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MINIREVIEWS

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

Matteo Colombo, Edoardo Forcignanò, Leonardo Da Rio, Marco Spadaccini, Marta Andreozzi, Carmelo Marco Giacchetto, Silvia Carrara, Roberta Maselli, Piera Alessia Galtieri, Gaia Pellegatta, Antonio Capogreco, Davide Massimi, Kareem Khalaf, Cesare Hassan, Andrea Anderloni, Alessandro Repici, Alessandro Fugazza

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Abstract

Benign biliary strictures (BBS) might occur due to different pancreaticobiliary conditions. The etiology and location of biliary strictures are responsible of a wide array of clinical manifestations. The endoscopic approach endoscopic retrograde cholangiopancreatography 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 cholangiopancreatography; Endoscopic management; Biliary stent

Core Tip: The aim of this narrative review is to describe the best treatment for benign biliary strictures caused by the most common diseases. Our attention will be focused on the evaluation of the different types of stents currently available in the market, their main characteristics, and the most relevant technological innovations.

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INTRODUCTION

Biliary strictures refer to the narrowing or obstruction of the bile ducts, which can be classified as malignant biliary strictures (MBS) or benign biliary strictures (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 postoperative 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 present[2]. Orthotopic liver transplantation (OLT) is the second most common cause of postoperative 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 a worse prognosis with significant mortality and morbidity[6]. Less common causes of postoperative biliary strictures are stenosis after biliary reconstructions, bilio-enteric anastomosis or post-endoscopic retrograde cholangiopancreatography (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-related sclerosing cholangitis, infective disease like tuberculosis or histoplasmosis, and trauma are less common etiologies of BBS. The etiology and location of biliary strictures are responsible of a wide array of clinical manifestations, ranging from asymptomatic or paucisymptomatic patients to those that present with jaundice, abdominal colic pain, and even sepsis. Regardless of the etiology, it is of paramount importance to rule out an underlying malignant process: Targeted radiological investigations, computed tomography, magnetic resonance imaging, or positron emission tomography, possibly complemented with a bioptic approach with endoscopic ultrasound or ERCP, are indispensable in such cases. After confirming the benign nature of the strictures, several treatment modalities are available, including surgery, interventional radiology, and endoscopy. Nowadays, the endoscopic approach 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 stricture 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 stent positioning was associated with higher success, defined as stricture resolution, and lower recurrence rates compared with dilation alone[9]. Traditionally, plastic biliary stent placement (Figure 1) across the stricture was the milestone of treatment, although the introduction of self-expandable metal stents (SEMS) has sparked a growing interest in this relative new technology. This narrative review aims to describe the treatment of BBS 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, a larger part of the studies included different heterogeneous etiologies of BBS, which limits their findings.

PLASTIC STENTS

BBS 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.

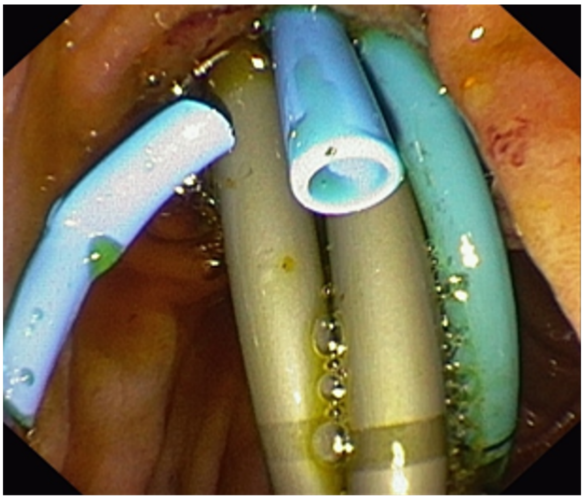

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Figure 1 Endoscopic appearance of multiple plastic stenting for benign biliary strictures.

