

Cholangioscopy-guided steroid injection for refractory post liver transplant anastomotic strictures: a rescue case series

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Ther Adv Gastrointest Endosc

2019, Vol. 12: 1–8

DOI: 10.1177/
2631774519867786

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Abstract

Background and aims: Post liver transplant biliary anastomotic strictures have traditionally been treated with balloon dilation and multiple plastic stents. Fully covered self-expandable metallic stents may be used as an initial alternative or after multiple plastic stents failure. Refractory strictures can occur in 10–22% and require revisional surgery. Alternatively, cholangioscopy allows direct visualization and therapeutic approaches. We aimed to assess the feasibility, safety, and efficacy of balloon dilation combined with cholangioscopy-guided steroid injection for the treatment of refractory anastomotic biliary strictures.

Methods: Three post-orthotopic liver transplant patients who failed standard treatment of their biliary anastomotic strictures underwent endoscopic retrograde cholangiopancreatography with balloon dilation followed by cholangioscopy-guided steroid injection at a tertiary care center. Patients had follow-up with images and laboratorial tests to evaluate for residual stricture.

Results: Technical success of balloon dilation + cholangioscopy-guided steroid injection was achieved in all patients. Cholangioscopy permitted accurate evaluation of bile ducts and precise localization for steroid injection. No adverse events occurred. Mean follow-up was 26 months. Two patients are stent free and remain well in follow-up, with no signs of biliary obstruction. No further therapeutic endoscopic procedures or revisional surgery were required. One patient did not respond to balloon dilation + cholangioscopy-guided steroid injection after 11 months of follow-up and required repeat balloon dilation of new strictures above the anastomosis.

Conclusion: Cholangioscopy-guided steroid injection combined with balloon dilation in the treatment of refractory post liver transplant strictures is feasible and safe. This method may be used as a rescue alternative before surgical approach. Randomized controlled trials comparing balloon dilation + cholangioscopy-guided steroid injection to fully covered self-expandable metallic stents are needed to determine the role of this treatment for anastomotic biliary strictures.

Keywords: balloon dilation, biliary anastomotic stricture, cholangioscopy, endoscopic retrograde cholangiopancreatography, steroids

Received: 9 April 2019; revised manuscript accepted: 12 July 2019.

Background and aims

Benign biliary strictures (BBS) most commonly occur after operative iatrogenic injuries, such as laparoscopic cholecystectomy (0.3–0.7%), or post-orthotopic liver transplantation (OLT) (20–30%).¹ Inflammatory disease is another possible cause,

such as chronic pancreatitis (10–30%)² and primary sclerosing cholangitis (PSC). Depending on the severity of the obstruction, BBS presents a challenge in terms of treatment and may still require surgical revision despite dedication to long durations of treatment with both plastic and metal stents.

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Currently, the first-line endoscopic strategy for BBS consists of balloon dilation combined with placement of multiple plastic stents (MPS).^{1,2} Stent exchanges are usually done every 3 months, with progressive increment in the number and diameter of stents, for approximately 1 year or until complete resolution of the stricture. Fully covered self-expanding metal stents (FCSEMS) have been successfully used in BBS.³ Its larger diameter provides higher patency and may result in the need for fewer procedures for stent exchange.⁴ Previous studies demonstrate that migration of FCSEMS can be a significant problem.^{5,6} However, a recent meta-analysis pointed no difference between FCSEMS and MPS regarding migration rate.⁷ A randomized study comparing FCSEMS with MPS for the treatment of anastomotic strictures in post-OLT patients demonstrated that FCSEMS are as effective as MPS in the management of stricture, with lower cost, but higher rates of adverse events and recurrence.⁸ A systematic review and meta-analysis from our institution, comparing the two different stent treatment options, showed no difference in resolution and recurrence of biliary stricture after liver transplantation, although the FCSEMS group required few number of stents, had lower duration of treatment, and had lower costs.⁹

