Endoscopic biliary drainage
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A prospective randomized study of hydrophilic polymer coated polyurethane versus polyethylene stents in distal malignant biliary obstruction


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ABSTRACT
Background and Study Aims: Hydrophilic polymer-coated polyurethane (HPCP) stents have a low friction coefficient and a hydrophilic layer, which may reduce biofilm formation and increase the period of stent patency. We compared the patency rates with this new stent with the standard Amsterdam-type polyethylene (PE) stent in a prospective randomized trial.

Patients and Methods: One hundred patients with an unresectable distal malignant bile duct stricture without a previous drainage procedure were randomly assigned to receive either a HPCP stent or a PE stent. The diameter (10 Fr), length (9 cm) and stent design (Amsterdam type) were similar in both stents. Nine patients were excluded. Forty-four patients received an HPCP stent and 47 patients a PE stent. The diagnoses included carcinoma of the pancreas (n = 78), papilla (n = 1), bile duct (n = 10), and metastases (n = 2).

Results: Stent insertion was successful in all patients. Stent dysfunction occurred in 27 of the HPCP stents and 20 of the PE stents, with median stent patency periods of 77 days (95% CI, 53 - 101 days) for HPCP stents and 105 days (95% CI, 42 - 168 days) for PE stents. The patency period was significantly longer for the PE stent (P = 0.04). Early complications occurred in four patients (4%), one in the HPCP group and three in the PE group.

Conclusion: Hydrophilic polymer-coated polyurethane stents do not prolong the patency period of biliary stents. In fact, the current standard treatment using polyethylene stents in patients with distal malignant biliary obstruction showed a significantly longer patency period.

INTRODUCTION
In patients with unresectable malignant biliary obstruction, the treatment of choice is insertion of an endoprosthesis during endoscopic retrograde cholangiopancreatography (ERCP). The main clinical problem with endoprostheses is late stent occlusion, which makes repeat intervention necessary. Various attempts to prolong the patency period by changing the stent diameter or stent design, or by altering bile composition, have so far been unsatisfactory.

The initial event in stent occlusion is adhesion of bacteria to the inner surface of the stent. Altering binding sites by changing the physical properties of the stent material may decrease the rate of biofilm formation. A hydrophilic polymer coating has been shown to be effective in reducing bacterial adherence in in-vitro studies (1). Costamagna et al. conducted a randomized study comparing hydrophilic polymer-coated polyurethane (HPCP) stents with standard polyethylene (PE) stents in patients with malignant biliary obstruction and suggested that the HPCP stent had a longer patency period (2).

The aim of the present study was to compare the patency periods of the HPCP stent and the standard PE stent in a prospective randomized trial.
PATIENTS AND METHODS

Criteria for Eligibility

Patients were included if they had obstructive jaundice caused by a malignant distal bile duct stricture and had not previously undergone a drainage procedure. The diagnosis was based on the presenting symptoms, biochemical tests, radiographic examinations (ultrasound and/or computed tomography) and ERCP. In some patients, final assessment of resectability had not been completed at the time of inclusion. The study protocol was approved by the local ethics committee. All patients provided informed consent prior to entry in the study.

Treatment

When a distal common bile duct stricture was visualized and deep bile duct cannulation was achieved, patients were randomly assigned to receive either a polyethylene (PE) or a hydrophilic polymer-coated polyurethane (HPCP) stent. Randomization was carried out using computer-generated random numbers. Both types of stents were straight, with an outer diameter of 10 Fr, with two side flaps to prevent dislocation, and one side hole at each end, with a total length of 9 cm. The materials used for stent construction were polyethylene (PBN Medicals, Denmark) or hydrophilic polymer-coated polyurethane (Biosearch, Somerville, New Jersey, USA). The HPCP stent was soaked in water for 5 min before use. Stent placement was carried out using standard techniques (3).

Follow-up and Definition of End Points

All patients were interviewed by telephone at monthly intervals until death or until the end of the follow-up period in October 2001. If patients developed jaundice, cholangitis (high spiking fever and cold chills), or a flu-like syndrome and cholestasis, an ERCP was performed to confirm obstruction of the stent. Subsequent treatment consisted of exchange of the occluded stent by insertion of a polyethylene stent or a self-expandable metal stent.

