World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v8.i2.77

World J Gastrointest Endosc 2016 January 25; 8(2): 77-85
ISSN 1948-5190 (online)

REVIEW

Drug eluting biliary stents to decrease stent failure rates: A review of the literature

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Author contributions: All authors contributed equally to the work, researched the topic and wrote the review.

Conflict-of-interest statement: The authors have no conflict of interest related to the manuscript.

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Received: April 3, 2015
Peer-review started: April 4, 2015
First decision: June 2, 2015
Revised: August 11, 2015
Accepted: October 17, 2015
Article in press: October 28, 2015
Published online: January 25, 2016

Abstract

Biliary stenting is clinically effective in relieving both malignant and non-malignant obstructions. However, there are high failure rates associated with tumor ingrowth and epithelial overgrowth as well as internally from biofilm development and subsequent clogging. Within the last decade, the use of prophylactic drug eluting stents as a means to reduce stent failure has been investigated. In this review we provide an overview of the current research on drug eluting biliary stents. While there is limited human trial data regarding the clinical benefit of drug eluting biliary stents in preventing stent obstruction, recent research suggests promise regarding their safety and potential efficacy.

Key words: Bile ducts; Cholangiocarcinoma; Endoscopy; Pancreas

Core tip: Despite the short life expectancies of patients with biliary tract cancers, biliary stenting suffers from high stent re-obstruction rates, provoking unneeded costs, morbidity and mortality. Drug eluting stents offer the possibility of decreasing stent failure rates from both biliary stent clogging, and external obstruction from tumor and epithelial ingrowth. In this inclusive review we outline the current body of experimental literature on drug eluting stents including bench, animal and human trials, and discuss possible targets for future research.

Shatzel J, Kim J, Sampath K, Syed S, Saad J, Hussain ZH, Mody K, Pipas JM, Gordon S, Gardner T, Rothstein RI. Drug eluting biliary stents to decrease stent failure rates: A review of the literature. *World J Gastrointest Endosc* 2016; 8(2): 77-85 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i2/77.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i2.77

INTRODUCTION

Obstruction of the bile duct results in serious clinical consequences such as cholangitis and death. Biliary stenting is an effective means of relieving obstruction, and is the preferred method of palliating patients with malignancy[1]. Malignant obstructions in particular cause high stent obstruction rates, despite the relatively short lifespan of patients with biliary tract cancers (Table 1). Stent failure is associated with recurrent morbidity, and often necessitates repeat endoscopy with stent retrieval and replacement. These procedures carry an increased risk for procedural complications such as pancreatitis, and can result in additional hospital admissions.

Stent failure can be stratified into four primary etiologies: Internal stent failure from biliary clogging, external failure caused by tumor ingrowth or overgrowth of excessive epithelial or malignant cells, and stent migration. The incidence of each type of failure in malignant obstruction has been documented in several small prospective trials (Table 2). For the purposes of this review, only internal and external failure will be addressed.

Drug eluting stents have been used for several decades in the setting of coronary artery disease to decrease the incidence of stent failure. Currently there have only been a limited number of human trials evaluating drug eluting biliary stents to prevent external obstruction[2,3], none of which showed a significant effect in decreasing stent failure rates. However, only one agent (paclitaxel) has been trialed in humans with malignant obstruction[2,3]. Both trials showed the hybrid stent was safe and well tolerated when compared to traditional stenting. There is a growing body of literature looking at *in vitro* and *in vivo* models of drug eluting biliary stents as prophylaxis against internal and external sources of failure. In this review, we divide stent failure pathophysiology into internal and external mechanisms and analyze the current literature on the use of stent drug elution as prophylaxis against the respective failure types.

INTERNAL STENT FAILURE

Internal stent failure results from the accumulation of obstructing material in the stent lumen. It is a complex process involving microbial colonization and biofilm generation[4]. This process is exacerbated by, but not dependent on, the reflux of duodenal contents into the biliary system.