Direct visualization of the bile ducts may be a useful adjunct to endoscopic retrograde cholangiopancreatography (ERCP) for the evaluation of biliary strictures.^{10,11} Cholangioscopy increases the ability to evaluate mucosal changes, presence of fibrosis, cast, or sutures, and allows for direct intraductal therapies,¹⁰ such as lithotripsy, ablation techniques, or foreign body removal.^{10–16}

Despite the various methods described above, a consensus regarding the adequate management of BBS has not yet been reached. Nevertheless, most biliary endoscopists tend to initially follow the balloon dilation + MPS strategy.

Although biliary dilation combined with MPS has allowed successful resolution of BBS in greater than 80% of cases, recurrence strictures may occur in 10–30% after initial resolution.^{1,2}

There are no standard recommendations for the management of these refractory BBS and new approaches are lacking. Recently, a new concept of large diameter balloon dilation associated with FCSEMS was reported as a possible approach to refractory BBS, but prospective studies are

lacking to confirm its effectiveness.¹⁷ In 2015, our group initially described the feasibility and safety of combination therapy with large diameter balloon dilation with biliary steroid injection under cholangioscopic visualization for the treatment of refractory BBS.¹⁸ The aim of this article is to report a case series of patients treated with this novel method, as well as long-term follow-up.

Patients and methods

Patients

Three patients with refractory post liver transplant anastomotic strictures were included in this series. All three underwent large diameter balloon dilation with cholangioscopy-guided corticoid injection (CSI) after failure of standard treatment with MPS or FCSEMS. Rescue procedures were performed from June 2015 to April 2017.

Refractory BBS were defined as either clinical or laboratorial, or both, abnormalities associated with inadequate diameter of the anastomosis, after treatment with one of the following methods: dilations with progressive plastic stents every 3 months for 1 year; or placement of FCSEMS for 6 months. In our series, all patients were endoscopically treated with balloon dilation + MPS for at least 1 year.

Methods

Conventional ERCP was performed under general anesthesia. Ciprofloxacin 400 mg IV was given as prophylaxis. Patient's informed consent was obtained as well as local research ethics committee approval. Multidisciplinary liver transplant team consultation approved the use of the novel approach.

Common bile duct (CBD) cannulation using a guide wire was performed, and cholangiography was obtained after contrast media injection to confirm and measure the stricture diameter. Balloon dilation of the stricture was performed under fluoroscopy (CRE; Boston Scientific, Natick, MA, USA), ranging from 8 to 15 ml, depending on biliary diameter.

After dilation, balloon sweeping was performed to clear stones and debris. Cholangioscopy was then performed using SpyGlass (both Legacy and DS) (Boston Scientific, Natick, MA, USA) through the 4.2 mm working channel of a therapeutic duodenoscope (TJF180; Olympus, Tokyo, Japan) and the

stricture was visualized. SpyGlass legacy was used in the first case and the DS version in two later cases. A prototype 26-gauge sclerotherapy needle (Montag, São Paulo, Brazil) was introduced through the 1.2 mm working channel of the Spyscope and 4 ml (40 mg) of triamcinolone acetate was injected circumferentially at four points using 10 mg of the medication at each site.

Results

Case 1

The first case was a 58-year-old male patient who underwent OLT due to nonalcoholic steatohepatitis (NASH) in November 2011. After 1 year, he developed BBS and was treated with five therapeutic ERCPs (over 24 months); however, he had a refractory stricture despite treatment with balloon dilation of up to 10 mm and placement of two 10Fr and one 8.5Fr plastic stents.

At rescue procedure, ERCP showed a 3-mm-diameter stricture and a sharp angulation. Multiple stones were identified proximal to stenosis. Previous sphincterotomy was expanded and a 10 mm balloon dilation of the stricture was performed followed by balloon sweep that allowed partial clearance of the biliary stones. Residual stones could not be removed due to the angulation of the stricture. CSI was performed and a 10Fr plastic biliary stent was inserted. ERCP was repeated 1 week later for stone clearance. At that time, large diameter balloon dilation to 13.5 mm was performed. Cholangioscopy showed moderate laceration of anastomosis, and a second session of steroid injection was performed. No stents were placed at the completion of the second procedure.

