Chapter 7

Endoscopic magnetic gastroenteric anastomosis for palliation of malignant gastric outlet obstruction: a prospective multicenter study

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Abstract

Background: Palliation of malignant gastric outlet obstruction remains challenging. Although there are 2 established treatment options, ie, surgical gastrojejunostomy and endoscopic duodenal stent insertion, there is an ongoing search for a technique that would combine the safety and rapid effect of duodenal stent placement with the long-term efficacy and low reintervention rate of a surgical gastrojejunostomy.

Objective: To investigate the safety and success rate of endoscopic creation of a gastroenteric anastomosis formed by magnetic compression and stent placement.

Design: Prospective, multicenter cohort study.

Setting: Four referral centers.

Patients: The expected number of patients with symptomatic malignant gastric outlet obstruction to be included at the participating hospitals during a year was 40. Because of a serious adverse device event, the study was terminated after inclusion of 18 patients.

Intervention: Creation of an endoscopic gastroenteric anastomosis by using the Cook Magnetic Anastomosis Device with transanastomotic deployment of a self-expandable stent.

Main outcome measurements: Primary endpoints were safety and success rate associated with the creation of an endoscopic gastrojejunostomy by using a magnetic anastomotic device with transanastomotic deployment of a self-expandable stent.

Results: Because of a serious adverse event, the study was terminated prematurely. A success rate of 66.7% (12 of 18 patients) was achieved; 1 serious adverse event (stent perforation) occurred leading to the death of the patient. Three patients (25%) experienced an adverse device effect (stent migration).

Limitations: Small sample size, lack of control group.

Conclusion: Endoscopic creation of a gastroenteric anastomosis by magnetic compression is feasible and safe; however, the necessity of a stent led to serious morbidity and even mortality in this study. The current system can therefore not be recommended for clinical use.

Introduction

Malignant gastric outlet obstruction (GOO) is often caused by advanced gastric, duodenal or periampullary malignancies.[1-3] GOO leads to significant morbidity, including nausea, vomiting, inability to eat, and weight loss. The aim of treatment is resolution of these debilitating symptoms.

A surgical gastrojejunostomy has long been the standard palliative therapy for these patients, but it carries considerable morbidity and even mortality.[4-6] As many as 57% of the patients have symptoms of delayed gastric emptying, often causing a prolonged hospital stay.[7-9] Once the gastrojejunostomy is functioning, recurrent obstruction is rare.[10]

Endoscopic placement of self-expandable metal stents has emerged as an alternative, minimally invasive treatment option. This endoscopic procedure leads to resumption of oral intake in about 90% of the patients within 4 days after stent placement, and it has a short procedure-related hospital stay and no intervention-related mortality.[1,3,11]

One of the most feared complications of enteral stent placement remains recurrent obstruction, caused by either stent migration or tumor infiltration.[1-3] A recently published randomized, controlled trial clearly underlined the previously cited shortcomings of the currently available techniques.[12]

Promising data on a new minimally invasive technique were reported by Chopita et al., who successfully created an endoscopic gastroenteric anastomosis by using magnetic compression. Based on these and other recent results of creation of an anastomosis with magnetic compression, the Magnetic Anastomosis Device (Cook Endoscopy Inc, Winston-Salem, NC) was developed.[13-15] This multicenter study was designed to evaluate the safety and technical success of the creation of a gastroenteric anastomosis with the Magnetic Anastomosis Device followed by transanastomotic deployment of a self-expandable stent as palliative treatment of malignant GOO.

Patients and Methods

Study design

The protocol of this multicenter, prospective, observational clinical trial (NCT00487552: Magnetic Anastomosis Device Relief of Malignant Gastric Outlet Obstruction [MAD]) was approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam and the local ethical committees of the other 3 participating centers (University Medical Center Utrecht; Hôpital Erasme, Brussels; and Catholic University, Rome). All participants provided written informed consent.

Patients

Between January 2008 and February 2009, patients older than 18 years of age with a histologically proven malignancy of the periduodenal area, who presented with symptoms compatible with GOO (GOO Scoring System [GOOSS] score ≤ 2) and a Karnofsky Performance Scale score of at least 60 (requires not more than occasional care for most needs) were considered for this study. Exclusion criteria were the inability to give informed consent, pregnancy, implanted cardiac device, coagulopathy, use of medication impairing wound healing, small-bowel strictures, and surgically altered gastrojejunal anatomy.

Material and Interventions

All endoscopic procedures were performed with the patient under conscious sedation or general anesthesia. Standard gastroscopy was performed to assess whether the endoscope could be passed through the obstruction. If this was not possible, a guidewire and a 5 French catheter were advanced through the endoscope and manipulated through the narrowed bowel lumen with fluoroscopic guidance. The malignant stricture was dilated to at least 16.5 mm with a through-the-scope balloon dilator (CRE balloon; Boston Scientific, Natick, Mass).

