Etiologic and clinical studies in primary sclerosing cholangitis
Ponsioen, C.Y.

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Four years experience with short term endoscopic stenting in primary sclerosing cholangitis

C.Y. Ponsioen\textsuperscript{a}, K. Lam, A.W.M. van Milligen de Wit\textsuperscript{a}, K. Huibregtse\textsuperscript{a}, G.N.J. Tytgat\textsuperscript{b}

\textsuperscript{a}Department of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, The Netherlands
\textsuperscript{b}Department of Internal Medicine, Elisabeth Hospital, Tilburg, The Netherlands

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SUMMARY

Background and Study Aims: Symptomatic dominant strictures in primary sclerosing cholangitis are often treated with endoscopic stent therapy, but the optimal treatment duration is not well established. After a promising pilot study, we now report our four year experience with short term endoscopic stent therapy for relief of dominant strictures.

Patients and Methods: Between January 1994 and October 1997, 32 patients with symptomatic primary sclerosing cholangitis with a dominant stricture at endoscopic retrograde cholangiopancreatography (ERCP) were treated with insertion of a 7- or 10-Fr polyethylene endoprosthesis, which was extracted after a mean of 11 days (range 1-23 days). Primary endpoints were changes in complaints and cholestasis after two months, and time interval until a repeat endoscopic treatment was deemed necessary. A secondary endpoint was the occurrence of treatment-related complications.

Results: Cholestatic complaints improved after two months in 83% of patients. Mean scores for pruritus, fatigue, and right upper quadrant pain decreased from 0.94, 1.0, and 0.87 to 0.26, 0.39, and 0.26, respectively. All improvements were significant. Of 14 patients presenting with jaundice, 12 regained normal serum bilirubin levels two months after short term endoscopic stenting. The mean levels of conjugated bilirubin, alkaline phosphatase, and γ-glutamyl transpeptidase dropped significantly from 36 µmol/L, 309 U/L, and 426 U/L to 7 µmol/L, 205 U/L, and 258 U/L, respectively. The reintervention-free proportions after one and three years were 80% and 60%. Seven transient procedure-related complications occurred in 45 therapeutic ERCPs.

Conclusions: Short term endoscopic stenting for symptomatic dominant strictures in primary sclerosing cholangitis is effective and safe, and the beneficial effect is sustained for several years.
INTRODUCTION

During the course of primary sclerosing cholangitis (PSC), many patients experience, at some point in time, the sudden development or worsening of complaints such as pruritus, right upper quadrant pain (RUQP), fever with rigors, and fatigue. When these symptoms do not subside within a few days, they may well be caused by a dominant stricture.

A dominant stricture in PSC is defined as a narrow stricture arising in either the common bile duct, the common hepatic duct, or the left or right main hepatic duct, impeding normal bile flow. The prevalence of these strictures is not well known, but in a large series the frequency was estimated at 10% (1, 2). Most experts agree that some form of dilatation is indicated when a symptomatic dominant stricture occurs, to relieve the obstruction. Depending on technical expertise, some favour the percutaneous route, but mostly the endoscopic approach, e.g., stenting or balloon dilatation is preferred (2-7). It is unknown how long an endoprosthesis should be left in situ to achieve optimal dilatory effect. Furthermore, stent therapy in PSC is accompanied by a substantial risk of suppurative cholangitis due to stent clogging (6). Therefore, the stenting period should be as short as possible. To determine the efficacy of short term stent placement for symptomatic dominant strictures in PSC, a pilot study was initiated in our institution in 1994 (8). Sixteen patients were treated with endoscopic stent therapy for a median of nine days. An intended stenting period of one week was chosen for practical reasons and because it is known from clinical observation that stent clogging in the first few weeks is extremely rare. The results after a median follow-up of 19 months compared favourably to those in a historical control group, in which stents were inserted for a duration of about 3 months (6).

The aim of the present study is to report our four years experience with short term stent placement for dominant strictures in PSC in a consecutive series of patients.

