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DYNAMIC MANUSCRIPTS

Short-term stenting using fully covered self-expandable metal stents for treatment of refractory biliary leaks, postsphincterotomy bleeding, and perforations

Jorge Canena · Manuel Liberato · David Horta · Carlos Romão · António Coutinho

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Abstract
Background Fully covered self-expandable metal stents (FCSEMS) have been used as a rescue therapy for several benign biliary tract conditions (BBC). Long-term stent placement commonly occurs, and prolonged FCSEMS placement is associated with the majority of the complications reported. This study evaluated the duration of stenting and the efficacy and safety of temporary FCSEMS placement for three BBCs: refractory biliary leaks, postsphincterotomy bleeding, and perforations.
Methods This was a retrospective case series with long-term follow-up of 25 patients who underwent FCSEMS placement for BBCs. This study included 17 patients with postcholecystectomy refractory biliary leaks who had previously undergone unsuccessful sphincterotomy and plastic stent placement, 4 patients with difficult-to-control postsphincterotomy bleeding, and 4 patients with a perforation following endoscopic sphincterotomy. Stents were removed according to clinical evidence of problem resolution. The review included stenting duration, safe FCSEMS removal, clinical efficacy, complications, and long-term outcomes. During the follow-up period, ERCP and cholangioscopy procedures were performed to exclude the possibility of bile duct lesion development.
Results Complete resolution of the initial condition was achieved in all patients. Patients with biliary leaks had a median stent duration time of 16 days (range 7–28 days). Patients with bleeding had stents removed after a median time of 6 days (range 3–15 days). Patients with perforations had their stents removed after a median time of 29.5 days (range 21–30 days). There were no complications related to stenting.
Conclusions Temporary placement of a FCSEMS for 30 days or less is an effective rescue therapy for refractory biliary leaks, difficult-to-control post-endoscopic sphincterotomy bleeding, and perforations. Duration of stenting should be different for each type of condition. Stents can be safely removed, and short-term stenting is associated with the absence of early and late complications.

Keywords Fully covered self-expandable metal stents · Refractory biliary leaks · Benign biliary tract conditions · Endoscopic retrograde cholangiopancreatography · Postsphincterotomy bleeding · Duodenal perforations

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J. Canena · C. Romão · A. Coutinho
Faculty of Medical Sciences, Department of Gastroenterology, Pulido Valente Hospital, Lisbon, Portugal

J. Canena (✉) · M. Liberato · D. Horta · A. Coutinho
Center of Gastroenterology, Cuf Infanto Santo Hospital, Travessa do Castro n° 3, 1350-070 Lisbon, Portugal
e-mail: jmtcanena@live.com.pt

J. Canena · D. Horta
Department of Gastroenterology, Professor Doutor Fernando Fonseca Hospital, Amadora, Portugal

J. Canena
Department of Endoscopy, José Joaquim Fernandes Hospital, Beja, Portugal

Since its introduction in 1968 [1], endoscopic retrograde cholangiopancreatography (ERCP) has evolved into a sophisticated therapeutic endoscopic examination, and the placement of biliary plastic stents has become one of the cornerstones of the procedure. Initially, due to the small

diameter of the working channel of the endoscope, it was only possible to place small-caliber plastic stents. However, the 1982 [2] development of duodenoscopes with 4.2-mm working channels allowed the use of large-bore (10–11.5-French) plastic stents. Ten-French stents are now the standard caliber, because use of 11.5-Fr plastic stents is more technically challenging and does not increase stent patency [3]. Plastic stents are routinely used to treat benign biliary conditions (BBCs) such as biliary leaks [4–6], strictures [7], postsphincterotomy bleeding (post-ES bleeding) [8], and perforations [9, 10].

Clinically significant biliary leaks can occur after hepatobiliary surgery and are the main cause of postoperative bile leaks following laparoscopic cholecystectomy procedures [4, 5]. Despite the widespread use and efficacy of ERCP in the diagnosis and treatment of biliary leaks [4–6, 11, 12], a variety of percutaneous and surgical treatments have been proposed [13, 14]. Biliary sphincterotomy alone [5], use of large-bore transpapillary biliary stents [5], or a combination of both therapies have become the first-line interventions for the treatment of bile leaks [4, 5]. Although there is no consensus as to the optimal endoscopic intervention, recent data suggest that a combination of biliary sphincterotomy and placement of a transpapillary biliary stent has a better outcome for the treatment of high-grade biliary leaks [4, 14]. Endoscopic management of bile leaks is safe and efficacious with a high success rate [4–6, 11, 12]. Nevertheless, there are reports of difficult-to-treat, refractory bile leaks that require multiple endoscopic interventions and sometimes surgery [4, 5].

Endoscopic sphincterotomy (ES) is a fundamental procedure of therapeutic ERCP. Complications following ES can include bleeding [8, 9, 15] and perforations [9, 10]. The incidence of post-ES bleeding varies from 0.76–2 to 10–48 % [8, 15], depending on the definition applied. Post-ES bleeding is classified as immediate or delayed according to the time of presentation [8, 15, 16], and it is associated with increased morbidity and mortality [8, 9, 17]. Endoscopic treatments include injection treatment, thermal therapy, endoclips, and balloon tamponade, which can be applied individually or in combined treatments. These procedures are associated with the placement of large-bore plastic stents to further tamponade the bleeding site and to maintain biliary drainage [8, 15]. In a small percentage of cases, refractory bleeding requiring angiographic embolization or surgery occurs [8, 15]. Another post-ES complication is perforation, which occurs in 0.35 % and 0.48–0.72 % of cases [9, 10]. Although conservative management with intravenous antibiotics, fluids, a nil-by-mouth regimen, and the placement of large-bore plastic stents is efficacious, surgery is sometimes required [9, 10].

