Endoscopic biliary drainage
van Berkel, A.M.

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Self-expandable metal stents in benign biliary strictures due to chronic pancreatitis


Department of Gastroenterology and Hepatology
Academic Medical Center, Amsterdam, The Netherlands

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ABSTRACT
Background: In selected patients with chronic pancreatitis (CP) in whom conventional plastic stenting fails and who have a contraindication or refuse surgery, insertion of a biliary self-expandable metal stent (SEMS) might be a valuable treatment.
Methods: Between 1994 and 1999, thirteen CP patients received SEMS for benign biliary strictures (mean age 56 years, 4 women and 9 men). The indication for SEMS placement was: contraindication to surgery (n=10), presumed inoperable pancreatic carcinoma (n=1), concomitant non-resectable lung cancer (n=1), rejected surgery (n=1). Success of treatment was defined as adequate biliary drainage by SEMS therapy.
Results: Mean follow-up time was 50 months (range 6 days-86 months). Nine patients (69%) were successfully treated by SEMS therapy: a patent first SEMS (n=5), a patent second SEMS inserted through the first SEMS (n=3), and one patent SEMS after balloon cleaning. In four patients SEMS treatment was not successful (migration n=1, occlusion n=3). Mean SEMS patency was 60 months (95% CI 43 months-77 months). At 33 months the probability of adequate biliary drainage with SEMS therapy was 75%.
Conclusion: SEMS therapy is safe and provides successful and prolonged biliary drainage in benign biliary strictures due to CP in whom surgical intervention is not possible or desirable.

INTRODUCTION
In patients with chronic pancreatitis (CP) 10-30% develop symptomatic biliary strictures(1-3). Endoscopic insertion of plastic stents provides excellent short-term results in terms of relief of jaundice. Long-term results, however, are disappointing. First, long-term stenting with plastic stents is limited by stent clogging which can only partly be avoided by elective stent exchanges(3,4). More importantly, after one year of stent therapy up to 80% of patients have a persistent stenosis and need to undergo surgical bypass (e.g hepaticojejunostomy)(4).
There is, however, a subset of patients in whom surgery is contraindicated because of an increased surgical risk due to concomitant portal hypertension or advanced cardiac or pulmonary disease. Some patients reject surgery for fear of the operation. It is in this highly selected group of patients that the use of self-expandable metal stents (SEMS) might be a valuable treatment option, potentially precluding problems of stent clogging associated with conventional stents.
SEMS have a larger diameter compared to conventional polyethylene stents (30 Fr versus 10 Fr) and longer patency rates, which has been well documented in case of malignant biliary obstruction(5,6). Drawback of SEMS is the impossibility to remove them once they are inserted, which withheld many clinicians to use them in cases with benign strictures. Published data comprises case reports and small series, and results are contradictory with only limited follow-up data(7-13).
The aim of this study was to evaluate the safety and long-term outcome of SEMS in a selected group of patients with benign biliary strictures due to chronic pancreatitis in whom surgical intervention is not possible or desirable.

**Patients and Methods**

**Patients**

All patients with CP who received a SEMS to relieve obstructive jaundice due to a benign biliary stricture between 1994 and 1999 were retrieved from an endoscopic database. Data were collected retrospectively until the end of the follow-up period in November 2002.

**Treatment**

If after removal of the plastic biliary stent the cholangiogram showed a persistent distal bile duct stricture, a SEMS (Wallstent®, Schneider, Switzerland) was inserted using standard techniques described elsewhere (5). In all patients a 30 Fr 10 cm SEMS was used which expands to 8-10 mm and shortens to 6.8 cm. No prophylactic antibiotics were prescribed. If not already performed at a previous ERCP procedure, biliary sphincterotomy was performed in all cases.

**Follow-up**

Patients were evaluated in the outpatient clinic every three to six months by means of clinical examination and laboratory tests. Ultrasonography was performed whenever indicated by abnormal clinical or biochemical findings. In case of stent dysfunction, an ERCP was performed for confirmation SEMS obstruction and restore biliary flow by various means (see results). At the end of the follow-up period in November 2002, all patients (or relatives in case of death) and their physicians were interviewed by telephone.