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 SEMS. SEMS is a particularly fascinating alternative for treatment of BBS, as a 10 mm SEMS corresponds to a bile duct caliber reached by three or four 10-Fr plastic stents. Three type of metal stents are available: Uncovered SEMS (U-SEMS), partially covered SEMS (PC-SEMS), and fully covered SEMS (FC-SEMS). The placement of uncovered metal stents in BBS was first reported in 1991, but their use has been limited by the stent occlusion due to epithelial hyperplasia leading to the embedding of prothesis into the bile duct mucosa, making removal difficult or even impossible[11,12]. Therefore, U-SEMS in BBS is not recommended by the European Society of Gastrointestinal Endoscopy (ESGE) because of removal issues[13]. PC-SEMS have a plastic polymer in the central part of the prothesis, 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]. FC-SEMS have been designed with a plastic polymer covering the entire prothesis, in order to avoid epithelial hyperplasia seen with U-SEMS and PC-SEMS and consequently facilitating their removal. According to the ESGE guidelines, the FC-SEMS are the recommended metallic prothesis to use in BBS, thanks to their ease of removal[13]. The ideal dwell time of FC-SEMS is still unknown; generally, their removal is indicated after 6 mo, because it has been reported that a 6-mo compared with a 3-mo dwell time is associated with a lower recurrence rate[15], even though longer dwell time has been described. The main drawback of FC-SEMS is the high migration risk, reported as 9% in a large meta-analysis by Zheng *et al*[16]. Thus, reducing the migration risk and enhancing stent dwell time of FC-SESM have encouraged some innovations in the technology of metal stents, 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 of 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 strictures 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*[18] 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 with 7.4% of patients who experienced adverse events. Only two patients underwent surgical reconstruction because of failed treatment. 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 stents was suggested. Tringali *et al*[19], in a recent prospective multicenter study, evaluated the efficacy of FC-SEMS with scheduled removal after 6-12 mo in patients with BBS. A subgroup analysis in 18 patients with post-cholecystectomy stricture was performed. At the 5-year follow-up, the resolution rate was 72%, with adverse events occurring in 38.9% of the patients, mainly cholangitis. They reported a migration rate in 16.6% of patients in which the stricture was healed. Temporary placement of a FC-SEMS could be considered as a safe alternative to MPS placement in biliary stricture due to cholecystectomy, even though MPS approach remains the first-line therapy (Figure 2) unless more conclusive data will be published.

BILIARY STRICTURES AFTER OLT

OLT is a frequent cause of BBS. 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 PSC[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 condition, with strictures that are usually longer compared with the anastomotic ones and located in multiple sites. The time of presentation of the strictures plays an important prognostic role; indeed the anastomotic strictures with an early presentation (less than 30 d) are linked to favorable outcome compared with anastomotic strictures with a later presentation (more than 90 d)[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 FC-SEMS has been described in early 2011 by Hu *et al*[25]. Multiple randomized clinical trials (RCT) have compared the results obtained with plastic stents or SEMS in the anastomotic strictures after liver transplantation (Table 1). The first one was published in 2014 by Kaffes *et al*[26], in which ten patients were randomized to the FC-SEMS arm and ten to the plastic stents arm. Stricture resolution was obtained in 100% of patients in the FC-SEMS group compared with 80% in the plastic stents group (P value was not significant) with a median number of 2 ERCP per patient obtained with metal stents compared with 4.5 with plastic stents (P = 0.0001). Complications, mainly cholangitis, occurred in 10% of patients in the FC-SEMS arm *vs* 50% in the plastic arm (P = 0.0505), with an identical overall number of recurrences in both groups. Interestingly, no stent migrations were observed in the FC-SEMS arm, but it must be noted that stents with antimigration waist have been used. Driven by these encouraging results, other authors have designed further trials. Tal *et al*[27] conducted a multicenter RCT with 24 patients randomized to the SEMS group and 24 to the plastic stents group. 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 FC-SEMS group was 33.3%, of which half occurred in healed strictures. Fewer ERCP (2 *vs* 4, P < 0.0001) were needed in the FC-SEMS arm compared with the plastic stents arm to obtain treatment success. The recurrence rate was 33.9% in both groups, Martins *et al*[28], in a RCT, compared the outcomes of FC-SEMS 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 significantly higher overall adverse event rate and higher migration rate in the SEMS group. Conversely, no statistically significant difference was seen regarding stricture resolution, which 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).