Because the use of plastic stents is not able to resolve problematic cases, gastroenterologists have looked to self-expandable metal stents (SEMSs), which have large diameters and demonstrate a prolonged duration of patency, as a rescue therapy for difficult-to-treat patients. Because uncovered SEMSs soon become embedded into body tissues, their removal is difficult, if not impossible, which limits their use in BBCs [3, 18, 19]. Covered SEMS were designed to prevent tumor ingrowth and reactive tissue hyperplasia through the stent mesh. This cover prevented the metal from embedding into the biliary tract, allowing for removability [3, 19–22]. The first covered stents were coated in the middle and had both ends uncovered. Although efficacy has been shown [19–22], studies using partially covered SEMS in several BBCs reported early complications, including duodenal or proximal migration and pancreatitis [21]. Later complications also occurred and included duodenal or proximal migration and cholecystitis [20, 21]. Furthermore, because the initial portion of the partially covered SEMS can be embedded in the bile duct, its removal can be difficult, particularly in cases of proximal migration. This embedding can result in late stricture formation at the site of embedding [19–23].

Fully covered SEMSs (FCSEMSs) were designed to maintain long-term patency and can be used to treat BBCs. The full coverage of the stent decreased the incidence of complications and made stent removal safer and easier [3, 24–26]. Although not approved by the Food and Drug Administration, temporary FCSEMS placement is an excellent option in a subgroup of patients with BBCs that do not respond to plastic stent placement or to the usual endoscopic therapies [3, 24–26]. However, recent papers using FCSEMSs in BBCs [3, 24–26] reported complications, including duodenal migration [24, 26], bile duct ulcerations [25], de novo choledocholithiasis [25], strictures [3, 25], and even periampullary adenoma [25]. Furthermore, optimal stenting duration has not been well studied, and long-term stent placement commonly occurs [3, 19, 25]. Prolonged FCSEMS placement is associated with the majority of the complications reported and has not been shown to increase efficacy [3, 25, 26], except in the treatment of strictures [3, 24, 27].

This study evaluated the optimal duration of stenting and the efficacy and safety of temporary FCSEMS placement for the treatment of three BBCs: refractory biliary leaks, difficult-to-control post-ES bleeding, and perforations. Our primary hypothesis was that short-term stenting (30 days or less) would effectively treat the examined BBCs without the development of early or late complications.

Materials and methods

Patients and setting

An interventional endoscopy database was retrospectively reviewed to identify all of the patients referred for ERCP who were treated with an FCSEMS as a rescue treatment for refractory biliary leaks, difficult-to-control post-ES bleeding, and perforations between March 2007 and May 2011. As an additional inclusion criterion, all stents were required to have been removed within 30 days of placement. The endoscopic and medical reports and the radiological findings of these patients were reviewed to collect the following data: patient demographics, indication for ERCP, duration of stenting, treatment outcomes, complications, and specific information for each group of patients. This study was conducted at a total of four institutions: three tertiary referral academic centers (Pulido Valente Hospital, Faculty of Medical Sciences, Lisbon, Portugal; Cuf Infanto Santo Hospital, Lisbon, Portugal; Professor Doutor Fernando Fonseca Hospital, Amadora, Portugal) and one community hospital (José Joaquim Fernandes Hospital, Beja, Portugal). All patients provided informed written consent prior to their procedures. Each institutional review board involved approved this retrospective study.

Definitions

Refractory biliary leaks were defined as leaks that failed to close after endoscopic intervention with a combination of biliary sphincterotomy and placement of a large-bore (10-Fr) transpapillary biliary stent regardless of biliary leak location (cystic stump, common bile duct/common hepatic duct, Luschka). All the plastic stents used had, at least, a length of 7 cm. High-grade biliary leaks were defined as leaks observed fluoroscopically prior to intrahepatic opacification [4]. Ceased bile output was defined as biliary drainage of less than 5 ml/day in percutaneous drains.

Difficult-to-control post-ES bleeding was defined as a hemorrhage where usual endoscopic measures [8, 15, 16] were attempted but failed to achieve hemostasis. Immediate post-ES bleeding episodes were defined as episodes that occurred at the time of sphincterotomy [8, 15], while delayed post-ES bleeding episodes were defined as bleeding that began hours to several days after the end of the ERCP procedure [8, 16]. Bleeding severity was graded as mild, moderate or severe using the following previously described validated grading system [16]: Mild bleeding was defined by clinical evidence of gastrointestinal bleeding, hemoglobin decrease of less than 3 g/dl, and no need for transfusion, while moderate bleeding was defined by the need for transfusion (4 units or less); severe bleeding was defined by the need for transfusion (5 units or more) or rescue intervention (angiographic or surgical). Immediate post-ES bleeding that required endoscopic treatment was considered, at minimum, as mild bleeding. At the time of the procedures, perforations were recognized by the characteristic contrast extravasation and retroperitoneal air on computed tomography (CT) scans, regardless of their association with subcutaneous emphysema.

Complications were defined as any adverse events related to FCSEMS placement. Early complications were defined as complications that occurred while stents were in place. Early complications, if any, were reported separately for FCSEMS insertion and removal. Late complications were defined as those complications that occurred after FCSEMS removal. Migration (distal or proximal), pancreatitis, cholecystitis, bile duct and duodenal ulcerations, de novo choledocholithiasis, and late strictures were carefully monitored using previously defined definitions [16, 20, 23, 25, 27].