After dilation a guidewire was passed beyond the ligament of Treitz under fluoroscopic control, and the endoscope was removed. The jejunal magnet (14-mm diameter) was mounted on a catheter and advanced over the guidewire to the horizontal part of the duodenum under fluoroscopic guidance. Finally, the gastric magnet (16-mm diameter) was inserted in the stomach attached to the endoscope with a forceps and manipulated under fluoroscopic guidance until mating with the previously placed jejunal magnet occurred. The location of the magnet was marked with an endoscopic clip (Figure 1) or with India ink, to easily identify the location of the placement should the magnets be passed into the intestine.

Approximately 8 to 10 days after magnet placement, a gastroscopy was repeated to identify the gastroenteric fistula and to remove the magnet pair by the retrieval suture if the magnets were free in the stomach. In case the magnets were still attached to the wall, gastroscopy was repeated 2 to 4 days later at the discretion of the endoscopist.

Once the magnets had been removed or had passed into the small bowel, a self-expanding metal stent with a 15-mm body and wide flanges (Figure 2) was delivered through the gastroenteric fistula (Figure 3) by using direct vision and/or fluoroscopy. The stent's proximal flanged edge (Figure 4) was positioned in the gastric lumen to prevent migration.

Data collection

After obtaining informed consent, the GOOSS (a 4-point scale with 0 being the inability to intake orally and 3 the ability to eat a low-residue or full diet) scores were determined

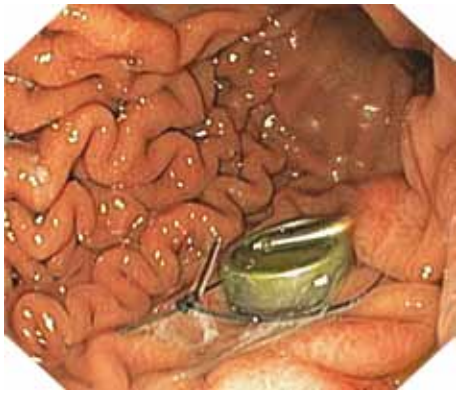

Figure 1. Gastric magnet marked with an endoscopic clip.

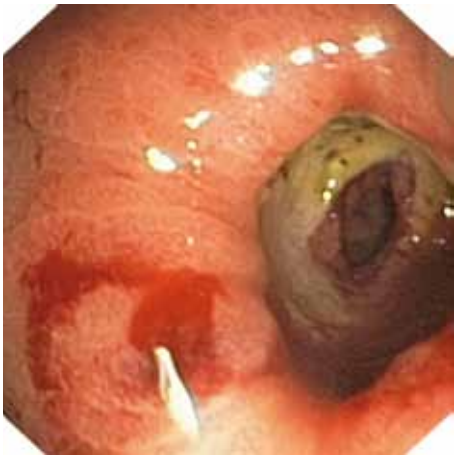

Figure 3. Gastrojejunal fistula formed by the Magnetic Anastomosis Device.

Figure 2. "Yo yo"-shaped stent.

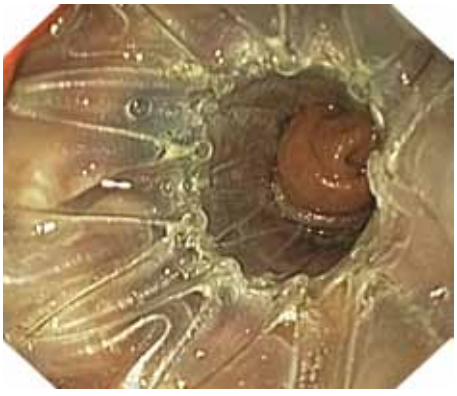

Figure 4. The stent's proximal flanged edge positioned in the gastric lumen.

as previously described.[16] Patients were followed up by telephone between magnet and stent placement and 24 hours after stent placement. The GOOSS score was determined before and 24 hours after stent placement. Thereafter, the patients were contacted every 5 to 7 days during the initial 3 weeks and every 25 to 30 days thereafter to assess the GOOSS score and to detect any adverse events or adverse device effects until an endpoint was reached. Patients returned 4 weeks after stent placement (25–30 days) for physical evaluation and an abdominal radiograph to check the position of the stent. Patients were followed for 180 days or until stent occlusion, recurrence of GOO, or death. Procedure-related data such as endoscopic difficulty of placement, technical difficulties and immediate post-placement complications were also assessed.

