Endoscopic stent placement throughout the gastrointestinal tract
van den Berg, M.W.

Citation for published version (APA):
van den Berg, M. W. (2014). Endoscopic stent placement throughout the gastrointestinal tract

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CHAPTER 7

High proximal migration rate of a partially covered “big cup” duodenal stent in patients with malignant gastric outlet obstruction.

M.W. van den Berg,  
D. Walter 
F.P. Vleggaar 
P.D. Siersema 
P. Fockens 
J.E. van Hooft

*Endoscopy* 2014; 46:158-161
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ABSTRACT

Endoscopic placement of self-expandable metal stents (SEMS) has emerged as a palliative treatment for patients with malignant gastric outlet obstruction (GOO). Recently, a new partially covered big-cup SEMS has been developed to prevent both stent migration and tissue ingrowth. Our aim was to evaluate safety and efficacy of this SEMS in a cohort study of patients with incurable malignant GOO. The study was terminated prematurely due to 3 proximal stent migrations in 6 patients. Migrations occurred at 2, 4 and 29 days respectively and necessitated endoscopic removal and placement of another SEMS. The remaining 3 patients had a patent SEMS at the end of follow-up.

The high proximal migration rate of this new SEMS should be taken into account when considering routine clinical use in malignant GOO. Further research is warranted in order to find an optimal stent design that prevents both stent migration and tumor ingrowth.
INTRODUCTION

Endoscopic placement of self-expandable metal stents (SEMS) has become an attractive alternative to surgical gastrojejunostomy for palliative treatment in patients with malignant gastric outlet obstruction (GOO). The majority of studies reveal high technical and clinical success rates and no intervention-related mortality. However, studies comparing duodenal SEMS placement with gastrojejunostomy have shown higher rates of re-obstruction and re-interventions after stent placement.

Conventional duodenal SEMS mostly have an uncovered design. The mesh-like framework of uncovered SEMS prevents migration by providing an anchoring function, which is achieved by embedding tissue within the meshes after expansion. Logically, the disadvantage of this design is obstruction due to tissue ingrowth through the stent mesh, occurring in 12-21% of patients. Covered SEMS have been investigated as a promising alternative. Although effective in preventing tissue ingrowth, the covering membrane caused reduced anchoring and subsequently covered stents tended to migrate more frequently.

The newly developed Hanaro DPC-stent (Hanaro, M.I. Tech, Ltd., Seoul, Korea) is intended to overcome these shortcomings with an uncovered proximal big cup, which fits the pyloric area and is supposed to prevent distal stent migration, and a fully covered duodenal part that should withstand tissue ingrowth. Furthermore this stent can be placed through the endoscope in order to facilitate accurate stent release.

We hypothesized that placement of this SEMS would achieve good technical and clinical success rates, that are at least comparable to previously reported results in the literature. Moreover, we expected low re-obstruction and migration rates resulting in a prolongation of stent patency and a reduced number of re-interventions.

PATIENTS AND METHODS

This study was designed as an investigator initiated single-arm, prospective clinical trial to evaluate the efficacy and safety of the Hanaro DPC-stent in 40 patients with malignant GOO in two academic hospitals, the Academic Medical Center in Amsterdam and the University Medical Center Utrecht in Utrecht (Dutch Trial Register number NTR3555). The protocol was approved by local hospital ethics committees.

Patients
From August 2012, all consecutive patients 18 years or older, presenting with symptoms of GOO (early satiety or nausea and/or vomiting and a Gastric Outlet Obstruction Scoring System (GOOSS) score ≤ 2) due to malignant duodenal obstruction at the pylorus, duodenal bulb (D1) or descending part (D2) were considered for inclusion in this study.
Exclusion criteria were the following: absence of significant stenosis during endoscopy (i.e. stenosis traversable with therapeutic endoscope), potentially curable disease, pre-procedural evidence of stenoses in the small bowel or colon, previous treatment with SEMS for the same condition, a stenosis length requiring two (overlapping) SEMS or inability to undergo upper GI endoscopy.

We only included patients with a stenosis of duodenal part D1 or proximal D2 in order to prevent occlusion of the ampulla of Vater by the covered part of the SEMS. By doing so, biliary access was preserved for endoscopic intervention in case of a new or recurrent biliary obstruction after duodenal SEMS placement.

**Follow-up and study endpoints**

After stent placement, follow-up was performed at 7 and 14 days and thereafter monthly by telephone interviews. Follow-up continued until withdrawal of informed consent, death, or stent failure requiring placement of another SEMS, whichever came first.

Outcomes included clinical success, defined as improvement of GOOSS score of at least one point and/or relief of symptoms compatible with GOO one week after intervention; technical success defined as successful stent placement and deployment at the site of stricture and procedure- and stent-related adverse events.