The procedure was technically and clinically successful. Cholangioscopic identification of the site of the dilated stricture was easily achieved, with very good image quality. Adequate needle positioning and puncturing was accomplished for the steroid injection. Luminal steroid extravasation could be seen if the needle did not reach deep position, permitting adjustments. There were no intra procedural or post-procedural adverse events. Repeat MRCP 48 h after procedure demonstrated that diameter of the stricture to have increased to 4.5 mm. The patient was discharged the next day. The patient was followed out to 42 months post-procedure and remained asymptomatic with no evidence of recurrent stricture as per laboratories or imaging.

Case 2

A 53-year-old female patient, post-OLT for autoimmune hepatitis, who developed an anastomotic stricture 4 years post transplant, failed treatment despite undergoing five therapeutic ERCPs, with a maximum dilation performed to 13.5 mm with placement of three 7Fr plastic stents.

At rescue procedure, cholangiography revealed a proximal CBD of 11 mm diameter, with a 4-mm-diameter stricture at the anastomosis. Balloon dilation of the anastomosis up to 13.5 mm was performed. Cholangioscopy identified the stricture, and steroid injection was performed. No stents were placed.

After 11 months, the patient presented with abdominal pain and increased liver function tests. MRCP showed mild dilation of the intrahepatic bile ducts and stricture of the proximal portion of the common bile duct, above biliary anastomosis. ERCP detected stenosis at sphincterotomy site, an axis deviation of the anastomosis, and stones below the anastomosis. Sphincteroplasty was performed up to 10 mm, and balloon sweep removed the stones and biliary sludge. The anastomosis was dilated up to 10 mm, without adverse events. Control MRCP revealed new strictures above the anastomosis.

Case 3

A 72-year-old male patient transplanted in June 2015 due to liver cirrhosis caused by alcohol. This patient developed biliary stricture 3 months post transplantation and underwent six consecutive ERCPs before this treatment with maximum balloon dilation of 10 mm and four 10Fr plastic stents inserted. MRCP showed refractory BBS. (Figure 1)

Rescue procedure ERCP identified an anastomosis stricture diameter of 3.5 mm. Balloon dilation up to 10 mm was performed, followed by biliary balloon scanning and biliary sludge removal (Figure 2(a) and (b)). Cholangioscopy followed by CSI were performed and no stents were placed (Figure 3(a) and (b)). No immediate or delayed adverse events occurred.

A 17-month post-procedure control abdominal ultrasound indicated mild bile duct dilation and suggested stenosis, thus a new ERCP was performed for confirmation. The exam showed no signs of stricture, with good anastomosis diameter and easy contrast and bile flow (Figure 4).

There were no signs of residual stricture up to 22 months post procedure, and the anastomosis measured 6 mm. The patient's clinical summary cases are presented on Tables 1 and 2.

Discussion

In this study, we performed three cases of cholangioscopy with SpyGlass associated with steroids injection. Two cases had good evolution and one had to be submitted to another ECRP with biliary dilation after 11 months. The first have the longest follow-up, with great results. This case was submitted to two sessions of steroids injection, which may have influenced the final result. The second case had the worst outcome, evolving with a long stricture of the proximal common bile duct. Control MRCP revealed new strictures above the anastomosis; this finding may suggest a

vascular component in the etiopathogeny, which may be the cause of steroid failure.