**Definitions**

Success of treatment was defined as adequate biliary drainage by a SEMS, including placement of a second SEMS through the first in case of stent dysfunction of the latter or cleaning of SEMS by means of saline flushing and balloon sweeping. Stent drainage was considered to be successful if serum bilirubin dropped more than 20% within one week after stent insertion. If jaundice failed to resolve or if a patient developed jaundice, cholangitis, or a combination of a flu-like syndrome and cholestasis, an ERCP was performed to confirm obstruction of the stent. Stent patency represented the interval between the time of stent insertion and the time of re-ERCP. Complications of ERCP and sphincterotomy were evaluated according to the criteria of Cotton(14). The end of follow-up was defined as the time of removal of the SEMS, death, or the end of the follow-up period in November 2002.
Statistics
Data are presented as means (± standard deviation). Patient survival and stent patency was calculated according to Kaplan-Meier. With this type of 'survival' analysis there is a limitation in reporting the 50% (median) value when this value is not reached in case of a prolonged 'survival'. In such cases, the calculated mean is an underestimation of the actual 'survival' (i.e. SEMS patency). For accurate data representation the 75% value is reported. The Chi-square test was used for comparison of categorical data. A p-value < 0.05 was considered statistically significant.

RESULTS
Patients
A total of 13 patients were identified from the endoscopic database, 9 men and 4 women, with a mean age of 56 years (range 40-79 years) (Table 1). The cause of chronic pancreatitis was alcohol abuse (n=8), pancreas divisum (n=1) and idiopathic (n=4). All patients had been treated with conventional plastic stents before insertion of a SEMS (mean 6 stents, range 1-18). Indications for SEMS placement were: (relative) contraindication to surgery (e.g. portal hypertension) (n=10), presumed inoperable pancreas carcinoma which after long-term follow-up turned out to be a benign stenosis due to CP (n=1), no candidate for surgery because of concomitant non-resectable primary lung malignancy (n=1), patient rejected surgery (n=1). Two patients had undergone previous surgery of the pancreas (pancreaticojejunostomy n=1; pancreatic tail resection with Roux-Y anastomosis n=1).

Early results
Endoscopic SEMS placement was successful in all patients. Sphincterotomy was performed in one patient. All other patients had already undergone a sphincterotomy at previous ERCP procedures.
Early complications occurred in one patient: an initial optimal placed SEMS migrated into the duodenum and was removed by a polypectomy snare after 6 days (Table 2). Eleven days after stent removal this patient underwent a choledochoduodenostomy and pancreaticojejunostomy and had an uneventful recovery. The 30-day mortality was zero.

Late results
Nine patients (69%) had adequate biliary drainage by SEMS therapy at the end of follow-up: a patent first SEMS (n=5), a patent second SEMS inserted through the first SEMS (n=3), and one patient with a patent SEMS after cleaning by a balloon (Table 2).
In four of the five patients who were successfully treated by a patent first SEMS, the stent remained patent after 80, 66, 43 and 39 months, respectively. One of these patients developed a liver abscess in the left liver lobe 14 months after SEMS place-
ment which was considered a late complication. Treatment consisted of antibiotics and percutaneous drainage of the abscess. One patient died of an unrelated cause with a patent SEMS 18 months after insertion.

In three patients a second SEMS was inserted through the first SEMS, after respectively 65, 57 and 45 months. The second SEMS remained patent for a minimum duration of 27, 34 and 13 months, respectively.

In one patient, the SEMS was cleaned by a balloon on three different occasions (8, 11, and 26 months) during which sludge and debris was removed. This patient died 48 months after SEMS placement due to pulmonary cancer with a patent SEMS.

In four patients SEMS treatment was not successful (31%). In one patient the SEMS migrated into the duodenum 6 days after placement and was removed by a polypectomy snare as described earlier. This patient underwent a choledochoduodenostomy and pancreaticojejunostomy and died 40 months later from an unrelated cause. In the remaining three patients a polyethylene stent was inserted through the SEMS after 6, 25 and 33 months, respectively. One of these patients underwent a successful hepaticojejunostomy after 5 polyethylene stent exchanges due to stent clogging. In this patient the SEMS remained in situ for 52 months after surgery without complications.

Overall mean follow-up was 50 months (range 6 days-86 months). At the end of the observation period, three patients died of whom two with a patent SEMS in situ and one patient with the removed SEMS. At 33 months the probability of adequate biliary drainage with SEMS therapy was 75%. The calculated mean SEMS patency (Kaplan Meier method) was 60 months (95% CI 43 months-77 months) (Figure 1).