Intervention and follow-up

All procedures were performed or supervised by two experienced pancreatobiliary endoscopists (J.C. and M.L.). ERCP procedures were performed in the prone position under sedation with propofol administered by an anesthesiologist. All of the endoscopic examinations were performed using a therapeutic duodenoscope (TJF-160R, TJF-160 VR, TJF-Q180 V; Olympus, Tokyo, Japan). Although all FCSEMSs used had a 10-mm luminal diameter, the length varied from 40 to 80 mm (Tables 1, 2, 3). From March 2007 to December 2009, two different stents were used: the Hanarostent (M. I. Tech, Seoul, South Korea) and the Niti-S (Taewoong Medical, Seoul, South Korea). After January 2010, the Wallflex (Boston Scientific, Natick, MA, USA) biliary stent was used in all cases. All patients underwent or had previously undergone a biliary sphincterotomy prior to FCSEMS placement. When the gallbladder was still present, FCSEMSs were placed below the cystic-duct insertion. In patients with bile leaks, the stent length (Table 1) was selected to enable leak coverage. After clinical evidence of the complete resolution of the initial condition, patients were scheduled for a second ERCP where the FCSEMS was removed through the scope using rat-toothed forceps or a cold snare at the discretion of the endoscopist. If, after pulling the stent, resistance was encountered, the stent was fixed to the tip of the duodenoscope with the forceps or the snare, and the instrument and the stent were removed together. After stent removal, a cholangiogram was performed to evaluate the initial problem and possible ductal

Table 1 Demographics, indications, detailed treatment data, and follow-up for patients with refractory biliary leaks

Age (years)/ sex	Origin of leak	Time interval (days) between ES + plastic stent (initial ERCP) and FCSEMS delivery	External drain bile output ceased (days after FCSEMS)	Duration of stenting (days)/ FCSEMS length (cm)	Follow-up (weeks)/control ERCP (weeks)/ choledochoscopy (yes/NA)
39/F	CBD/CHD	12	6	18/8	14/NA/NA
45/M	Cystic stump	10	2	28/6	30/24/yes
38/M	CBD/CHD	10	8	21/8	52/48/yes
32/M	CBD/CHD	8	6	18/8	104/90/yes
73/F	Cystic stump	18	3	20/6	36/30/NA
47/F	CBD/CHD	14	5	21/8	124/110/yes
73/F	Cystic stump	7	2	7/6	208/50/NA
84/M	Cystic stump	14	2	14/6	206/52/NA
62/F	Cystic stump	7	2	14/6	205/70/NA
74/F	Cystic stump	7	3	14/8	214/54/NA
89/F	Cystic stump	7	2	14/6	154/100/NA
62/F	Cystic stump	7	3	14/8	123/60/NA
39/F	Cystic stump	8	4	15/8	165/NA/NA
48/M	Cystic stump	10	3	15/6	180/NA/NA
42/F	Cystic stump	10	3	16/6	125/NA/NA
55/F	Cystic stump	12	4	16/8	130/NA/NA
64/M	CBD/CHD	10[a]	5	18/8	104/NA/NA

F female, *M* male, *CBD/CHD* common bile duct/common hepatic duct, *ES* endoscopic sphincterotomy, *ERCP* endoscopic retrograde cholangiopancreatography, *FCSEMS* fully covered self-expandable metal stent, *NA* not available

[a] Patient was submitted, on day 6, to a second ERCP to place a second large-bore plastic stent

injury. Patients were maintained several days on antibiotics due to the initial clinical condition, but not because of the stent itself. We do not advocate maintaining patients on antibiotics while covered stents are in place. With a large-diameter stent in place there is no obstruction of bile flow and there is no risk of cholangitis. The majority of patients underwent a follow-up ERCP procedure weeks to months after FCSEMS removal to determine if late strictures had developed.

At the moment of control ERCP a subset of patients with normal cholangiogram and previous history of one or more episodes of transient cholestasis were submitted to choledochoscopy to exclude minor bile duct defects (tissue hyperplasia). Cholangioscopy procedures were performed using the "mother–baby" technique. In this approach, a fiber-optic cholangioscope (CHF-BP30; Olympus, Tokyo, Japan) connected to a high-resolution system (Olympus, Tokyo, Japan) was utilized.

Long-term follow-up was obtained by reviewing clinical notes provided by regular clinic visits, laboratory results, imaging, cholangiography procedures performed weeks to months after stent removal (when available), cholangioscopy data, and structured telephone interviews with patients or family at the time of manuscript preparation.

Results

A total of 6,267 records for ERCP procedures that occurred between March 2007 and May 2011 were identified in the endoscopy database. Twenty-nine patients who met the inclusion criteria were identified. Four of these patients were excluded for the following reasons: incomplete data concerning endoscopic procedures and follow-up (three patients) and unavailability of informed written consent (one patient).

A total of 25 patients (9 male and 16 female) with a median age of 55 years (range 29–91 years, mean 56.2 years) were enrolled in the study. All stents were safely removed with a snare or rat-toothed forceps. Complete resolution of the initial BBC was confirmed in all patients. Patients were followed up for a median of 123.5 weeks (range 14–214 weeks, mean 113.3 weeks) following FCSEMS removal. One patient in the post-ES bleeding group was lost to follow-up because he underwent surgery for an ampullary tumor and died 5 days post surgery. Nevertheless, he was included in the study because his FCSEMS was removed and his initial clinical condition had resolved. All other patients completed the follow-up. For further detailed analysis, patients were divided into the following three

Table 2 Clinical characteristics and treatment data of patients with postsphincterotomy bleeding

Age (years)/ sex	Indication	Comorbid conditions/risk factors for bleeding	PT (s/INR)/ platelet count (100,000/μl)	Bleeding time after ERCP (days)/type	No. of units of blood transfusions/Hg drop (g/dl)	Attempted treatments	Duration of stenting (days)/ FCSEMS length (cm)	Follow-up/ control ERCP (weeks)
91/F	Stones	Atrial fibrillation anticoagulation therapy[a]	17.6/1.4/195	7/clot, oozing	2/NA	Epinephrine injection, balloon tamponade	3/4	20/14
37/M	Stones	Hepatitis C; no evidence of cirrhosis	10.8/1.0/239	3/clot, oozing	0/2,4	Epinephrine injection, endoclips	6/6	16/14
80/F	Stones	Periampullary diverticulum	12.4/1.2/231	Immediate/ pulsatile	0/1.3	Epinephrine injection, balloon tamponade	6/6	14/12
40/M	Ampullary tumor	Hepatitis B AIDS *Mycobacterium avium* complex	11.0/1.0/207	2/clot, oozing	10/NA	Epinephrine injection	15/6	NA[b]

