

Bile Flow Phantom Model and Animal Bile Duct Dilation Model for Evaluating Biliary Plastic Stents with Advanced Hydrophilic Coating

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See editorial on page 499.

Background/Aims: The efforts to improve biliary plastic stents (PSs) for decreasing biofilm formation and overcome short patency time have been continued. The aim of this study is to evaluate the effect of advanced hydrophilic coating for patency and biodurability of PS. **Methods:** Using an *in vitro* bile flow phantom model, we compared patency between prototype PS with hydrophilic coating (PS+HC) and prototype PS without hydrophilic coating (PS-HC). We performed an analysis of the degree of luminal narrowing by microscopic examination. Using an *in vivo* swine bile duct dilation model made by endoscopic papillary closure and stent insertion, we evaluated biodurability of hydrophilic coating. **Results:** In the phantom model, PS+HC showed less biofilm formation and luminal narrowing than PS-HC at 8 weeks ($p < 0.05$). A total of 31 stents were inserted into the dilated bile duct of seven swine models, and 24 stents were successfully retrieved 8 weeks later. There was no statistical difference of stent patency between the polyethylene PS+HC and the polyurethane PS+HC. The biodurability of hydrophilic coating was sustained up to 8 weeks, when assessing the coating layer by scanning electron microscopy examination. **Conclusions:** Advanced hydrophilic coating technology may extend the patency of PS compared to uncoated PS. (**Gut Liver 2016;10:632-641**)

Key Words: Plastic stents; Biliary stents; Hydrophilic coating; Biodurability

INTRODUCTION

Plastic stents (PSs) are easy to apply and less expensive than self-expandable metal stents (SEMS) in biliary obstructive diseases, in addition to being easier to remove. Limitations, however, can include insufficient luminal diameter and short patency period. PS are prone to occlusion by biliary sludge and/or development of bacterial biofilm formation.^{1,2} According to a prospective study comparing different diameters of PS, there was no additive draining effect of PS larger than 10 F.³ Also, stent material and its shape did not add advantages in draining effect.⁴⁻⁶

Clogging of PS was mainly associated with biliary sludge and biofilm that can be synergistically affected by mixed bacterial infections and dietary fiber.⁷⁻⁹ As effort to overcome clogging of PS, innovative attempts or newly improved PS have been continued, focusing on improving biodurability (e.g., coadministration of drugs such as ursodeoxycholic acid and/or antibiotics, antibiotic-eluting stents, incorporating with hydrophilic coating technology, and adding of antireflux valve).¹⁰⁻¹⁷ However, promising outcomes have not derived until now. For instance, results between *in vitro* and *in vivo* studies were not consistent.

This study aimed to develop PS that may demonstrate longer patency and higher biodurability, by novel design with advanced hydrophilic coating technology.

MATERIALS AND METHODS

The current study is a preclinical, proof-of-concept study. This animal study was approved by the institutional animal care committee of Medi Kinetics Co., Ltd, contract research organization for preclinical test prior to the commencement of the study

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(MK-IACUC: 140103-001). Using an *in vitro* bile flow phantom model, we compared the patency between prototype PS with hydrophilic coating (PS+HC) and prototype PS without hydrophilic coating (PS-HC). Using an *in vivo* swine bile duct dilation model, we evaluated biodurability of hydrophilic coating. We compared four kinds of PS; polyethylene PS without hydrophilic coating (PE-HC), polyethylene PS with hydrophilic coating (PE+HC), polyurethane PS without hydrophilic coating (PU-HC), and polyurethane PS with hydrophilic coating (PU+HC).

1. Prototype PS with hydrophilic coating

Two types of commercially available 10-F plastic tubing (polyurethane tube of outer diameter 3.3 mm and inner diameter 2.0 mm; polyethylene tubing of outer diameter 3.3 mm and inner diameter 2.0 mm) were used as PS by cutting into 5 cm segments without any flap or side-hole. For the advanced hydrophilic coating on inside of PS, a bilaminar coating method was utilized with a base coating solution (Hydak B-23K; Biocoat Inc., Horsham, PA, USA) and a top coating solution (Hydak T-060; Biocoat Inc.). Bilaminar coating is commercially known to enhance coating durability and uniformity as compared to

single laminar coating. Compared to single coating, which has coating coherence and performance deviations because the

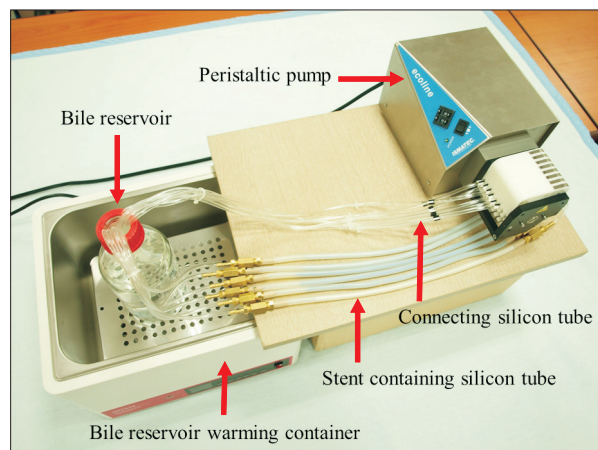


Fig. 1. An experimental perfusion system for the bile flow phantom model. This system consists of a bile reservoir, a peristaltic pump, a bile reservoir warming container, six connecting silicone tubes and six stent-containing silicone tubes. Six types of 10-F plastic tubes were inserted into the silicon tubes (36 stents in total).

