

Biodegradable Pancreatic and Biliary Stents—Still Searching For Disappearing Wonder?

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Abstract

Biodegradable stents hold considerable promise in the treatment of benign biliary or pancreatic diseases with the major advantage being avoidance of repeated interventions for stent removal or stent exchange. They have been confirmed to have good biocompatibility and current evidence shows acceptable rates of clinical efficacy and safety. In the current news and views, we discuss an interesting study that has evaluated a new type of biodegradable biliary and pancreatic stent (the Archimedes stent) in benign biliary and pancreatic diseases.

Keywords

- ▶ pancreatitis
- ▶ stent
- ▶ stricture

Introduction

The stents currently used in management of benign biliary and pancreatic diseases are either plastic stents made up of polyethylene or fully covered self-expanding metallic stents (FCSEMS). These stents are not ideal stents and several attempts are being made to improve upon the conventionally available stents. An ideal stent for benign biliary and pancreatic disease would be the one that has adequate radial expansile force for a sufficient period of time, provides drainage for a sufficient period of time, and does not elicit a tissue response or epithelial hyperplasia that may contribute to the formation of a new stricture.^{1,2} Apart from these necessary requirements, biodegradability of the stent with biocompatible breakdown products would be an added advantage, making it an ideal stent. A biodegradable stent (BDS) with the above-mentioned properties has a potential to replace conventional plastic and FCSEMS biliary and pancreatic stents for managing benign diseases like postcholecystectomy biliary strictures, bile leaks, and benign fibrotic pancreatic duct strictures.

The main advantage of BDSs is avoidance of repeated endoscopic retrograde cholangiopancreatography (ERCP) for stent removal and thus saving treatment costs and decreasing patient's discomfort.² This spontaneous degradation is an attractive option in patients who are expected to have poor compliance to regular follow-up, especially in developing countries like ours and the problem of difficult removal of

impacted stents in situ because of prolonged indwelling times can be avoided. Also inadvertent stent migration would be of less concern if the stent is biodegradable. A major problem with FCSEMS is an inability to place them across the hilum and cystic duct because of risk of occlusion of the ducts. However, BDS has a meshed design and therefore they can be deployed across the hilum and cystic duct without fear of occlusion.^{1,3} The initial data on the use of biodegradable stents look promising but studies on efficacy of these stents are still limited and there are teething problems, like reduced expansile force and fragmentation of the stent during degradation causing duct obstruction that are yet to be resolved.

Initially, BDS was used in animal models and the results on biocompatibility and degradation were encouraging. The initial BDS was made with biodegradable polymers that were similar to the materials used in biodegradable surgical sutures. These materials had proven biocompatibility and reliable degradation times and have been in use for a long time. These biodegradable synthetic polymers include polyglycolic acid, polylactic acid, and their copolymers, poly-p-dioxanone (PDX), and copolymers of trimethylene carbonate and glycolide.⁴ A biodegradable stent made up of polylactide (PLA) and loaded with barium sulfate powder for radio-opacity was evaluated in the bile ducts of pigs and the authors reported that the stent can be deployed endoscopically, is self-expanding, can be visualized on fluoroscopy and remains functionally patent for more than 6 months.⁵

There was no bile duct integration or proliferative changes but stent migration and occlusion were important concerns. PLA BDS was also evaluated in the pancreatic duct of a swine model.⁶ The authors reported that this novel biodegradable pancreatic stent appeared to be safe for use in the pancreatic duct (PD). Other biodegradable polymers have also been evaluated but studies have shown that BDS made up of PDX is the best as they offer good expansion force and patency that is very similar to that provided by FCSEMS and importantly, have controlled degradation.⁷

