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NEW TECHNOLOGY

A novel gallbladder umbrella stent (the Shai™ Stent) for prevention of stone migration and impaction: results on feasibility and short-term safety in a porcine model

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Abstract

Background and aims Cholelithiasis is the most common biliary tract disorder. Surgery is the treatment of choice for symptomatic gallstones. Aims of this study were to investigate the feasibility and short-term safety of a new endoscopic procedure with a specially designed Nitinol gallbladder stent for blockage of gallstone migration, the Shai™ Stent. The Shai stent is designed to enable free bile flow, which will be supposed to prevent recurrent attacks.

Methods The Shai™ Stent was inserted into the gallbladder during a standard ERCP procedure using a conventional metal stent delivery system. The aim of the present study was to investigate the feasibility and safety of insertion and deployment and removal of the stent into the gallbladder of pigs. In addition, the short-term safety of the stent was evaluated.

Results Fifteen stents were placed in the gallbladder of 15 pigs. Mean procedure time was 25 min (15–37). The maximum follow-up before sacrifice was 42 days. The stent in 1 pig had migrated at the 42 days follow-up but there were no macroscopic changes in its gallbladder or other organs. The stent remained in place in the remaining 12 pigs at autopsy, and the gallbladder and bile ducts were macroscopically normal. Stent removal was easily done in two pigs immediately after placement.

Conclusions Correct placement and removal of the Shai™ Stent in the gallbladder is safe and feasible in pigs. Further clinical trials are warranted to confirm these results and to effectively evaluate the capability of this stent as an innovative biotechnology to block gallstones from migration and impaction.

Keywords Gallbladder stones · Cholecystitis · Endoscopic retrograde cholangiopancreatography · Gallbladder stent · Innovative biotechnology

Cholelithiasis is the most common biliary tract disease worldwide and affects large segment of the population in developed nations (up to 15%) [1].

Gallstones can be asymptomatic when confined to the gallbladder. However, if stones become lodged in the neck of the gallbladder or migrate from the gallbladder, thereby blocking the flow of bile from the gallbladder, they can manifest different symptoms. These may vary from nonspecific abdominal complaints and dyspepsia to true biliary pain, with or without complications, such as cholecystitis and acute cholangitis or acute pancreatitis (in the case of stone migration into the common bile duct—CBD) [1]. It is estimated that common bile duct stones are present in 10–20% of individuals with symptomatic gallstones [2]. Stones that migrated into the CBD require endoscopic retrograde cholangiopancreatography (ERCP) for clearance [2].

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Today cholecystectomy is commonly performed in symptomatic patients with gallstones and also to prevent complications. In 90% of cholecystectomy cases, the procedure is performed with a laparoscopic approach, with approximately 2–15% of cases requiring an open surgery [3–5].

Both laparoscopic or open cholecystectomy can be high-risk procedures or even contraindicated in symptomatic patients with severe comorbidities. Stone movement in these patients can lead to cholecystitis, and therefore other methods, less invasive than ERCP are usually performed: (double-pigtail plastic stent placement, endoscopic ultrasound with cholecystoduodenostomy, and percutaneous cholecystostomy) [6–11]. These procedures, even if less invasive, can lead to severe complications. For instance, double-pigtail plastic stents and percutaneous cholecystostomy can lead to recurrent cholangitis with hospital readmissions and with this the health care costs can rise [6–8, 10]. Recently, lumen-apposing metal stents (LAMS) have been used for gallbladder drainage in acute cholecystitis, but to our knowledge, no stents have been designed for the prevention of episodes of recurrent gallbladder colic pain and cholecystitis.

In this paper, we present the results of endoscopic placement in pigs of a new nitinol gallbladder stent (The Shai™ Stent, Kiryat Gat, Israel). The idea of this stent is to prevent gallstones from migration into the CBD and impaction into the cystic duct, and with this, the onset of symptoms of gallbladder obstruction.

The Shai™ Stent is intended to be used as an innovative biotechnology device to prevent recurrent attacks of pain and cholecystitis and is not intended as a treatment in cases of acute cholecystitis.