F female, *M* male, *PT* prothrombin time, *INR* international normalized ratio, *Hg* hemoglobin, *ES* endoscopic sphincterotomy, *ERCP* endoscopic retrograde cholangiopancreatography, *ICU* intensive care unit, *NA* not available, *AIDS* acquired immune-deficiency syndrome

[a] Patient was receiving anticoagulant therapy within 4 days of procedure. Anticoagulants were held for 5 days post procedure and for five more days after stent removal

[b] Patient was submitted to surgery for ampullary tumor and died 5 days post surgery

Table 3 Characteristics, treatment, and outcome data of patients with perforations

Age (years)/ sex	Indication	Motive of perforation[a]	Perforation diagnosis	Number of days in ICU	Duration of stenting (days)/FCSEMS length (cm)	Follow-up (weeks)/ control ERCP (weeks)/ choledochoscopy (yes/ NA)
55/F	Stones	Zipper cut ES with bleeding and attempted balloon tamponade	Subcutaneous emphysema Extravasation of contrast Retroperitoneal air on CT scan	4	21/4	108/66/yes
29/F	Stones	Zipper cut ES	Extravasation of contrast Retroperitoneal air on CT scan	1	30/6	72/48/yes
31/M	Stones	Large balloon dilation followed by attempted removal of stones	Extravasation of contrast Retroperitoneal air on CT scan	2	30/6	160/58/NA
76/F	Stones	Zipper cut ES	Subcutaneous emphysema Extravasation of contrast Retroperitoneal air on CT scan	3	29/6	156/48/NA

F female, *M* male, *ES* endoscopic sphincterotomy, *ERCP* endoscopic retrograde cholangiopancreatography, *ICU* intensive care unit, *NA* not available

[a] According to the endoscopist who performed the procedures

groups that were defined earlier in the "Materials and methods" section: refractory biliary leaks (Table 1), postsphincterotomy bleeding (Table 2), and perforations (Table 3).

Refractory biliary leaks

FCSEMSs were placed in 17 patients with postcholecystectomy refractory biliary leaks. The median patient age

was 55 years (range 32–89 years, mean 56.8 years). Final diagnoses included 12 cystic-stump high-grade leaks and five common bile duct/common hepatic duct leaks. During the first ERCP procedure, all patients had high-grade leaks (four), and they were treated with a combination of biliary sphincterotomy and placement of a large-bore (10-Fr) transpapillary biliary stent, at least 7 cm long. Patients who were nonresponsive to the initial endoscopic therapy were identified according to clinical grounds and individual assessment. Similar or increased levels of percutaneous drainage and worsening images were the most commonly utilized criteria to determine endoscopic treatment failure. The second ERCP procedure with FCSEMS placement was performed after a median time interval of 10 days (range 7–18 days, mean 10.1 days) after the first procedure. One patient had a second ERCP on day 6 post ERCP to place a second large-bore (10-Fr) plastic stent without success, leading to FCSEMS placement on day 10 post ERCP.

Subsequent to FCSEMS placement, percutaneous drain output ceased after a median time of 3 days (range 2–8 days, mean 3.7 days). When comparing the drainage output of the common bile duct/common hepatic duct leaks with the cystic-stump leaks, drainage ceased more quickly in the patients with cystic-stump leaks, with a median time to cessation of 3 days compared with 6 days. FCSEMSs were removed after a median time of 16 days (range 7–28 days, mean 16.6 days). Follow-up was completed for all patients after a median time of 125 weeks (range 14–214 weeks, mean 127.8 weeks).

The five patients with common bile duct/common hepatic duct leaks exhibited major bile duct injuries with associated strictures detected at the time of the first ERCP. After FCSEMS removal, patients were treated with multiple plastic stents for 9–12 months. Four patients had clinical resolution of their strictures while maintaining minor bile duct defects, and one patient was still in endoscopic treatment at the time of manuscript preparation.

Postsphincterotomy bleeding

FCSEMSs were placed in four patients with difficult-to-treat post-ES bleeding. Patients had a median age of 60 years (range 37–91 years, mean 62 years). Bleeding was immediate in one patient with a periampullary diverticulum (Fig. 1) and was delayed in three patients, occurring on days 2, 3, and 7 post ERCP. All patients were submitted to endoscopic measures to achieve hemostasis without success. Two hemorrhages were considered minor, with both patients exhibiting melena and hemoglobin drop; moderate and severe bleeding were observed in the remaining two patients. The first three patients underwent the second ERCP procedure on the day following clinical presentation of bleeding. In the patient with severe bleeding, the second ERCP procedure was delayed 4 days (due to a long holiday weekend). We hypothesize that the delay in treatment was the main cause of the severity of bleeding; the patient required the transfusion of 10 units of blood. Following FCSEMS placement, there were no signs or symptoms of recurrent gastrointestinal (GI) bleeding. Stents were removed after a median time of 6 days (range 3–15 days, mean 7.5 days). Follow-up was completed for three patients after a median time of 16 weeks (range 14–20 weeks, mean 16.7 weeks).

Perforations

Four patients with a median age of 43 years (range 29–76 years, mean 47.8 years) underwent FCSEMS placement as a rescue therapy for perforation closure following endoscopic biliary sphincterotomy. All the perforations were recognized at the time of the procedure based on characteristic contrast extravasation. All patients had a CT scan showing retroperitoneal air and leaks, and two patients exhibited associated subcutaneous emphysema (Fig. 2). According to the endoscopist who performed the procedures, a zipper cut during ES was the most common cause of perforation. None of the patients underwent precut papillotomy, which has been suggested as a risk factor for perforation [10]. The four patients were admitted to the intensive care unit (ICU) and treated with intravenous antibiotics, fluids, and a nil-by-mouth regimen. The median length of ICU stay was 2.5 days (range 1–4 days). The two patients with subcutaneous emphysema required mechanical ventilation for bilateral pneumothorax for 1 day. Patients were discharged from the hospital after a median of 10 days (range 7–12 days) post FCSEMS placement, and stent removal was performed as an outpatient procedure. FCSEMSs were left in place for a median time of 29.5 days (range 21–30 days, mean 27.5 days). Follow-up was completed for all patients after a median time of 132 weeks (range 72–160 weeks, mean 124 weeks).