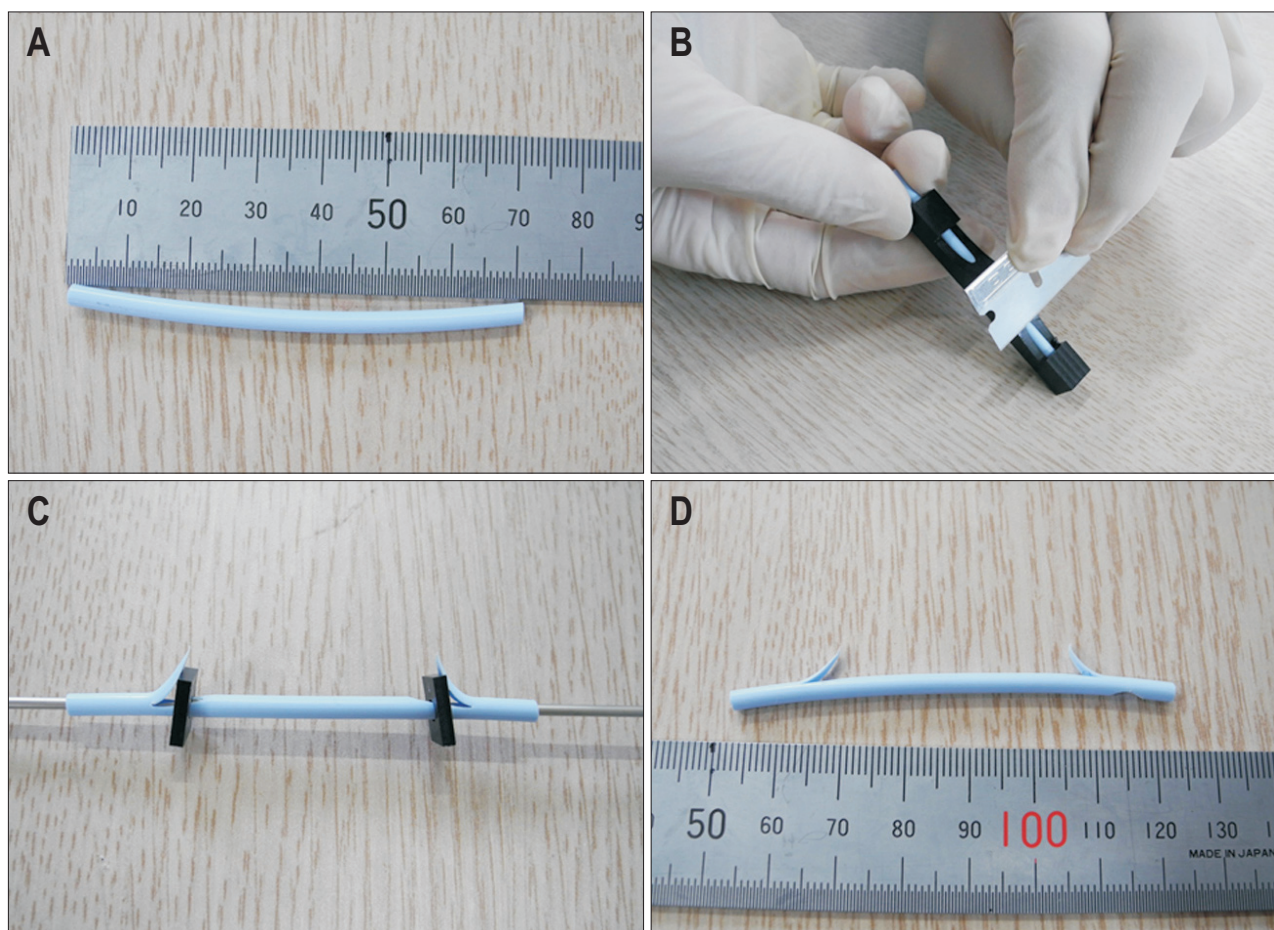


Fig. 2. The production of 10-F plastic tubes with bilateral flaps. (A) A commercially available plastic tube was cut to 7 cm (actual length of the 5 cm straight plastic stents). (B) The tube was fixed to a frame, and flaps were made on both sides using a blade. (C, D) The flaps were fixed to the frame so that they could maintain the shape, and a side hole was made at the proximal end.

coating materials have to be combined directly with the PS, the bilaminar coating uses a highly coherent coating material for the base coating and a highly lubricative coating material for the top coating to make surface uniformity, regardless of the material or surface condition of the PS. The tubes were coated with the coating materials by using syringes with repeated dry process. As for the drying condition in a drying oven (Sungchan science, Pocheon, Korea), the optimal parameters (1 L/min for 20 minutes at 60°C) were determined by attempting different dry temperatures and dry flow parameters.