A normal functioning sphincter of oddi helps to preserve the relative sterility of the biliary tree compared to the duodenum. Stenting across the papilla allows for the reflux of intestinal contents and bacteria into the biliary system[5]. After placement, biliary stents are quickly colonized by a diverse poly-microbial community[6-10]. Aerobic and anaerobic bacteria are readily isolated from occluded biliary stents with *Enterococcus*, *Escherichia coli* and *Klebsiella* the most common aerobic bacteria isolated from biliary sludge, while *Clostridium* is the most common anaerobe isolated[6-8,11]. Anaerobic bacteria may be the first to attach and may play a crucial role on biofilm initiation[7].

Electron microscopy and biochemical analyses of explanted stents has shown that the occluding material is formed by the accumulation of multispecies bacterial colonies, fungi, microbial byproducts, crystals of calcium bilirubinate, crystals of fatty acid calcium salts, and by semi digested fibers arising from duodenal reflux[6,7,12-14]. Surface irregularities in the stent have been postulated to facilitate the initial biofilm generation[6,12,15].

The process of internal failure is self-perpetuating. As the stent lumen narrows with increasing biofilm generation, or external compression, bile flow decreases by an exponential rate. The precipitous decrease in bile flow seen with small decreases in stent diameters is explained by Poiseuille's law, which states that when a fluid with a stable viscosity flows through a tube, halving the radius of the tube will decrease the flow rate to $1^{st}/16^{th}$ the original flow[9] (Figure 1). Viscous fluids also display a parabolic flow, with the lowest flow rates against the surfaces of the tube. Slowing of bile flow promotes both spontaneous and bacteria-driven bile salt precipitation, thus exacerbating the likelihood of internal failure[4]. This has been proven clinically as failure rates have been shown to be well correlated with the diameter of the stent[16].

DRUG ELUTION TO PREVENT INTERNAL FAILURE

Drug insertion into the biliary stent lumen can theoretically improve internal failure rates by decreasing bacterial colonization and biofilm formation. There has been a small amount of research looking at internal drug coating or drug elution to prevent internal failure (Table 3), comprising *in vitro*, *in vivo* animal and one human trial. Drugs selected for analysis can be loosely grouped into two categories: those theorized to inhibit bacterial attachment and biofilm generation and antimicrobials theorized to inhibit bacterial growth and induce sterilization of the biliary tree.

The first published example of incorporating pharmaceuticals into the internal stent lumen was bench modeling done in the late 1990's. An *in vitro* model was developed by submerging test material in culture broth and bile; it was shown that an addition of benzalkonium chloride, a commonly used antiseptic, as well as Teflon, decreased the incidence of microbial colonization[17]. However, these studies did not accurately model the

Table 1 Current stent failure rates

Stent type	Stent failure rates in malignant obstruction
Plastic stents	30%-70%
Self expanding metal stents	19%-46%

Adapted from Ref.[31-37].

Table 2 Causes of stent failure

Causes of stent failure	Percent of total failures
Tumor ingrowth	66%-68%
Epithelial ingrowth	
Biliary clogging	17%-21%
Tumor overgrowth	2%-11%
Stent migration	0%-4%

Adapted from Ref.[31-37].

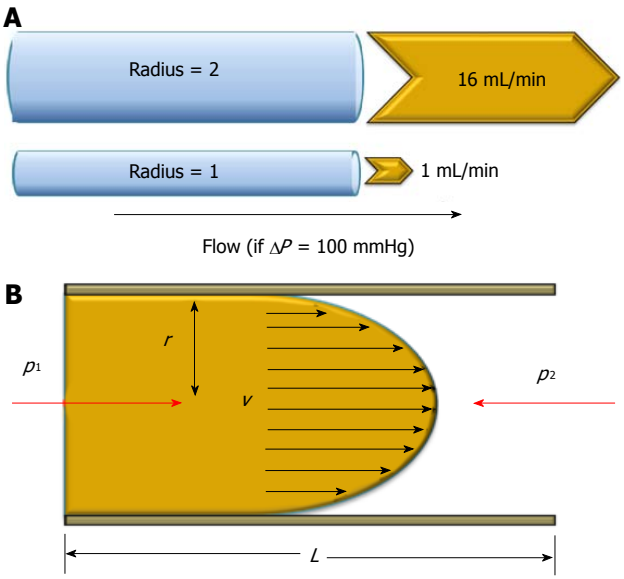

Figure 1 Change in biliary flow determined by stent radius, as described by Poiseuille's law (A) and laminar flow of viscous fluids (B). Flow= (π • pressure difference • radius^4)/(8 • viscosity • length).

