to relieve symptoms [2]. However, complex strictures, which are long, tortuous, or associated with a severely compromised luminal diameter, are usually more difficult to treat with conventional bougie or balloon dilation techniques, and often have high recurrence rates [3].

Although the permanent placement of self-expandable metal stents (SEMS) has been used to manage refractory benign esophageal strictures, this procedure is associated with additional problems, such as stricture from tissue hyperplasia, stent migration, and fistula formation. Thus, several new types of stents have been developed, including temporary SEMS [4][5], self-expandable plastic stents (SEPS), and biodegradable stents [6][7][8][9]. The use of these new products has produced varied results. Temporary SEMS that have been used to relieve benign esophageal conditions have caused granulation tissue at both ends of the stent because of contact between the mucosa and the exposed metal components of

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the stent, thus hindering stent removal. SEPS were developed to minimize the tissue response but these stents require a large-diameter delivery catheter [7]. The concept of a biodegradable, self-expandable esophageal stent is very appealing as it would provide patency without concern for long-term complications associated with nonremovable stents. However, if remodeling of the esophagus does not occur within 6 weeks, which is the life span of the stent, dysphagia may return [8].

Benign, refractory esophageal strictures are an important therapeutic challenge. Self expandible metal stents (SEMS) occasionally have been used, but results are still disappointing. SEMS is hard to be removed because the both ends of SEMS cause marked tissue reaction and overgrowth into it. Therefore, it can results in restricture at the end of stent. We studied to verify the effectiveness of the new design of SEMS through an animal experiment [10].

2. METHODOLOGY

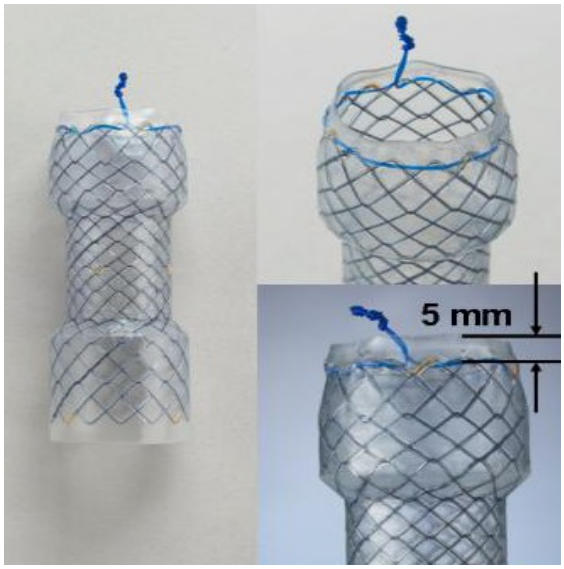
Six dogs with the weight of 8-10kg were grouped into three. Three different types of SEMS have been inserted into each group. The first group was a flange type of SEMS with silicon membrane coated onto the inside of metal mesh (Fig. 1). The second group was a flange type with thicker silicon membrane coated onto the outside of metal mesh (Fig. 2). The third group was a straight type with thicker silicon membrane coated onto the outside of SEMS (Fig. 3). SEMS insertion was preceded as follows: after the exposure of esophagus by incision of cervical region of a dog, SEMS were inserted with endoscopic guidance, and fixed in an operation way. Tissue reaction has been observed every 2 weeks until the 8th week according to endoscopic guidance.

We also developed a new type of DES (Fig. 4) to minimize tissue hyperplasia [13]. To minimize contact between the metal part of the stent and the esophageal mucosa, which may result in tissue hyperplasia and esophageal stricture, the ends of the DES were flange-shaped. Paclitaxel was dissolved in a nondegrading silicon polymer and is eluted by diffusion. The diffusion velocity test results showed a concentration of 3 % w/v. 14 dogs (5 – 10 kg) were randomly allocated to two groups. Drug-eluting stents (DES, n = 7) or nondrug-eluting stents (non-DES, n = 7) were endoscopically inserted and fixed in the esophagus of healthy dogs. Every 2 weeks, for a maximum period of 8 weeks, an endoscopic examination was performed to evaluate the status of stent insertion, the grade of tissue hyperplasia, and mucosal change at both ends of the stent.