2. *In vitro* phantom model

Using an *in vitro* bile flow phantom model, we compared patency between PS+HC and PS-HC. An experimental perfusion system for the bile flow phantom model was constructed following the previously reported method (Fig. 1).^{13,18} This system consists of a bile reservoir, a peristaltic pump, a bile reservoir warming container, six connecting silicone tubes, and six stent-containing silicone tubes (six different types of stents were inserted serially into each silicone tube). Four PS groups were prepared; PE-HC, PE+HC, PU-HC, and PU+HC. Two types of commercially available 10-F PS from two different companies (A stent: Cotton-Leung® biliary stent, Cook Medical, Winston-

Salem, NC, USA; B stent: Percuflex™ biliary stent, Boston Scientific Corp., Natick, MA, USA) were used as control PS. These controls were made into the same shape as the test PS by cutting out both flanged-areas and leaving the 5-cm center area. The outer and inner diameters of control PS A were 3.3 mm and 2.0 mm, respectively. The outer and inner diameters of control PS B were 3.4 mm and 2.5 mm, respectively. A total of 600 mL of human bile obtained by drainage catheter in patients with cholangitis was replaced every 2 days in the bile flow phantom. The peristaltic pump was set so that the bile could recirculate at 1 mL/min. At 4 weeks and 8 weeks after bile exposure, the stent-containing silicone tubes were removed to examine the stents.

3. *In vivo* animal model

For the *in vivo* studies, the PS were cut into 7 cm (actual length of the 5 cm straight PSs) and flaps were made to prevent migration at both ends. A side hole was made at the proximal portion of the stents, making the stents look almost similar to a 5-cm, 10-F conventional stents (Fig. 2).

1) Animals

Seven mini-pigs (*Sus scrofa*, mean age 14 months, mean body weight 29.9 kg) were used for current study. The pigs were

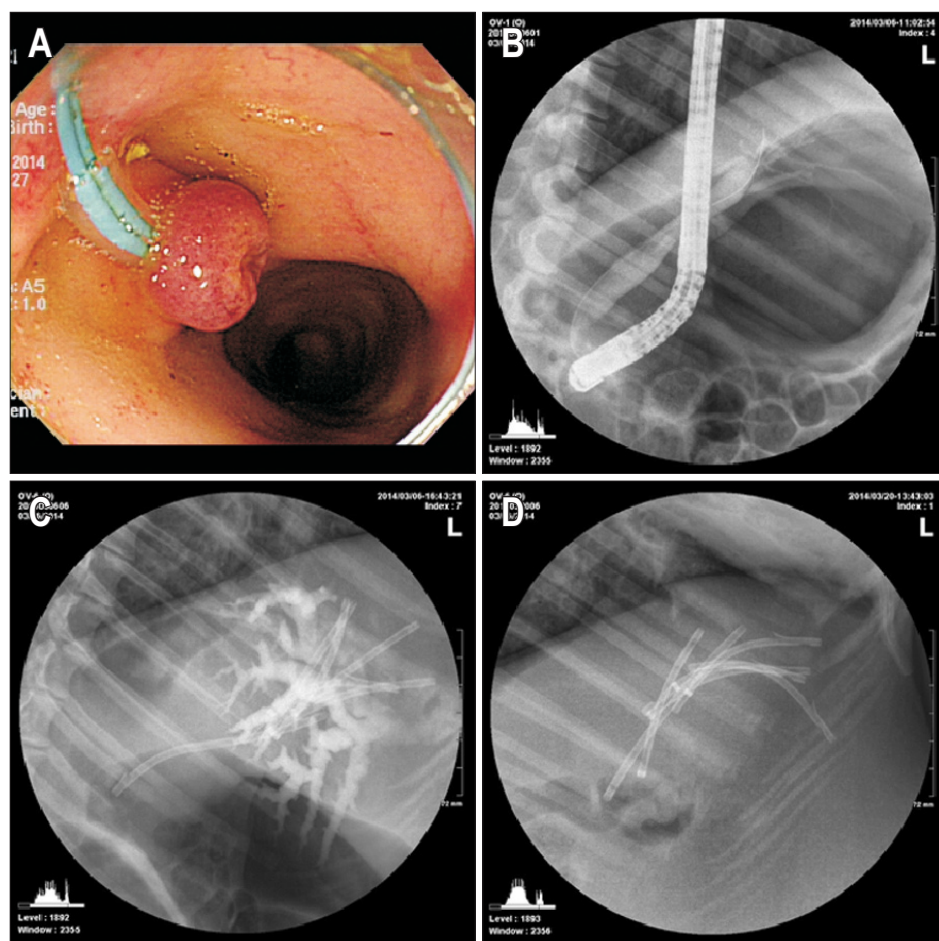


Fig. 3. Endoscopic procedures in the animal bile duct dilation model. (A) A detachable snare obstructed the major duodenal papilla. (B) Representative cholangiography showing marked biliary dilation 2 weeks after endoscopic papillary closure. (C) Six plastic stents were successfully inserted into the dilated biliary duct on a representative specimen. (D) Follow-up fluoroscopic examination of the same specimen reveals plastic stents that remain in the biliary tract.

fasted overnight, except for water that was given *ad libitum*, before the endoscopic procedure. Preanesthesia sedation consisted of an intramuscular injection of atropine sulfate (0.04 mg/kg), xylazine (2 mg/kg), and tiletamine-zolazepam (5 mg/kg). Animals were intubated and general anesthesia was achieved using 0.5% to 2% isoflurane through an endotracheal tube with 70% nitrous oxide and 30% oxygen provided by a ventilator, and then placed on their sides on a fluoroscopy table.

2) Endoscopic procedures

Endoscopic papillary closure was performed with a transparent cap-fitted conventional endoscope (GIF-Q260J; Olympus Co., Tokyo, Japan) using a detachable snare (MAJ-340; Olympus Co.), according to previously reported our method (Fig. 3A).¹⁹ After positioning the endoscope close to the major papilla, a detachable snare was positioned around the base of the papilla and tightened, and then the stopper was detached from the device.