polymicrobial environment of the biliary tree, utilizing just 3 cultured pathogens.

Several more *in vitro* models have been reported in the literature evaluating luminal drug elution. Of the materials tested, heparin coating has proven promising in both *in vitro* and human trials. Cetta *et al*[18] examined stents internally coated with heparin and hyaluronic acid. The coated stents were then placed in bacterial cultures which were generated from culturing previously occluded biliary prostheses. Compared to uncoated polyurethane stents, heparin coated stents had significantly reduced biofilm formation. Later, some researchers found that stents coated with both hydrophobin and heparin decreased encrustation detected by the electron microscopy compared to hydrophobin alone in their *in vitro* model. This work was followed up by Farnbacher *et al*[19], who devised a prospective human trial. In their study they found that explanted heparin coated stents had significantly decreased rates of luminal encrustation by visual inspection and weight.

Antibiotics, while an intuitive possibility for decreasing bacterial colonization, have failed to show any effect in decreasing internal failure rates when given both systemically or locally through drug elution. There has been a continuous effort since 1989 to identify systemic treatments which could decrease internal stent failure rates, among which antibiotics, ursodiol, mucolytic agents, and anti-inflammatory agents have been trialed (Table 4). Multiple studies as well as meta-analysis[20] have failed to show a direct benefit from any systemic treatment in decreasing internal failure rates.

Along with a lack of benefit when given systemically, antibiotics have also failed to show any benefit when given locally. In 2011, Weickert *et al*[21] analyzed the effect of antibiotic elution on internal failure by incubating stents in human bile. Their experiment examined the combined effect of stents combined with hydrophobin and ampicillin/sulbactam, as well as hydrophobin and levofloxacin showed that the neither antibiotic reduced the amount of biofilm generation compared to hydrophobin alone. In 2012, Gwon *et al*[22] developed a cefoxitime eluting stent and for testing in a canine model. Upon both gross inspection and analysis with electron microscopy they found no effect from cefotaxime in preventing biofilm development. The reasons behind the lack of local antibiotic efficacy can only be surmised, but may include the selection of resistant organisms in the polymicrobial biliary environment, the inability of antibiotics to permeate through biofilms, or local breakdown and inactivation of antibiotics.

EXTERNAL STENT FAILURE

Biliary obstruction is the first presenting sign of disease in 70% of patients with cancer of the pancreas and biliary system[23]. Pancreatic cancer is common and carries significant morbidity and mortality. In the year 2000 for example, there were 217000 new cases of pancreatic cancer with 213000 pancreatic cancer deaths worldwide[24]. Survival rates are dismal at an estimated five-year rate of 5%[25] and have been generally stagnant with no recent advances improving mortality[26]. Although biliary duct and gallbladder cancers have a lower incidence, their mortality is equally dismal. External stent obstruction is not only a concern in patients with pancreatobiliary malignancy, as there is also a notable population of patients with nonmalignant obstructions at risk for stent failure who could benefit from drug elution as a possible means of decreasing failure risk. Prospective studies on patients with chronic pancreatitis, autoimmune pancreatitis, and liver transplants for instance have shown that respectively up to 20%[27], 83%[28], and 22%-49%[29] of patients developed biliary strictures.

