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Chapter 2

Endoscopic treatment of benign anastomotic
esophagogastric strictures with a
biodegradable stent (ESBIO study)

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Submitted

Abstract

Background: Benign postsurgical esophagogastric anastomotic strictures are a cumbersome complication requiring repetitive endoscopic intervention before a remission is achieved. An effective one-step technique is eagerly awaited.

Objective: To investigate the efficacy and safety of a biodegradable uncovered expandable stent (SX-ELLA Biodegradable Esophageal Stent) for the treatment of postsurgical esophagogastric anastomotic strictures.

Design: Prospective, single-center, feasibility cohort study.

Setting: Tertiary referral center.

Patients: Ten patients with dysphagia grade 2 to 4 caused by a benign postsurgical esophagogastric anastomotic stricture were included.

Intervention: Endoscopic placement of a self-expandable biodegradable esophageal stent.

Outcome measurements: Primary endpoint was defined as number of re-dilations within 6 months after stent placement. Secondary endpoints: improvement of dysphagia score, 7-day visual analogue pain score, stent dissolution, and other complications.

Results: Stents were successfully inserted in all 10 patients. In 6 patients placement of the biodegradable stent proved an effective one-step treatment. Four patients developed signs of re-obstruction treated with re-dilations in 3 and removal of an impacted food bolus in one patient. Compared to baseline, dysphagia score at 1 week, 3 months, and 6 months follow-up improved significantly. The stent appeared to be well tolerated with low pain score in the first week after stent placement. No stent collapse with blockage of the esophageal lumen or serious adverse events were observed.

Limitations: Small patient group, short follow-up, single center.

Conclusion: Placement of a biodegradable esophageal stent may be an effective and safe one-step treatment in patients with dysphagia caused by postsurgical esophagogastric anastomotic strictures.

Introduction

Postoperative benign fibrotic strictures of a cervical esophagogastric anastomosis occur in 5 to 46% of patients, mostly within 6 months after the esophageal resection.¹⁻³ Factors independently related to development of benign anastomotic strictures are cardiovascular disease, gastric tube compared to colonic interposition and postoperative anastomotic leakage.⁴ These strictures bring about morbidity because of dysphagia and weight loss, leading to a decreased quality of life. Esophagogastric anastomotic strictures belong to the group of complex esophageal strictures.³ Several methods have been described to treat these strictures, including balloon dilation, Savary bougy dilation and Eder Puestow olive dilation. None of these conventional methods proved to be superior over others with regard to efficacy and safety.^{1-3;5-7} Complex esophageal strictures require a median of 3 to 7.5 dilation sessions when using a conventional dilation technique to achieve remission.^{3;8;9} To reduce the number of treatment sessions dilation has been combined with intralesional steroid injections, revealing a reduction of dilation sessions in uncontrolled series.^{10;11}

Another treatment modality is electrocautery incision of the stricture: a recently published randomized controlled trial showed electrocautery incision to be equivalent to Savary bougy dilation in previously untreated anastomotic strictures.¹²

Self-expandable metal stents (SEMS) have also been considered as dilation therapy for the treatment of anastomotic strictures. In several clinical series however significant problems were encountered after stent placement.¹³ These included difficulty to remove the stent, ingrowth of granulation tissue with subsequent obstruction of the uncovered part of the stent, as well as pain. As a consequence self-expandable plastic stents (SEPS) were developed to preclude these complications. The first results with SEPS for the treatment of benign anastomotic strictures revealed easy removal of all SEPS 6 weeks after stent placement and a long-term relief of dysphagia in 80% of the patients.¹⁴ In the mean time several studies on SEPS have revealed a long-term clinical success rate of well below 50%, a migration rate of about 50% and severe complications in 6% of the patients.¹³

Embroidering on these techniques the ideal stent for a benign stricture should not migrate and should overcome ingrowth of granulation tissue which often occurs after having a stent in situ for a longer period. In this regard an interesting option could be an uncovered biodegradable stent which dissolves spontaneously after placement.