3) Endoscopic retrograde cholangiography and biliary stents insertion

Two weeks after the endoscopic papillary closure, endoscopic retrograde cholangiography (ERC) using a side-viewing duodenoscope (TJF-240; Olympus Co.) was implemented to confirm biliary tree dilation and to insert the PS (Fig. 3B-D). After duodenal intubation of the scope, biliary cannulation (ERCP catheter, bottle-shaped metal tip; MTW Endoskopie, Wesel, Germany) was performed using the wire-guided cannulation method with a 0.035-inch hydrophilic tipped guidewire (Boston Scientific Corp.). After obtaining cholangiogram, two types of PS+HC and two types of conventional PS were inserted serially into each bile duct of seven swine bile duct dilation models. According to the degree of bile duct dilation, maximum number of PS insertion was determined in each swine as many as possible. Fluoroscopic images were repeated every 2 weeks after the procedures for the identification of remaining PS in the biliary tract. After fluorography at 8 weeks, all live swine were euthanized and all

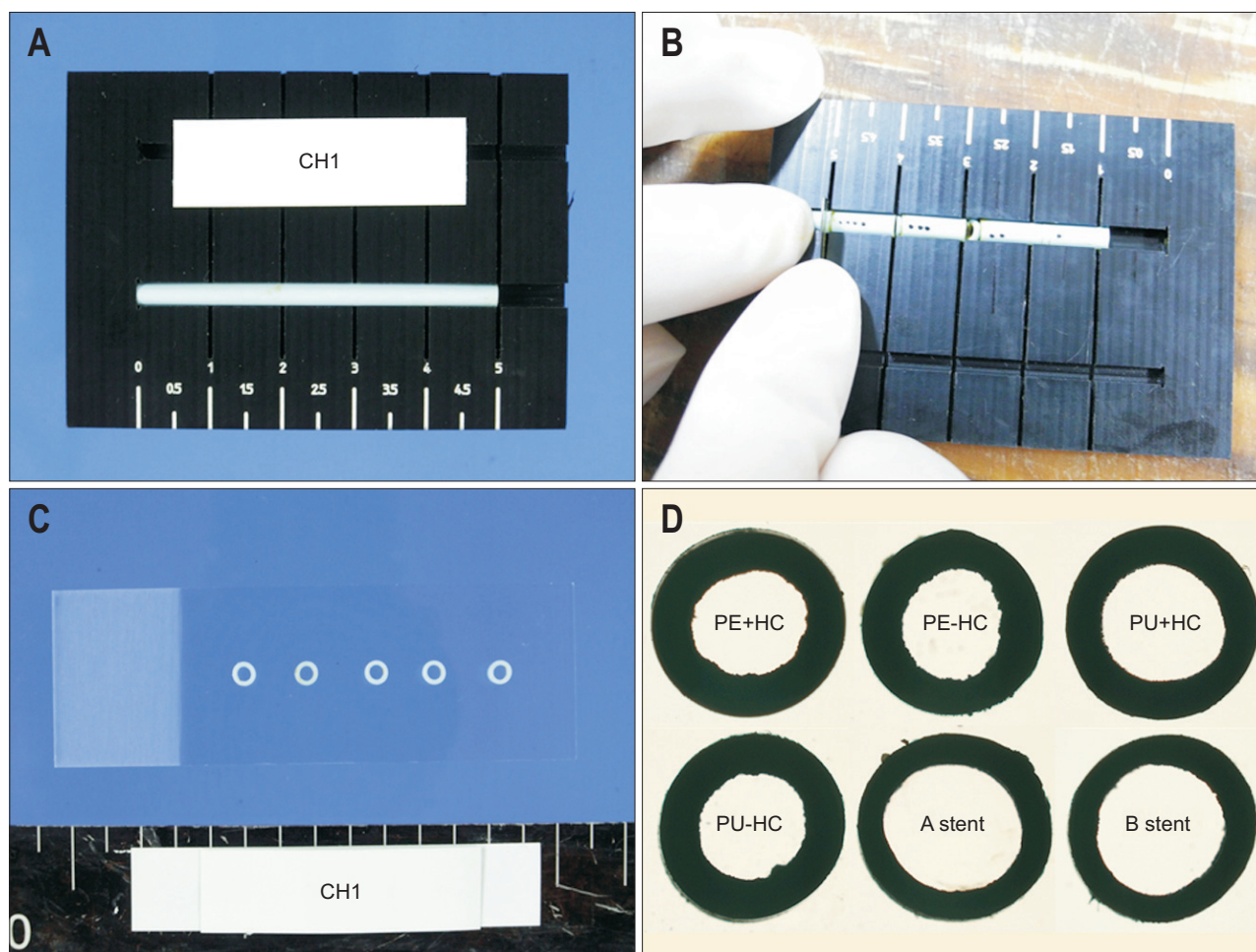


Fig. 4. Light microscopic patency evaluation for the retrieved stents. (A) The retrieved 5-cm plastic stents were fixed to a self-produced frame. (B) The stents were cut into sections at 10-mm intervals using a blade, and then, a 1-mm small section was made again at one end of the 10-mm sections. (C) Five small sections made from one stent were placed on a slide, and their luminal patency was observed microscopically. (D) Representative samples of the lumens were observed at 8 weeks with a microscope ($\times 12$). PE, polyethylene; PU, polyurethane; HC, hydrophilic coating.

remaining PS in the bile ducts were removed.