In 2019, a systematic review and meta-analysis of the four RCTs[26-29] available at that time was performed, including 205 patients[30]. The authors reported no statistically significant difference between groups in stricture resolution [odds ratio (OR): 1.05, 95% confidence interval (95%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 a lower mean number of ERCP in the FC-SEMS group (mean difference -2.08) was confirmed.

Recently, a multicenter RCT has been published in which 30 patients with anastomotic strictures after liver transplantation were randomized to undergo FC-SEMS or MPS placement. 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 73% and 93% in the SEMS and MPS groups (P value was not significant), with a migration rate of 29% and 2.6% in the SEMS and MPS arms, 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 FC-SEMS group [31].

Data from RCT 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 stents.

There are insufficient data to make a comparison, due to the heterogeneity of the disease, between plastic stents and metal stents in non-anastomotic strictures. In a recent retrospective study by Zhang *et al*[32], 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, FC-SEMS in 12.7%, while balloon dilation was the approach of choice in other cases; however, no comparison was performed by the authors. Comparative studies are needed to better understand which type of stent has to be chosen in these particularly conditions.

Table 1 Main outcomes of randomized clinical trials comparing multiple plastic stents to fully covered self-expandable metal stents in anastomotic stricture after liver transplantation

Ref.	Arm	Number of patients	Success rate (%)	Recurrence (%)	Number of ERCP/patients	Migration rate (%)	Follow-up time (mo)
Kaffes *et al*[26], 2014	MPS	10	8 (80%)	3 (37.5%)	4.5 (2-6)	1 (10%)	25.5 (3-44)
	FC-SEMS	10	10 (100%)	3 (30%)	2 (2-2)	0 (0%)	26 (6-40)
Coté *et al*[29], 2016	MPS	36	31 (86.1%)	1 (3.2%)	3.13 ± 0.88	8 (22.2%)	24
	FC-SEMS	37	33 (89.2%)	5 (15.2%)	2.21 ± 0.48	15 (40.5%)	24
Tal *et al*[27], 2017	MPS	24	23 (95.8%)	5 (21.7%)	4 (3-12)	0 (0%)	16.9 (2-39.4)
	FC-SEMS	24	24 (100%)	5 (20.8%)	2 (2-12)	5 (20,8%	13.3 (6.3-34.9)
Martins *et al*[28], 2018	MPS	29	28 (96.6%)	0 (0%)	4.9 (4-6)	3 (10,3%)	32.9
	FC-SEMS	30	25 (83.3%)	8 (32%)	2 (2-2)	3 (10%)	36.4
Cantù *et al*[31], 2021	MPS	15	14 (93.3%)	1 (7.1%)	4 (3-7)	2 (13.3%)	55 (34-74)
	FC-SEMS	15	11(73.3%)	4 (36.4%)	3 (2-8)	5 (33.3%)	63 (41-80)

ERCP: Endoscopic retrograde cholangiopancreatography; FC-SEMS: Fully covered self-expandable metal stents; MPS: Multiple plastic stents.

