EDITORIAL

Biodegradable pancreatic stent: A 1-step "magical" procedure to resolve pancreatic duct strictures?

The treatment of patients with painful chronic pancreatitis (CP) and dominant main pancreatic duct (MPD) stricture remains a challenge. The current recommendations suggest, as the standard modality of endoscopic treatment, the insertion of a single pancreatic plastic stent (PPS) in the MPD with the aim of relieving pain related to outflow obstruction, and for MPD strictures persisting beyond 1 year after the initial PPS insertion, to consider other options such as surgical pancreaticojejunostomy, the insertion of multiple plastic stents, or a trial of 3 to 6 months with a fully covered-self expandable metal stent (FC-SEMS).[1]

Long-term clinical results after these combined procedures were reported in 5 selected retrospective studies, including a total of 431 patients in whom a single PPS was inserted in more than 90% of cases, and reporting data about pain relief at least 1 year after single PPS removal. Pain improved in 55% to 83% of patients at a mean follow-up time of 27 to 46 months, and surgery was avoided in 84% (74%-96%) of patients.[2-6] A recent systematic review and meta-analysis identified a subgroup of CP patients with pancreatic duct stricture(s) (n = 536 patients, 9 studies) in which the pooled estimate of the proportion of patients with long-term pain relief was 67.5% (95% confidence interval, 51.5%-80.2%).[7]

Although these series were relatively homogeneous regarding the baseline characteristics of the included patients (mostly middle-aged men with pain, alcohol abuse as the main cause of CP, average duration of disease before endoscopic treatment around 3 to 5 years, severe CP with endocrine/exocrine insufficiency at baseline in around 30% of the cases), they had the biases of retrospective studies, including the use of unstandardized pain relief assessment, various follow-up times after "definitive" stent removal, various sample sizes, various sizes and types of stents, and different stent exchange schedules.

The obvious drawbacks of endotherapy include possible pain recurrence after endoscopic treatment in about a third of patients because of migration of stone fragments, persistence or recurrence of stricture, or both, and the need for repeated ERCP for stent exchanges in order to calibrate the MPD stricture.[2,4,8-11] The duration of this "calibration" period has most often been reported to be more than 1 year in the largest series, given that a shorter duration of stenting (6 months) was already reported to be insufficient more than 20 years ago.[12] Predictive factors of long-term clinical success after endoscopic treatment have been identified and include (1) a shorter duration of disease before treatment,[2,13] (2) a lower number of ERCP procedures,[11,14] (3) a lower rate of constant pain,[13] (4) a lower proportion of patients taking daily narcotics,[13] and (5) a higher proportion of smokers who quit smoking.[11,14]

Similarly, a multivariate analysis identified a pain duration ≤3 years, the absence of preoperative use of opioids, and ≤5 endoscopic procedures before surgery as independent and significantly associated factors with higher rates of pain relief after surgery in patients with painful CP.[15] Patients with all 3 risk factors had a probability of 23% for achieving postoperative pain relief compared with a probability of 75% in the absence of these 3 risk factors.

> It seems premature to qualify the results as promising (as compared with the standard policy of single or multiple PPS placement), given the observed clinical outcome and adverse events. These BD-SESs, however, as mentioned by the authors, surely deserve further evaluation in larger studies with longer follow-up times.

The insertion of multiple plastic stents was shown as feasible and effective for obtaining resolution of the MPD stricture in a single study of 19 patients.[16] Temporary placement of multiple plastic stents (median of 3 simultaneous stents, 8.5F to 11.5F) for 6 to 12 months (mean, 7 months) resulted in pain relief for 84% (16/19) of patients during a mean follow-up time of 38 months after stent removal. Relapsing pain after "definitive" stent removal and need for restenting seemed to be lower than after temporary single plastic stent placement: 11% and 16%, respectively,[16] compared with 25% and 26% in series reporting these data after single plastic stent placement.[2,4,5,8-11] Despite this limited evidence, multiple stent placement has been adopted in several centers as

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initial therapy and might offer the additional advantage of reducing the number of stent exchange required when the procedure is performed "on-demand."[17]

For refractory MPD stricture, the temporary insertion of FC-SEMS could be an option; pain improvement was reported in 52 of 61 (85%) patients in a systematic review of 4 case series but with a short follow-up time after stent removal.[18] Less encouraging results with the need of early FC-SEMS removal and a 63% recurrence rate of symptoms were recently reported in 2 small studies,[19,20] migration and stent-induced MPD stenosis (at the proximal edge of the stent) being the major matters of concern.