4. Light microscopic evaluation

Gross inspection and light microscopic (LM) examination were performed by a pathologist (G.K.) who was blinded to the types of PS. The retrieved 5-cm PSs were fixed to a custom-made frame and cut each section into 10-mm tubes using R35 Feather disposable microtome blades (Feather Safety Razor Co., Osaka, Japan). A small section of 1-mm length was made again at one end of each of these 10-mm sections. LM examination was performed to observe luminal patency of these small sections (Fig. 4). The exact quantitative measurements of the patency of retrieved stents were performed using ImageJ 1.47v (National Institute of Health, Bethesda, MD, USA). The percent of remaining cross-section area of the inner lumen was calculated by dividing the area of inner patent lumen at 4 weeks and 8 weeks by the area of original inner lumen of each stent.

5. Scanning electron microscopy examination

Apart from the above mentioned 1-mm section for LM examination, the remaining 4-mm sections were cut vertically to perform scanning electron microscopy (SEM) (S-4800; Hitachi, Tokyo, Japan) on the inner surface. After coating the surface with 200 nm of platinum, constant magnification was performed to evaluate hydrophilic coating durability and biodurability.

6. Statistical analysis

One-way ANOVA test and the Student t-test were used to analyze the difference of % stent patency area. A p-value <0.05 was considered significant. Statistical analysis was performed with IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. *In vitro* assessment of stent patency area in six types of PS

Four weeks after the stent insertion, three silicon tubes harboring PS were removed from the *in vitro* bile flow phantom and the 18 PS were retrieved. Biofilm was not visibly formed via LM examination in any of the 18 stents regardless of their

Table 1. Detailed Statistical Analysis of Stent Patency at 8 Weeks after Stent Insertion in the Bile Phantom Model

Group	p-value				
	PE+HC	PE-HC	PU+HC	PU-HC	A stent
PE-HC	0.131	-	-	-	-
PU+HC	0.322	0.017	-	-	-
PU-HC	0.004	0.048	<0.001	-	-
A stent	0.42	0.065	0.794	0.002	-
B stent	0.063	0.006	0.158	<0.001	0.419

Student t-test.

PE, polyethylene; PU, polyurethane; HC, hydrophilic coating.

types at 4 weeks (data not shown). The remaining three silicon tubes were removed after 8 weeks and when these stents were examined under LM (Fig. 4D), PS without hydrophilic coating (PS-HC) showed significantly decreased stent patency compared to PS+HC and conventional stents ($p < 0.05$) (Table 1, Fig. 5). The percent patency areas according to stent types are as follows: PE-HC, 92.9 ± 2.7 ; PE+HC, 94.3 ± 2.0 ; PU-HC, 90.2 ± 6.4 ; PU+HC, 94.9 ± 1.2 ; A stent, 95.1 ± 3.7 ; B stent, 96.1 ± 3.5 . However, there was no significant difference between hydrophilic coating groups and conventional stent groups.

2. *In vivo* assessment of stent patency area according to four types of PS

Two weeks after papillary obstruction, the porcine bile duct diameter was dilated to a mean of 16.4 ± 3.2 mm. A total of 31 stents (8 PE+HC, 8 PU+HC, 7 A stents, and 8 B stents) were inserted into the bile ducts of the seven swine models, ranging from minimum 3 to maximum 6 stents in each swine bile duct. Although most stents were inserted with the above the papilla method for preventing stent migrations, some final stents were necessarily inserted with the across the papilla method. The swine fared well without any remarkable event throughout 8 weeks. The number of inserted stents was followed by fluoroscopic images every 2 weeks. Seven out of the 31 inserted stents were lost during the observation period (stents loss rate, 22.6%), and 24 stents (6 PE+HC, 7 PU+HC, 5 A stents, and 6 B stents) were retrieved from the dilated bile ducts at 8 weeks after the insertion.

On the LM examination of the retrieved stents, biofilms were definitely formed and the decrease in patency was much more prominent compared to the *in vitro* phantom (Fig. 6). The difference among the groups was not statistically significant ($p = 0.407$). Also, there was no statistical difference of stent patency between the PE+HC and the PU+HC ($p = 0.062$) (Fig. 7). The percent

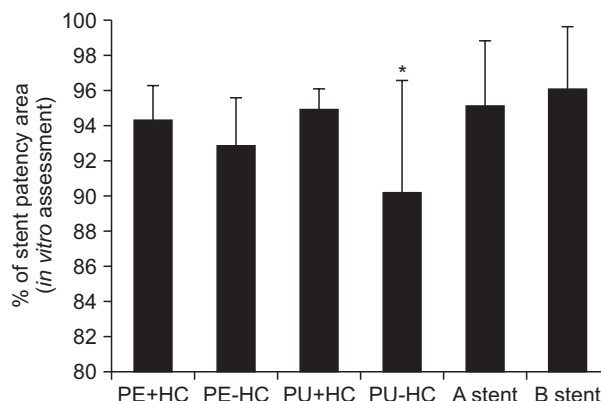


Fig. 5. Result of stent patency at 8 weeks after stent insertion in the bile phantom model. The % of stent patency area was measured low in the stent groups without hydrophilic coating (one-way analysis of variance, * $p < 0.001$).

PE, polyethylene; PU, polyurethane; HC, hydrophilic coating.

