Development of a new endoscopic treatment for bile duct injury using bioabsorbable covered stents

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【Background and Aim】 In laparoscopic cholecystectomy, bile duct injury can occur and treatment can be difficult. Endoscopic repair of bile duct injury is the least invasive method, but currently, no tools or techniques have been developed to repair and regenerate the bile duct. We are developing a bioabsorbable bile duct substitute (artificial bile duct: ABD) that allows regeneration of bile duct injury without stenosis. At this conference, we would like to introduce an endoscopic treatment for bile duct injury using ABD, which is currently under investigation.

(Bile duct regeneration using ABD) In the past, we have successfully regenerated a ring-shaped bile duct with a long diameter of 3 cm using a bioabsorbable bile duct substitute (BBDS) (Am J Transplant 2005, World J Gastroenterol. 2022). Furthermore, using this ABD, we have demonstrated that it is possible to perform patch repair of bile duct damage (Surgery 2010), circular bile duct regeneration between native bile ducts (J Gastrointest Surg 2012), and bile duct regeneration at infection foci (Int Surg. 2015), and have aimed to develop a treatment method to restore the bile duct at the bile duct resection site.

(Endoscopic bile duct injury treatment using ABD) A hole of about 5 mm is made in the extrahepatic bile duct of a pig, and a bioabsorbable covered stent is inserted to endoscopically close the hole (the stent part is also made of bioabsorbable material). In early studies, this ABD was used to repair damaged bile ducts, and no stenosis was observed after treatment, showing promising results for clinical application.

(Conclusion and Discussion)
By using the ABD we are developing, it will be possible to treat bile duct damage (part of bile leakage) minimally invasively. It is expected that in the near future, endoscopic treatment using such bioabsorbable materials will provide a new minimally invasive treatment for bile duct damage.

Background and Aim

Bile duct injury often occurs during laparoscopic cholecystectomy. For such bile duct injury, endoscopic self-expandable metal stents and plastic stents are used, but these are not necessarily sufficient and reliable treatment methods. When bile duct injury occurs, the most ideal treatment is to directly repair the damaged area and prevent complications such as stenosis after repair. To achieve this treatment minimally invasively, it is necessary to repair the damaged area endoscopically and regenerate good bile duct epithelium. We have previously developed a bioabsorbable tube (artificial bile duct) that enables bile duct regeneration. In this study, we investigated the possibility of treating bile duct injury with a novel self-expandable biodegradable covered stent (SEBCS), which combines this artificial bile duct with a bioabsorbable stent.

Methods

Bioabsorbable tube

The bioabsorbable tube, which forms part of the sheet covering the SEBCS, is composed of a 50:50 copolymer of lactic acid and caprolactone, reinforced with polyglycolic acid fibers. It is designed to be fully absorbed in vivo within 6–8 weeks. In its natural state, the tube maintains its annular shape (Fig. 1a). It has a cylindrical structure with a diameter of 5 mm, length of 5 cm, and wall thickness of approximately 1 mm. With a porosity exceeding 95%, the tube is designed to facilitate cell adhesion. It is spongy and easy to handle, does not feel rigid, and quickly regains its original shape after manual compression. The braided glycolic acid fibers reinforce the structure, allowing for surgical suturing without tearing when a needle passes through. During implantation, bile permeates the polymer, turning it yellow. Notably, the tube remains impermeable to water and bile, preventing leakage.

Bioabsorbable stent

The SEBCS stent is made of a 75:25 copolymer of lactic acid and caprolactone, with a complete in vivo degradation time of approximately 20 weeks. When fully expanded, the stent measures 5 mm in diameter and 5 cm in length11(Fig. 1b).

SEBCS

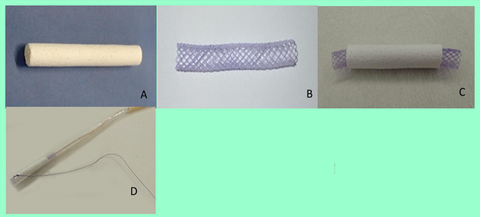
At the start of the experiment, a bioabsorbable stent was inserted into the bioabsorbable tube, forming an SEBCS (Fig. 1c).

Measurement of hepatobiliary enzymes

Blood samples were collected before stent insertion, 10 days after insertion, and 10 weeks after stent insertion for evaluation of liver function after SEBCS insertion.

Cholangiography (postoperative week 10)

Cholangiography was performed to examine bile flow in the bile ducts. A 76% urographin solution was diluted 1:1 with saline and injected into the body of the gallbladder. A C-arm (OEC One; GE Healthcare Japan) was used to position and capture the entire bile duct.

