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Endoscopic management of benign biliary strictures: Looking for the best stent to place

Endoscopic management of benign biliary strictures: Which is the best stent?

Abstract

Benign Biliary Strictures (BBS) might occur due to different pancreaticobiliary conditions. The etiology and the location of biliary strictures are responsible of a wide array of clinical manifestations. The endoscopic approach with ERCP represents the first-line treatment for BBS, considering interventional radiology and surgery when endoscopic treatment fails or it is not suitable. The purpose of this review is to provide an overview of possible endoscopic treatments for the optimal management of this subset of patients.

Key Words: Benign biliary strictures; Endoscopic Retrograde Cholangio Pancreatography; Endoscopic management; Biliary stent

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Core Tip: The aim of this narrative review is to describe the treatment of BBSs caused by the most common diseases, with a main focus on the use of the stents and their characteristics.

INTRODUCTION

Biliary strictures refer to the narrowing or obstruction of the bile ducts, which can be classified as malignant (MBS) or benign (BBS), based on their underlying causes. BBS can be caused by a variety of pancreaticobiliary disorders, and they can be further split into strictures caused by iatrogenic sources and inflammatory diseases. Complications following cholecystectomy surgery are the first cause of post-operative strictures with an overall incidence of up to 0.1% [1]. Post-cholecystectomy biliary strictures could develop as a result of ischemic damages or due to the clipping of the biliary tree especially when anatomic variants are presents [2] Orthotopic Liver Transplantation (OLT) is the second most common cause of post-operative biliary strictures with an overall incidence between 4% to 20% [3]. Biliary strictures after OLT are further classified as anastomotic biliary strictures, when the stenosis occurs at or adjacent to the end-end anastomosis or non-anastomotic biliary strictures if the stenosis develops elsewhere in the biliary tree [4]. Although, the non-anastomotic strictures are less common (2%-15%) than the anastomotic ones (5%-36%) [5] they are linked to worse prognosis with significant mortality and morbidity [6]. Less common causes of post-operative biliary strictures are stenosis after biliary reconstructions, bilio-enteric anastomosis or post Endoscopic Retrograde Cholangio Pancreatography (ERCP) injury. Chronic pancreatitis is a well-known disease that could lead to BBS in up to 46% of patients [7]. The stricture usually develops in the intra-pancreatic tract of the common bile duct due to the compression applied by the fibrotic and stiff pancreatic parenchyma on the distal biliary tree. Autoimmune disease like Primary Sclerosing Cholangitis (PSC), immunoglobulin G4 (IgG4)-related sclerosing cholangitis, infective disease like tuberculosis or histoplasmosis and trauma are less common etiologies of BBS. The etiology and the location of biliary strictures are responsible of a wide array of clinical manifestations, ranging from asymptomatic or pauci-asymptomatic patients to those that present with jaundice, abdominal colic pain until sepsis. Regardless of the etiology, it is of paramount importance to rule out an underlying malignant process: targeted radiological investigations (Computed Tomography (CT), Magnetic Resonance Imaging (MRI) or

Positron Emission Tomography (PET), possibly complemented with a bioptic approach with Endoscopic Ultrasound (EUS) or ERCP, are indispensable in such cases. Confirmed the benign nature of the strictures, several treatment modalities are available including surgery, interventional radiology and endoscopy. Nowadays, the endoscopic approach with ERCP represents the first-line treatment for BBS, considering interventional radiology and surgery when endoscopic treatment fails or it is not suitable [8]. Endoscopic management consists of balloon dilation of the strictures with or without placement of one or more biliary stents with the aim of applying a radial force on the stricture and thus ensuring patency of the biliary duct and solving the stricture. Additional stents positioning was associated with higher success, defined as stricture resolution, and lower recurrence rates compared with dilation alone [9]. Traditionally, plastic biliary stents placement (Figure 1) across the stricture were the milestone of treatment, although the introduction of Self-Expandable Metal Stent (SEMS) has sparked a growing interest in this relative new technology. This narrative review aims to describe the treatment of BBSs caused by the most common diseases, with a main focus on the use of the stents and their characteristics. The major limitation of the available studies on this topic is that most of them are retrospective, with few cases described in each of them; moreover, larger part of the studies included different heterogeneous etiology of BBS which limits their findings.