Patients and Methods

The current ESBIO study, was designed as a prospective, single-center, feasibility study to evaluate the efficacy and safety of a self-expandable biodegradable uncovered

stent. The protocol was approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam. The study has been conducted at the department of Gastroenterology and Hepatology of the Academic Medical Center at the University of Amsterdam. All participants provided written informed consent.

Patients

From January 2009 to February 2010, consecutive patients older than 18 years of age with an esophagogastric anastomotic stricture presenting within 6 months after surgery and a dysphagia score 2 to 4 were considered for this study.

Exclusion criteria were previous endoscopic treatment of the anastomotic stricture, suspicion of malignancy, anastomotic stricture longer than 3 cm, and upper esophageal sphincter within 1.5 cm of the stricture.

Materials and intervention

In this study a biodegradable uncovered expandable stent (Figure 1), 60 mm long with a body diameter of 25 mm and a flare diameter of 31 mm, was used (SX-ELLA Biodegradable Esophageal Stent BD, ELLA-CS, Hradec Kralove, Czech Republic). This stent has been Conformité Européenne (CE) approved and holds an indication for the use in benign strictures (peptic, anastomotic, caustic and post-irradiation). The stent is made of polydioxanone monofilaments and dissolution occurs 11 to 12 weeks following implantation. The stent has to be manually mounted on a delivery system shortly before implantation, the outer diameter of the delivery system is 9.4 mm.

Stent placement was done with the patient under conscious sedation (midazolam or fentanyl). If a pediatric endoscope (Olympus XP-160 or similar) could not pass the stricture, a guidewire was placed under fluoroscopic guidance and dilation with Savary bougies till 10 mm was performed. After reintroduction of the endoscope, the length of the stricture

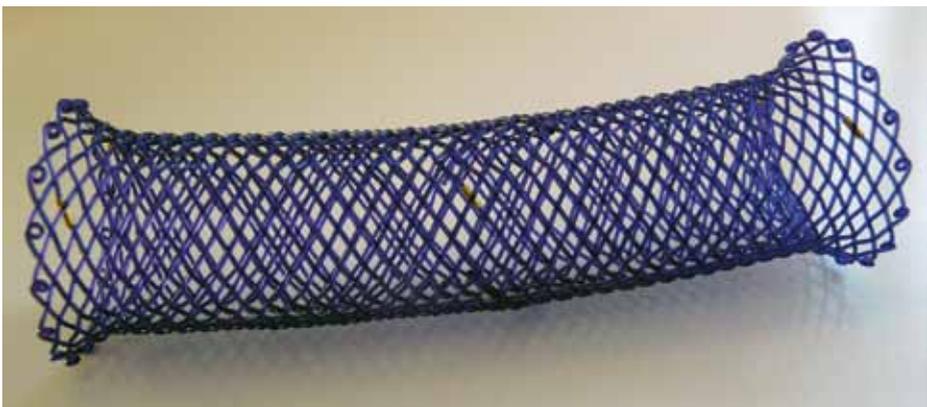


Figure 1. Biodegradable Esophageal Stent.

was measured. The proximal part of the stricture was marked with intramucosal injection of a radiopaque contrast agent to facilitate accurate stent placement. A guidewire was placed in the antrum of the stomach. The biodegradable uncovered expandable stent was placed with the proximal end 1.5 cm above the anastomotic stricture. The correct position of the stent was confirmed using fluoroscopy and endoscopy.

Data collection

After obtaining informed consent and before stent placement (baseline) patients' demographics, clinical characteristics, medication use, severity of dysphagia and pain score were gathered by a research nurse. Procedure-related data were noted down by the treating physician.

After stent placement patients were contacted by a research nurse to investigate on the pain score at day 1, 2 and 7, and on dysphagia score and complications weekly for the first month and thereafter monthly. At 3 months a follow-up gastro-duodenoscopy was planned to check for stent dissolution. Patients were followed for 6 months.