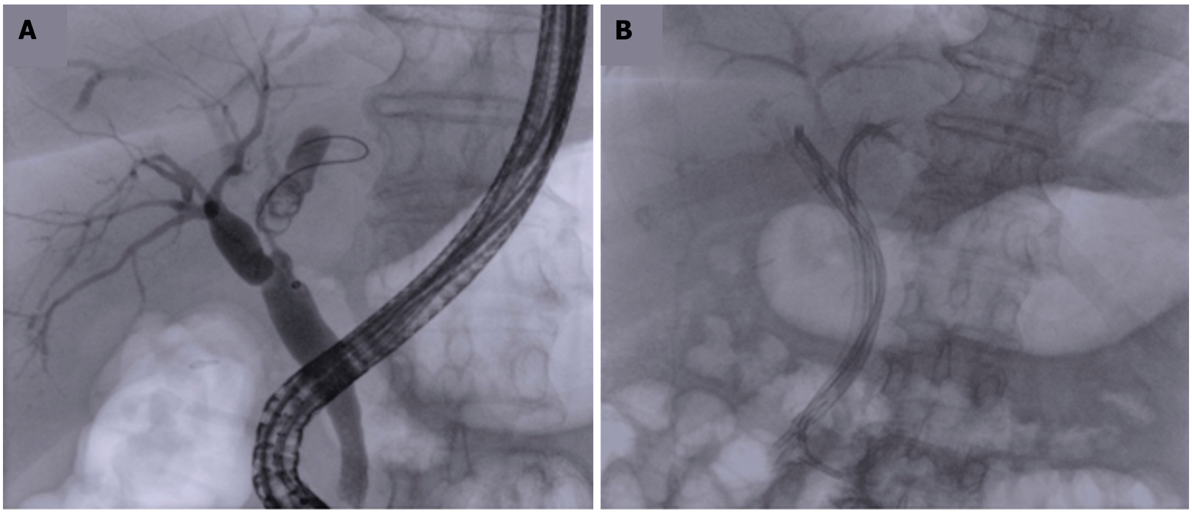

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Figure 2 Endoscopic treatment of a post-cholecystecomy biliary stricture. A: Fluoroscopic appearance of the biliary stricture at the confluence of the intrahepatic bile ducts; B: Fluoroscopic result after multiple sessions of balloon dilation and multiple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

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 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 FC-SEMS has been described in the treatment of patients with benign bile duct obstruction associated with chronic pancreatitis, nevertheless only two dedicated RCT have been reported (Table 2). The first one was published by Haapamäki *et al*[34], in 2015, in which 30 patients per arm were randomized in the FC-SEMS or MPS group. Three months after the initial ERCP with related sphincterotomy and 10-Fr plastic stent placement, the original stent was replaced with either three plastic stents or a single FC-SEMS, 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 was reported. Recently, Ramchandani *et al*[35] published a newer multicenter noninferiority RCT, comparing MPS and FC-SEMS to treat symptomatic patients with biliary stricture associated with chronic pancreatitis. Overall, 164 patients were randomized: 84 to the MPS arm and 80 to the FC-SEMS group. At the

Table 2 Main outcomes of randomized clinical trials comparing multiple plastic stents to fully covered self-expandable metal stents in common bile duct structure associated with chronic pancreatitis

Ref.	Arm	Number of patients	Success rate (%)	Recurrence (%)	Number of ERCP/patients	Migration rate (%)	Follow-up time (mo)
Haapamäki *et al*[34], 2015	MPS	30	22 (73.3%)	3 (13.6%)	-	3 (15%%)	37 (3-61)
	FC-SEMS	30	20 (66.6%)	2 (10%)	-	2 (10%)	41 (1-66)
Ramchandani *et al* [35], 2021	MPS	84	54/70 (77.1%)	-	3.9 ± 1.3	18 (21.4%)	23.7
	FC-SEMS	80	47/62 (75.8%)	-	2.6 ± 1.3	15 (18.8%)	23.7

ERCP: Endoscopic retrograde cholangiopancreatography; FC-SEMS: Fully covered self-expandable metal stents; MPS: Multiple plastic stents.

index ERCP, plastic or metal stents were placed according to the randomization process. FC-SEMS were removed after 12 mo, whereas plastic stents were changed every 4 mo and finally removed after 12 mo of treatment. At the 2-year follow-up, the stricture resolution rate was 77.1% *vs* 75.8% for MPS and FC-SEMS, respectively (P = 0.008 for noninferiority intention-to-treat analysis). The authors reported a statistically significant higher mean number of ERCP in the MPS group compared with the FC-SEMS group (3.9 ± 1.3 *vs* 2.6 ± 1.3, P < 0.001). No statistical significance difference for adverse events among the treatment arms was reported. The overall migration rate in the FC-SEMS group was 18.8%, mainly complete distal migration, whereas only a 7% migration rate was reported by Haapamäki *et al*[34]. An interesting technical contribution showed by this trial is the safety profile of leaving in place the FC-SEMS for a time of 12 mo, a longer period of time than that previously reported, with the aim to reduce the recurrence rate, as suggested by other authors[36]. Although the risk of pancreatic cancer in these patients should be remembered, indeed in the trial 6.7% of patients had a pancreatic cancer diagnosis over the follow-up period, without any difference between groups; 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. FC-SEMS are a concrete alternative (Figure 3) to MPS in the treatment of biliary strictures related to chronic pancreatitis without any difference in safety profile and with similar stricture resolution rates 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.