Complications and follow-up

There were no initial complications related to FCSEMS placement or removal. Four patients, two in the post-ES bleeding group and two in the perforation group, exhibited two- to threefold increases in serum amylase values in the absence of pain following FCSEMS placement; these increases were assumed to be a consequence of the ERCP procedures. At the time of extraction, the endoscopist thought that seven stents had slid several millimeters into the duodenum. Because the largest portion of the stent was still inside the bile duct and there was clinical resolution of the initial conditions, these movements were not

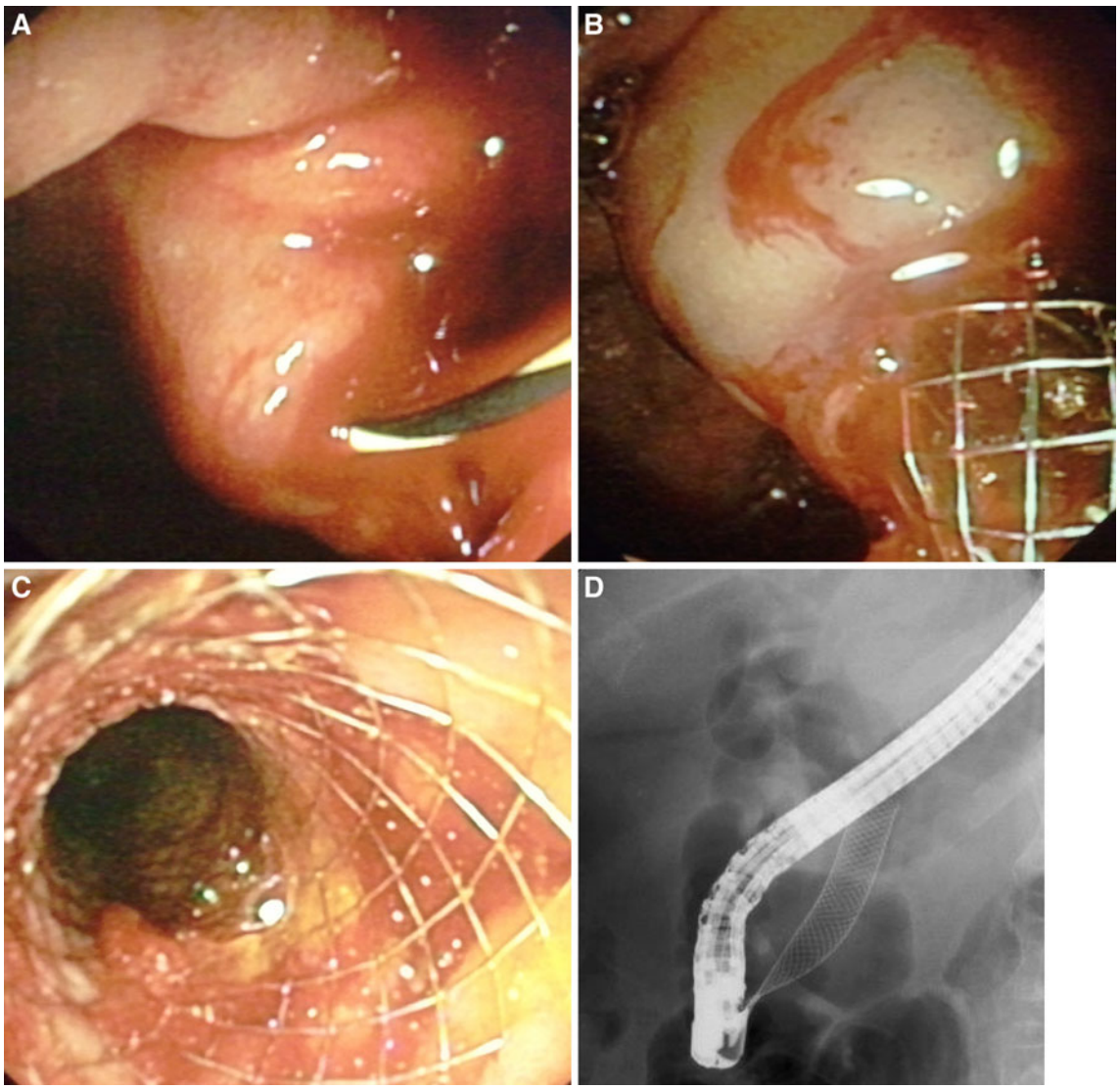

Fig. 1 Use of fully covered self-expandable metal stent (FCSEMS) for treatment of difficult-to-control bleeding immediately after sphincterotomy: **A** Endoscopic image of active bleeding after biliary sphincterotomy in a patient with a periampullary diverticulum. **B** Endoscopic lateral view of a fully deployed FCSEMS that resulted in mechanical tamponade and hemostasis. Note the *blue tone* of the papilla of Vater after epinephrine injection. **C** Inside view of a FCSEMS across the ampullary orifice showing the immediate tamponade of the bleeding site. **D** Fluoroscopic image of a FCSEMS removal through the scope

considered stent migration. None of the five patients (two in the bleeding group and three in the perforation group) who had an intact gallbladder presented with cholecystitis. There were no cases of duodenal ulcerations or de novo choledocholithiasis found within FCSEMS and bile duct at the time of stent removal.