**Stent placement**

Details of the duodenal stent placement procedure have been reported previously. All procedures were performed by two dedicated pancreaticobiliary endoscopists (JvH, PF) with extensive experience in duodenal stent placement.

The Hanaro DPC-stent is a recently developed Conformité Européenne (CE) approved through-the-scope SEMS stent made of nitinol. It combines a proximal uncovered big cup (length 20 mm, diameter 40 mm), which fits the pyloric area, as anti-migration feature with a fully silicone membrane covered intra-duodenal part (length 70mm, diameter 20mm) for prevention of tissue ingrowth. In this study solely SEMS with a length of 9 cm were placed, because only patients with a proximal duodenal stricture (D1 or proximal D2) were treated. A total of 22 radiopaque markers, 4 on each stent-end and 14 on the proximal end of the covering membrane, made a clear fluoroscopic view of the stent possible (Figure 1a-c). When stent dysfunction required placement of a new SEMS, a conventional uncovered SEMS was placed.
Proximal migrations with new duodenal stent for malignant GOO

Figure 1 | a) Picture of the Hanaro DPC-stent b) Endoscopic view of the proximal big cup of the Hanaro DPC-stent at the pyloric area c) Fluoroscopic control of stent deployment with contrast agent filling stent
RESULTS

In total, 6 patients were included in the Academic Medical Center between August and December 2012. Unfortunately, the study was terminated prematurely in January 2013 due to proximal stent migration in 3 patients. There were no patients included in the University Medical Center Utrecht because the study was terminated before an eligible patient presented there. Baseline patient characteristics are summarized in Table 1.

Stenoses were located at the pylorus in 1 patient, at D1 in 4 patients and at D2 in 1 patient. Median stenosis length was 3 cm (range 2-4). At baseline GOOSS-scores were 0 in 1 patient, 1 in 2 patients, 2 in 2 patients and 3 in 1 patient. The latter patient had severe nausea and vomiting.

Regarding biliary drainage, 3 patients were already adequately drained with a biliary SEMS. In the remaining 3 patients liver function tests revealed no signs of biliary obstruction and these patients had no plastic biliary stent in situ. Therefore no biliary interventions were performed prior to duodenal stent placement in the 6 study patients.

Outcomes and adverse events

Endoscopic control after stent placement showed that all stents were well in place with the proximal big-cup fitted at the pylorus (Figure 1b) and fluoroscopic control demonstrated sufficient stent deployment in all six patients. Therefore, the technical success rate was 100%. Clinical success was achieved in 4 patients (67%). At one week of follow-up, the GOOSS scores in these patients improved from 1 to 2 in 2 patients and from 0 and 2 to 3 in 2 patients. Moreover, symptoms of vomiting declined in all 4 patients. The clinical failures in 2 patients were caused by a complete proximal migration of the SEMS into the stomach, which was discovered by endoscopy after 2 and 4 days, respectively. Furthermore, endoscopy for recurrent GOO symptoms in a third patient revealed another full proximal migration 29 days after stent placement. All 3 proximal migrations were treated with endoscopic removal of the Hanaro DPC-stent using a snare and placement of an uncovered conventional SEMS. Consequently follow-up was discontinued in these 3 patients.

One patient presented with recurrent biliary obstruction 45 days after duodenal stent placement due to tumor ingrowth of the previously placed biliary SEMS. This was treated with stent-in-stent placement of a new biliary SEMS using endoscopic retrograde cholangiopancreatography (ERCP).

Finally, two patients developed recurrent GOO symptoms at 49 and 30 days after stent placement respectively. In both patients upper endoscopy showed a fully open stent and no evidence of additional stenoses. In the first patient recurrent symptoms started directly after the start of palliative chemotherapy and were therefore graded as toxic side effects. This was confirmed by the fact that symptoms subsided after chemotherapy was stopped. In the absence of an alternative diagnosis, obstructive symptoms in the second patient were most likely caused by a motility disorder.
Two patients with a patent Hanaro-DPC stent in situ died due to disease progression after a follow-up of 60 and 69 days, respectively, and 1 patient was lost to follow-up with a functional stent 228 days after insertion.

Study outcomes are summarized in Table 1.

DISCUSSION

In this prospective cohort study we aimed to evaluate safety and efficacy of the newly designed Hanaro-DPC stent in patients with malignant GOO. Unfortunately, a high number of proximal stent migrations resulted in the premature termination of the study, which was decided in consent among principal investigators of both study sites and after consultation of a biomedical statistician.