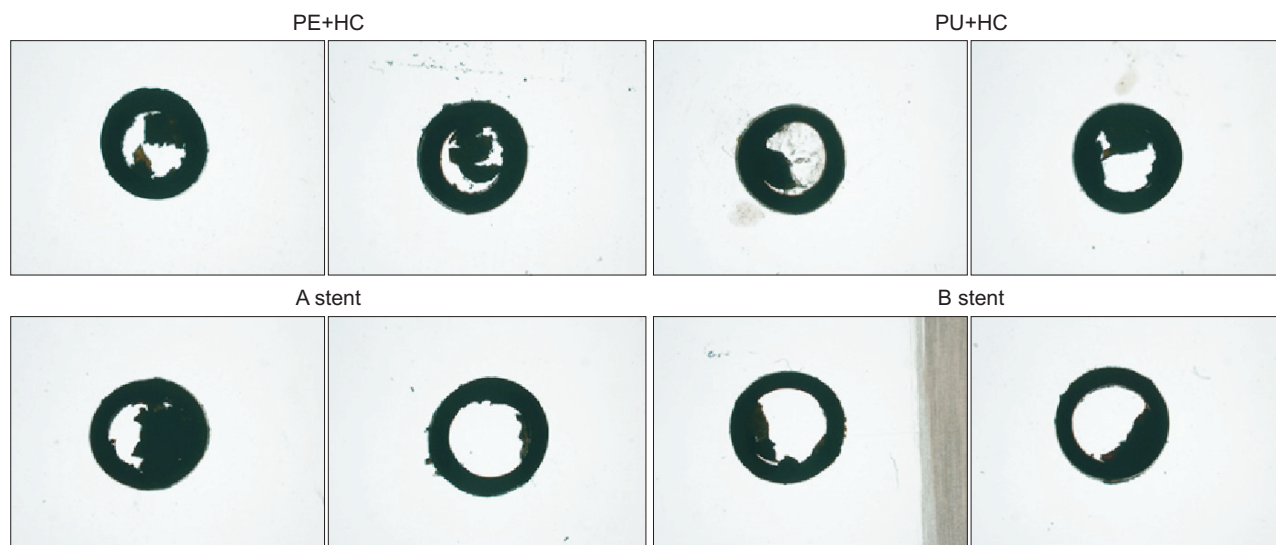


Fig. 6. Examples of light microscopic examination for retrieved stents in the animal bile duct dilation model. Biofilm formation was observed and the patency area was reduced in the sections ($\times 12$). PE, polyethylene; PU, polyurethane; HC, hydrophilic coating.

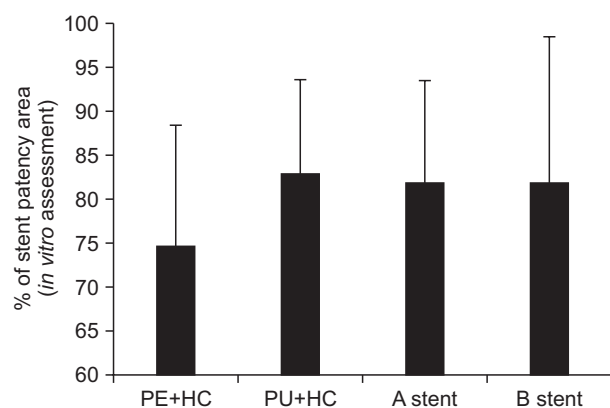


Fig. 7. Result of stent patency at 8 weeks after stent insertion in the animal bile duct dilation model. The PE+HC had a tendency to form more biofilm and constrict the lumen than the other types of stents (one way analysis of variance, $p=0.407$). PE, polyethylene; PU, polyurethane; HC, hydrophilic coating.

patency areas were as follows: PE+HC, 74.6 ± 11.4 ; PU+HC, 82.8 ± 10.7 ; A stent, 81.9 ± 11.6 ; B stent, 81.8 ± 16.7 .

3. SEM examination

SEM examination was performed to observe the hydrophilic coating layer in all sections of the stents retrieved from the two models. On the SEM analysis of the stents at 4 weeks of *in vitro* bile exposure, biofilm formation was almost nonexistent and the top coating layer was virtually invisible, but most of the base coating layer was still in place (Fig. 8). On the analysis of the stents at 8 weeks of *in vitro* bile exposure, biofilm formation was almost formed in all types of stents and most of the base coating layer still existed (Fig. 9A and B). In the swine model, the biofilm layer was generally thicker and the base coating

layer was relatively thinner (Fig. 9C and D).

DISCUSSION

To overcome stent occlusion in biliary PS, SEMS with a larger diameter or new SEMS with additional function have been or are currently being developed. However, as SEMS is hard to insert and remove, and more of a burden in price, many researches on PS are also continuously ongoing these days. For instance, to improve the function and patency of PS, inserting multiple PS, and changing the internal diameter or shape of PS have been tried.^{17,20-23} In spite of these efforts, these attempts are not supported by additional clinical researches or follow-up studies confirming the effectiveness.

Based on the fact that bacterial adhesion to the plastic surface is closely related to the surface hydrophobicity,^{14,24} multiple studies regarding hydrophilic coating onto PS have been started.^{15,25} However, further advancements are still prerequisite because they just covered short-term changes and they could not quantify total amount of biofilm formation itself. Two prospective randomized controlled studies were performed based on the results of *in vitro* studies that hydrophilic coating had positive effects on stent patency. A randomized controlled trial by Costamagna *et al.*¹⁶ showed a tendency toward longer patency in PU+HC group, but the difference was not statistically significant. The other clinical study is a prospective randomized trial by van Berkel *et al.*¹² showed contradictory result that PE stent yielded higher stent patency than PU+HC stent.