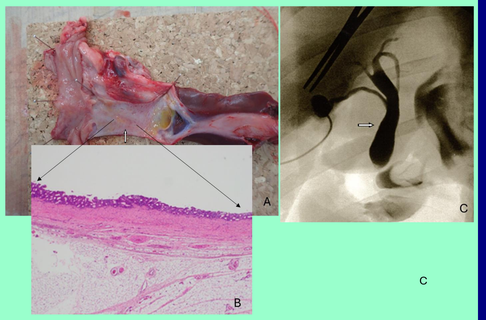


A. This bioabsorbable tube is a (50:50) copolymer of lactic acid and caprolactone reinforced with polyglycolic acid fibres, designed for in vivo absorption over 6-8 weeks. In its natural state, it retained its annular shape. B. Self-expanding bioabsorbable stent. This stent is made of a lactic acid/caprolactone (75:25) copolymer with a complete in vivo degradation rate of approximately 20 weeks. It becomes fragile in the presence of the digestive fluid. C. SEBCS. This stent was created by inserting a self-expanding bioabsorbable stent into the tube. D. SEBCS insertion introducer. A SEBCS was attached to this introducer and inserted through the papilla of Vater. The stent is secured with a thread for removal (arrow).

Animal operation

All animal experimental procedures were conducted in accordance with the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals and were approved by the Animal Experiment Committee of Saitama Medical University.
Hybrid pigs (n=5) weighing 15–25 kg were fasted for 12 hours before surgery. Anesthesia was induced with an intramuscular injection of ketamine (20 mg/kg), followed by an intravenous injection of propofol (1 mg/kg). The animals were then intubated intratracheally and mechanically ventilated. During surgery, anesthesia was maintained with a continuous infusion of propofol (4 mg/kg/h). A midline incision was made to open the abdomen. The extrahepatic bile duct within the hepatoduodenal mesentery was identified and dissected. A 5-mm diameter opening was created in the anterior wall of the extrahepatic bile duct, approximately 3 cm from the superior border of the duodenum. A 5-cm incision was then made in the anterior wall of the descending duodenum to expose the papillary region of Vater. The Vater papilla was dilated using Pean forceps, and the SEBCS was inserted into the introducer, advanced through the Vater papilla, and positioned so that the opening in the bile duct was centered within it. A balloon catheter was introduced through the Vater papilla and expanded to ensure proper adhesion of the stent to the perforated area. To maintain patency, a 6Fr plastic stent was inserted through the Vater papilla as a lost tube to bridge the opening. The proximal end of the lost tube extended into the liver-side lumen, while the distal end extended 5 cm into the duodenum. A nylon thread attached to the SEBCS (Fig. 1d) was passed through the pyloric ring, exiting via the anterior wall of the gastric body toward the abdominal wall. The duodenum and abdominal incision were then closed, with the nylon thread secured to the right side of the abdominal wound before final closure. Postoperatively, the animals were provided with a normal diet and received antibiotic therapy until postoperative day 3.

Results



Histological findings 10 weeks after SEBCS insertion: (a) Grossly, the perforated area appears slightly reddish compared to the surrounding areas and is identified in the fresh specimen. (b) Histologically, the perforated area is indistinguishable from the surrounding areas. On the bile passage side, the epithelium shows numerous peribiliary glands.
Cholangiography (10 weeks after SEBCS insertion): (c) When contrast was injected through the gallbladder, the perforated portion of the extrahepatic bile duct is not identified, and the contrast flowed smoothly into the duodenum. No intrahepatic bile duct dilation is observed.

	Postoperative day 0	Postoperative day 10	Postoperative week 10
ALT (IU/L)	23.0 (19.3–26.6)	31.4 (26.5–36.2)	22.0 (19.6–28.0)
ALP (IU/L)	179 (165–192)	253 (236–280)	208 (178–220)
T-Bil (mg/dL)	0.8 (0.7–0.8)	1.0 (0.8–1.1)	0.9 (0.7–1.0)

Blood biochemistry tests showed a slight increase in biliary enzymes 10 days after surgery, but these had returned to preoperative values by 10 weeks

Results

- In histological evaluation 10 weeks after insertion of the SEBCS, there was no distinction between the perforated area and the rest of the area, and numerous bile duct accessory glands were observed on the epithelial surface.
- Blood biochemistry tests showed a slight increase in biliary enzymes 10 days after surgery, but these had returned to preoperative values by 10 weeks.
- Cholangiocarcinoma was unclear, and flow to the duodenum was good.

Conclusion and discussion

- In order to regenerate good epithelium in the area of bile duct injury, it is essential to prevent severe crushing on the epithelial surface after stent removal in order to prevent stenosis after treatment. This SEBCS is capable of regenerating the bile duct in the area of extrahepatic bile duct defect, and may be a promising endoscopic treatment for bile duct injury.

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Disclosure
First Author: Mitsuo Miyazawa MD, PhD, FACS
There are no conflicts of interest to disclose.