The stent patency period represented the interval between the time of stent insertion and the time of its replacement, or the presence of both jaundice and fever at the time of death. In patients with hyperbilirubinemia, drainage was considered successful if stent placement resulted in a bilirubin decline greater than 20% of the pre-procedure value within 1 week after stent insertion. In patients without hyperbilirubinemia, drainage was considered successful if alkaline phosphatase and/or γ-glutamyl transpeptidase decreased by 20% of the preprocedure value within 1 week after stent insertion. Complications of ERCP and sphincterotomy were evaluated according to the criteria published by Cotton et al. (4).

Patient survival and stent patency periods in the two groups were analyzed using the Kaplan-Meier method and compared using the log-rank test.
**Scanning Electron Microscopy**

Scanning electron-microscopic examination of two out-of-package HPCP stents was carried out: one unused HPCP stent and one HPCP stent after manipulation of the stent through the endoscope over a guiding catheter. Stent segments of about 2 cm in length were mounted on stubs and sputter-coated with approximately 15 nm of gold, and random areas were examined with a scanning electron microscope (SEM 525; Philips, Eindhoven, The Netherlands) at an accelerating voltage of 12 kV, with special emphasis on surface characteristics.

**RESULTS**

**Enrollment and Exclusion of Patients**

From June 1999 to October 2000, 100 consecutive patients were included in the study. At the time of inclusion, not all patients had undergone total work-up for resectability. Nine patients were excluded - two because of chemotherapy before stent obstruction occurred; one turned out to have had a previous drainage procedure; two had a benign stricture; three patients were treated by flushing of the stent during an elective repeat ERCP in the referring hospital; and one patient was lost to follow-up. The remaining 91 patients were followed until October 2001.

Patient characteristics were comparable between the two groups (Table 1). Presenting symptoms included jaundice (n = 87), abdominal pain (n = 37), pruritus (n = 24), fever (n = 12), and weight loss (n = 72). Ultrasonography was carried out in 85 patients (93%) and computed tomography in 63 patients (69%), showing a pancreatic mass in 69 (76%) and dilatation of both the intrahepatic and extrahepatic ducts in 88 (97%).

The final diagnosis of malignancy was based on brush cytology, clinical follow-up until death, or histology from surgical specimens, and was confirmed in 96% of the cases. Twenty-nine patients ultimately underwent resectional surgery (pylorus-preserving pancreaticoduodenectomy) after stent placement.

Previous attempts to cannulate the bile duct in the referring hospital failed in 40 patients (44%). We achieved bile duct cannulation during the first attempt in all patients. A previous precut papillotomy had been performed in 11 of these patients.

**ERCP and Stent Placement**

Thirty-six patients had a stent placed through an intact papilla. In three patients, the previous precut papillotomy was sufficient to cannulate the common bile duct. In 42 patients, a precut papillotomy was performed. Endoscopic sphincterotomy was performed in 10 patients. The pancreatic duct was cannulated in 63 patients (70%). A stricture of both the pancreatic duct and the distal common bile duct (double-duct sign) was found in 53 of these patients (84%). Brush cytology was performed in 26 patients, and evidence of a malignancy was found in eight. Forty-seven patients received a PE stent and 44 patients an HPCP stent. Stent placement was successful in all patients.
Drainage
Biliary drainage was equally effective in both groups: 93% in the HPCP group (n = 41) and 91% in the PE group (n = 43). The remaining seven patients had no decline of bilirubin > 20% of the preprocedure value within 1 week after stent insertion. One patient (in the PE group) died 11 days after stent placement due to cholangitis and septicemia. A repeat ERCP and stent exchange was performed in six patients (PE group three, HPCP group three). Five patients received a PE stent and one patient a self-expandable stent. After stent exchange, jaundice subsided in all patients.