Total length: 60 mm
Body diameter: 18 mm
Flange diameter: 24 mm
Inner coating silicone membrane
Membrane thickness: 0.07-0.11 mm

Fig. 1 Conventional fully covered self expandable metal stent

This picture shows conventional fully covered SEMS. It's total length is 60 mm and body diameter is 18 mm. This stent is a flange type with silicon membrane coated onto the inside of metal mesh. This membrane thickness is 0.07-0.11 mm. The distance between end of metal mesh and end of silicone membrane is less than 2 mm.



Length: 60 mm
Center diameter: 18 mm
Flange diameter: 24 mm
Outside silicone membrane
Membrane thickness: 0.2-0.24 mm

Fig. 2 A newly designed fully covered self expandable metal stent-flange type

This picture shows newly designed fully covered SEMS. It's total length is 60mm and body diameter is 18 mm. This stent is a flange type with thicker silicon membrane coated onto the outside of metal mesh. This membrane thickness is 0.2-0.24 mm. The distance between end of metal mesh and end of silicone membrane is 5 mm.

Length: 60 mm
Diameter: 18 mm
Outside silicone membrane
Membrane thickness: 0.2-0.24 mm

Fig. 3 A newly designed fully covered self expandible metal stent - straight type

This picture shows newly designed straight type fully covered SEMS. It's another condition is same with newly designed flange type fully covered SEMS.

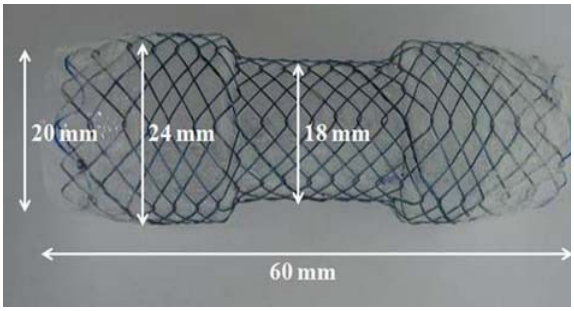


Fig. 4 A self-expanding metal stent used in the study. The flange-shaped stent was 60 mm in length, 20 mm in diameter at both ends, 24 mm in diameter at the flange, and 18 mm in diameter throughout the body.

3. RESULTS

Endoscopically in the first group, an exuberant tissue reaction was found at the 2nd week, and in the entire region of both ends of SEMS at the 4th week. In one case of the second group, the tissue reaction was noted in small region of the proximal end of SEMS at the 4th week, and was not progressed at the 4th and the 8th week. In the other case of the second group, the tissue reaction was not found in the 4th week, but the SEMS has migrated upward in the 6th week. In the third group, the tissue reaction was not found at the 4th week, and the SEMS had migrated upward in the 6th week. In a pathological view, in the first group, the tissue overgrowth and ulceration were found even on the body of SEMS as well as the both ends of SEMS. In the second group, the tissue overgrowth was confined to a small region of the proximal end of SEMS at the 8th week for the second case. In the third group, the tissue overgrowth was not found.

The results of DES in this study was as follows. One case of stent migration was observed after 4 weeks in the non-DES group. In this group, tissue reaction and hyperplasia remained for more than 4 weeks after stent insertion (Fig. 5, 7, 9). By contrast, an endoscopic examination of the surrounding esophageal mucosa in the DES group showed very little tissue reaction (Fig. 6, 8, 10), and the stent was easily separated from the esophageal tissue.