There are two main categories of commercially available biliary stents for endoscopists to select from:

Table 3 Studies evaluating drug elution or coating to prevent internal failure

Ref.	Journal	Study design	Study results
In vitro			
Rees *et al*[17]	*Journal of Hospital Infection* (1998)	*In vitro* - control (polyurethane) - benzalkonium chloride (BZC) - ePTFE (Teflon)	BZC and Teflon reduced the number of organisms attached to stents
Cetta *et al*[18]	*The European Journal of Surgery* (1999)	*In vitro* 5 stents - control (polyurethane) 5 stents - heparin + hyaluronic acid	Heparin and hyaluronic acid coating reduced biofilm development
Weickert *et al*[21]	*Advances in Medical Sciences* (2011)	*In vitro* 7 stents - control (polyethylene) 4 stents - hydrophobin (H) 3 stents - H + ampicillin/sulbactam 3 stents - H + levofloxacin 3 stents - H + heparin	Stents coated with hydrophobin or both hydrophobin and heparin reduced clogging material scanning electron microscopy (SEM) images
Animals			
Gwon *et al*[22]	*Acta Radiologica* (2012)	Canine model 3 stents - control (ePTFE) 3 stents - 10% wt/vol cefotaxime 3 stents - 20% wt/vol cefotaxime	Cefotaxime did not prevent biofilm development (gross inspection, SEM images)
Humans			
Farnbacher *et al*[19]	*Scandinavian Journal of Gastroenterology* (2012)	Randomized prospective 13 stents - control (polyethylene) 13 stents (same patients) - heparin	Heparin is effective in preventing encrustation on stents (encrustation weighed)

plastic or metal-based stents. In regards to malignant obstruction, self-expanding metal stents (SEMS) have been found to have a decreased incidence of cholangitis, stent failure, and overall hospitalizations when compared to plastic stents[30]. Median patency rates for SEMS have been evaluated in several studies and generally found to be at approximately 270 d in malignant obstruction[31-33]. Biliary stents have a sub-optimal failure rate, and will occlude in 30%-70% of patients with plastic stents and in 19%-46% of patient with bare metal stents (Table 1)[31,32,34,35]. The most common cause of failure are tumor or epithelial ingrowth (66%-68%), followed by sludge and clogging (17%-21%), tumor overgrowth (2%-11%), and stent migration (0%-4%) (Table 2)[33,36,37].

From analysis of biopsied obstructing tissue, it was found that 44% of the tissue ingrowth was non-malignant in nature, suggesting epithelial hyperplasia plays a significant role in stent obstruction[35]. Other studies have suggested that up to 50% of SEMS occlude secondary to epithelial hyperplasia[35]. Considering the major mechanisms of stent obstruction, tumor ingrowth, tumor overgrowth, and epithelial hyperplasia, a stent externally coated with agents that effectively hinder tissue growth could theoretically reduce failure rate by 50%-79%. Drug incorporation into the external stent membrane appears to be an intuitive next step in stent development capable of significantly reducing stent obstruction rates[34].

CURRENT RESEARCH ON DRUG-ELUTING BILIARY STENTS TO PREVENT EXTERNAL FAILURE

Drug-eluting stents have been well validated in the intravascular setting and have become a staple in the management of coronary artery disease for several decades. However, despite the theoretical promise of drug-eluting biliary stents (DEBS), there has been little research on the subject to date (Table 5). Ideal agents to incorporate into the stent exterior would serve to (1) effectively inhibit the growth of malignant pancreaticobilary cells; (2) retard the proliferation of biliary epithelial hyperplasia; and (3) display favorable histologic changes when exposed to biliary epithelium, without necrosis or risk of biliary perforation.