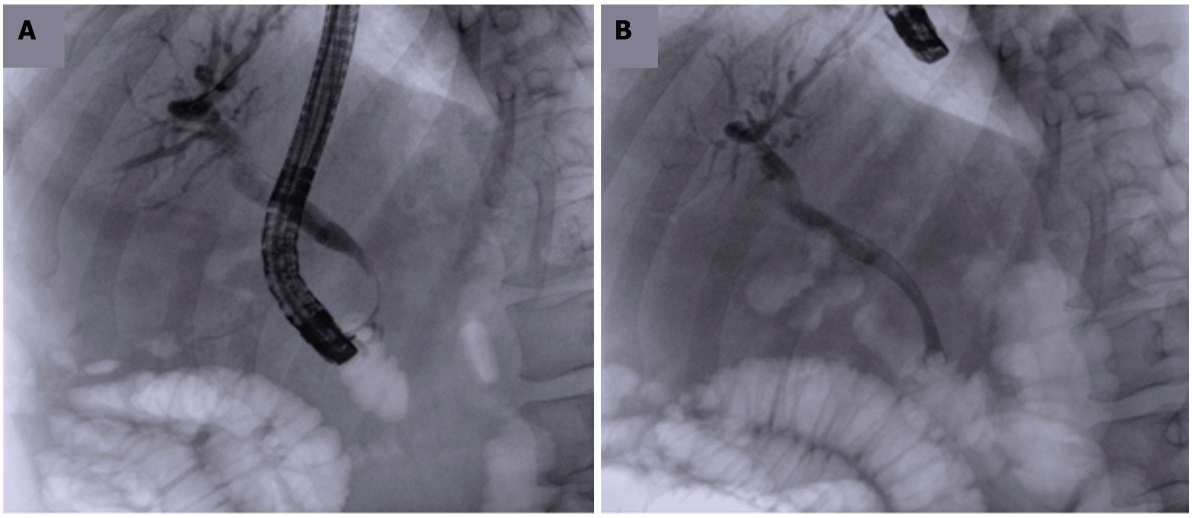
BILIARY STRICTURES IN PSC

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 is 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 option. In an early retrospective study, Kaya *et al*[39] 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, and in the remaining part of the patients, the stent was placed percutaneously or using both interventions. No significant difference between groups was reported in success rate in terms of improving cholestasis, although balloon dilation plus stent positioning was associated with a higher number of ERCP per patient and nevertheless with a 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. A recent multicenter RCT comparing balloon dilation with plastic stents placed for a short-term of 7 d was published by Ponsioen *et al*[40]. The study was interrupted after a planned interim analysis due to concern about the safety profile of the plastic stent placement. Indeed, at the 2-year follow-up, the recurrence-free rate did not differ significantly between groups, instead the rate of serious adverse events was significant higher in the stent arm compared with dilation arm (45% *vs* 6.7%, respectively, P = 0.001). Considering the disease course and these outcomes, in which plastic stent placement in dominant stricture related to PSC is not more effective and even harmful compared with endoscopic balloon dilation alone, it might be expected that even fully covered metal stents are unlike to add some benefit in the treatment of stricture due to PSC; however, data from RCT or even from retrospective study are required to better understand the role of FC-SEMS 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



DOI: 10.12998/wjcc.v11.i31.7521

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

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 RCT. Both of stents have comparable success rate in stricture resolution, even though FC-SEMS guarantee the heal of the structure with a lower number of ERCP, although their use is burdened with a higher migration rate compared with MPS, which nowadays remains the most common and a viable strategy to treat BBS. Additional studies based on larger sample size and on new technologies in metal stents are demanded to better understand which type of stent is the best to place in BBS.

FOOTNOTES

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