The aim of this study was to evaluate feasibility and short-term safety of this novel gallbladder stent in pigs.

Materials and methods

Landrace pigs with a weight of 30 kg (± 5) and 3 months of age were chosen for this experiment. The procedures were done at the animal facility of the Catholic University of Rome (Italy) and IHU of Strasbourg (France) with prior authorization from the ethical committees of both institutions (CESA/A/45/2012 for Rome and 38.2015.01.069 for Strasbourg).

The Shai™ Stent is an 'umbrella-like,' memory-shaped, self-expandable, nitinol metal stent, rounded at its ends to support easy fixation in the gallbladder (Fig. 1). The Shai™ Stent is delivered by a common biliary 7–8.5 French delivery system (chosen according to the dimensions of the cystic duct). Upon its release from the delivery system, the Shai™ Stent gently accommodates itself in the gallbladder facing the cystic duct orifice. Once in place, the stent opens to its memory shape and the umbrella meshes are faced to the orifice on the infundibulum (Fig. 2). These meshes are designed to prevent migration of stones bigger than 2 mm in diameter. Stones smaller than 2 mm in diameter can freely pass through the meshes and through the biliary sphincterotomy.

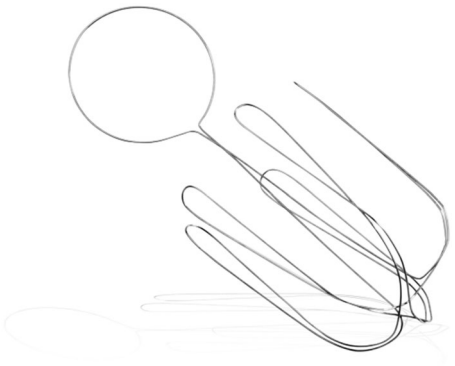

Fig. 1 The Shai™ Stent an 'umbrella-like,' memory-shaped, self-expandable, nitinol metal stent

Fig. 2 Animation of the appearance of the Shai stent in the gallbladder after deployment

Prior to stent placement, abdominal ultrasound was done in every animal in order to determine the size of the gallbladder (Fig. 3). The procedures were done with a standard Olympus duodenoscope (TJF 180 Olympus Tokyo, Japan) under fluoroscopic control and general anesthesia. After biliary cannulation, cholangiography, and sphincterotomy, the gallbladder was cannulated with a J-shaped hydrophilic guidewire through the cystic duct under direct fluoroscopic guidance. The Shai™ Stent was introduced over the same guidewire into the gallbladder with a 7–8.5 French standard delivery system. The stent (available between 4 and 8 cm in length) was deployed in the gallbladder under direct fluoroscopy control (Fig. 4A–C). The stent delivery device has also incorporated a stent removal device (Fig. 4C). Stent removal should be done in case of stent misplacement or request for subsequent removal of the Shai™ Stent. The stent removability device has three hooks (Fig. 5) that when are opened

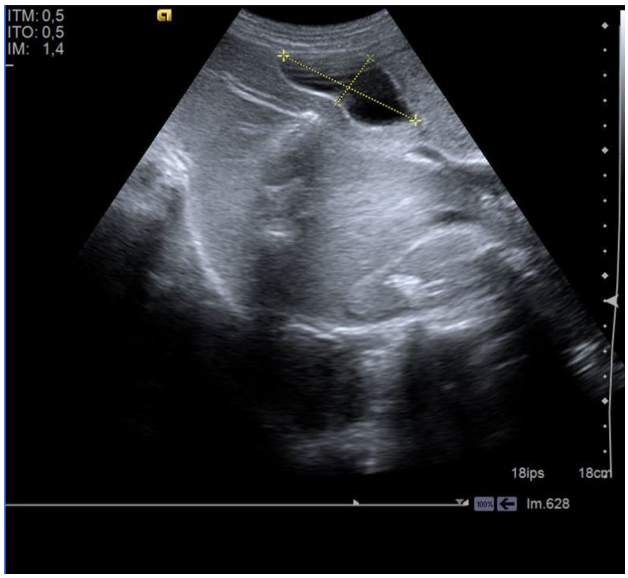

Fig. 3 Measuring the dimensions of the gallbladder for best choice of the stent

in proximity of the umbrella of the stent capture the wires and reload the stent into the delivery system. The animals in which the stent was removed were sacrificed immediately after the procedure in order to assess any damage of the cystic duct, gallbladder, and the common bile duct.