DISCUSSION

In this series of selected patients with benign biliary strictures due to chronic pancreatitis in whom surgical intervention was not possible or desirable, SEMS therapy provided adequate biliary drainage in the majority of patients (69%) after a overall mean follow-up time of 50 months. The probability of adequate biliary drainage by means of SEMS therapy at 33 months was 75%.

In patients with chronic pancreatitis (CP) 10-30% develop symptomatic biliary stenoses(1-3). If the biliary stenosis is due to compression by an edematous inflamed pancreatic head or a pseudocyst, biliary obstruction will resolve if the inflammation subsides or the pseudocyst is drained. If, however, biliary obstruction is caused by a fibrotic stricture due to repeated or ongoing inflammation, the obstruction will not resolve spontaneously. In these cases, medical intervention is mandatory. The gold standard treatment is surgical biliary diversion (e.g. hepaticojejunostomy). This has been challenged by endoscopic interventional therapy, but studies have now shown that complete resolution of a biliary stricture due to CP and permanent removal of standard polyethylene stents is achieved in only 10-30% of patients(4,13,15,16). Continued stent therapy (>1 year) is not regarded as a valid treatment option because
of the need of frequent elective stent exchanges (every 3 months) and the risk of repeated stent clogging with associated complications such as cholangitis and secondary biliary cirrhosis. For these reasons, many institutions have adopted the policy to endoscopically stent a CP induced fibrotic stricture for one year and refer the patient for surgical biliary diversion in case of failure.

There is a subset of patients in whom surgery is contraindicated because of an increased surgical risk due to concomitant portal hypertension (in patients with CP) or complicated cardiac or pulmonary disease. Some patients reject surgery for fear of the operation. It is in this highly selected group of patients that the use of self-expandable metal stents (SEMS) might be a valuable treatment option, potentially precluding problems of early stent clogging and frequent plastic stent exchanges. SEMS have significantly longer patency rates compared to polyethylene stents in malignant biliary obstruction\(^5,6\). This is mainly due to a larger diameter compared to conventional polyethylene stents (30 Fr versus 10 Fr). Theoretically, SEMS might perform better in benign strictures because, obviously, obstruction due to tumor ingrowth does not occur. Drawback of SEMS is the impossibility to remove them once they are inserted, which, together with fear of complicating future surgical intervention, withheld many clinicians to use them in cases with benign strictures. Although SEMS have been successfully removed wire by wire, this seems neither practical nor necessary\(^{17,18,19}\). In case of obstruction, standard polyethylene stents can be inserted through the SEMS. So far, it has not been shown that a deployed SEMS in the distal common bile duct complicates future surgical intervention and long-term outcome. In our series, one patient underwent a hepaticojejunostomy with a SEMS left in situ. This patient had an uneventful recovery and remains free of symptoms with the SEMS in situ 52 months after surgery.

Studies on the use and outcome of SEMS in benign biliary strictures have shown contradictory results\(^7-13\). Most publications comprise of case reports. There are only very few patient series with limited number of patients and follow-up time. Outcomes are difficult to compare because of differences in patient population (postsurgical benign strictures versus CP induced benign stricture), the route of SEMS placement (endoscopic versus percutaneously) and SEMS stent design.

Deviere and co-workers reported an overall SEMS patency rate of 90% in 20 patients with benign biliary strictures due to CP after a mean follow-up of 33 months\(^7\). Only 2 patients developed SEMS occlusion. They concluded that if SEMS occlusion occurs, it does so within 6 months after insertion, because it was postulated that in this time interval abnormal intima hyperplasia occurs and becomes symptomatic. Macconi and co-workers reported on 18 patients with postsurgical strictures who were treated by SEMS which were inserted percutaneously. The patency rate at 3 year follow-up was 69%\(^8\). Although obtained in a different patient population, these results are in agreement with our data. In another study with percutaneously inserted SEMS in a group of patients with miscellaneous causes of benign strictures, the median SEMS patency was 32 months\(^9\).
The cause of SEMS occlusion is not fully understood and seems multifactorial. O’Brien and co-workers performed baby scope examination 1 year after SEMS insertion and complete epithelialization of the metal stent was seen in all patients(12). Hyperplastic biliary epithelium may be the result of localized trauma to the mucosal layer triggered by the edges of the uncovered metal stent. If excessive intima hyperplasia causes SEMS obstruction, this might be overcome with the use of a covering. Until now, covered SEMS have only been used in malignant strictures without showing any additional benefit because of tumor overgrowth(20). Other experimental strategies to re-establish biliary drainage in case of intima hyperplasia include intraductal radiotherapy, photodynamic therapy or endoscopic diathermy (13,21,22). A relatively new but fascinating observation is that some drug compounds applied as a coating on the metal meshes, such as sirolimus or paclitaxel, are effective in reducing neointimal tissue proliferation in intravascular stents (23). Bacterial adherence may also play a role, followed by sludge and stone formation as was seen in different studies(9,11,21); re-canalisation was performed by lithotripsy or cleaning by a balloon.