PLASTIC STENTS

Benign biliary strictures are historically treated by ERCP with balloon dilation of the stricture and then by positioning a plastic stent. There are several models of plastic stents available in the market, with different caliber, length, material and shape to best suit the extent of the stricture and the size of the bile duct. The usage of plastic stents is essentially limited by the risk of obstruction caused by biliary sludge accumulation inside the stent lumen that requires frequent stent exchange usually no later than 3 mo. To overcome this limitation and to obtain a progressive and acceptable dilation of the stricture, a Multiple Plastic Stent (MPS) technique was proposed by means of simultaneously placement of an increasing number of plastic stents [10]. The main disadvantage of this approach is related

to multiple ERCP procedures for stent exchange that are usually performed every 3-4 mo for a time frame of 12 mo with associated costs and risk of adverse events.

METAL STENTS

Using MPS, stricture resolution generally requires several endoscopic procedures, with the placement of larger caliber stents or an increasing number of stents during each session. Considering these downsides and the short-term patency of plastic stents, some endoscopists have considered to place Self-Expandable Metal Stents. SEMS is a particularly fascinating alternative for treatment of BBS, as a 10mm SEMS corresponds to a bile duct caliber reached by three or four 10-Fr plastic stents. Three types of metal stents are available: Uncovered SEMS (USEMS), Partially Covered SEMS (PCSEMS) and Fully Covered SEMS (FCSEMS). The placement of uncovered metal stents in BBS was firstly reported in 1991, but their use has been limited by the stent occlusion due to epithelial hyperplasia leading to embed of prosthesis into the bile duct mucosa, making removal difficult or even impossible [11,12]. Therefore, USEMS in BBS is not recommended by the European Society of Gastrointestinal Endoscopy (ESGE) because of removal issues [13]. PCSEMS have a plastic polymer in the central part of the prosthesis, being uncoated at both distal ends. This kind of stent has been designed to extend the stent's patency preventing tissue ingrowth through the mesh, thus allowing easier removal. However, the uncovered distal ends are still subject to tissue ingrowth, so their removal could not always be easily performed [14]. FCSEMS have been designed with plastic polymer covering the entire prosthesis, in order to avoid epithelial hyperplasia seen with USEMS and PCSEMS and consequently facilitating their removal. According to the ESGE guidelines the FCSEMSs are the recommended metallic prosthesis to use in benign biliary strictures, thanks to their ease of removal [13]. The ideal dwell time of FCSEMSs is still unknown; generally, their removal is indicated after 6 mo, because it has been reported that a 6-month compared with a 3-month dwell time is associated with a lower recurrence rate [15], even though longer dwell time has been described. The main drawback of FCSEMS is the high migration risk, reported as 9% in a large meta-analysis by Zheng *et*

al ^[16]. Thus, reducing the migration risk and enhance stent dwell time of FCSESM has encouraged some innovations in the technology of metal stent, including flared ends, anchoring fins and flaps and totally intraductal short stents.

BILIARY STRICTURES AFTER CHOLECYSTECTOMY

Even though numerous methods for avoiding biliary injury during cholecystectomy have been described, this procedure still accounts for the majority of BBS cases. Not all of the strictures are associated with the direct trauma occurred during the surgical procedure, but also as a consequence of ischemic microvascular injury. Endoscopic treatment by means ERCP with MPS positioning is generally the first-line approach in case of biliary stricture after cholecystectomy, reserving percutaneous drainage and surgical reconstruction when endoscopic treatment fails. The stricture resolution rate with MPS approach is reported to range between 80% and 100%, with stricture involving the distal part of the common bile duct having better outcomes compared with strictures nearby the hepatic hilum ^[17]. In a recent retrospective study, in which 154 patients were enrolled, Costamagna *et al*, reported the long-term follow-up of multistenting therapy in patients with post-cholecystectomy biliary strictures. The overall resolution rate was 96.7% with a recurrence rate of 9.4% after a follow-up of 11 years. A mean of 4.2 ERCP per patient was needed, without procedure related mortality in the cohort and 7.4% of patients who experienced adverse events. Only 2 patients underwent surgical reconstruction because of failed treatment ^[18]. Based on these results, endoscopic multistenting therapy is a safe and an effective treatment in post-cholecystectomy biliary stricture. The major drawback of multistenting is the need of numerous ERCP to add or exchange the clogged plastic stents. In order to surmount this weakness, the use of fully covered metal stent was suggested. Tringali *et al*, in a recent prospective multicenter study evaluated the efficacy of FCSEMS with scheduled removal after 6-12 mo in patients with benign biliary strictures. A subgroup analysis in 18 patients with post-cholecystectomy stricture were performed. At 5 years follow-up, the resolution rate was 72% with an adverse events rate in 38.9% patients, mainly cholangitis. They reported a migration rate in 16.6% patients in

which the stricture was healed. ^[19]. Temporary placement of a FCSEMS could be considered as a safe alternative to MPS placement in biliary stricture due to cholecystectomy, even though MPS remain the first-line therapy (Figure 2) unless more conclusive data will be published.