Early Complications and 30-Day Mortality
Procedure-related complications occurred in four of the 91 patients (4.4%) - one patient in the HPCP group and three patients in the PE group (Table 2). One patient (in the HPCP group) had both bleeding and a perforation. In this patient, an extensive precut sphincterotomy had been carried out with a false route and was treated conservatively. This patient also developed bleeding, which was initially treated with blood transfusions. Because of persistent bleeding, a gastroduodenoscopy was performed; arterial bleeding (Forrest IA) was seen at the cut margins of the precut and treated with sclerotherapy. One patient (in the PE group) had pancreatitis, which was treated with antibiotics, but the patient died 11 days after the procedure from ongoing septicemia. The fourth patient (in the PE group) had a perforation during sphincterotomy and was treated conservatively.
The 30-day mortality was 9% in the HPCP group and 15% in the PE group.

Stent Patency and Patient Survival
Stent occlusion occurred in 47 patients (52%) (Table 2). ERCP was performed in 42 patients; the remaining five were considered unfit for further treatment. The indications for repeat ERCP were cholangitis (n = 14), jaundice (n = 14) and a flu-like syndrome and cholestasis (n = 14). Median stent patency was 77 days (range 8 - 536; 95% CI, 53 - 101 days) in the HPCP group and 105 days (range 3 - 286; 95% CI, 42 - 168 days) in the PE group (Figure 1). There was a significantly longer patency period in the polyethylene stent group (P = 0.04).
If there was stent dysfunction, patients received a polyethylene stent (n = 32) or a self-expandable metal stent (n = 7). One patient was treated in a referring hospital by flushing of the stent instead of stent removal. The indication for this ERCP was cholestasis and fever. ERCP was not successful in two patients; in one, cannulation was not possible after stent removal, and the patient underwent surgery after 3 days; in the other patient, stent exchange was not possible because of duodenal obstruction, and this patient died 5 days later.
The median patient survival periods were 132 days in the HPCP group and 145 days
in the PE group. There was no significant difference between the two groups in this regard \((P = 0.25)\).

**Scanning Electron Microscopy**

Both out-of-package HPCP stents (one unused HPCP stent and an HPCP stent that had been manipulated through the endoscope over a guiding catheter) showed an extremely smooth inner surface, virtually free of irregularities except for places with marked signs of release of the hydrophilic polymer coating (Figure 2). No form of mechanical trauma was visible after manipulation of the stent through the endoscope.

**DISCUSSION**

The mechanism of stent clogging is multifactorial. The initial event is adherence of bacteria to the inner wall of the stent, followed by biofilm formation \((5,6)\). Favored sites for microbial adherence are side holes and irregular surfaces \((7-9)\), due to microturbulence of bile flow. Coene et al. showed that the rate of sludge formation correlated with the frictional coefficient of the stent material \((7)\).

In theory, a stent design without side holes and an ultrasmooth inner surface may decrease microturbulence of bile flow and therefore decrease adherence of bacteria and proteins. Teflon is the material with the lowest friction coefficient, but contradictory results were reported with a Teflon stent design without side holes \((10-13)\). Also, omitting side holes in PE stents or using Teflon material in a conventional design did not improve stent patency \((14,15)\). In a scanning electron-microscopic study, we showed that the inner surface of different stent materials showed marked irregularities, which may explain the conflicting results obtained in clinical studies. We postulated that the irregularities result from the manufacturing process used for these stents, with extrusion, which creates surface irregularities \((16)\).

Surface modification using a coating might therefore contribute to reducing bacterial adherence. Firstly, the coating can produce an ultrasmooth surface by using a specific material with a low friction coefficient. The coating is added after the manufacturing process, and this may increase the smoothness of the instrument, as shown by scanning electron microscopy of these stents. Secondly, it is possible to add substances to the coating that may reduce bacterial adherence. The hydrophilic polymer coating used in the present study not only has a low friction coefficient, but also a coating that absorbs water and provides a hydrophilic sheath. Because bacteria initially attach by hydrophobic interactions, this coating may decrease bacterial adherence and therefore increase the stent's patency period \((17)\).