Definitions and endpoints

Safety and the technical success rate associated with the creation of a gastroenteric anastomosis by using the Cook Magnetic Anastomosis Device with transanastomotic deployment of a stent was the primary endpoint. Safety was defined as the absence of serious adverse events, serious being defined as those events leading to death, life-threatening situations, hospitalization, or prolongation of hospital stay. Technical success was defined as placement of the gastric and jejunal magnets, creation of the anastomosis, and deployment of a stent through the anastomosis. Possible adverse device effects included perforation of interposed organs or tissue, proximal or distal migration of the gastrojejunal stent, small-bowel obstruction because of failure of the magnets to pass a distal intestinal stricture, and any adverse event occurring during endoscopic placement. Secondary endpoints were improvement in tolerance of oral feeding by using the GOOSS score, the rate of stent migration, and the duration of patency of the stented anastomosis. Technical difficulties were defined as the inability to dilate the stricture, inability to successfully fuse the magnets or to deploy the stent, and failure of any component of the delivery system for the magnet or stent. Ease of placement of magnets and the stent was graded on an analogue 5-point scale (1 being very easy and 5 being very difficult).

Statistical analysis

We expected to be able to include 40 patients at the participating hospitals during 1 year. This was based on 2 recently concluded prospective studies on duodenal stent placement including 20 patients per year in the Amsterdam Medical Center, combined with the assumption that half of these patients might not meet the more strict entry criteria of the current study. All participating centers were expected to have a similar patient recruitment.

Descriptive statistics were used for data of all included patients (intention to treat), except for those patients who died between the time of providing informed consent and the first endoscopic procedure. Wilcoxon matched-pairs signed-rank test was used to assess improvements from baseline (GOOSS score), after calculating the average score per patient from available follow-up assessments until death, weighed for the length of the preceding time interval between planned assessments. Duration of patency of the stented anastomosis was defined as time to first occlusion and was assessed by Kaplan-Meier analysis with stent dysfunction taken as event and death before stent dysfunction as censored observation. The date of occlusion was judged from the date of first reported symptoms. Statistics were performed using the SPSS (version 16.0) software package (SPSS, Inc, Chicago, Ill). Statistical significance in all analyses was set at $P < .05$.

A data safety monitoring board consisting of independent physicians convened on a regular basis to evaluate study progress and review adverse events and adverse device effects.

Results

Inclusion of patients started in January 2008. In July 2008, after the inclusion of 12 patients, the study was placed on hold because of 2 adverse device effects both of which were stent migration. The study was reopened in November 2008 after approval of the medical ethical committees to continue with a different stent. In February 2009, the enrollment was suspended by the data safety monitoring board because of a serious adverse event leading to the death of a patient. Until this suspension, 18 patients with malignant GOO had been included.
Patient demographics and clinical characteristics are summarized in table 1.

Table 1. Patient demographics and clinical characteristics at baseline.

No. of patients	18
Age, (y), mean (SD)	68.8 (11.0)
Sex: male/female, no.	15 / 3
Tumor characteristics, no. (%)	
Pancreatic cancer	12 (66.7)
Cholangiocarcinoma	3 (16.7)
Duodenal cancer	1 (5.6)
Gastric cancer	1 (5.6)
Metastatic disease	1 (5.6)
Severity of obstruction	
GOOSS score, no. (%)	
0: No oral intake	11 (61.1)
1: Liquids only	3 (16.7)
2: Soft solids	4 (22.2)
General condition	
Body mass index, mean (SD)	21.8 (3.5)
Karnofsky Performance Scale score, mean (SD)	72.2 (9.4)

GOOSS, Gastric outlet obstruction scoring system; SD, standard deviation.

Primary endpoint

In 3 of the 18 patients, adequate alignment of the magnets could not be achieved. Two patients died 2 and 10 days after magnet placement and before stent placement. Autopsy on both patients did not show a stent-related cause of death, and disease

progression was considered the most likely cause of death. In 13 patients, placement of a stent through the gastroenteric fistula was attempted. This procedure took place a median of 10 days (range 8-21 days) after magnet placement. Stent placement failed in 1 patient because of technical difficulty to release the stent from the delivery system. Placement of the stent was therefore successful in 12 out of 13 patients with a magnetic anastomosis (92%) and 12 out of the 18 original patients (66.7%).
During follow-up, adverse device effects occurred in 3 patients (25%), all being stent migrations, proven by radiography at 7, 11 and 81 days after stent placement. These patients were all treated with either a new gastrojejunal stent through the anastomosis (2 patients) or a duodenal stent (1 patient). Stents that had migrated were left and did not lead to symptoms. In 1 patient, a serious adverse event (free peritoneal perforation of the stent) occurred 7 days after stent placement, used in the second part of the study. The perforation was located in the jejunum at the distal margin of the stent, leading to fatal sepsis. Because of this serious adverse event further enrollment was suspended.