PATIENTS AND METHODS

From January 1994 through September 1997, 77 PSC patients underwent one or more endoscopic retrograde cholangiopancreatographies (ERCP) for suspicion of a symptomatic dominant stricture. In one patient, adequate depiction of the biliary tree could not be obtained due to failed cannulation. In 44 of 76 patients (58%) one or sometimes multiple dominant strictures were observed. Patients with cholangiocarcinoma (n=6), prior endoscopic treatment within six months (n=5),
impossibility to pass a guidewire through the stricture (n=2), and those without an obvious dominant stricture (n=26) were excluded. A total of 37 patients had a dominant stricture amenable to endoscopic treatment. Five patients were treated by balloon dilatation as part of a study. The remaining 32 patients were treated by short term placement of a 10-Fr polyethylene, Amsterdam-type endoprosthesis for an intended period of one week. If direct placement of a 10-Fr stent was technically impossible, initial dilation with Soehendra dilators, nasobiliary catheters, and/or temporary placement of a 7-Fr endoprosthesis for one week, were performed.

All patients were kept overnight in the hospital and received antimicrobial prophylaxis with a combination of intravenous gentamycin and amoxicillin before, and for 24 h after, the ERCP.

**Primary endpoints:**

These included changes in liver tests pre-and 2-months post-ERCP. Before ERCP serum was sampled for determination of conjugated bilirubin (cbili, normal range < 7 µmol/L), alkaline phosphatase (AF, normal range 26-103 U/L), and gamma-glutamyl-transpeptidase (γGT, normal range < 60 U/L). This was repeated two months after the procedure.

As parameters pertaining to increased cholestasis, the degrees of pruritus, fatigue, RUQP, and the occurrence of cholangitis (defined as sudden fever, RUQP, and increase in liver tests) were assessed prior to the ERCP and two months later. These parameters were scored using a semiquantitative scale, which is outlined in Table 1. The time interval until a renewed ERCP with endoscopic treatment was performed, if necessary, was also assessed. Follow-up data were collected from the charts or by inquiring of the referring physician. All patients were seen back on our outpatient clinic at least once after two months, and all repeat ERCPs were done in our unit.

**Table 1.**

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>None</td>
<td>Sometimes</td>
<td>Daily</td>
<td>Wakes me up/need medication</td>
<td>Intolerable</td>
</tr>
<tr>
<td>Fatigue</td>
<td>None</td>
<td>Cannot do everything</td>
<td>Have to rest</td>
<td>&lt; 50% daytime in bed</td>
<td>Fully bedridden</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>No fever</td>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUQ pain</td>
<td>None</td>
<td>Sometimes</td>
<td>Daily</td>
<td>Wakes me up/need analgesics</td>
<td>Intolerable</td>
</tr>
</tbody>
</table>

RUQ=right upper quadrant
Secondary endpoints:
The occurrence of procedure-related complications such as suppurative cholangitis, hydropic gallbladder, bleeding, pancreatitis, and perforation were recorded and graded according to Cotton (9).

Statistical analysis
For statistical analysis, the SPSS 7.0 package (SPSS Inc., Chicago, IL, USA) was used. Differences in serum biochemical cholestatic parameters before and after the treatment were compared by the paired samples two-tailed t-test. To correct for skewness or differences in variance, log transformation was performed when necessary. Changes in complaints were compared using the Wilcoxon paired signed rank test. Values of $p < 0.05$ were considered significant. Long term patency of the therapy was estimated by Kaplan-Meier survival analysis.

RESULTS

Patient characteristics:
There were 19 men and 13 women, 18 (56%) of whom had a concurrent diagnosis of inflammatory bowel disease. Twenty-two patients were already known to have a diagnosis of PSC. The mean age was 41 years. Nineteen patients used ursodeoxycholic acid at the time of the intervention. Two patients used prednisolone and one was on azathioprine for coexisting inflammatory bowel disease. Medical therapy had been started more than three months before the intervention and was not altered during the follow-up in these three patients. At entry, four patients had liver cirrhosis Child B/C. All but two patients had intrahepatic involvement to a variable degree on cholangiography.

