Partially covered self-expandable metallic stents for benign biliary strictures due to chronic pancreatitis

Behm B, Brock A, Clarke BW, Ellen K, Northup PG, Dumonceau JM, Kahaleh M.


In this study by Behm and colleagues from the University of Virginia, USA, a total of 20 patients with benign biliary strictures (BBS) due to chronic pancreatitis underwent temporary placement of a partially covered metal stent (PCMS) over a 6-year period. The primary outcome of interest was the proportion of patients with stricture resolution persisting 6 months after stent removal. Secondary outcomes included the stent failure rate, number of endoscopic sessions required to achieve biliary drainage, total duration of stenting, and complication rate. Adequate biliary drainage was achieved in 19 patients with PCMS (95%). Eighteen of the 20 patients (90%) had persistent stricture resolution 6 months after PCMS removal. Complications occurred in four patients (20%). Median duration of PCMS placement was 5 months, requiring a median of two endoscopic procedures. The authors concluded that temporary placement of PCMS achieved persistent stricture resolution in the majority of patients with BBS due to chronic pancreatitis.

Commentary

Distal BBS may be found in 2.7%–45.6% of patients with chronic pancreatitis. ERCP with single or multiple plastic stent placements have been associated with a poor long term outcome. Complete resolution of the biliary stricture and permanent removal of plastic stents is achieved in only 10%–30% patients with chronic pancreatitis. Therefore, many investigators have studied the use of uncovered-, fully covered-, or partially covered-metal stents in benign indications. Uncovered metal stents are associated with epithelial hyperplasia, leading to chronic inflammation of the bile duct and occlusion. The advantages of fully covered metal stents over partially covered metal stents include elimination of epithelial hyperplasia and a decreased rate of migration. The disadvantage of the former includes difficult removal because of anchoring fins or barbs.

There have been two previous studies on the use of PCMS in patients with BBS due to chronic pancreatitis. Both these studies did not attempt to remove the metal stent prior to occlusion. In the study by Cantu et al, 14 patients were treated with PCMS. At 22 months half of the patients had developed stent dysfunction due to tissue hyperplasia or migration. In the second study by Tringali et al published in an abstract form, stent dysfunction occurred in 4 of 6 patients at a mean follow up of 20 months.

In the present study, the authors used biliary Wallstents of 10 cm diameter, and 4 cm or 6 cm in length. The choice of stent was based on the length of the stricture, and importantly the site of cystic duct insertion. In patients with gallbladder in situ, the authors were careful not to occlude the cystic duct, by ensuring the placement of the stent below the level of its insertion. Six patients were excluded at ERCP because the cystic duct insertion was found to be approximating the biliary stricture. The authors did not have a predefined time interval for stent removal. They removed the stent when the biliary dilatation resolved, and the hepatic enzymes had normalized. The median duration of stenting in this study was 5 months (range: 1-21 months). The primary study endpoint, defined as persistent stricture resolution 6 months after PCMS removal, was achieved in 18 of 20 patients (90%). Of the two failures, one patient developed recurrent stricture 3 months after PCMS removal, and the second developed a pseudocyst 1 month after PCMS placement. It should be noted that, of the 18 patients defined as clinical success, two subsequently developed recurrent biliary obstruction 9 months and 41 months, respectively, after stent removal and underwent repeat PCMS placement. The median follow up of the cohort after stent removal was only 22 months. Hence long-term follow up is required. The etiology of chronic pancreatitis was alcohol related in 15 of the 20 patients, and stones were seen in 75%. The period of abstinence, active alcohol use, and the presence of inflammatory head mass have not been mentioned in the study.