In the current edition of *Gastrointestinal Endoscopy*, Cahen et al[21] report for the first time the use of biodegradable self-expandable stents (BD-SESs) for refractory MPD stricture in CP patients and emphasize that the potential advantages of this stent are the absence of proximal migration into the MPD, less hyperproliferative tissue response, and, without the need for stent removal or stent exchange procedures, the possible 1-step procedure for MPD stricture resolution by ERCP in CP patients.[21]

In their bicenter prospective study, 19 patients with painful CP (4 years of disease duration, median initial Izbicki pain score 76 [range, 54-88]) were included over a 30-month period after the failure of MPD stricture resolution, defined as the absence of stricture resolution after at least 6 months of stent placement with a single PPS. This definition of failure is similar to the one they used in a previous study,[22] even though this duration of stent placement is considered insufficient to achieve calibration and impact the clinical outcome.[1]

In contrast with the treatment by single PPS, requiring (in the largest study) a median number of 3 stent replacements during a total median stent placement duration of 23 months,[4] this new stent type allows resolution of MPD stricture in a 1-step procedure in 58% (11/19) of cases. This is, however, not really a 1-step treatment because all patients had at least 6 months of previous plastic stent placement. This rate of resolution of MPD stricture is lower than the >90% reported with multiple plastic stent placement[16] and with FC-SEMSs.[18] However, complete stricture resolution is not needed for resolution of pain,[3,23] as also shown by the authors: 2 patients (out of 8) without stricture resolution becoming asymptomatic.

The current study reported a rate of 53% of clinical success at a median follow-up time of 12 months after BD-SES as "promising results." The patients included in this study met the criteria that the same authors previously defined as "failure of endoscopic treatment" in their previous randomized controlled trial,[22] where the success of endotherapy was particularly poor (32% pain relief). According to their past recommendation, those patients should have undergone surgery at the time of inclusion. It is, however, interesting to observe that more than half (53%) of patients experiencing such failure ultimately had midterm pain relief after an additional calibration period and that only 26% (5/19) of those patients experiencing initial failure required surgical treatment. These findings could prompt the authors to reconsider their own definition of failure of endotherapy and the adequate timing of surgical option.

Along the same lines, it was previously shown that only 79% of pain recurrences requiring a new period of pancreatic stent placement occurred during the first year after single PPS removal, whereas almost all relapses (97%) have occurred by 24 months.[4,23] Therefore, a slightly longer follow-up period after BD-SES disintegration might help the authors to draw more firm conclusions.

For more than 15 years, BD-SESs have been used in the bile ducts,[24] and although the short-term results were promising, hyperplasia, early dislocation, and tumor ingrowth (in malignant strictures) were observed and limited the enthusiasm for further development, including in benign indications. Even though the rate of adverse events reported in the present study was low, migration, hyperplasia, and early dislocation of the stent were observed. The most worrying adverse event, in our opinion, is, however, the occurrence of a new stricture, proximal to the stent, a feature similar to the previously reported stenosis at the proximal edges of FC-SEMSs.[18-20]

The advantage of this new stent might be to obviously simplify MPD stricture calibration in painful CP. It seems premature to qualify the results as promising (as compared with the standard policy of single or multiple PPS placement), given the observed clinical outcome and adverse events. These BD-SESs, however, as mentioned by the authors, surely deserve further evaluation in larger studies with longer follow-up times. If such a study were to be designed as a real "1-step" procedure (ie, initial insertion of a BD-SES without a previous PPS), the developers should pay attention to the time to degradation of these stents, 3 to 6 months being probably, again, not enough to achieve long-term calibration.

It is, in any case, encouraging to see new developments in biliopancreatic stents, even though such BD-SESs (along with pancreatic FC-SEMSs) should currently be strictly used in the setting of clinical trials and are obviously not yet appropriate for routine use.

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Abbreviations: BD-SES, biodegradable self-expandable stent; CP, chronic pancreatitis; FC-SEMS, fully covered self-expandable metallic stent; MPD, main pancreatic duct; PPS, pancreatic plastic stent.

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