During the long-term follow-up of the 24 patients, bile leak recurrence, episodes of rebleeding, or delayed complications (e.g., abscesses or strictures) related to perforations were not observed in any of the patients. Follow-up ERCP procedures were performed in 18 patients (11 in the bile leak group, 3 in the bleeding group, and 4 in the perforation group) after a median time of 51 weeks (range 12–110 weeks, mean 52.7 weeks). In 15 patients, the results of the ERCP were normal. The other three patients had minor stricture/bile duct defects that were without clinical significance and were related to injuries obtained during cholecystectomy. When the bile duct dimensions at the moment of FCSEMS placement and the follow-up cholangiography performed months later were compared, there was no evidence of bile duct enlargement due to FCSEMS placement. In the 25 patients mid bile duct diameter was initially measured with values ranging from 6 to 12 mm. After FCSEMS placement the bile duct assumed the shape and diameter of the stent (for bile duct <10 mm), returning to normal after FCSEMS removal.

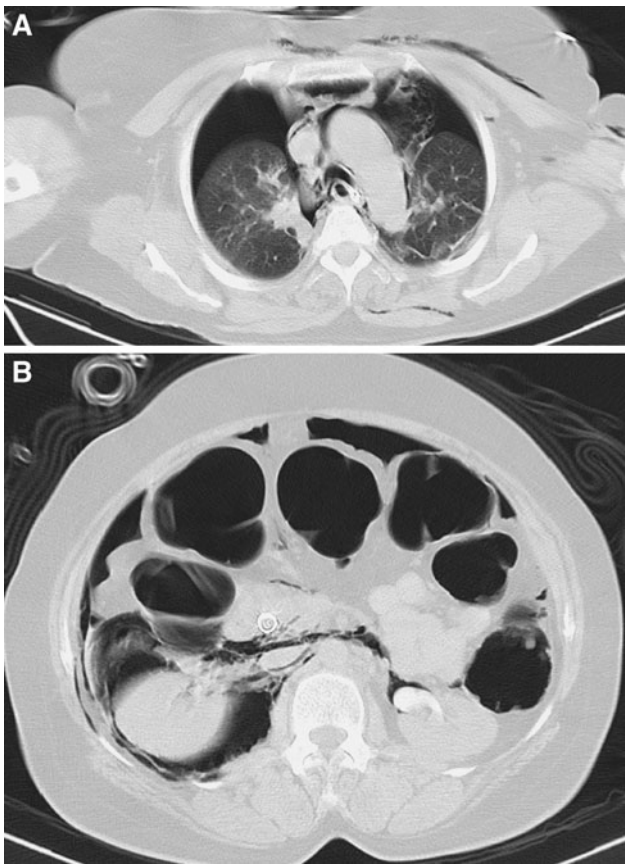

Fig. 2 CT scan images following postsphincterotomy perforation: **A** CT scan of the chest. Axial view showing bilateral pneumothorax, pneumomediastinum, and subcutaneous emphysema. **B** CT scan of the abdomen. Axial view showing significant pneumoperitoneum and retroperitoneal air. The fully covered self-expandable metal stent that was used to seal the perforation can be seen in the bile duct

Cholangioscopy procedures were performed in six patients (four in the bile leak group and two in perforation group). In the perforation group patients and in one of the bile leak group patients who had a cystic-stump leak (Video 1), the choledochoscopy results were normal without evidence of minor bile duct defects or tissue hyperplasia. The other three patients, who presented with bile duct/common hepatic duct leaks, exhibited minor strictures (fibrous ring) of the bile duct at the site of strictures being treated with long-term plastic stenting. Above the minor defect/stricture, in the place where the initial portion of the FCSEMS was placed, no defects or evidence of reactive tissue hyperplasia were observed (Video 2).

Discussion

According to our findings, temporary placement of a FCSEMS for 30 days or less is an effective rescue therapy for several BBCs and is free from early complications. The median time of FCSEMS removal varied depending upon the BBC; FCSEMSs were removed after 6 days in patients with difficult-to-control post-ES bleeding, after 16 days in patients with complex biliary leaks, and after 29.5 days in patients with perforations. Patients underwent long-term follow-up, including cholangiography and cholangioscopy procedures, without evidence of late complications. These results suggest that the short duration of stenting was a key factor for the absence of FCSEMS-related complications.

Bile leaks after cholecystectomy are traditionally managed with endoscopic techniques consisting of transpapillary placement of large-bore (10-Fr) plastic stents with or without biliary sphincterotomy [4, 5, 19, 22]. For simple leaks such as small cystic duct leaks (low-grade leaks) and Luschka's duct leaks, the success rate of endoscopic treatment is high. Bile leak closure is achieved because the transpapillary high-pressure gradient is decreased or eliminated with the endoscopic procedures. However, in a small subset of patients with more complex leaks (high-grade cystic-stump leaks, common bile duct/common hepatic duct leaks, bile leaks after liver transplantation or large leaks following partial cholecystectomy) successful closure can be more problematic, leading to an increased number of procedures or even surgery [4, 5, 19, 22]. Refractory bile leaks can be treated by FCSEMS. The large stent diameter diverts more flow away from the leak site, causing a significant decrease of the pressure gradient at the ampullary level. Furthermore, the FCSEMS directly covers the leak site. Baron et al. [19] first reported the use of partially ($n = 2$) and fully covered ($n = 1$) SEMSs in three patients with complex biliary leaks of the gallbladder bed following open subtotal cholecystectomy procedures. In two patients, the leaks had not responded to the endoscopic intervention of a combination of ES and a large-bore plastic stent; in the third patient, a FCSEMS was the initial option. Stents were removed 9, 5, and 3 weeks later, and no major complications were reported. The authors suggested that, until more data were available, stents should remain in place for an arbitrary time of $\leq$3 months. Interestingly, bile drainage output decreased markedly in 1 week or less following SEMS placement.

A study with 16 patients used partially covered SEMS to treat 8 cystic-stump leaks, 5 Luschka's duct leaks, 2 partial cholecystectomy leaks, and 1 liver transplant anastomotic leak [20]. These patients had previously undergone unsuccessful plastic stent placement or had severe comorbidities that prevented multiple interventions. Of the patients studied, 15 responded to partially covered SEMS placement. Stents were left in place for a median time of 3 months (range 1–17 months), and the authors reported complications in two patients (one proximal and one distal migration). Information regarding external drainage or

recommendations concerning stenting duration were not available.