Definitions and endpoints

The primary endpoint of the study was defined as number of re-dilations per patient because of recurrent esophageal stricture within 6 months after stent placement. Secondary endpoints were improvement of dysphagia score at 1 week, 3 and 6 months; pain score at day 1, 2 and 7; stent dissolution and other complications.

Esophageal stricture was defined as a stricture in the esophagus which could not be traversed by a therapeutic endoscope (diameter 11 mm). A re-dilation was performed in case of clinical recurrence of dysphagia (score 2 to 4) with an apparent stricture at endoscopy.

Dysphagia was scored as follows: score 0 - ability to eat a normal diet; score 1 - ability to eat some solid food; score 2 - ability to eat semisolids only; score 3 - ability to swallow liquids only; score 4 - complete obstruction.^{15;16} A visual analogue scale (VAS) pain score ranging from 0 (no pain) till 10 (worst possible pain) was used to investigate thoracic pain. Stent dissolution was graded as follows: completely dissolved stent, partially dissolved stent without blocking the esophageal lumen, partially dissolved stent with blocking the esophageal lumen (collapsed stent), stent configuration unchanged since placement. The following complications were defined: perforation, bleeding requiring blood transfusion, stent migration, esophageal re-obstruction, gastrointestinal obstruction because of stent migration, stent-related pain requiring treatment with morphinomimetics for over 24 hours, removal of the stent because of intolerable foreign object feeling or untreatable pain.

Safety was defined as absence of serious adverse events related to the procedure or device, serious being defined as those events leading to death, requiring admission to the intensive care or leading to surgical (re-)intervention.

Statistics

The aim of this feasibility study was to investigate the efficacy of a biodegradable uncovered expandable stent as reflected by the need of re-dilations. This pilot study is descriptive by nature, therefore no formal power calculation has been performed. In this study 10 patients with an untreated anastomotic esophageal stricture were planned to be included.

Descriptive statistics were used for data of all included patients (intention-to-treat). Depending on distributional proportion, Wilcoxon matched-pairs signed-rank test (dysphagia score) was used to assess improvements from baseline. Dysphagia and pain score data are graphically depicted as means \pm 1 standard error for visualisation purposes. Statistics were performed using the SPSS (version 16.0) software package (SPSS, Chicago, Ill). Statistical significance was set at $P < 0.05$.

Results

Between January 2009 and February 2010 16 patients were screened for inclusion, 10 patients (8 men, 2 women; mean age \pm standard deviation (SD) 62 \pm 6.8 years) fulfilled all criteria and were included. Nine patients had undergone esophagectomy because of esophageal carcinoma, 1 patient because of a Boerhaave's syndrome. Two patients had anastomotic leaks postoperatively. Patient demographics, stricture and stent placement characteristics are further summarized in table 1.

Primary endpoint

In 6 patients, placement of the biodegradable stent proved an effective one-step treatment for their stenosis without the need for re-intervention during 6 months follow-up. Signs of re-obstruction occurred in 4 patients. One patient had food impaction 74 days after stent placement for which an endoscopic desobstruction was performed, the remaining 15 weeks of follow-up were uneventful. Two patients had obstruction caused by hyperplasia in the area of the stent and 1 patient had a recurrence of the anastomotic stricture: 103, 109 and 132 days after stent placement. Symptoms resolved after 3, 5 and 9 additional dilation sessions respectively.

Table 1. Patient demographics, stricture and stent placement characteristics.

Patient demographics	
Number of patients, n	10
Sex, male; female, n	8;2
Age in years, mean (SD)	62 (6.8)
Dysphagia score, mean (SD)	2.5 (0.71)
Number of patients on proton pump inhibition, n	4
Number of patients using analgetics*, n	2
Stricture characteristics	
Days to stricture formation, median (range)	83 (29-170)
Upper margin stricture** (cm), mean (SD)	21.4 (1.6)
Length stricture (cm), median (range)	1 (0.5-3)
Stent placement characteristics	
Procedure time (min), mean (SD)	23.3 (7.1)
Upper margin stent** (cm), mean (SD)	19 (1.1)
Number of dilatations prior to stent placement, n	2
Number of technical problems, n	0
Number of complications during placement, n	0
*One patient used paracetamol combined with diclofenac and one only paracetamol.	
**Measured from the incisors.	