ANIMAL MODELS OF DRUG ELUTING BILIARY STENTS

Lee *et al*[38] developed the first published animal models of DEBS in 2005. Their team developed a paclitaxel eluting stent for trial in a porcine model. The decision to use paclitaxel was based on bench data from Kalinowski *et al*[39] which showed that paclitaxel, inhibited human gallbladder cells, human fibroblasts, and pancreatic cells in a dose-dependent fashion. Their model was designed to evaluate drug release dynamics and bile duct histological changes resulting from extended direct stent contact after implantation in pigs for 4 wk. Stents were developed with paclitaxel concentrations of 0%, 10% and 20%. Inflammatory cell infiltration and fibrous reactions were the commonly noted histologic changes which corresponded to the level of paclitaxel incorporated into the stent. Although the model was not designed to evaluate long term failure rates, no pigs showed clinical or laboratory signs of biliary obstruction during the trial. Their results were promising, finding acceptable histologic changes at all drug levels. Epithelial denudation, mucin hypersecretion, and epithelial metaplasia were noted in

Table 4 Trials evaluating systemic treatments to prevent internal failure

Ref.	Journal	Study design	Study results
Humans			
Barrioz *et al*[48]	*Lancet* (1994)	Randomized prospective 25 - conservative treatment 21 - ursodeoxycholic acid and norfloxacin	Drugs were associated with longer stent patency and shorter hospital stay
Coene *et al*[49]	*Scandinavian Journal of Gastroenterology* (1994)	Randomized prospective 60 patients received either co-trimoxazole or N-acetylcysteine	Bile clogging did not correlate with bile viscosity. Mucolytic agents or antibiotics only effective when bile is highly viscous
Smit *et al*[50]	*Gastrointestinal Endoscopy* (1989)	Randomized prospective 30 patients received either placebo or doxycycline or aspirin	Both doxycycline and aspirin reduced the dry weight of sludge. Doxycycline improved patient survival
Halm	*Endoscopy* (2001)	Randomized prospective 26 - ursodeoxycholic acid 26 - ursodeoxycholic acid + ofloxacin	No difference in patient survival or stent occlusion
De Lédinghen *et al*[51]	*Digestive Diseases and Sciences* (2000)	Randomized prospective 29 - conservative treatment 33 - ursodeoxycholic acid and norfloxacin	No difference in stent patency and patient survival
In vitro			
Tsang *et al*[52]	*Journal of Laboratory and Clinical Medicine* (1997)	*In vitro* 4 - porcine bile 4 - porcine bile + ampicillin + sulbactam	Ampicillin and sulbactam inhibited biofilm formation

the bile ducts that were in contact with stents containing 20% weight/volume (wt/v) paclitaxel; there was no incidence of transmural necrosis or perforation in any animal. Furthermore, the amounts of paclitaxel released over 1 wk and over 6 wk were similar, regardless of the concentration of paclitaxel incorporated in the stent. The authors ultimately found that stents with 10% (wt/v) paclitaxel in the covering membrane was superior to those with 20% (wt/v) in regards to histologic changes and drug release dynamics. The 10% (wt/v) paclitaxel stent had a more favorable histologic profile without evidence of epithelial metaplasia or other concerning local changes from excessive cytotoxic effects which could suggest a risk for necrosis or perforation, while still displaying a favorable drug release profile.

There are four other previously published animal studies involving paclitaxel eluting stents. In 2009, Lee *et al*[40] undertook a canine model also to assess biliary duct histological changes, evaluating 20% wt/v paclitaxel DES. The authors noted biliary mucosal hyperplasia in 3/6 dogs who received paclitaxel stents (none in the control group) along with no distinct stent complications. They concluded that more research is warranted to determine the proper concentration of drug to obtain optimal tumor control in and histological remodeling of the biliary duct. In 2012, Jang *et al*[41] used a porcine model to examine a 10% wt/v paclitaxel-eluting biliary stents using a membrane containing Pluronic F-127 in an attempt to bolster drug delivery. They again found acceptable histologic changes based on inflammatory cell infiltration and fibrotic reaction, with no incidence of obstruction or perforation. Paclitaxel was detected for 28 d in porcine serum with the 10% Pluronic concentration. However, released paclitaxel was observed for only 7 d with incorporation of higher or lower concentrations of Pluronic. Most recently, Shi *et al*[42] used a canine model to study the effect of paclitaxel biliary stents when used as biliary-enteric anastomosis following Roux-en-Y cholangiojejunostomy. Histology of the bile duct was observed 1, 3, 6, 9 and 18 wk following the surgery. Paclitaxel-coated stents were found to release paclitaxel for 9 wk, and dogs that had paclitaxel-coated stents placed had less granulation tissue and granular hyperplasia of the biliary-enteric anastomosis. No adverse effects of paclitaxel were observed. Lastly, Bang *et al*[43] recently developed a mouse model xenografted with both pancreatic cancer and cholangiocarcinoma cell lines which they exposed to paclitaxel-eluting membranes, in an attempt to determine the molecular mechanisms of tumor inhibition. Paclitaxel, they discovered, inhibited tumor angiogenesis, through multiple mechanisms including suppression of mammalian target of rapamycin (mTOR) through regulation of hypoxia inducible factor 1 and increased apoptosis, as well as inhibiting tumor-stromal interaction by effecting regulation of CD44, SPARC, matrix metalloproteinase-2, and vimentin.