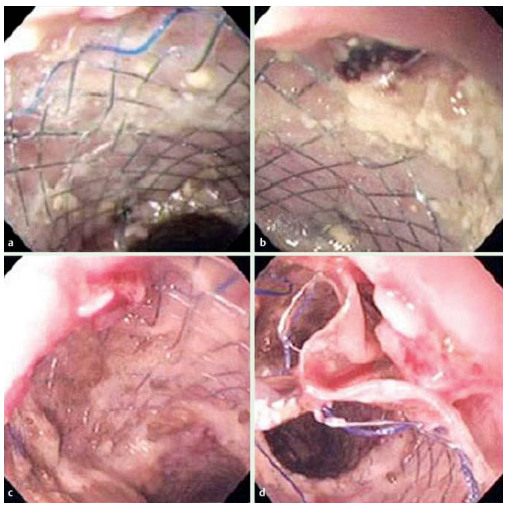


Fig. 5 Endoscopic findings in the non-DES group. **a** At 2 weeks after stent insertion, moderate granulation tissue with mucosal discoloration and multiple ulceration was noted. **b** At 4 weeks, the ulcers at the distal end of the stent were worse and moderate granulation tissue had formed. **c** At 6 weeks, the distal end of the stent was buried into the esophageal mucosa under moderate-to-severe granulation tissue. **d** At 8 weeks, the distal end of the stent was buried deep into the esophageal mucosa under severe granulation tissue.

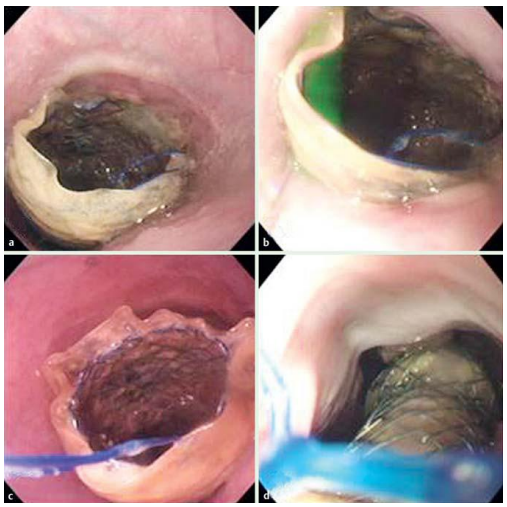


Fig. 6 Endoscopic findings in the DES group. **a** At 2 weeks after stent insertion, mild-to-moderate granulation tissue formation and a small number of ulcers could be seen. **b** At 4 weeks, mild granulation tissue without ulcers were seen. **c** At 6 weeks, only minimal tissue reaction was seen. **d** At 8 weeks, the esophageal mucosa was almost normal and the stent was easily removed from the esophageal tissue, allowing for easy endoscopic access between the stent and esophagus.

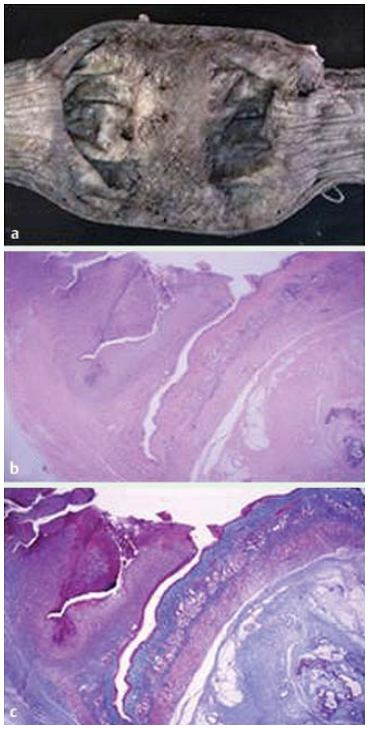


Fig. 7 Pathologic findings in the non-DES group within 4 weeks after stent insertion (death at day 19). **a** Macroscopically, the esophageal mucosa was discolored with multiple ulcers and granulation tissue. **b, c** Deep ulceration, exuberant granulation tissue, and abscess throughout the esophageal wall were observed in association with a loss of normal structure (**b** H&E staining × 12.5; **c** Masson's trichrome stain × 12.5).