Secondary endpoints

Figure 2 reflects the mean dysphagia score over time: dysphagia score at 1 week, 3 months, and 6 months improved significantly compared to baseline ($p=0.004$, $p=0.006$, $p=0.004$). Figure 3 shows the mean VAS pain score at baseline and during the first week after stent placement. No stent-related pain requiring treatment with morphinomimetics occurred. The per-protocol follow-up endoscopy 3 months after stent placement revealed that 3 stents were completely dissolved. None of the partially dissolved stents, however, were obstructing the esophageal lumen. Signs of tissue hyperplasia in the area of the stent was noticed in 6 out of 10 patients, yet in only 2 patients this was associated with symptoms of dysphagia. These two cases have been described in the paragraph on the primary endpoint.

Apart from signs of re-obstruction in 4 patients (as presented above) no complications were observed.

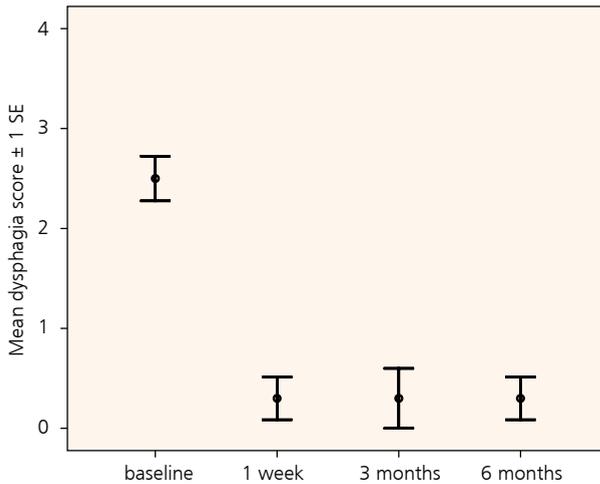


Figure 2. Mean dysphagia scores over time on dysphagia score scale ranging from score 0 (ability to eat a normal diet) till score 4 (complete obstruction). Bars represent 1 times standard error (SE).

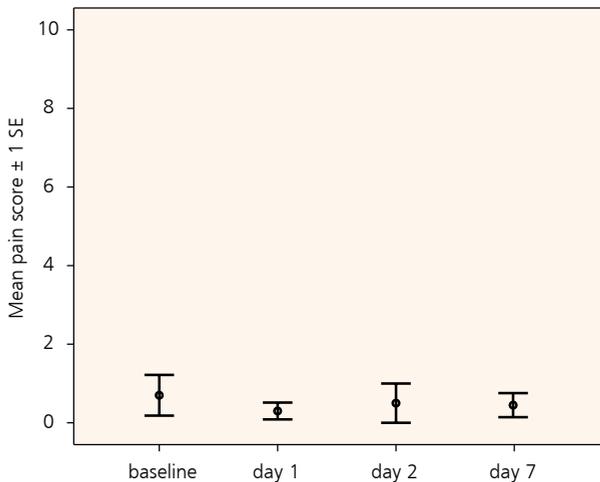


Figure 3. Mean pain scores over time on VAS pain score scale ranging from score 0 (no pain) till score 10 (worst possible pain). Bars represent 1 times standard error (SE).

Discussion

Benign cervical postsurgical esophagogastric anastomotic strictures cause major morbidity and occur in many patients after esophagectomy.³ Endoscopic per oral dilation with bougies or balloons is considered the treatment of choice for these strictures.³ Because of extensive fibrosis and a severely narrowed esophageal lumen anastomotic strictures are considered complex, and often require repeated dilation with intervals of 1 to 2 weeks. Dilation of complex strictures have to be performed with a median of 3 to 7.5 sessions but incidentally up to 28 sessions are needed to achieve remission.^{2,3;8;9} Several new techniques have been studied recently: intralesional steroid injections,

electrocautery incisions of the stricture, SEMS and SEPS placement.¹⁰⁻¹³ The major drawback of SEMS appeared to be ingrowth or overgrowth of hyperplastic tissue while SEPS revealed a high migration rate. Only intralesional steroid injection led, in uncontrolled studies, to a reduction of the number of interventions and a longer time-interval between dilation sessions. We conducted this pilot study to see if a biodegradable stent would be able to further reduce the number of re-dilation sessions and could overcome the drawback of SEMS and SEPS.