In the literature, duodenal stent dysfunction has been reported to vary between 14-30%. The main cause of stent dysfunction is tissue ingrowth through the meshes of uncovered SEMS. The use of covered stents has therefore been investigated as an alternative. A recently published randomized trial indeed found a significantly lower tissue ingrowth rate for covered stents; however, this was offset by a significantly higher migration rate, which ultimately resulted in comparable overall stent patency and stent dysfunction rates. Nevertheless, distal stent migration has the potential risk of intestinal obstruction or perforation requiring emergency surgery in a small number of patients. For this reason, placement of uncovered duodenal stents is still the standard of care in the majority of endoscopy units.

We believed that the design of the newly developed Hanaro DPC-stent was promising with regard to prevention of both tissue ingrowth and distal stent migration. However, in 3 of 6 patients the stent migrated proximally into the stomach, resulting in recurrent GOO symptoms and necessitating endoscopic stent removal and placement of a different stent. A large prospective series found a significant association between the use of chemotherapy and stent migration, however in the current study none of the patients with a migrated stent was treated with chemotherapy. Moreover, proximal stent migrations are less frequently observed in the literature when compared to distal migrations. Therefore, the explanation for the high migration rate of the Hanaro DPC-stent is probably related to the stent design. Adam et al. described a ‘soap bar’ effect as an explanation for proximal migration of partially covered esophageal stents with a proximal flare as anti-migration feature in malignant esophageal stenosis. They speculated that peristalsis in combination with a relatively short stenosis, the smooth surface of the covered stent part and the conical shape of the stent resulted in upward forces that tended to push the stent in a proximal direction. Because all these factors were present in our study the ‘soap bar’ effect is likely a valid explanation for the high proximal migration rate. One
Table 1 | Patient demographics and outcomes after duodenal stent placement

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Malignancy</th>
<th>Palliative chemotherapy</th>
<th>Technical success</th>
<th>Clinical success</th>
<th>Adverse Events</th>
<th>Follow-up, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>M</td>
<td>Cholangio Carcinoma</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>Proximal stent migration (29)</td>
<td>29 (stent failure)</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>Gastric cancer</td>
<td>yes*</td>
<td>yes</td>
<td>yes</td>
<td>Nausea and vomiting due to chemotherapy (49)</td>
<td>228 (lost to follow-up)</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>F</td>
<td>Pancreatic cancer</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>Motility disorder (30)</td>
<td>60 (death)</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>F</td>
<td>Pancreatic cancer</td>
<td>yes*</td>
<td>yes</td>
<td>yes</td>
<td>Biliary obstruction (45)</td>
<td>69 (death)</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>M</td>
<td>Pancreatic cancer</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>Proximal stent migration (4)</td>
<td>4 (stent failure)</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>M</td>
<td>Pancreatic cancer</td>
<td>yes§</td>
<td>yes</td>
<td>no</td>
<td>Proximal stent migration (2)</td>
<td>2 (stent failure)</td>
</tr>
</tbody>
</table>

y, years; M, male; F, female

*Palliative chemotherapy was started 42 and 3 days after stent placement respectively
§Palliative chemotherapy was already completed before stent placement
could argue that adding extra length to the covered stent part might prevent migration. However, that would require placement of a biliary SEMS in all patients, regardless of the presence of biliary obstruction, because this would result in occlusion of the ampulla of Vater. Another option to prevent proximal migration could be the addition of anchoring flaps to the covered part of the stent.\textsuperscript{11}

The remaining 3 patients developed no stent-related problems and therefore the overall stent dysfunction rate was 50\% (3/6) with a 95\% confidence interval (CI) of 11.8\%-88.2\%, which is very wide due to the small study population. As the lower limit of the 95\% CI of 11.8\% is still below stent dysfunction percentages of other studies, one could argue that our study should have been continued in order to exclude sample error.\textsuperscript{1-5} However, stent migrations were observed after 2, 4 and 29 days respectively. This resulted in a clinical success rate of 67\%, which is low when compared to previously reported data.\textsuperscript{1-5} Moreover, stent migration occurred after short time intervals when compared to median stent patency times ranging between 147-307 days for uncovered stents\textsuperscript{2, 5, 12}, especially taken into account that the majority of patients suffering from malignant GOO have a life expectancy of less than 3 months\textsuperscript{13}. Despite the very limited number of patients, we therefore felt that we needed to terminate this study prematurely.

**Conclusion**

Although limited by a small number of patients, this prematurely terminated study showed a high proximal migration rate of the Hanaro DPC-stent in malignant GOO. This finding should be taken into account when considering routine clinical use of this stent. Further research is warranted in order to find an optimal stent design that prevents both stent migration and tumor ingrowth.
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REFERENCE LIST