Abdominal ultrasound was done in every animal also after ERCP with stent placement in order to determine the correct position of the stent (Fig. 6).

All the animals were held in the facility on an overnight fast before ERCP.

In order to evaluate the functionality and the removability of the device and exclude immediate and late organ lesions, animals were divided in three groups. Animals in Group 1 were sacrificed up to 6 h after the procedure, while animals in Group 2 were followed up from 24 h to 42 days. The removability of the device was evaluated in the animals in Group 3, and these were sacrificed immediately after positioning and removal of the stent. Animals in Group 1 and 2 were held at the facility, had water and food ad libitum, and were clinically monitored for procedure-related adverse events. Abdominal ultrasound was performed in all pigs before sacrifice to assess the presence of the stent and exclude complications such as cholecystitis. A single dose of antibiotic was given immediately before the procedure. Sacrifice was done with Tanax 3 ml/10 kg, according to standardized protocol.

Statistical analysis

All the parameters (e.g., animal weight, temperature during facility maintenance, gallbladder dimensions) were collected in an Excel database.

Outcomes

The primary endpoint of the study was to evaluate the degree of facility of insertion and deployment of the stent. The secondary endpoints were the evaluation of the stent removability and the short-term safety of the device.

Results

The Shai™ Stent was placed in 15 pigs during standard ERCP procedure. Technical success was 100%. Group 1 consisted of nine pigs, Group 2 of 4 (Table 1), and Group 2 of 2.

The mean ERCP procedure time was 25 min (15–37 min), including the procedure for stent removal. No immediate procedure or device-related complications were observed. On abdominal ultrasound, there was no evidence of cholecystitis and in 12 out of 13 animals the

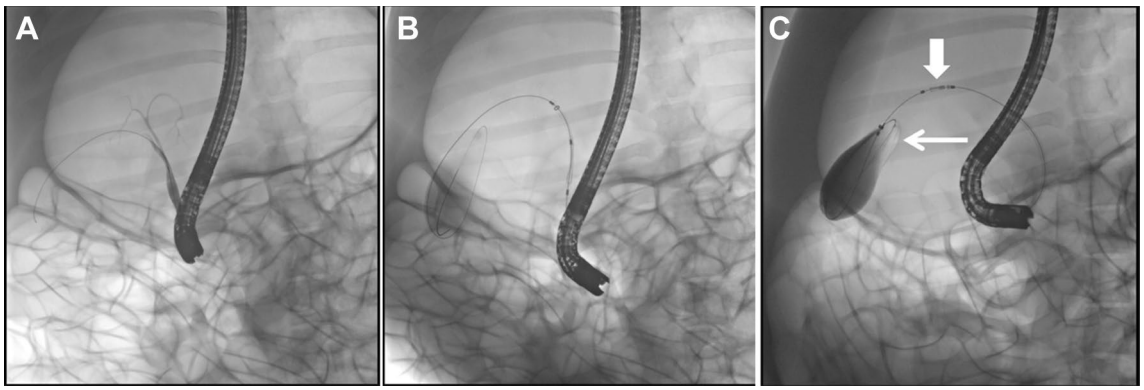

Fig. 4 **A** Gaining access into the gallbladder. **B** Inserting the Shai™ Stent into the gallbladder. **C** The Shai™ Stent in place and well expanded (thin arrow). The three hooks for stent removal (thick arrow)