The techniques for removal of metal biliary stents have been described in detail previously by Familiari et al. The stent mesh is grasped close to the papilla with a foreign-body forceps, and the stent pulled back and forth to assess its mobility in the bile duct. Mobile stents that do not appear to be involved by ingrowth are simply removed by pulling back on the forceps, and then extracting the stent through the endoscope channel. Fixed stents are gently disimpacted from the bile duct wall by grasping them with a forceps or snare and pulling the scope with a clockwise torque, similar to stone extraction with a basket. If the distal end is inaccessible, the stent mesh is grasped with a rat-toothed forceps at the proximal end and pulled back with the forceps to invaginate the stent. In this way, the stent can be peeled away from the CBD. The ingrowths can also be removed with electro-coagulation, the stent trimmed with APC, or plastic stents placed inside the metal stents to induce necrosis of ingrowth followed by a second attempt at removal after a few months. The characteristic of the stent mesh may also be important when considering removing a biliary metal stent. Wallstents, Shim-Hanarostents, and Niti-S biliary stents are made from a woven, braided mesh of stainless-steel alloy or nitinol filaments in a crisscross pattern. They are amenable to removal because they are very resistant to longitudinal traction. On the other hand, Zilver stents have a zigzag design without any crossing struts in the mesh. This allows them to be flexible, but they easily tear on attempted removal, because their mesh is not resistant to longitudinal traction.

In summary, placement of PCMS may be one option in the case of BBS due to chronic pancreatitis. However, careful patient selection is needed. The anatomy of the stricture and cystic duct...
insertion should be defined meticulously, and malignancy must be ruled out. Uncovered metal stent placement has been associated with epithelial hyperplasia, embedding the stent in the bile duct, making their removal extremely difficult. This can seriously compromise any future surgical treatment. Although the authors do not mention any difficulty in covered stent removal, there is still very limited experience with metal stent removal. The use of PCMS in a subset of patients with increased surgical risk due to concomitant portal hypertension, or advanced cardiac or pulmonary disease may be an option.

References

Endoscopic ultrasound-guided fine-needle aspiration biopsy coupled with K-ras mutation assay to distinguish pancreatic cancer from pseudotumoral chronic pancreatitis


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The differentiation between pancreatic adenocarcinoma and pseudotumoral forms of chronic pancreatitis remains difficult. Mutations of K-ras oncogene are present in 75% to 95% of pancreatic adenocarcinoma. This French multicenter study evaluated whether the combined analysis of K-ras mutation with traditional EUS-FNA cytology might improve the discrimination between pancreatic adenocarcinoma and chronic pancreatitis. A total of 178 patients with solid pancreatic masses (men 104, women 74; mean age 64.5 years) who underwent EUS-FNA at four large French referral centers (Clichy, Marseille, Montpellier, and Toulouse) were included. Cytopathological examination and K-ras mutation analysis (codon-12 and codon-13, restriction fragment length polymorphism, and direct sequencing) were performed on EUS-FNA material. The final diagnosis were ductal adenocarcinoma (n=129), chronic pancreatitis (n=27), other neoplasms (n=16), and benign lesions (n=6). Codon-12 K-ras mutation was found in 66% of adenocarcinoma samples, and in none of chronic pancreatitis samples. The sensitivity, specificity, positive and negative predictive values, and overall accuracy of cytopathology alone for diagnosis of adenocarcinoma versus chronic pancreatitis were 83%, 100%, 100%, 56% and 86%, respectively. When K-ras mutation analysis was combined with cytopathology, these values reached 88%, 100%, 100%, 63% and 90% respectively. The authors conclude that although the value of adding K-ras analysis in addition to EUS-FNA cytology is limited for distinguishing between pancreatic mass lesions, when chronic pancreatitis presented as a pseudotumor a negative finding (wild-type K-ras), was useful in strongly suggesting a benign lesion.

Commentary

There are several important messages from this study: Firstly, despite being a multicenter study with several endosonographers performing the procedures, and absence of on-site pathologist to certify sample adequacy, the samples were adequate for K-ras mutation analysis in 100% cases. There were no failures of amplification and sequencing. No additional passes were made, and only ‘left-over’, air-expelled material from the needle was used. Hence the analysis can be technically done in the majority, if not all the cases, with a very small sample volume without adding procedure time or risks.

Secondly, in patients with clinical and radiological suggestion of pancreatic adenosarcoma and an inconclusive biopsy, the presence of a K-ras mutation is highly suggestive of adenocarcinoma. In this situation a repeat biopsy would be indicated. However, mutation analysis improved the accuracy of cytopathology alone only from 86% to 90%, when the subgroup of patients with adenocarcinoma was considered. Thus, routinely adding K-ras mutation analysis to cytopathology does not seem to make a major contribution to the positive diagnosis of pancreatic adenocarcinoma.