There are two possible explanations for the conflicting results. The first one is the same as the speculation in the previous study; manipulation at the time of stent placement and coating surface damage from duodenal reflux, although the SEM

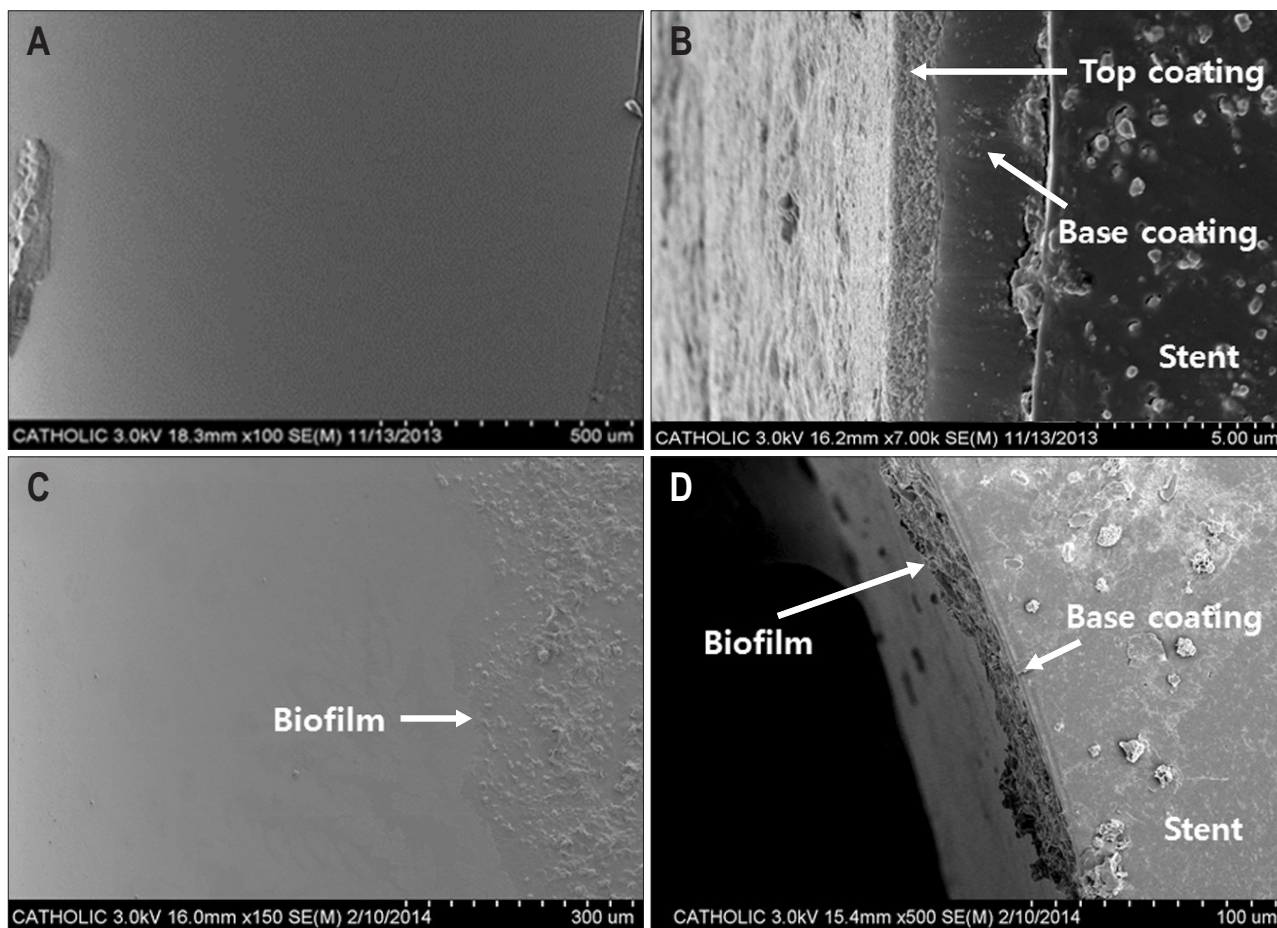


Fig. 8. Scanning electron microscopy images of the polyethylene plastic stents with a hydrophilic coating. After bilaminar hydrophilic coating and drying processes, the bilaminar coating was performed relatively well (A, $\times 100$; B, $\times 7,000$). At 4 weeks of *in vitro* bile exposure, biofilm formation was almost nonexistent and the top coating layer was virtually invisible, but most of the base coating layer was still in place (C, $\times 150$; D, $\times 500$).

examination after manipulation did not support this idea. The second one is that the coating layer would have been degraded with time, which was a mere speculation.

Stimulated with these contradictory results, we conducted this study. According to our results of the *in vitro* phantom model, biofilm formation by human bile was almost nonexistent in the stents retrieved at 4 weeks, which was why it was impossible to measure inner diameter change. It has been known that a stent design without side holes reduces micro-turbulence of bile flow, producing less biofilm formation in theory, although the theory has not been supported by clinical evidences.^{5,26-28} Lowered formation of biofilm at 4 weeks might be possibly explained by the removal of both flanges areas before inserting the stents. In the stents retrieved at 8 weeks, the PS+HC showed less biofilm formation and less luminal narrowing than PS-HC ($p < 0.05$). Given that biofilm in the phantom model at 8 weeks was not as apparent as *in vivo* model, it would have been useful to extend the trial beyond 8 weeks. But this period was selected because it is generally deemed safe for PSs before total obstruction. If a total occlusion occurs in one stent, serial occlusions can quickly

occur in other stents in a same harboring silicon tube. At any rate, measurements at 4 and 8 weeks seem to have yielded interesting results for the purpose of evaluating the biodegradability of the hydrophilic coating, which will be described again in the SEM analysis.