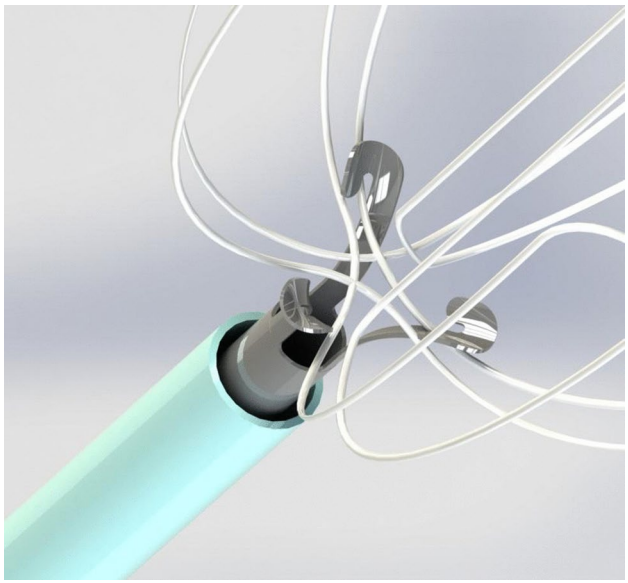

Fig. 5 Animation showing the mechanism of the Shai™ Stent removal

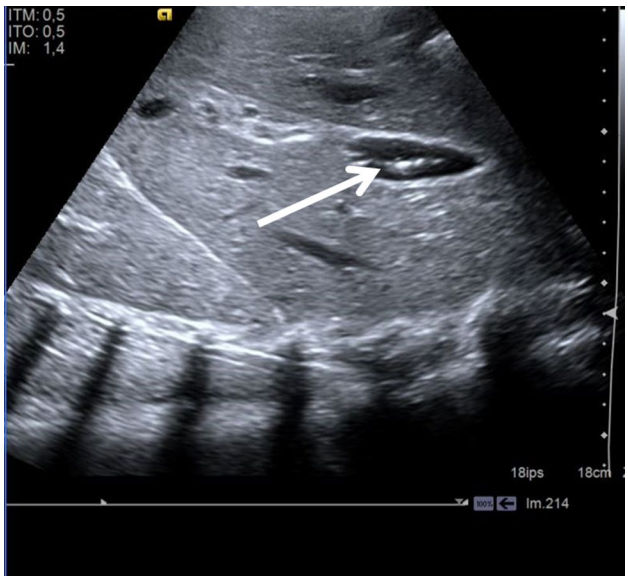

Fig. 6 Abdominal ultrasound showing the Shai™ Stent in place in the gallbladder (arrow)

stents remained in place in the gallbladder (Fig. 6) while in one pig there was complete stent migration, without any consequence.

In neither group was there any evidence of organ or mucosal damage during the procedure or at autopsy and the stent was intact and in a correct position in the gallbladder in all animals (Fig. 7), but one. Furthermore, there were no macroscopic alterations on the level of the gallbladder, the CBD, the duodenum, or other organs.

Table 1 Summary data on procedures and outcomes

Animal	Group 1						Group 2						
	1	2	3	4	5	6	7	8	9	10	11	12	13
Technical success	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Procedure duration (minutes)	20	19	35	35	25	40	37	28	17	19	15	14	16
Time to sacrifice	1 h	1 h	1 h	6 h	6 h	6 h	24 h	10 days	21 days	42 days	42 days	42 days	42 days
Complications	None	None	None	None	None	None	None	None	None	None	None	None	None
Gallbladder and bile ducts at autopsy	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Device at autopsy	In place	In place	In place	In place	In place	In place	In place	In place	In place	Migrated	In place	In place	In place

Fig. 7 The Shai™ Stent correctly in place on autopsy

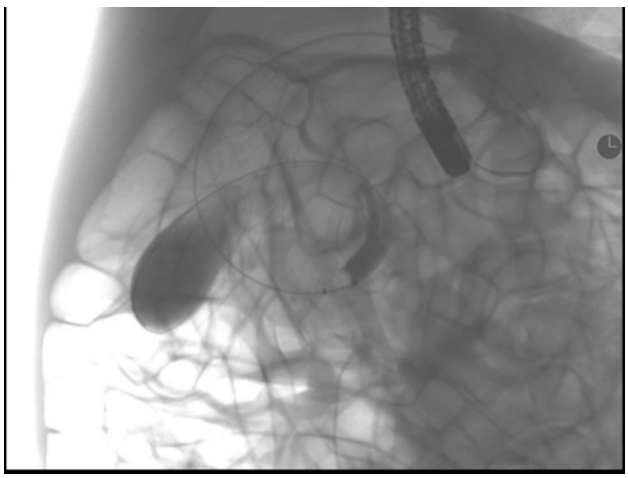

Fig. 8 The gallbladder after removal of the Shai™ Stent. The occlusive cholangiography shows no leakage of contrast