One of the limitations of our retrospective study is the fact that SEMS dysfunction was treated at the endoscopists’ discretion in various ways and not by protocol. Placement of a second SEMS through an occluded SEMS was performed in three patients. In all three patients the second SEMS remained patent until the end of the follow-up period. In one patient the SEMS was cleaned on multiple occasions by a balloon with favourable results. Clearly, SEMS occlusion in this patient was due to sludge formation and debris and not to intima hyperplasia. Standard treatment in case of SEMS obstruction in malignant stricture consists of placement of a polyethylene stent through the SEMS and this was performed in our study in three patients. Although effective in establishing immediate drainage, the problems of frequent stent occlusion remains and these patients underwent multiple polyethylene stent exchanges thereafter. It remains uncertain whether these patients would have been more adequately treated with a second SEMS.

In conclusion, SEMS therapy is safe and provides successful and prolonged biliary drainage in a selected group of patients with benign biliary obstruction due to CP in whom surgical intervention is not possible or desirable. If the SEMS becomes obstructed it should be evaluated at ERCP whether this is due to excessive intima hyperplasia or sludge formation. In the latter case only flushing with saline and cleaning by a balloon should be performed. In case of the former the initial indication for SEMS placement must be reconsidered. In case of a relative contraindication for surgery, a surgical biliary diversion should be reconsidered. In all other cases placement of a second SEMS through the first seems a valid alternative.
Table 1. Characteristics of patients with benign biliary strictures due to chronic pancreatitis receiving SEMS therapy (n=13).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>56 (40-79)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>9/4</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>8</td>
</tr>
<tr>
<td>Divisum</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>4</td>
</tr>
<tr>
<td>Mean previous plastic stents (range)</td>
<td>6 (1-18)</td>
</tr>
<tr>
<td>Indication SEMS</td>
<td></td>
</tr>
<tr>
<td>Relative contraindication surgery</td>
<td>10</td>
</tr>
<tr>
<td>Presumed inoperable pancreatic cancer</td>
<td>1</td>
</tr>
<tr>
<td>Other malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Refused surgery</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Outcome of SEMS therapy in patients with benign biliary strictures due to chronic pancreatitis (n=13).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early complications</td>
<td></td>
</tr>
<tr>
<td>SEMS migration</td>
<td>1</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>0</td>
</tr>
<tr>
<td>Late complications</td>
<td></td>
</tr>
<tr>
<td>liver abscess</td>
<td>1</td>
</tr>
<tr>
<td>Mean follow-up*</td>
<td>50 months</td>
</tr>
<tr>
<td>(6 days-86 months)</td>
<td></td>
</tr>
<tr>
<td>Mean adequate drainage by SEMS §*</td>
<td>60 months</td>
</tr>
<tr>
<td>(6 days-80 months) [43 months-77 months]</td>
<td></td>
</tr>
<tr>
<td>successful treatment</td>
<td>9</td>
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<tr>
<td>not successful treatment</td>
<td>4</td>
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<tr>
<td>Overall mortality</td>
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</tr>
<tr>
<td>procedure related</td>
<td>0</td>
</tr>
<tr>
<td>not procedure related</td>
<td>3</td>
</tr>
</tbody>
</table>

§ Kaplan Meier method
* (range), [95% confidence interval]
**Figure 1.** Kaplan Meier plot for adequate biliary drainage by SEMS therapy in patients with benign biliary strictures due to chronic pancreatitis (n=13).
REFERENCES