Endoscopic intervention:
A total of 45 therapeutic ERCPs were performed in 32 patients. In 21 patients, insertion of a 9, 11, 14, or in two cases because of peripheral dilated branches a 19-cm-long, 10-Fr polyethylene Amsterdam-type endoprosthesis was successful in one step. Six patients initially received a 7-Fr stent, which was exchanged after one week for a 10-Fr endoprosthesis. Sphincterotomy was performed in 10 cases, only when pre-cut papillotomy had to be performed for access to the common bile duct or to facilitate stent insertion. In two patients, sphincterotomy had been performed in the
past. In one case, a common bile duct stone was found and extracted. In five cases, it proved possible to insert only a 7-Fr endoprosthesis, despite 1-4 attempts. Mean *in situ* time of the endoprostheses was 11 days (range 1-23). Figure 1 shows the effect on a distal common bile duct stricture of one-week stenting with a 10-Fr endoprosthesis. Upon removal of the endoprosthesis, a control cholangiogram was done. All patients showed improvement of the luminal diameter of their dominant strictures.

**Fig 1.** Detail of a cholangiogram showing a dominant stricture (→) in the distal common bile in a PSC patient: Before therapy (left panel). With a 9-cm 10-Fr stent in situ (middle panel). After removal of the stent one week later (right panel). Improvement of the stricture is easily appreciated.
Effect on complaints:
Data on cholestasis related complaints, i.e., pruritus, fatigue, cholangitis, and right upper quadrant pain were complete in 30 cases.
Half of the patients presented with some degree of pruritus, 70% experienced fatigue, 50% had right upper abdominal pain, and in six cases acute cholangitis was the presenting clinical picture. Acute cholangitis at entry was not correlated with prior ERCPs or cholecystectomy, (Chi-square test, Fisher exact: $p = 0.172$ and $p = 1.0$, respectively). Two months after short term stent therapy, cholestatic complaints had improved in 25 (83%) of patients. One patient complained of more intense itching, one experienced more fatigue, one patient had an episode of acute cholangitis, and two still had right upper quadrant pain. For the whole group the mean scores of the various complaints improved considerably. Mean pruritus scores at $t=0$ and $t=2$ months were 0.94 and 0.26, respectively ($p<0.01$). Mean fatigue scores at $t=0$ and $t=2$ months improved from 1.0 to 0.39, respectively ($p<0.002$). Mean pain score lowered from 0.87 to 0.26 ($p<0.002$). Mean cholangitis score dropped from 0.19 to 0.03 ($p=0.056$), (Figure 2).

![Fig 2. Mean scores (+SEM) of cholestatic complaints before, and two months after, stent therapy. Data shown are for 30 of 32 patients whose data sets were complete. Comparisons by Wilcoxon signed rank test.](image-url)
Effect on serum biochemical cholestatic markers:

All but two patients who had elevated conjugated bilirubin levels at entry (n=14) had normal levels after two months. These two patients both had advanced liver cirrhosis. Alkaline phosphatase and γGT levels dropped substantially in 81% and 71% of cases, respectively. Mean levels for serum conjugated bilirubin, alkaline phosphatase, and γGT before and at t=2 months decreased from 36 μmol/L, 309 U/L, and 426 U/L to 7 μmol/L, 205 U/L, and 258 U/L, respectively. The improvements were all significant, \( p<0.001, n=30; \) \( p<0.001, n=32; \) and \( p<0.002, n=30; \) paired samples t-test), (Figure 3).

Fig 3. Mean serum levels (+SEM) of cholestatic parameters before stenting and at two months. Data shown are for all patients whose data sets were complete (cbili: μmol/L, n=30; AF: U/L, n=32; γGT: U/L, n=30). Comparison of means by paired sample t-test.

Long-term effects:

No patient was lost to follow-up. Median follow-up was 35 months (range 9-54). Figure 4 shows the Kaplan-Meier plot for the cumulative proportion of patients that remained free of endoscopic reintervention. At one and three year, 80% (95% confidence interval (95% CI) 66-93%) and 60% (95% CI 41-79%) of patients, respectively, were still free of renewed endobiliary therapy.
Short term stenting in PSC

Cumulative proportion of patients without endoscopic reintervention

Fig 4. Kaplan-Meier survival curve of interval until renewed stent therapy was necessary. Estimated "survival" of the therapy after one year was 80% (95% CI 66-93%), and after three years 60% (95% CI 41-79%).