BILIARY STRICTURES AFTER ORTHOTOPIC LIVER TRANSPLANTATION

OLT is a frequent cause of benign biliary stricture. Well known risk factors associated with strictures are ischemic damages, hepatic artery thrombosis, living donor liver transplantation, usage of T-tubes, non-heart beating donor, donor-recipient ABO incompatibility and PCS ^[20]. Strictures may occur at the level or adjacent to the biliary anastomosis, usually performed with an end-to-end reconstruction technique, or elsewhere in the biliary tree, usually with the involvement of the donor hepatic ducts, defined as anastomotic biliary stricture and non-anastomotic biliary stricture, respectively. Non anastomotic biliary strictures represent a more challenging conditions, with stricture that are usually longer compared with the anastomotic ones and located in multiple sites. The time of presentation of the strictures play an important prognostic role, indeed the anastomotic strictures with an early presentation (less than 30 days) are linked to favorable outcome compared with anastomotic strictures with later presentation (more than 90 days) ^[21]. Regardless of the stricture site, ERCP is the mainstay treatment with an overall success rate of 75% for the anastomotic strictures and of 50%-70% for the non-anastomotic ones ^[22,23]. ERCP with balloon dilatation alone has a low success rate but additional plastic stenting has proven high success rate and less overall recurrences ^[24]. In order to reduce the need of multiple stents exchange due to the MPS approach the use of FCSEMS has been described in early 2011 by Hu *et al* ^[25]. Multiple Randomized Clinical Trials (RCT) have compared the results obtained with plastic stent or SEMS in the anastomotic strictures after liver transplantation (Table 1). The first one was published in 2014 by Kaffes *et al*, in which 10 patients were randomized in the FCSEMS arm and 10 in the plastic stents arm. Strictures resolution were obtained in 100% of patients in the FCSEMS group compared with 80% of patients in the plastic stents

group ($p = ns$) with a median number of 2 ERCP per patients obtained with metal stents compared with 4.5 in with plastic stents ($P = 0.0001$). Complications, mainly cholangitis, occurred in 10% of patients in the FCSEMS arm *vs* 50% in the plastic arm ($P = 0.0505$), with an identical overall number of recurrences in both groups. Interestingly, no stents migrations were observed in the FCSEMS arm, but it must be noted that stents with antimigration waist have been used [26]. Driven by these encouraging results, other authors have designed further trial. Tal *et al*, conducted a multicenter RCT with 24 patients randomized in the SEMS group and 24 randomized in the plastic stents ones. Stricture resolution, was achieved in all of the patients treated by SEMS compared with 95.8% in which plastic stents were used ($P = 1.000$). The migration rate in the FCSEMS group was of 33.3%, of which half occurred in healed strictures. Fewer ERCP (2 *vs* 4, $p < 0.0001$) were needed in the FCSEMS arm compared with the plastic stent arm to obtain treatment success. The recurrence rate was 33.9% in both groups [27], Martins *et al*, in a RCT, compared the outcomes of FCSEMS with the plastic stents' ones in 64 patients with anastomotic strictures after liver transplantation, in which the outcomes of SEMS appeared less encouraging than in the previous trials. Particularly, a higher stricture recurrence rate was reported in the SEMS group compared with the plastic stents group (32 % *vs* 0%, $p < 0.01$), in addition to a significant higher overall adverse events and higher migration rate in the SEMS group. Conversely, no statistically significant difference was seen regarding stricture resolution, that was reached in 83.3% of patients in the SEMS *vs* 96.5% in the multi stents arm ($P = 0.019$) with a mean of 2 *vs* 4.9 ERCP, respectively (no available p value) [28].

In 2019, a systematic review and meta-analysis of the 4 RCTs [26-29] available at that time was performed, including 205 patients [30]. The authors reported no statistically significant difference between groups in strictures resolution (odds ratio [OR] 1.05, 95% confidence interval [CI] 0.43-2.56, $P = 0.92$), recurrence (OR 2.37, 95%CI 0.54-10.38, $P = 0.25$), adverse events (OR 0.91, 95%CI 0.84-3.48, $P = 0.86$) and migration rate (OR 1.31, 95%CI 0.46-3.71, $P = 0.61$). Although it was confirmed a lower mean number of ERCP in the FCSEMS group (mean difference [MD] -2.08).