Wang et al. [25] reported the first case series using FCSEMS to treat a heterogeneous group of patients with complex leaks that were defined as biliary leaks that failed ERCP intervention, bile leaks after cadaveric orthotopic liver transplantation, and complicated cholecystectomies with large bile leaks. The bile leaks in all 13 patients resolved, and FCSEMSs were removed in 11 patients after a median time of 103 days (range 67–493 days). However, several complications were reported. Ten of the 11 patients had de novo choledocholithiasis within the FCSEMS. Two patients presented with strictures that developed after stent removal; the strictures were located at the previous location of the proximal edge of the FCSEMS. One of the strictures required treatment with balloon dilation and stent placement for 7 months. In five of seven patients who underwent choledochoscopy at the time of stent removal, ulceration was seen where the fins anchored the stent into the bile duct. Again, no information regarding external bile drain output was available. The authors advocated that the stents may be reasonably left in place for more than 6 weeks.

In a prospective study of FCSEMS placement for a variety of BBCs [3], one patient with a large intrahepatic fistula after excision of a hydatid cystic was treated with a FCSEMS. The FCSEMS remained in place for 36 days, despite the fact that external drainage stopped 24 h after insertion. In a recent case report [28], a patient with a Luschka's duct leak treated with an FCSEMS after unsuccessful endoscopic management with ES and plastic stent placement had the stent removed after 28 days. Again, the authors reported an almost immediate decrease in the bile output from the percutaneous drain.

In this study, we examined two types of refractory biliary leaks that exhibited a 100 % success rate following FCSEMS treatment, comparable to other reports using partially or fully covered SEMS [19, 20, 25]. The leaks in our study (high-grade cystic-stump leaks or common bile duct/common hepatic duct leaks) failed initial endoscopic treatment with placement of large-bore (10-Fr) plastic stents and biliary sphincterotomy which has been reported by other studies [5, 19, 20, 25]. A variety of endoscopic techniques other than placement of FCSEMS could have been chosen in the cases presented here. One option is the placement of multiple large-bore (10-Fr) plastic stents at lower cost to further decrease transpapillary high pressure gradient. However, plastic stents can occlude possibly before leak closure, and furthermore one of our patients was treated with two large-bore plastic stents without success, increasing costs and leading to another ERCP for FCSEMS placement. In our series, the bile output from the percutaneous drains ceased after a median time of 3 days (range 2–8 days) following FCSEMS placement. This result is comparable to earlier studies [3, 19, 28], suggesting that stents could be removed earlier than previously reported (for both partially and fully covered SEMS). In our study, stents were removed after a median time of 16 days, which deviated from earlier studies [20, 25]. The median time interval between ceased biliary drainage and FCSEMS removal was 12 days (range 5–26 days). Bile drainage ceased after 2–4 days (median 3 days) for cystic-stump leaks, while bile drainage for even more complex leaks associated with major common bile duct/common hepatic duct injuries ceased between 5 and 8 days (median 6 days) following FCSEMS placement. Upon FCSEMS removal, leaks were sealed in all cases, suggesting that stents can be removed safely 10–15 days after cessation of bile drainage. Taken together, these findings suggest that, for refractory bile leaks, stents can be safely removed after no longer than 3 weeks.

In a recent report [26], five patients were treated with temporary FCSEMSs for difficult-to-control post-ES bleeding. The stent worked through mechanical tamponade of the bleeding site. Three patients were treated for immediate bleeding, and two patients were treated for delayed hemorrhage. Four patients were previously submitted to other endoscopic measures (including embolization in one patient) but failed to achieve hemostasis. The stents were removed in three patients at 2, 4, and 8 weeks; stents had completely migrated spontaneously without complications in two patients at 4 weeks. No other complications were reported. The authors estimated that a 2–4-week duration of FCSEMS placement would be appropriate in this setting.

We studied a cohort of patients submitted to FCSEMS placement after the failure of several endoscopic treatments for post-ES bleeding. Two mild cases, one moderate case, and one severe case of bleeding were treated. This treatment resulted in immediate hemostasis in all patients, and no further interventions were needed, which is consistent with the report of Shah et al. [26]. In our study, patients with post-ES bleeding had their stents removed after a median time of 6 days. In one patient in whom the stent remained in place for 3 days, anticoagulant therapy was resumed 5 days after stent removal, and no signs of rebleeding were observed. In a study by Shah et al. [26], anticoagulants were resumed with stents in place, and again no signs or symptoms of recurrent GI bleeding were detected. Because the hemostatic effect appears to be immediate and stenting works through a tamponade effect, this result suggests that stents can be safely removed no longer than 1 week after placement and patients with anticoagulant therapy can resume therapy while stents are in place. The repeated instrumentation on a very short time scale can be considered aggressive, and perhaps stents could be removed later. However, the intention in

removing the stents early is to repeat the procedure before discharging the patient from hospital. The early removal avoids the return of the patient to the hospital as an outpatient. Furthermore, the early removal of the stent avoids potential complications, namely migration of the stent.

Garcia-Cano et al. [3] used an FCSEMS to close two perforations after ES. Patients were managed conservatively, and stents were removed after a mean time of 96 days. The covering seals the perforation, perhaps with a strong occlusion pressure, allowing for a safe and faster recovery. We used FCSEMS to treat four perforations. All patients were admitted to the ICU, and two patients required mechanical ventilation. Perforations were detected during ERCP procedures on account of large extravasation of contrast in all four patients and subcutaneous emphysema in two patients leading to respiratory failure, suggesting that perforations were severe. With the FCSEMS approach, all patients recovered rapidly and resumed oral feeding less than 1 week after perforation detection. Furthermore, the patients were rapidly discharged from hospital, and FCSEMS removal, which occurred after a median time of 29.5 days, was performed as an outpatient procedure. More importantly, no complications, such as papillary strictures or abscesses, were detected during follow-up. These data suggest that FCSEMSs are effective in treating post-ES perforations and are associated with rapid, complication-free recovery. We do not advocate SEMS placement for microperforations with minor retroperitoneal air where most patients will do well with medical management and placement of a plastic stent. We suggest the use of FCSEMS in more severe perforations with major leaks and/or subcutaneous emphysema detected at the time of ERCP. The stents were removed within 30 days of placement, but eventually, due to the rapid recovery of all patients in our series, stents can be removed even earlier (i.e., before discharge from hospital).