In-vitro studies have shown reduced bacterial adherence in hydrophilic hydromer-coated stents. The reduction in adherence of bacteria was more pronounced in perfusion experiments with human bile \((1)\). Costamagna et al. conducted a prospective randomized trial comparing HPCP stents and PE stents and found a trend toward a
longer patency period with the HPCP stent (2). However, a high percentage of patients (29%) were excluded from the study. One of the exclusion criteria was early stent blockage, which was defined as stent replacement within 2 weeks after stent insertion. Costamagna et al. hypothesized that this was due to improper positioning or obstruction by blood or mucus plugs, in contrast to late obstruction caused by bacterial adherence and biofilm formation. This selection of patients makes it difficult to compare the results with other biliary stent trials, as most studies have used the intention-to-treat principle for analysis. In the present study, 7% presented with early clogging. If these early cloggers were excluded from this study, the patency rate would be 77 days for HPCP stents and 142 days for PE stents (P = 0.02) - an outcome even more favorable for the PE stent.

There was a significantly longer patency period with the PE stent in the present study. One of the possible explanations for this could be that the surface characteristics of the HPCP stents were altered by the manipulations required for stent placement during endoscopy. We therefore compared two HPCP stents using scanning electron microscopy before and after stent placement; however, no alterations in the stent were evident after manipulation of the stent through the endoscope over a guiding catheter. Secondly, the HPCP coating is fragile and may degrade over time, as shown by our scanning electron-microscopic pictures of an out-of-package HPCP stent. In addition, once the stent layer has been colonized by a biofilm, the surface characteristics are nullified. This may explain why in-vitro observations with a short follow-up period show encouraging results that cannot be confirmed in clinical trials.

In conclusion, no real progress has been made in extending the efficacy of plastic biliary endoprostheses since the introduction of the Amsterdam-type polyethylene stent in 1982. At present, the Amsterdam-type polyethylene stent is still the standard treatment in patients with an unresectable distal malignant biliary obstruction.
**Table 1.** Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Hydrophilic polymer-coated polyurethane</th>
<th>Polyethylene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Excluded</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Analyzed</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>22/22</td>
<td>23/24</td>
</tr>
<tr>
<td>Age* (years)</td>
<td>74 (53 - 94)</td>
<td>73 (47 - 88)</td>
</tr>
<tr>
<td>Serum bilirubin* (μmol/l)</td>
<td>212 (37 - 573)</td>
<td>209 (7 - 611)</td>
</tr>
<tr>
<td>Alkaline phosphatase* (U/l)</td>
<td>445 (65 - 1905)</td>
<td>465 (75 - 993)</td>
</tr>
<tr>
<td>Previous ERCP</td>
<td>15</td>
<td>25</td>
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<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
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<td>Pancreas carcinoma</td>
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<tr>
<td>Cholangiocarcinoma</td>
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<td>5</td>
</tr>
<tr>
<td>Metastatic</td>
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<td>1</td>
</tr>
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</table>

* Values are median (range). ERCP: endoscopic retrograde cholangiopancreatography.
Table 2. Results.

<table>
<thead>
<tr>
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<th>Hydrophilic polymer-coated polyurethane (n = 44)</th>
<th>Polyethylene (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent dysfunction</td>
<td>27 (61 %)</td>
<td>20 (43 %)</td>
</tr>
<tr>
<td>ERCP performed</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>No ERCP performed</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Stent patency, days*</td>
<td>77 (8 - 536) [53 - 101]</td>
<td>105 (3 - 286) [42 - 168]</td>
</tr>
<tr>
<td>Subsequent surgery</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Subsequent chemotherapy**</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Survival, days*</td>
<td>132 (15 - 715) [106 - 158]</td>
<td>145 (11 - 385) [102 - 188]</td>
</tr>
<tr>
<td>Complications</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Perforation</td>
<td>1**</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0**</td>
<td>1</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>0**</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1**</td>
<td>0</td>
</tr>
</tbody>
</table>

* Values are median (range), [95 % confidence interval].
** After stent exchange.
*** Same patient.

Figure 1. Cumulative patency of stents (n = 91), P = 0.04.
Figure 2. Scanning electron microscopy of an unused hydrophilic polymer-coated stent after manipulation through the endoscope over a guiding catheter, showing an extremely smooth inner surface virtually free of irregularities, except for places in which there are marked signs of release of the hydrophilic polymer coating. Bar = 1 mm.
REFERENCES