Recently, a multicenter RCT has been published in which 30 patients with anastomotic strictures after liver transplantation were randomized to FCSEMS or MPS. At a median follow up of 60 mo, including re-treatments, overall clinical success was obtained in 93.3% of patients in each group. Although, considering only the radiological success rate at first-line treatment, the success rate was of 73% and 93% in the SEMS and MPS group (p = not significant), with a migration rate of 29% and 2.6% in SEMS and MPS arm, respectively ($p < 0.01$). In the cost analysis performed by the authors there was no difference in overall treatment related costs between the two approaches, although in the patients with clinical success after first-line approach, the costs were 41% lower in the FCSEMS group [31].

Data from RCTs and meta-analyses suggest that an approach with SEMS compared to MPS guarantees comparable outcomes in stricture resolution rates with fewer ERCP procedures required in anastomotic strictures after liver transplantation. However, a higher stent migration rate and a trend toward a higher recurrence rate are reported after positioning of metal stent.

There are insufficient data to make a comparison, due the heterogeneity of the disease, between plastic stent and metal stent in non-anastomotic strictures. In a recent retrospective study by Zhang *et al*, 55 patients with non-anastomotic strictures were included. The balloon dilation in association with plastic stents was the approach used in 30.9% of patients, FCSEMS in 12.7% while balloon dilation was the approach of choice in other cases, however no comparison was performed by the authors [32]. Comparative studies are needed to better understand what type of stents have to be chosen in these particularly condition.

BILIARY STRICTURES IN CHRONIC PANCREATITIS

In advanced chronic pancreatitis, 3% to 23% of patients could develop, as a complication of the disease, a stricture of the common bile duct [7]. Generally, no treatment is required in asymptomatic patients with BBS associated with chronic pancreatitis, whereas, according to the ESGE guidelines, a treatment is demanded in case of symptoms, bile

duct stones, secondary biliary cirrhosis or in case of persistent (> 1 mo) cholestasis [33]. Usually, the endoscopic treatment is the approach of choice, reserving surgical operation for non-responding strictures and in the suspicion of malignancy. ERCP using MPS and FCSEMS have been described in the treatment of patients with benign bile duct obstruction associated with chronic pancreatitis, nevertheless only two dedicated RCTs have been reported (Table 2). The first one was published by Haapamaki *et al*, in 2014, in which 30 patients per arm were randomized in the FCSEMS or MPS group. Three months after the initial ERCP with related sphincterotomy and 10Fr plastic stent placement, the original stent was replaced with either three plastic stents or a single FCSEMS, according to randomization method. Plastic stents were changed or added every 3 mo while metal stent was removed after 6 mo of treatment. The 2-year overall success rate was 90% in the plastic stent and 92% in the SEMS group ($P = 0.405$). No difference between groups in terms of adverse events, recurrences or stent migration were reported [34]. Recently, Ramchandani *et al*, published a newer multicenter non inferiority RCT, comparing MPS and FCSEMS to treat symptomatic patients with biliary stricture associated with chronic pancreatitis [35]. Overall, 164 patients were randomized: 84 to the MPS arm and 80 in the FCSEMS group. At the index ERCP, plastics or metal stents were placed according to the randomization process. FCSEMS were removed after 12 mo, whereas plastic stents were changed every 4 mo and finally removed after 12 mo of treatment. At 2 years follow-up, the strictures resolution rate was 77.1% vs 75.8% for MPS and FCSEMS, respectively ($P = 0.008$ for noninferiority intention-to-treat). The Authors reported a statistical significance higher mean number of ERCPs in the MPS group compared with FCSEMS group (3.9 ± 1.3 vs 2.6 ± 1.3 , $p < 0.001$). No statistical significance difference for adverse events among the treatment arms were reported. The overall migration rate in the FCSEMS group was 18.8%, mainly complete distal migration, whereas only 7% of migration rate was reported by Haapamaki *et al*. An interesting technical contribution showed by this trial is the safety profile of leaving in place the FCSEMS for a time of 12 mo, a longer period of time previously reported, with the aim to reduce the recurrence rate, as suggested by other authors [36]. Although it should be remembered the risk of pancreatic cancer in these

patients, indeed in the trial 6.7% of patients had a pancreatic cancer diagnosis over the follow-up period, without any difference between group; thus, it is possible that repeated cholangiograms would not affect the possibility of an earlier cancer diagnosis. Instead, it is crucial to exclude an underlying malignancy before the starting of treatment protocol. FCSEMSs are a concrete alternative (Figure 3) to MPSs in the treatment of biliary stricture related to chronic pancreatitis without any difference in safety profile and similar stricture resolution rate obtained with less total procedures. Additional studies with longer-term follow up are needed to help determine the best option in chronic pancreatitis related BBS.