Studies evaluating clinical use of BDS are limited and majority of published work on safety and efficacy of BDS is on its use through the percutaneous route. Petrtýl et al in 2010, studied two patients with postbilioenteric anastomotic strictures who were successfully treated with percutaneous placement of PDX stents.⁸ Mauri et al reported their experience with percutaneous placement of PDX stents in 10 patients with benign biliary strictures and reported that stent placement was successful in all patients with no major procedure related complications. Also, stent degradation occurred within 6 months and stricture resolution was documented at a median follow-up of 16.5 months with none of the patients requiring any further intervention.⁹ The same investigators in 2015 published further data on percutaneous placement of 7- to 12-mm diameter PDX stents in 107 patients with benign biliary strictures refractory to bilioplasty. Technical success rate was 98% with an acceptable stent migration rate of 2%. At a median follow-up of 23 months, stricture recurrence was seen in 18% and the estimated stricture recurrence rates were 26 and 29%, at 2 and 3 years, respectively.¹⁰ Although, the technical, as well as clinical success rates of these studies were impressive, up to 30% patients treated with BDS developed episodes of transient cholangitis that was hypothesized to be due to transient bile duct obstruction by stent fragments during the process of stent degradation.

The clinical experience with endoscopic insertion of BDS is limited due to challenges in development of endoscopic delivery devices for BDS. However, the development of an endoscopic implantation device for deployment of PDX BDS has led on to studies evaluating its clinical utility. Siiki et al published the first successful endoscopic biodegradable biliary stent placement in a patient with postcholecystectomy cystic duct stump leak. An 8-mm custom made braided PDX self-expandable stent was successfully deployed using a novel insertion device.¹¹ Further, successful stent placements in benign biliary strictures and iatrogenic biliary leaks were reported by the same investigators ($n = 13$). 8- to 10-mm PDX stents (Ella CS, Hradec Králové, Czech Republic) with radiopaque markers at both ends were placed using 10.5 French insertion devices. Stent deployment was successful in all patients even though some of the stents had to be adjusted into position using grasping forceps or extraction balloons postdeployment. On radiological follow-up, all the stents degraded within 6 months. Stricture resolution was seen in 83% patients at a median follow-up of 21 months and resolution of bile leak was seen in all the treated cases. The adverse events documented were cholangitis and pancreatitis, in one

patient each.¹² Same group also reported a prospective non-randomized trial comparing BDS ($n = 8$) with plastic stents ($n = 24$) for management of iatrogenic bile leaks. Clinical success rates were similar (BDS 100% vs. plastic stents 75%, $p = 0.059$). One patient in BDS group developed cholangitis but overall adverse events, length of hospital stay, and readmission rates were similar between the two groups.³

BDS has also been studied for treating benign pancreatic diseases. Cahen et al published the first endoscopic placement of biodegradable pancreatic stents. PDX stents (Ella-DV biliary stent, ELLA-CS, Hradec Králové, Czech Republic) with 6-mm diameter and length of 3 to 4 cm were placed in 19 patients with pancreatic duct strictures. Stent placement was successful in all patients with no major periprocedural adverse events. Stricture resolution was seen in 58% at 6 months of follow-up and two stents got occluded necessitating balloon clearance of stones and sludge. Stent degradation occurred in a predicted manner within 6 months.¹³ Despite these encouraging results, progressive decrease in radial force with stent degradation that may be insufficient to dilate and remodel benign strictures, and duct obstruction due to stent fragments are a matter of concern. Therefore, there is a need to further improve upon the design of BDS before they can be put into routine clinical use.

In this news and views we discuss, an interesting study by Anderloni et al that has evaluated a new type of biodegradable biliary and pancreatic stent (the Archimedes stent, Amg International GmbH, Winsen, Germany) in benign biliary and pancreatic diseases.¹⁴ The Archimedes stent has a helicoidal shape that is presumed to facilitate bile or pancreatic juice flow through the outer surface of the stent while supporting the duct opening, and are available in a wide range of lengths and outer diameters. Importantly, these stents are made up of varying combinations of polymeric mixtures so that they have different degradation times: (1) fast (12 days): polymeric mixture of PDX, polyethylene glycol (PEG), and barium sulfate; (2) medium (20 days): polymeric mixture of PDX and barium sulfate; and (3) slow (11 weeks): blend of poly (lactide-co-caprolactone-co-trimethylene carbonate) and barium sulfate. This varying degradation times can be of use in differing clinical indications. The stent degradation occurs via hydrolysis of polyester polymers and stent migration is minimized by proximal and distal flaps. These stents have a central channel for a 0.035" guidewire and are available in three outer diameters: 2 (6 F), 2.6 (8 F), and 3.4 mm (10 F), and in lengths ranging from 4 to 12.5 cm. An important advantage of this novel stent is that it does not require a special delivery device and can be inserted over the guidewire like conventional plastic stents.