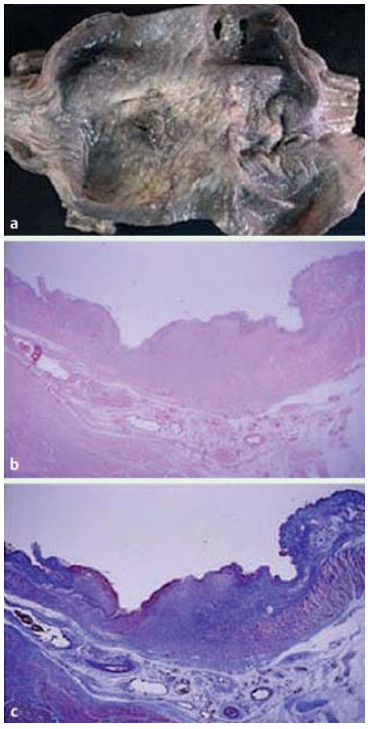


Fig. 8 Pathologic findings in the DES group within 4 weeks after stent insertion (death at day 18). **a** Focal ulceration with a small amount of granulation tissue and mucosal regeneration was observed. **b, c** Microscopic findings demonstrated small, focal ulcers, submucosal thickening by granulation tissue and fibrosis, and surrounding epithelial regeneration (**b** H&E × 12.5; **c** Masson's trichrome × 12.5).

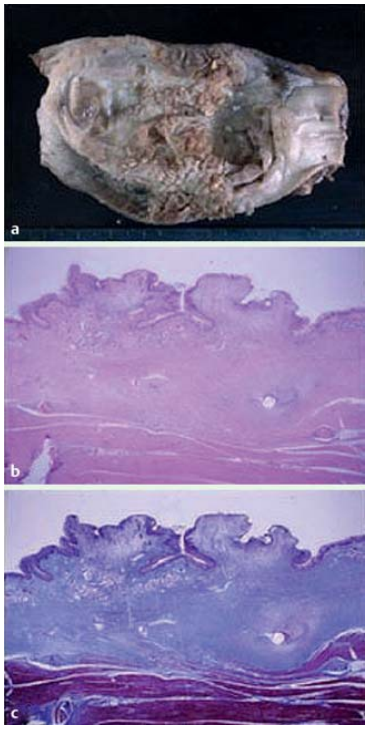


Fig. 9 Pathologic findings in the non-DES group 8 weeks after stent insertion. **a** Macroscopically, the esophageal mucosal surface was replaced by marked verrucous proliferation of granulation tissue. **b** Microscopically, the surface was extremely irregular and thickly covered by regenerating squamous epithelium (H&E × 12.5). **c** The submucosa was markedly thickened by fibrosis, and the superficial muscle layer was also affected by fibrosis (Masson's trichrome × 12.5).

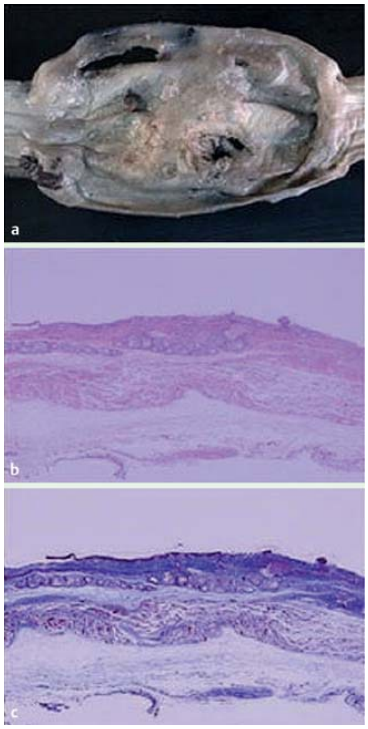


Fig. 10 Pathologic findings in the DES group 8 weeks after stent insertion. **a** Macroscopically, the esophageal mucosa was relatively smooth and intact. **b** Microscopic examination revealed an intact mucosa covered by squamous epithelium and abundant submucosal mucous glands (H&E × 40). **c** Mild submucosal fibrosis and a relatively well preserved muscle layer were observed (Masson's trichrome × 40).