Thirdly, in the presence of clinical and morphological
data suggesting a pseudotumoral form of chronic pancreatitis, where FNA is frequently nondiscriminatory, malignancy can be ruled out in the presence of a wild-type \textit{K-ras} gene. Based on the combined findings of cytology and \textit{K-ras} mutation analysis, surgery could be avoided in all 27 patients with pseudo-tumoral pancreatitis.

**Deep sedation with propofol does not precipitate hepatic encephalopathy during elective upper endoscopy**

Amorós A, Aparicio JR, Garmendia M, Casellas JA, Martínez J, Jover R


In this single-center, cohort study from Alicante, Spain it was studied whether the use of propofol for endoscopy in patients with cirrhosis induces minimal or overt hepatic encephalopathy (HE). Twenty patients with cirrhosis who received propofol sedation during endoscopy were compared with 20 patients without cirrhosis undergoing endoscopy. Patients with clinical HE or upper gastrointestinal bleeding in the previous 3 months were excluded. Minimal HE (MHE) was diagnosed by using the psychometric hepatic encephalopathy score (PHES) battery of psychometric tests. Cognitive status before and 1 hour after the endoscopy was evaluated by measuring the critical flicker frequency (CFF). Psychometric tests and the CFF measurement were done immediately before endoscopy and were repeated 1 hour after the procedure. None of the 20 cirrhotic patients (65%) had MHE before the endoscopy. No patient developed overt HE after sedation. There was no difference in CFF before and after sedation in patients with or without MHE. None of the patients who were without MHE before endoscopy, showed a decrease in the CFF under the cutoff of 39 Hz after sedation. The authors concluded that the use of propofol for the sedation of patients with cirrhosis during endoscopic procedures does not precipitate minimal or overt HE.

**Commentary**

Although propofol is predominantly cleared by the liver, dose adjustments are not necessary in the presence of liver disease or other comorbidities, such as renal insufficiency or obesity. Hence propofol has ideal pharmacokinetics for use in patients with liver disease.

In the present study, 13 patients had Child B cirrhosis, and one had Child C cirrhosis, which suggests that most patients had advanced liver disease. Endoscopy was done with the patient under deep sedation by using propofol. The dose of propofol was a 0.4 mg/kg IV bolus, followed by a continuous infusion of 3 to 6 mg/kg/h, with additional bolus doses of 10 to 20 mg IV if necessary. A trained nurse administered the propofol in all the procedures. With these doses, the authors encountered no severe complication associated with the endoscopic procedure.

Patients with cirrhosis and MHE are known to develop episodes of overt HE more frequently than those without MHE. In this study however, there was no increased risk with deep sedation in the subgroup of patients with pre-existing MHE.

The small sample size is the major limitation of this study. Because overt HE is very infrequent after endoscopic procedures, a large sample size would be required to determine the frequency of overt HE after propofol sedation. Even if one were to detect a higher frequency of new onset of MHE immediately after propofol, its long-term relevance is unknown, because MHE in this situation could be self limiting, unlike spontaneous MHE. Also a more clinically relevant comparison would have been with cirrhotic patients undergoing endoscopic procedures with conventional sedation using midazolam and/or meperidine. A previous randomized controlled trial has compared propofol with meperidine-midazolam in patients with cirrhosis who underwent upper-GI endoscopy for variceal screening. This study demonstrated that the use of propofol was associated with significantly faster induction and recovery times, with a trend toward a more rapid return to the baseline functioning and greater patient satisfaction (1).

Despite the above limitations, the current study explored the neuropsychometric impact of propofol by using well-tested tools, including a battery of established neuropsychometric tests and CFF, and provides reassurance to the endoscopist about the safety of propofol use in cirrhotic patients.

**References**

Precut papillotomy: The Mystery Continues

Cennamo V, Fuccio L, Repici A, Fabbri C, Grilli D, Conio M, D’Imperio N, Bazzoli F


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The ERCP is widely established as an invaluable and effective modality for undertaking a variety of biliary intervention procedures. The selective bile duct cannulation which is a requirement for biliary interventions at ERCP fails in 5-10% of patients despite the use of number of specialized techniques such as use of specialized catheters, papillotomes, guide wires, transpancreatic stenting and some others (1-4). To further improve the success rate of accessing bile duct selectively, a specialized procedure called precut papillotomy was introduced by Siegel in 1980 (5) and it subsequently underwent further modifications and refinements (6-10).