In 6 patients, placement of the biodegradable stent proved an effective one-step treatment for their stenosis without significant side-effects.

Whereas conventional techniques are typically executed on an interval basis applying "the rule of 3" (corresponding with a total of 3 times 1 mm increase in diameter) and thus require multiple endoscopic procedures, the biodegradable stent causes a gradual dilation during several weeks with a continuous increase in diameter till 25 mm.

Signs of re-obstruction occurred in 4 patients: three underwent re-dilation and 1 had a partially occluded stent caused by food impaction which was cleaned endoscopically. In 2 of these patients the re-obstruction was caused by tissue hyperplasia at the level of the stent. In fact, the per-protocol endoscopy 3 months after stent placement showed signs of tissue hyperplasia in 6 out of 10 patients but it had only clinical consequences in 2 patients as mentioned above. In a recent overview hyperplastic tissue ingrowth or overgrowth was the cause of recurrent dysphagia in 17% of patients treated with a partially/uncovered SEMS for benign esophageal strictures.¹³ It is speculated that this hyperplasia is related to the radial force, the size of the stent and the duration of stenting. Since we used a biodegradable stent, we can not exclude the possibility that the chemical dissolution of the stent may also have influenced tissue hyperplasia.

It is unknown if reflux of gastroduodenal contents may contribute to hyperplasia formation. Because of a lack of data suggesting a protective effect we did not routinely prescribe acid suppressant medication following stent placement.

The dysphagia score improved in 1 week in all but 1 patient, all patients were free of dysphagia 1 and 2 months after stent placement; thereafter re-obstruction caused by stricture formation requiring re-dilation occurred in 3 patients. The reoccurrence of the stricture appeared to be related to changes in stent integrity and decrease of radial forces that occurred 6 to 8 weeks after placement caused by dissolution of the polydioxanone monofilaments. Dissolution was expected to be complete 11 to 12 weeks after implantation. In our series the follow-up gastro-duodenoscopy at 3 months showed complete stent dissolution in 3 patients, while in the other 7 patients the stent had partially dissolved without actually blocking the esophageal lumen, which had been a severe problem in several patients according to the reports of two study groups in the mid-1990s.^{17;18}

Because of the relatively large diameter of our esophageal stent, flare 31 mm and body 25 mm, thoracic pain and foreign object feeling were anticipated, especially during

the first days after stent placement because of the gradual expansion of the stent. We therefore registered pain medication and pain score at baseline and did an intensive follow-up during the first 7 days. Our pilot study revealed however that neither during the first week, not even for a short period, nor during the remainder of the follow-up morphinomimetics had to be prescribed.

Besides re-obstruction no other complications such as perforation, bleeding, stent migration or gastrointestinal obstruction due to stent migration occurred.

We realize that the limited number of patients in our pilot study is a drawback although all published series on biodegradable stents for esophageal strictures were small, describing between 2 and 13 patients. In addition stents in these studies were placed for a variation of indications: anastomotic as well as caustic and post endoscopic mucosal resection.^{19;20} We carefully selected consecutive patients with benign cervical postsurgical esophagogastric anastomotic strictures without prior treatment of their strictures and all occurring within 6 months after surgery which makes our cohort much more homogeneous than other published series. To further determine the position of this new, in our view promising technique in the treatment algorithm for benign cervical anastomosis, larger and preferably randomized studies are needed.

Conclusion

Placement of the SX-ELLA biodegradable esophageal stent in patients with dysphagia caused by benign anastomotic esophageal strictures appears to be an effective and safe one-step treatment.

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