4. DISCUSSION

The newly designed SEMS with outer coating thicker silicon membrane can be one of alternative to treat refractory benign esophageal stricture as the tissue reaction is obviously minimized compared to the old design of SEMS with inner coating silicon membrane.

In benign esophageal strictures, pressure imposed by the stent decreases the blood supply to the wall of the esophagus, resulting in ischemic damage. As time passes, complications, such as granulation tissue due to ischemic necrosis, ulcers, and fibrosis, lead to esophageal restenosis [10]. However, the same DES used in percutaneous coronary intervention can also be used to decrease restenosis rates in refractory benign strictures, although most of these have been used in cases of malignant disease of the biliary tract [11][12].

We also developed a new type of DES (Fig. 4) to minimize tissue hyperplasia [13]. To minimize contact between the metal part of the stent and the esophageal mucosa, which may result in tissue hyperplasia and esophageal stricture, the ends of the DES were flange-shaped.

In an animal study where a metal stent coated with 10 % or 20 % (% w/v) paclitaxel was inserted into the bile duct of a pig to examine whether intraductal hyperplasia could be prevented, moderate inflammation, mucinous metaplasia, and fibrosis of the bile duct were noted but no specific sequelae were seen, providing supportive evidence on the safety of

paclitaxel-eluting stents [14]. In another animal study, a paclitaxel-eluting metal stent was inserted into the bile duct of a pig to observe the prevention of benign stent epithelial growth. At 6 months after stent insertion, progressive mucosal hyperplasia was observed in the noncoated stent, and 25 % total obstruction was observed in the ethylene vinyl acetate (EVA)-coated stent. However, the paclitaxel-coated stent was found to control the epithelial growth almost completely and was virtually the same as it was when the stent was initially inserted, providing positive evidence that paclitaxel can prevent benign stent intraductal hyperplasia even in normal cells [15].

The stent used in this study was manufactured based on the study results noted above. Paclitaxel was dissolved in a nondegrading silicon polymer and is eluted by diffusion. The diffusion velocity test results showed a concentration of 3 % w/v. And the direction of the drug emission was toward the esophageal mucosa rather than the lumen, so the effects of the drug on the distal esophagus and the stomach should be negligible. Although the paclitaxel dose used in this study was smaller than that used in other studies, the death rate was high during the follow-up period. The number of deaths before 4 weeks was three animals each in both groups and after 4 weeks one animal each in both groups.

Based on the results, we can surmise that the test animals died not because of the adverse effects of paclitaxel but because of other causes. On a side note, we would like to declare that the animals used during this study underwent no undue suffering and that they were treated in the most humane way possible. The small sample size, the lack of objective data such as the serum level of paclitaxel, surgical fixation of the stent rather than endoscopic fixation such as clipping, and insufficient postprocedural management are limitations of this study. Further experiments addressing these problems and including a larger number of animals are of course needed. However, unlike for the bile duct, there are almost no published papers on the paclitaxel-eluting stent in the esophagus, and therefore the fact that the paclitaxel-eluting stent caused almost no tissue hyperplasia in the surviving animals in this study is an encouraging result.

5. CONCLUSION

Although further study in more cases would be needed, the newly designed DES could be one alternative to manage refractory benign esophageal stricture as the tissue hyperplasia is minimized compared to the conventional SEMS. Further evaluation including clinical study, optimal concentration of drug, and coating method would be necessary.

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