Besides paclitaxel, two other chemotherapeutics have been evaluated in DEBS animal models. In 2012, Lee *et al*[44] developed a gemcitabine eluting stent membrane applied to a self-expanding Nitinol stent. They performed both *in vitro* modeling using a SK-ChA-1 cholangiocarcinoma cell line as well as *in vivo* modeling using a mouse model with colorectal carcinoma cells (CT-26). They analyzed stents developed with 0%, 8%, 10%, and 12% gemcitabine PU by weight and found the 12% concentration to be superior in terms of tumor inhibition and pro-inflammatory markers in both the *in vivo* and *in vitro* models. The authors concluded that gemcitabine eluting stents show considerable feasibility for the treatment of malignant obstruction[44]. Furthermore, in 2012, Chung

Table 5 Studies evaluating drug elution or coating to prevent external failure

Ref.	Journal	Study design	Study results
Animals			
Lee *et al*[38]	*Gastrointestinal Endoscopy* (2005)	Porcine model 2 pigs - control (metallic) 2 pigs - 10% wt/v Paclitaxel 2 pigs - 20% wt/v Paclitaxel	Paclitaxel-eluting stents caused mild adverse effects, but are safe to use in porcine models
Lee *et al*[40]	*Gastrointestinal Endoscopy* (2009)	Canine model 5 dogs - control (metallic) 6 dogs - 20% wt/v paclitaxel	Paclitaxel-eluting stents caused mild adverse effects, but are safe to use in canine models
Lee *et al*[44]	*International Journal of Pharmaceutics* (2012)	*In vitro*, murine model 5 mice - no stenting 5 mice - polyurethane 5 mice - 0% wt/v gemcitabine 5 mice - 8% wt/v gemcitabine 5 mice - 12% wt/v gemcitabine	Stents coated with gemcitabine reduced the size of subcutaneous tumor *in vitro* and in mice
Chung *et al*[45]	*Journal of Gastroenterology and Hepatology* (2012)	Porcine model 2 pigs - 0% wt/v gemcitabine 2 pigs - 10% wt/v gemcitabine 2 pigs - 15% wt/v gemcitabine 2 pigs - 20% wt/v gemcitabine	Gemcitabine-eluting stents cause mild to severe inflammation, but are safe to use in porcine models
Jang *et al*[41]	*Endoscopy* (2012)	Porcine model 2 pigs - 0% wt/v paclitaxel 2 pigs - 0% Pluronic + 10% taxol 2 pigs - 10% Pluronic + 10% taxol 2 pigs - 20% Pluronic + 10% taxol	Greater patency observed when stents were coated with pluronic with paclitaxel. Stents are safe to use in porcine models
Kim do *et al*[46]	*International Journal of Nanomedicine* (2013)	*In vitro*, murine model 10 mice - control (no stenting) 10 mice - PCL film 10 mice - sorafenib-loaded film	Sorafenib-loaded film inhibited the growth of human cholangiocarcinoma cells *in vitro* and in mice
Shi *et al*[42]	*European Journal of Gastroenterology and Hepatology* (2013)	Canine model 10 dogs - control (no stenting) 10 dogs - Poly-L-lactic acid coated metallic stents (PLLA) 10 dogs - PLLA + 1 mg paclitaxel/stent 10 dogs - PLLA + 2 mg paclitaxel/stent	No adverse effects less granulation tissue and glandular hyperplasia in dogs with paclitaxel stents
Bang *et al*[43]	*Gastroenterology Research and Practice* (2015)	Murine model 8 mice - control (polyurethane) 8 mice - control + Pluronic 8 mice - Pluronic + 5% paclitaxel 8 mice - Pluronic + 10% paclitaxel	Tumor angiogenesis inhibited in mice with Paclitaxel stents through multiple molecular mechanisms
Humans			
Suk *et al*[2]	*Gastrointestinal Endoscopy* (2007)	Randomized prospective 21 patients - 10% wt/v paclitaxel	Paclitaxel-eluting stents are safe and effective. Occlusion in 9 patients, mean patency was 429 d
Jang *et al*[3]	*Digestive Diseases and Sciences* (2013)	Randomized prospective 46 patients - control (metallic) 60 patients - 10% wt/v paclitaxel	No significant differences in stent patency or patient survival, but stents proved safe to use in humans