The majority of patients had a follow-up ERCP following FCSEMS removal. These examinations were scheduled by treating physicians to evaluate possible late bile duct injury several months after stent removal. Concerns have been raised in literature [3, 25, 29] about the development of late strictures several months after FCSEMS removal, and this was the main cause for the referral of patients to a control ERCP. Patients contacted the authors for further information about the development of late strictures and possible methods for diagnosis. They were told that a control ERCP may not be the standard of care because it is an invasive procedure and could be avoided by carrying out magnetic resonance imaging (MRI) associated with periodic blood samples. However, 18 patients chose to undergo a control ERCP, providing informed written consent before this additional procedure. No concerns were raised by each institutional review board that approved this study. Seven patients did not undergo the follow-up ERCP; one patient died, one patient was still in endoscopic treatment at the time of manuscript preparation, and the remaining five patients declined further endoscopic procedures despite being available for follow-up using the MRI strategy associated with blood samples.

The FCSEMS used had no fins for anchoring. Nevertheless, the proximal edge of the stent can potentially cause bile duct damage, leading to reactive tissue hyperplasia and possibly to the development of a late stricture. Although this stent effect on the biliary epithelium may be related to long-term stent placement, we intended to exclude this possibility after short-term stenting with cholangioscopy screenings. At the time of follow-up ERCP, patients with normal cholangiogram but who had previous history of at least one episode of transient cholestasis were submitted to cholangioscopy to determine if tissue hyperplasia/minor bile defects had developed. Choledochoscopy results were normal in three patients. The other three patients had previously been treated for a stricture caused at the time of cholecystectomy. In all cases, there were no bile duct lesions above the remaining minor stricture, which had an endoscopic appearance of a fibrous ring.

Patients with bile duct/common hepatic duct leaks had associated strictures, and their FCSEMSs were removed following the clinical resolution of leaks. Strictures were subsequently treated by multiple placements of plastic stents (not FCSEMS). Although reports exist suggesting that temporary FCSEMS placement in benign strictures offers a potential alternative to the multiple plastic stent strategy [21, 24, 27], these findings have been challenged in literature [30]. We treated seven patients with benign biliary strictures using FCSEMS (unpublished data), and we observed complications in six patients. Three patients developed de novo choledocholithiasis and stent occlusion, one patient exhibited proximal stent migration, and two patients exhibited distal stent migration. The FCSEMS were removed, and the patients were subsequently treated with multiple plastic stents. Until more data are available, we use plastic stents to treat benign biliary strictures.

When FCSEMS placement is considered for BBCs, cost is an important issue. Although no studies are available on this matter, FCSEMS placement as a rescue therapy is likely to be cost-effective because the prevention of several procedures (including surgery) offsets the cost of the stents. Complications have been reported in papers using FCSEMS to treat BBCs [3, 24–27]. One common complication is stent migration, which has been reported previously [24, 26]. Stent migration is associated with short stents (i.e., 4 cm) that tend to migrate easily. In our series we did not observe any migration and we only used two short stents in two patients with an intact gallbladder and low cystic-duct insertion. In our study complications did not

develop in any patients following FCSEMS placement. Furthermore, after long-term follow-up, no patients exhibited signs of FCSEMS-related complications. We believe that most of the FCSEMS-associated complications are related to the duration of stenting, especially the nearly 10 % stricture rate of the literature [3, 25, 29], which is a major concern before additional FCSEMS placement for a refractory biliary leak. The association between short-term stenting and the absence of complications strongly support this hypothesis. A subset of our patients underwent one additional ERCP after FCSEMS removal on account of safety reasons. As suggested by our study, short-term placement of FCSEMS is safe and we do not advocate control ERCPs in the future for patients submitted to short-term (i.e., 30 days or less) FCSEMS placement.

Several limitations of our study should be taken into account. This was a retrospective study where stent removal was not scheduled according to specific endpoints. In the leak group, no patients with bile leaks after cadaveric orthotopic liver transplantation or with large leaks following partial cholecystectomy were included; these types of leaks can be problematic, leading to increased stenting durations [22, 25, 29, 31]. Nevertheless, in a report of three patients outlining the SEMS treatment of bile leaks after open subtotal cholecystectomy, Baron et al. [22] noted a dramatic decrease of bile output in a short period of time, suggesting that these leaks can also be treated with short-term stenting. Patients with post-ES bleeding had a shorter follow-up compared with the other groups; the effect of the stents appeared to be immediate, and very late rebleeding was unusual. These patients had a median time of stenting of 6 days, and there was no evidence that such very short-term stenting was associated with late bile duct injury. We suggest that further studies are needed with a prospective design, where time of stent removal should be a primary endpoint. In these proposed studies, biliary drainage should be carefully monitored and used as a marker for scheduled stent removal in patients experiencing bile leakage.

The strengths of our study are the early removal of stents, the long-term follow-up, the use of control cholangiography and choledochoscopy procedures in a subset of patients, and the relatively large sample size. To our knowledge, this is the first study concerning the duration of FCSEMS placement and the largest series of patients treated with FCSEMS for BBCs other than benign strictures.

In conclusion, our data suggest that FCSEMS placement for 30 days or less is efficacious at resolving complex biliary leaks, difficult-to-control post-ES bleeding, and perforations. Duration of stenting should be different for each type of condition. Stents can be safely removed, and short-term stenting is associated with the absence of early and late complications.

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