The Shai™ Stent was removed in the two animals in Group 3 immediately after placement. The removal procedure was easy to perform and was done under fluoroscopic control (Fig. 4C). In order to exclude any perforation of the cystic duct or the gallbladder an occlusive cholangiography was done after the stent removal and no contrast leakage was observed (Fig. 8). At autopsy there were no signs of tissue injuries of the cystic duct, the gallbladder, the common bile duct, or any adjacent organs.

Follow-up

Follow-up was done in animals in Group 1 and 2 (Table 1). Follow-up in Group 1 was done with nine animals up to 24 h.

Follow-up in Group 2 was done as follows: one animal for 10 days, one animal for 21 days, and 2 animals for 42 days (Table 1).

One animal in Group 2 that reached the 42-day follow-up, on autopsy had complete stent migration without macroscopic alteration of the gallbladder, the CBD, the duodenum, or other organs. Complete stent migration in this pig was confirmed on X-ray images.

Discussion

The prevalence of gallstones has increased with the advent of ultrasonographic surveys as opposed to previous studies based on clinical or necropsy evidence [12, 13].

Surgery is the treatment of choice for symptomatic gallstones and to our knowledge there are no other less invasive methods for blocking gallbladder stones from migration. Patients with high surgical risk and symptomatic gallstones are basically without recourse to surgery and in the case of cholecystitis internal (with LAMS), double-pigtail stents or external gallbladder drainage is the only solution.

The idea of the Shai™ Stent is to prevent stone migration and symptoms related to the obstruction of the gallbladder flow.

We tested the Shai™ Stent in 15 animals, with excellent technical success, proof of feasibility, removability, and a short-term safety. It is important to mention that we placed the Shai™ Stent in pigs with normal CBD and the cystic ducts and alithiasic gallbladders and even if, in some pigs the cystic duct was tortuous, cannulation of the gallbladder was easily managed with a J-shaped hydrophilic guidewire.

Obviously, the gallbladders of the pigs in this study were alithiasic, and, to our knowledge, there are no models of pigs with gallstones. Therefore, the exact ability of the Shai™ Stent to block stones migrating from the gallbladder can only be evaluated in a future clinical trial.

In this experiment, we proved that the Shai™ Stent can be easily placed in the gallbladder of a pig and removed without any immediate- or short-term complications. In one pig, there was a stent migration which nevertheless caused no adverse events.

In any future feasibility clinical trials, the best candidates for the Shai™ Stent would probably be high-risk surgery patients with multiple symptomatic gallstones and CBD stones. The most realistic scenario could be performing an ERCP with stone removal from the CBD and placement of the Shai™ Stent in the gallbladder to prevent further stone migration and to prevent future cholecystitis.

Another scenario could be to insert this stent as a bridge to cholecystectomy, and after CBD stone extraction in fragile patients who are temporarily poor candidates for surgery.

In conclusion, the Shai™ Stent seems to be a promising innovative biotechnology that could prevent gallstones from migration and impaction. Clinical trials are warranted, not only to confirm results already obtained, but to effectively evaluate the capability of the Shai™ Stent to block gallbladder stones from migration.

Compliance with ethical standards

Disclosures Mr. Shmuel Ben Muvhar is the CEO of Lithiblock. On the 8th of April Dr. Ivo Boskoski won a research Grant from Apollo endosurgery and also a consultancy agreement was signed. Prof. Guido Costamagna, Dr. Andrea Tringali, Prof. Fred M. Konikoff, and Dr. Jonathan Tsehori have no conflicts of interest or financial ties to disclose.

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