et al[45] developed a porcine model to analyze gemcitabine eluting stents, analyzing 0%, 10%, 15% and 20% gemcitabine wt/v drug DEBS. They found mild to severe inflammation in the 15% and 20% groups compared to mild inflammation in the 10% group. Fibrous reactions in the submucosal layer did not differ among groups and no biliary obstruction, necrosis or perforations were observed during the study. They found that the 10% GEM stents produced mild histologic changes and are likely most appropriate for clinical application.

Most recently in 2013, Kim do *et al*[46] loaded sorafenib on PCL film, which was then wrapped around a metal biliary stent. They cultured human cholangiocellular carcinoma cells with the PCL films in order to examine the effect of sorafenib on angiogenesis and tumor cell growth. Additionally, a mouse model was developed using human cholangiocarcinoma cells. The study concluded that sorafenib successfully inhibited local angiogenesis and tumor cell growth both *in vitro* and in murine models.

HUMAN TRIALS OF DRUG ELUTING BILIARY STENTS

There have been limited human trials involving DEBS. The initial human trial of paclitaxel DEBS was a single arm trial of 21 patients undertaken by Suk *et al*[2] in 2007 in which a mean patency of 429 d and a mean survival of 350 d were found. Occlusion was observed in 9 patients due to bile sludge or clogging in 4, tumor overgrowth in 3, and tumor in-growth in 2. Furthermore, cumulative patency rates at 3, 6, and 12 mo were 100%, 71%,

and 36%, respectively. Blood levels of paclitaxel were monitored in 6 patients showing systemic levels were low, peaking between 1-10 d, suggesting systemic effects are minimal compared to local effects. This trial showed promising safety and efficacy data and prompted a follow up prospective trial[3], comparing a 10% wt/v paclitaxel eluting bare metal stent with a traditional covered metal stent. Stents were 5-8 cm in length and 10 mm in diameter in both groups. The study was altered due to a patient preference for the DEBS, and the planned randomized controlled trial was changed to consecutively enrolling 60 patients to the paclitaxel-coated stent arm and then enrolling 46 patients to standard covered SEMS[41]. Mean duration of stent patency was 199 ± 235 d in the paclitaxel-DEBS group and 149 ± 99 d in the covered SEMS group. Mean survival was 270 in the in the paclitaxel-DEBS arm *vs* 260 d in the control arm. The rates of cholangitis, pancreatitis, and stent migration were similar between the two groups. Although there was a trend towards improved patency and survival in the DEBS arm, the results did not display statistical significance. The authors concluded that although no significant difference was detected with paclitaxel DEBS, they were shown to be equally safe in human use, and further research is needed. The relatively small number of patients, as well as the shift from a prospective concurrent randomized trial to a trial with staggered accruement likely inhibited the power of the study to detect a clinical benefit from paclitaxel eluting biliary stents. These studies aside, there are multiple avenues for future human research, as well as a significant need to perform large prospective trial to evaluate the effectiveness of drug eluting biliary stents, both with paclitaxel and innumerous other compounds.