At present, nonsurgical minimally invasive approaches have largely replaced reoperation as the initial treatment of BBS. Endoscopic treatment is considered to be the preferred first-line modality, for patients who have duct-to-duct anastomosis, as it is less invasive, safe, effective, more easily accessible, and more convenient for the patient.¹⁹

In this study, we demonstrated the feasibility, safety, and long-term results of treatment with large diameter balloon dilation and cholangioscopically directed steroid injection as an alternative treatment for anastomotic strictures. All three cases demonstrated resolution of the anastomotic stricture; however, one patient developed a secondary stricture that required further endoscopic intervention. The exact mechanism for improvement with intralesional steroid injection (in combination with balloon dilation) is not clear; however, intralesional steroid injections have been shown to inhibit stricture formation by interfering with collagen synthesis, fibrosis, and chronic scarring processes.²⁰

Triamcinolone inhibits the transcription of matrix protein genes, including fibronectin and procollagen. It also reduces the synthesis of α 2-macroglobulin, an inhibitor of collagenase activity.²¹ Local steroid treatments have been used as a rescue approach in refractory benign esophageal strictures secondary to corrosive ingestion;²² moreover, it is an effective treatment for anastomotic strictures occurring after esophagectomy.²³ There is no

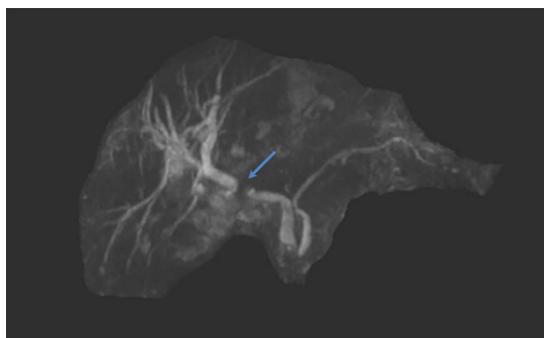


Figure 1. MRCP demonstrates stricture of the anastomosis (arrow). MRCP, magnetic resonance colangiopancreatography.

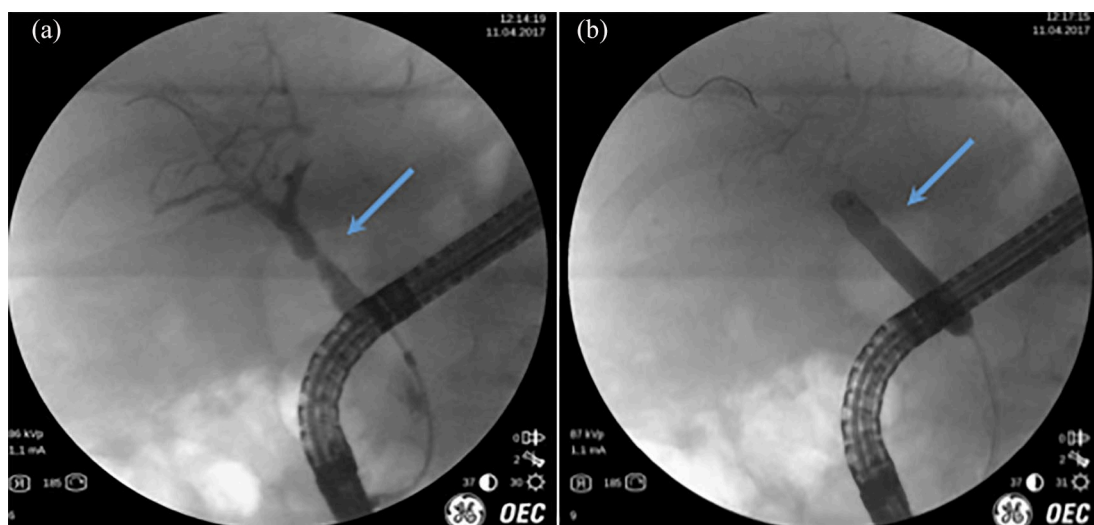


Figure 2. (a) Benign biliary stricture (BBS). (b) Refractory BBS balloon dilation fluoroscopy view.