Secondary end points

Because of the limited number of patients and follow-up assessments, the improvement from baseline of the GOOSS score and duration of patency of the stented anastomosis were not calculated. Failure of the stented anastomosis occurred twice after 7 days (1 perforation, 1 migration), once after 11 days (migration), and once after 81 days (migration). Seven patients died while having a functional anastomosis. One patient completed the follow-up of 180 days with a functional anastomosis.
The magnet placement procedure took a median of 48 minutes (range 21-168 minutes). In 12 of 18 patients the duodenum had to be dilated with a balloon to pass the jejunal magnet. Difficulty of placement was graded a median 4 out of 5 (difficult) for the jejunal magnet, 2 out of 5 (easy) for the stomach magnet, and 2 out of 5 for the entire procedure. Stent placement took median 30 minutes (range 15-93 minutes); the magnets were retrieved in 6 patients, and in 7, the magnets had migrated distally. In 1 patient, the anastomosis appeared to be immature and a second procedure took place 2 days later, 12 days after magnet placement. Difficulty of stent placement was graded a median 2 out of 5.

Discussion

Palliation of malignant GOO remains challenging. There seems to be a need for a technique that combines the safety of the duodenal stent with the long-term efficacy of a surgical bypass.
Our study revealed that the use of magnets to create an anastomosis between the stomach and jejunum is feasible and safe. None of the adverse events was related to the

magnets. It can, of course, not be excluded that the first endoscopic procedure to place the magnets may have worsened the condition of the 2 patients who died before stent placement.

Alignment of the magnets was not always easy and failed in 17% of the patients. Nevertheless, the overall magnet placement procedure was graded easy and took a median 48 minutes.

In the first instance, a specially designed fully covered "yo yo"-shaped stent was used. This stent was fully covered to minimize the risk of leakage of the anastomosis. Because of the well-known risk of migration of covered stents, wide horizontal flanges had been added at both sides of the relatively short body (15 mm).[11] During the study, it appeared that this special stent caused some difficulties: mounting it on the delivery system, releasing it accurately, and migration in 3 of 7 (42.8%) successful placements. Mainly because of the high migration rate it was decided to switch to the commercially available non-covered, 6-cm nitinol duodenal stent (Evolution Duodenal Stent, Cook Endoscopy Inc). This stent was successfully placed in 5 patients without migration but led to a fatal perforation in the last patient. This perforation probably occurred because of the distal end of the stent impinging on the opposite jejunal wall.

The median period of 10 days (range 8-21 days) between magnet placement and stent placement is a point of concern. We hypothesized that dilating the stricture at least 15 mm, which was needed to pass the 14 mm diameter magnet, would be sufficient for at least a liquid diet until stent placement.

As a consequence of the limited number of patients and follow-up assessments, we concluded that the data were insufficient to do a formal calculation of the secondary endpoints. Fifty percent of our patients either had a stent failure or died within 1 month after stent placement.

There is only 1 other clinical study on the creation of a gastroenteric anastomosis by using magnets for the palliation of malignant GOO.[13] In this single-center, prospective study, 15 patients were included; in 2 the procedures failed, 1 because of the inability to sufficiently dilate the stricture to allow passage of the duodenal magnet and the other because of a perforation that occurred as a result of manipulation of the fresh gastroenteric anastomosis, making emergency surgery necessary. During follow-up, 3 stent migrations and 1 stent obstruction occurred. All patients maintained oral intake of solids until death. As in our study, the procedural concept appears to be in order, but the design of the stent seemed to be one of the limitations. It is also interesting to note that in this single-center study no failures of alignment of the magnets were mentioned, indicating that a learning curve effect may have contributed to our 3 failures.

The current available data seem to justify further development of this innovative technique. Research could focus on improvement of the design of the stent, creating, for example, a "yo yo"-shaped, partially covered stent with larger flanges and a shorter body to prevent migration or an uncovered stent approximately 3 cm in length with flanges at

both sides. Ideally, an endoscopic magnetic bypass would not need any device to keep it open. Maturation of the anastomosis would preferably occur in 2 to 3 days or the magnets should have a central lumen that could be used to place a temporary feeding tube. Finally the option of combined placement of a duodenal stent for short-term palliation and creation of a gastroenteric anastomosis for long-term palliation could be considered.

The attractiveness of the concept of a compression magnetic anastomosis is underlined by recent studies on the creation of a choledochoduodenostomy, Roux-en-Y gastric bypass, and colonic anastomosis.[17-19] In our opinion, the endoscopic magnetic gastroenteric anastomosis is a very interesting and feasible concept. However, in this study, the necessity of a stent led to serious morbidity and even mortality. The current system can therefore not be recommended for clinical use, and further research is needed to make this technique safe as well as feasible.

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