CONCLUSION

The amount of direct research involving drug eluting biliary stents has been limited, with only a few drugs having been directly examined. Considering the myriad of possible drugs which could decrease the incidence of internal failure, external failure, or both, there is ample room for further research. As described earlier, small amounts of luminal narrowing from external compression can have exponential effects on the rate of biliary flow, resulting in a significantly increased propensity for internal failure. Drug elution has theoretical benefit in decreasing internal stent failure rates, and heparin coating in particular has shown promise in small studies, which warrants further research. However, antibiotic elution has not shown a benefit in decreasing biofilm formation, which parallels trials looking at the use of systemic antibiotics to prevent stent failure. This may be secondary to multiple possible etiologies including the inability of antibiotics to permeate within biofilms, or the polymicrobial environment of the biliary tree which may quickly lead to bacterial resistance.

Only three drugs, paclitaxel, gemcitabine and sorafenib have been evaluated as possible candidates to decrease the incidence of external failure, where paclitaxel is the sole drug evaluated in human trials. There are multiple drugs which theoretically could show a clinical benefit in decreasing stent failure rates in both malignant and nonmalignant sources of biliary stenosis. Development of an effective drug eluting stent would likely be cost effective due to the high costs involved in stent failure and has the possibility of directly decreasing patient morbidity and mortality. The high costs, and extensive time and labor requirements of large animal modeling, as well as the lack of an established reproducible bench model have likely inhibited the process of stent development thus far. Despite this, the raw theoretical benefit is evident, where the demand for new devices that reduce restenosis rates with their associated morbidity and mortality is ever present.

Among the possibilities for future DEBS research, the possibility of combination drug stents holds theoretical promise. In order to maximize stent patency rates, the ideal stent would feature both internal and external drug elution. Also, previously trialed drugs which failed to show efficacy as a single agent may have added efficacy when combined with other agents such as heparin or antibiotics, which could prove to have increase efficacy when used in concert. Future animal and human trials will benefit from the analysis of drug combinations.

One of the main limitations to the development of DEBS is the lack of cheap, reproducible models which accurately reflects the human bile duct. Internal stent failure can be reasonably modeled on the bench top by systems which propel biologically active bile through the stent[47]. Biofilm development can then be measured by direct inspection, weight and electron microscopy[17-19,21,22]. This model may be used to select optimal agents for further analysis. However, there are no cheap reproducible models which accurately depict the human biliary ducts tolerance to direct contact with drug elution. Drug eluting stents, particularly those with external drug elution, require animal modeling in order to assess histological changes resulting from the stent. As there are no adequate small animal models available for biliary stenting, this has previously been performed with porcine or canine modeling. This has multiple downsides including the high costs of endoscopists or surgeons to place stents, veterinarians, and the animal husbandry required for the several weeks while stents incubate in the bile duct. As the large animal model is also required to establish the ideal drug elution dosage based on histologic changes, costs inhibit the number of drug dosages trialed. Future investigators would benefit from the development of more streamlined and standardized bench top and animal models.

In conclusion, although the current research on DEBS is limited, promise is evident and holds the possibility for significantly increasing the rates of long-term stent patency. Drugs that inhibit malignant cells and non-malignant epithelia hyperplasia, while displaying reasonable histologic tolerance after exposure to the biliary epithelium, should be further examined. Previous models that are well defined can be implemented to

streamline further research. There is an obvious need in this population to decrease morbidity, and DEBS hold the possibility of a significant improvement in outcomes. Further analysis of both new pharmaceuticals and further modeling of current and combinatory drug eluting stents is needed.

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P- Reviewer: Paydas S, Sakata N **S- Editor**: Ma YJ **L- Editor**: A
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