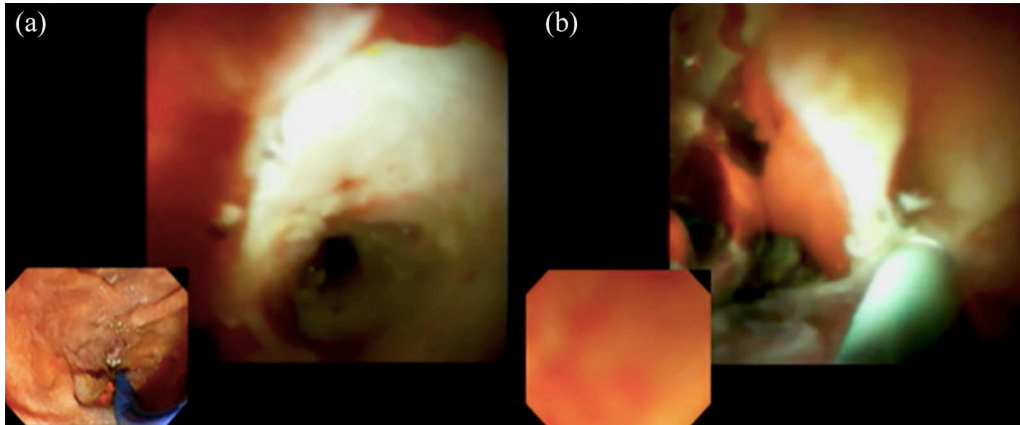


Figure 3. SpyGlass cholangioscopy. (a) BBS direct view after balloon dilation. (b) Cholangioscopy-guided steroid injection. BBS, benign biliary stricture.

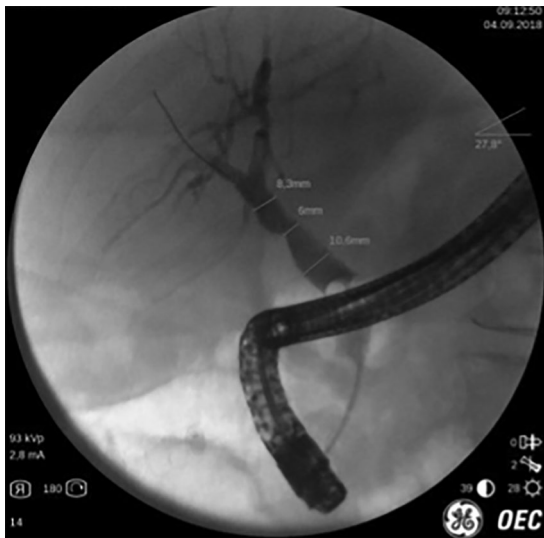


Figure 4. Control ERCP after 17 months of the procedure. Adequate anastomosis diameter. ERCP, endoscopic retrograde cholangiopancreatography.

consensus regarding the type, doses, and number of injections,²⁴ although triamcinolone acetate/acetone is the most widely used steroid. Most studies evaluated esophageal strictures and advocated a volume that varied from 0.5 to 2.8 ml of a 40 mg/ml triamcinolone solution, to a total of 40–100 mg in each session.²⁵ Similar protocols for dose and distribution of steroid injection were used in present cases, in which initial experience suggest that 1–2 sessions should be sufficient.

In a pilot study by Wehrmann and colleagues,²⁶ eight patients with BBS (six postoperative and

two with PSC) underwent balloon dilation and injection of 2×10 mg of triamcinolone into the bile duct wall using radiologic guidance, without direct visualization. The results showed significant increase of the anastomosis diameter (1.81 ± 0.65 mm to 3.86 ± 0.96 mm, $p < 0.01$). No adverse events were detected. Three patients had complete recovery after a third dilation and the remaining five patients were cured after two or three additional balloon dilations with intermittent stents exchange. No recurrence was observed during a follow-up of 12 months.