The successive publications reported that precut papillotomy significantly increased cannulation rate but its safety remains questionable (2,8,11,12). In earlier studies, it was reported to be a safe procedure but those reports were retrospective, nonrandomized and done by expert endoscopists only (2,3,13). Subsequently, various prospective and even large multicentric studies revealed it be an independent risk factor for overall post-ERCP complications with an odds ratio of 3.61 in an American study (14) and relative risk of 1.87 in an Italian study (15) This risk was still higher for post-ERCP pancreatitis with odds ratio of 4.34 in an American study and 2.80 in another Italian study (16). Consequently precut is often considered as a complicated procedure and it is emphasized that it should be reserved for experts (17). However, it remains unknown whether higher complication rate associated with precut papillotomy is as result of faulty technique or it is an unfair criticism as conceptualized by some investigators. The latter investigators thought that it may be due to repeated attempts for bile duct cannulation at ERCP in difficult cases by techniques other than precut papillotomy, and that results in more edema, trauma and inflammation to predispose them at risk. Hence it is believed that early use of precut papillotomy may circumvent these problems in difficult cases (19) but it remains largely undefined when to shift to precutting for biliary access in a difficult case (19).

Cennamo et al (20) attempted to answer this question in a prospective randomized study (Gastroint Endosc 2009;69:473-9) as to whether timing of precut for biliary access influences the success and complication rates. They considered patients for inclusion if biliary access failed after 5 minutes of deep biliary cannulation attempts or if up to 3 unintended cannulations of pancreatic duct occurred. The patients were randomly assigned in a 1:3 ratio to group A (early precut) or group B (who underwent standard cannulation attempts for further 20 minutes without any limit of pancreatic duct cannulations). If biliary access was achieved patients were included in subgroup B1 otherwise precut was carried out and patients were included in “delayed precut” subgroup B2. All precuts were carried out without placing pancreatic stents. All procedures were performed by two experienced endoscopists in prone position under conscious sedation (titrated 1% IV propofol and 10-20mg of hyoscine); no pharmacological prophylaxis for post ERCP pancreatitis was used. All patients were monitored for complications (pancreatitis, perforation, and bleeding).

Over the 2-year period, a total of 1078 therapeutic ERCPs were performed and of them 146 patients met selection criteria (mean age 68.5 years [range: 34-88 years], 67 men and 79 women). Thirty-six patients were assigned to group A, and 110 to group B. Among group B, biliary cannulation was achieved with standard approach in 78 (B1 standard access subgroup) whereas precut was performed in 32 (subgroup B2 - delayed precut subgroup). Success for deep biliary cannulation was 92% (33/36 patients) in group A. In group B it was successful in 95% (104/110), in 78 cases it was with standard cannulation in further 20 minutes and in other 32 patients delayed precut allowed cannulation in 26 patients. All patients with failed cannulation (Group A, 3 patients; Group B, 6) underwent second attempt at biliary cannulation after 48 hours which was achieved in all, one patient from each group required second precut. The overall complication in group A was 8 % (3/36) and 6 % (7/110) in group B. In group A one had retrodudenal perforation, one had bleeding and one had moderate pancreatitis). In group B all 6 complications were in subgroup B1, one had bleeding and others had moderate pancreatitis. All were managed conservatively without any mortality. In this study, the cannulation success rate were similar in two groups (group A 92%, group B 95%), and no significant difference in complications was observed in two groups (group A 8%, group B 6%). All complications in group B were observed in group B1 and no complication was observed in delayed precut group B2. A number of prospective randomized trials have reported that use of precut papillotomy for difficult biliary cannulation is safe and effective (21-23).

The present prospective study showed that delayed precutting after prolonged attempts with standard approach does not increase the complications and is equivalent to early precut in successful biliary cannulation in experienced hands. This study warrants further multicentre studies with larger number of patients with less experienced endoscopists so that the results can be applicable widely. This study points towards the safety of the precut procedure for achieving biliary cannulation.
References


Reprint requests and correspondence:
Dr. Gaurav Gupta, MD
Dr. Sandeep Nijhawan, MD, DM
Department of Gastroenterology,
S.M.S Medical College and Hospitals, Jaipur