BILIARY STRICTURES IN PRIMARY SCLEROSING CHOLANGITIS

PSC is a chronic cholestatic liver disorder associated with intrahepatic and extrahepatic biliary strictures. The disease is characterized by the development in almost 50% of patients of a so-called dominant stricture, which are defined as a narrowing of the common bile duct with a diameter of less than 1.5 mm or less than 1 mm in the left or right hepatic duct [37]. Stricture may degenerate to cholangiocarcinoma in up to 15% of patients, thus, it is indispensable to first exclude malignancy before starting stricture treatment [38].

In symptomatic patients ERCP with balloon dilation of the dominant stricture is indicated which represents the first line therapeutic options. In an early retrospective study, Kaya *et al*, compared the efficacy and safety of the endoscopic balloon dilation alone *vs* balloon dilation followed by plastic stent placement in dominant stricture related to PSC. In this study only 14 out of 37 patients in the stent group were treated endoscopically, in the remaining part of the patients the stent was placed percutaneously or using both interventions. No significant difference between groups were reported in success rate in terms of improving cholestasis, although balloon dilation plus stent positioning was associated with higher number of ERCP per patient and nevertheless with higher rate of adverse events in the plastic stent group compared with balloon dilation alone, even so it should be noted that most of the complications were subsequent to the percutaneous

approach ^[39]. A recent multicenter RCT comparing balloon dilation with plastic stent placed for a short-term of 7 days was published by Ponsioen *et al*. The study was interrupted after a planned interim analysis due to concern about the safety profile of the plastic stent placement. Indeed, at 2 years follow-up the recurrence-free rate did not differ significantly between groups, instead the serious adverse events were significantly higher in the stent arm compared with dilation arm (45% *vs* 6.7%, respectively. $P = 0.001$) ^[40]. Considering the disease course and these outcomes, in which plastic stents placement in PCS's dominant stricture is not more effective and even harmful compared with endoscopic balloon dilation alone, it might be expected that even fully covered metal stents are unlikely to add some benefit in the treatment of stricture due to PCS; however, data from RCT or even from retrospective study are required to better understand the role of FCSEMS in this disease.

CONCLUSION

BBS is a challenging condition in which endoscopic treatment provides good results in resolution rate in a minimally invasive fashion compared with surgery and percutaneous treatments. Endoscopic balloon dilation was the first available therapeutic option, even though the introduction of stents has improved the efficacy of the endoscopic treatment, with the exception of stricture in patients with PSC in which the balloon dilation alone is still the first-line treatment. Which stent, between plastic and metallic, is better to place in BBS would remain a partially unsolved question, considering the shortage of good randomized clinical trial. Both of stents have comparable success rate in stricture resolution, even though FCSEMS guarantees the healed of the structure with a lower number of ERCP, although their use is burdened with a higher migration rate compared with MPS, which nowadays still remain the most common and a viable strategy to treat benign biliary stricture. Additional studies based on larger sample size and on new technologies in metal stents are demanded to better understand which type of stent is best to place in BBS.

Figure Legends

Figure 1 Endoscopic appearance of multiple plastic stenting for benign biliary strictures.

Figure 2 . A: Fluoroscopic appearance of a post-cholecystectomy biliary stricture at the confluence of the intrahepatic bile ducts; B: Fluoroscopic result after multiple sessions of balloon dilation and multiple plastic stenting.

Figure 3 . A: Fluoroscopic appearance of a benign biliary stenosis of the distal common bile duct due to chronic pancreatitis; B: Fluoroscopic result after placement of a fully covered self expandable metal stent.

Table 1 Main outcomes of RCTs comparing MPS to FC-SEMS in anastomotic stricture after liver transplantation

Table 2 Main outcomes of RCTs comparing MPS to FC-SEMS in common bile duct stricture associated with chronic pancreatitis

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