Although injections can be made satisfactorily under radiologic guidance, improper localization of the needle's tip is a possible cause of failure. Our initial experience demonstrated that the direct cholangioscopy visualization could improve the goals of intralesional BBS steroid injection. Therefore, in the pilot study described above, as direct view injection was not performed, we cannot be sure if injection was truly successful and if the steroid was adequately injected into the stricture. By performing the injection under direct visualization, safe and accurate injection can be confirmed. In addition, postsurgical local fibrosis can be a local protection factor to prevent adverse events, such as leakages and perforations.

Even though this treatment may have a temporary effect, we would propose it as a new minimally invasive therapeutic option for refractory benign biliary strictures that might obviate the need for either repeat procedure or eventual surgical revision, or both. In addition, given that no stents are left in place, one can avoid complications such as

Table 1. Clinical summary cases.

Identification	Pretreatment				Treatment		
	Patient (sex), age	Disease	Liver transplant date	Stricture diagnosis	ERCP (N)	Triamcinolone dose	Balloon dilation
JFS (M), 62 years Case 1	NASH	28 November 11	17 August 2012	5	80 mg/8 ml (two sessions)	15 mm	Two stents of 10Fr + one stent of 8.5Fr
HPR (F), 54 years Case 2	Autoimmune hepatitis	21 November 11	27 April 2015	6	40 mg/4 ml	13.5 mm	Three stents of 7Fr
AFC (M), 73 years Case 3	Alcohol	03 June 15	09 September 2015	7	40 mg/4 ml	10 mm	Four stents of 10Fr

ERCP, endoscopic retrograde cholangiopancreatography.

Table 2. Patient follow-up.

Identification	Follow-up				
	Patient (sex), age	ERCP (N)	Time w/o ERCP	MRCP	Follow-up length
JFS (M), 62 years	0	42 months	24 June 15: tortuosity and irregularity of the extra hepatic bile duct, with places of narrowing and thickening.	44 months	Has the longest follow-up without clinical symptoms and with all normal lab tests after more than 3 years.
HPR (F), 54 years	1	11 months	2 March 18: stricture of the proximal portion of the common bile duct, with 1.2 cm of extension, above the anastomosis. At least four stones in the hepatocholedocus, up to 1.0 cm. The common bile duct measures 0.8 cm.	22 months	Worst outcome of the three cases. Needed another ERCP less than 1 year after the procedure. Control MRCP showed a long stricture of the proximal portion of the common bile duct.
AFC (M), 73 years	1	22 months	-	22 months	Good clinical outcome ERCP on 4 September 2018 showed no stricture. Anastomosis with 6 mm of diameter and good drainage.

ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance colangiopancreatography.

stent migration, cholangitis, obstruction, and duodenal perforation.²⁷ Our study limitations include the limited number of patients and that it is a single center experience. However, a considerably long follow-up interval is reported, which offers valuable results regarding durability of treatment. Further studies are required to demonstrate the long-term efficacy of this novel technique in a larger group of patients and evaluate its potential

to become a standard treatment for BBS, particularly for refractory cases.

Conclusion

Cholangioscopy-guided steroid injection combined with large balloon dilation in the treatment of refractory post-liver transplant anastomotic strictures is feasible, safe, and durable based on

long-term follow-up. This approach may be a new step in the algorithm of stricture management and may help prevent the need for surgical revision. Randomized controlled trial (RCT) comparing treatment with FCSEMS may be the next step to help understand the role for this novel technique.

Author contributions

T.F. and E.G.H.M. performed the procedures. W.A. and L.A.C.D'A. did patient selection and post-procedure follow-up. V.M.S., H.G.G., and T.F. performed the literature review and wrote the paper with A.S. and P.S. The final version was revised and approved for all the authors.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: T.F. is a consultant for Boston Scientific, E.G.H.M. is a consultant for Boston Scientific and Olympus, and A.S. is a consultant for Boston Scientific and Olympus.

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Supplemental material

Supplemental material for this article is available online.

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