Complications:
Seven (15%) transient, procedure-related complications graded as mild to moderate were recorded in 45 therapeutic ERCPs. Two ERCPs were complicated by perforation of the biliary tract, which was treated conservatively and healed without further sequelae. Three patients experienced mild to moderate pancreatitis, which was treated conservatively. In two patients the endoprosthesis had to be extracted after one day because of painful hydrops of the gallbladder, confirmed by ultrasonography. There were no bleeding complications.
DISCUSSION

The results of this retrospective analysis show that short term stenting of symptomatic dominant strictures in PSC is effective, reasonably safe, and that the beneficial effect is considerably long lasting.

These outcomes compare favourably with those of a historic control group from our institution (6). In this group of 25 patients with symptomatic dominant strictures between 1985-1994, stent therapy was employed for a median of three months. Endoscopic therapy was successful in 21 (84%). In 16 of these patients (76%), one or more stent episodes was followed by sustained clinical and biochemical improvement during a median follow-up of 29 months (range 2-120). Early procedure-related complications occurred in 15 (14%) of 105 therapeutic and stent-extraction ERCPs. However, during stent therapy, 50% of patients developed suppurative cholangitis or jaundice as a result of stent clogging, necessitating stent exchange. To minimize this risk would imply shortening the duration of the stent therapy as much as possible. However, it is not known how long an endoprosthesis should be left in situ to achieve optimal dilatory effect. For this reason, a pilot study with 16 PSC patients with symptomatic dominant strictures was performed, leaving the endoprosthesis in situ for only 1-2 weeks (8). During a median follow-up of 19 months serum biochemical cholestatic parameters decreased substantially and 81% of patients became asymptomatic. Transient procedure-related complications occurred in 7% of procedures. These results are corroborated by the present evaluation of our four years experience with short term stenting. Short term stenting is as good as leaving an endoprosthesis in situ for several months and is not associated with ascending cholangitis or jaundice due to stent clogging.

The fact that short term stenting is effective in keeping the majority of dominant strictures open for many months suggests that there must be a fair amount of rigid scar tissue in these strictures, the bands of which are effectively breached by the dilating effect of the endoprosthesis. If a dominant stricture were composed mainly of edematous inflammatory tissue, early stricture recurrence would, rather, be the rule. The long term results are quite favourable, so we do not advocate "surveillance" ERCPs for recurrent stricture formation as in some centers (10). ERCP is only repeated when there is clinical suspicion of recurrent stricture formation. Also, the policy of repeated endoscopic balloon dilatation at one-year intervals as employed by Johnson et al. and Wagner and co-workers does not seem to be necessary when short term stenting is used instead (3, 11). ERCP is still an intervention that bears some potentially serious risks for the patient and, although suppurative cholangitis is
encountered only occasionally with the routine use of prophylactic antibiotics, this complication can be particularly detrimental to the vulnerable biliary tree of PSC patients. We therefore hold the view that ERCP should only be done in PSC patients on strict indications such as suspicion of a symptomatic dominant stricture, choledocholithiasis, or jaundice.

Is one-week stenting of dominant strictures in PSC short enough? In two patients who both received a 7-Fr endoprosthesis through a mid-CBD stricture, these had to be extracted within 24 h, because of the occurrence of a painful hydrops of the gallbladder. Both have no signs of recurrent stricture formation after a follow-up of 10 and 16 months. We are currently undertaking a prospective randomized study to find out whether single-procedure balloon dilatation of dominant strictures in PSC performs as good as short term stenting.

Although on theoretical grounds quite conceivable, it is not known whether relieving biliary obstruction slows down disease progression, but since endoscopic therapy such as short term stenting gives such excellent results in palliation of symptoms and biochemical improvement, randomized trials addressing this issue are not feasible.

REFERENCES

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