In this pilot study, 38 patients (11 females [28.9%]; median age 68.05 ± 10.74 years), underwent placement of 53 biodegradable stents. Out of 53 stents, 34 were biliary stents placed for varied etiologies like iatrogenic bile duct strictures, strictures secondary to chronic pancreatitis, postampullectomy, in severe cholangitis, primary sclerosing cholangitis (PSC), and preoperative drainage of malignant biliary strictures and 19 were pancreatic stents placed for prevention of post-ERCP pancreatitis (PEP) or in pancreatic

ductal strictures secondary to chronic pancreatitis. The authors used 35 (66%) slow-degrading stents, 6 (11.3%) medium-degrading stents, and 12 (22.6%) fast degrading stents. The type of stent used depended on the clinical indication, fast degrading stents were used for prevention of PEP, and slow degrading stents were used in patients with benign strictures. Unlike previous stents where only the radiopaque markers could be seen on radiography, here radiopaque barium sulfate was incorporated into the stent material, and the entire stent could be visualized on fluoroscopy. The primary outcome of the study was to evaluate the degradation time of the stents. The secondary outcome of the study was to evaluate technical features related to stent performance at the time of stent positioning, particularly, loadability, pushability, and fluoroscopic visibility.

The authors reported technical success in all the patients. Stent loadability and pushability were excellent in the majority and fluoroscopic visibility was either good or excellent in 94% of the cases. Importantly, the safety profile was also excellent and there were no episodes of cholangitis. Though the study did not aim at evaluating clinical efficacy, none of the patients needed any further treatment during the follow-up period, and the subgroup with biliary strictures had significant reduction in bilirubin levels. Five (9.4%) stents prematurely migrated and this happened in patients where the stents were placed for indications other than strictures. Stent degradation, assessed at predefined intervals was as expected, 100% of fast stents degraded in 4 weeks, medium stents in 6 weeks, and slow stents in 6 months. The authors concluded that the biodegradation of the new biodegradable biliary and pancreatic stent is reliable and as expected. Moreover, the stent insertion was technically successful in a variety of benign biliary and pancreatic diseases.

Commentary

BDS is a dream that the pancreaticobiliary endoscopists have been chasing for a long time. Various technical issues have hampered the widespread use of BDS. The novel Archimedes stent used in the current study has many advantages compared with previously studied biodegradable stents. Foremost is the ease of deployment which is similar to conventional plastic stents. Moreover, multiple stents may be placed in a single sitting for the treatment of biliary and pancreatic strictures. Stents with different degradation times opens new avenues for use of biodegradable stents, including in the preoperative biliary drainage of malignant strictures and prevention of PEP. A cause of concern with previous stents were reports of cholangitis in up to 30% of cases due to stent fragmentation during degradation of the BDS. In the current study, none of the patients developed cholangitis on follow-up. The spiral design of the Archimedes stent along with the polymeric stent material might have contributed to better stent patency and more uniform degradation preventing duct obstruction.

There were initial concerns whether BDS could provide adequate radial force to cause biliary stricture remodeling and stricture resolution. Though PLA stents had less radial

force, PDX stents, especially those with 10-mm diameter have been found to have almost similar expansion force like FCSEMS.⁷ A recent systematic review and meta-analysis comparing BDS (three studies) with multiple plastic stents (six studies) for benign biliary strictures reported that BDS is not inferior to multiple plastic stents in resolving and maintaining long-term biliary duct patency.¹⁵ However, patients in BDS group had higher incidence of postprocedural cholangitis. The Archimedes stents used in this study did not have this adverse effect of cholangitis. Extrapolation of these results suggest that these stents may be as effective as FCSEMS for management of benign strictures with added advantage of biodegradability.

Conclusion

In conclusion, BDS does hold promise in the treatment of benign biliary or pancreatic diseases with the major advantage being avoidance of ERCPs for stent removal or stent exchange. They have been confirmed to have good biocompatibility and current evidence shows acceptable rates of clinical efficacy and safety. Larger control trials with long-term follow-up are needed before these stents can be advocated as a replacement for conventional plastic stents or FCSEMS.

Conflict of Interest

No conflicts of interest and No financial disclosures

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