The biggest concern in the *in vivo* animal model was that we could not be sure of the maximum number of PSs that can be inserted after biliary dilation and whether the stents could be maintained for 8 weeks, unlike the expectation that biliary duct dilation model would be made easily following the method we have previously reported.¹⁹ In the current study, three to six PSs were inserted in each swine bile duct and a total of 31 stents were inserted with both flanges intact unlike the *in vitro* phantom model. Seven out of the 31 inserted stents were lost, with a relatively good stent loss rate (22.6%). Under more severe conditions, considering the possibility of additional effects, such as duodenal reflux, unlike the *in vitro* phantom model, mean stent patency area was decreased in every type of stent. When SEM analysis was used to determine whether the severe conditions also affected the hydrophilic coating, the biofilm layer was

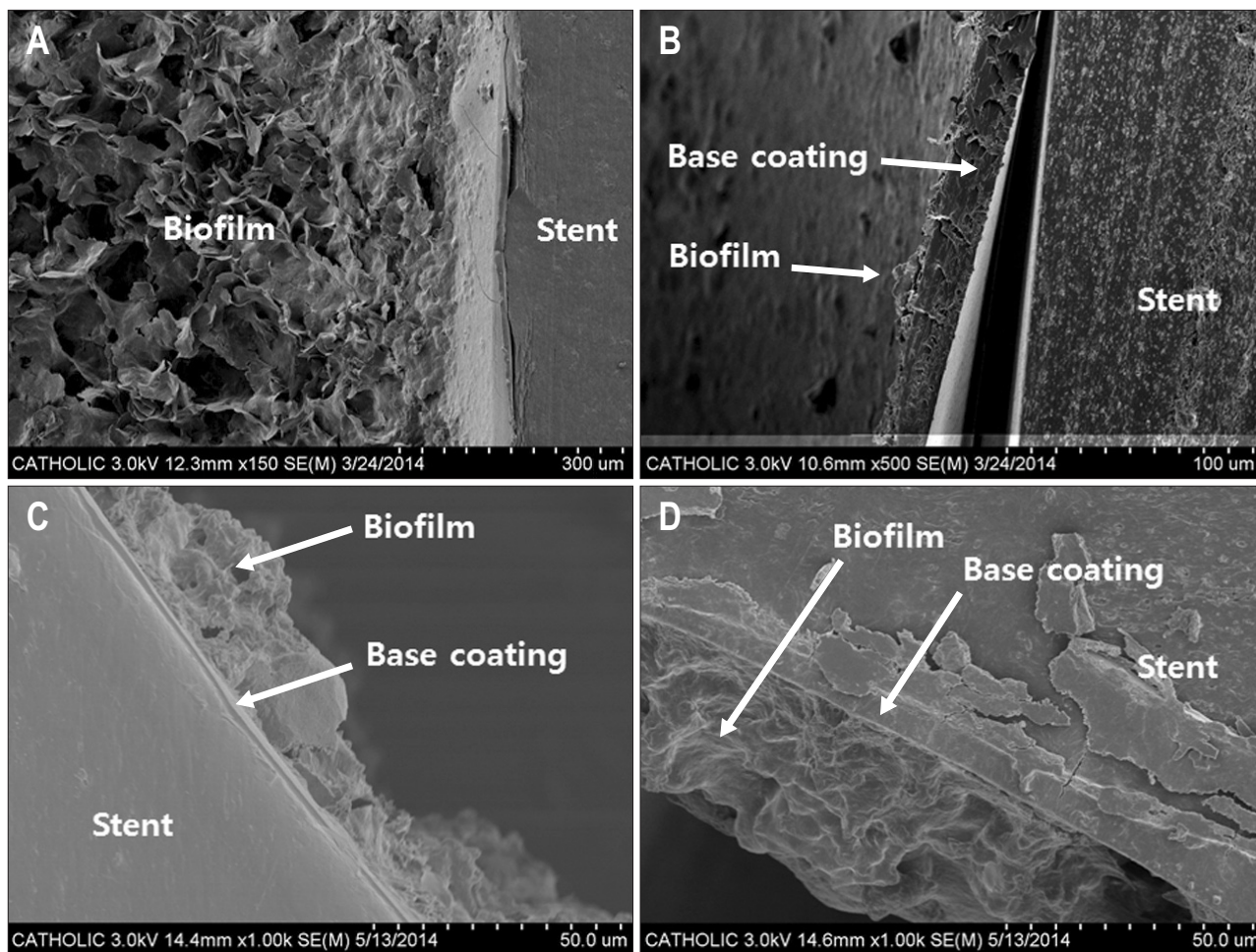


Fig. 9. Scanning electron microscopy images representing each stent type retrieved at 8 weeks. By 8 weeks, the top coating layer was invisible with biofilm formation, but the base coating layer was still present. (A) PE+HC in the *in vitro* phantom model ($\times 150$), (B) PU+HC in the *in vitro* phantom model ($\times 500$), (C) PE+HC in the *in vivo* animal model ($\times 1,000$), (D) PU+HC in the *in vivo* animal model ($\times 1,000$). PE, polyethylene; PU, polyurethane; HC, hydrophilic coating.

generally thicker and the base coating layer was thinner in the *in vivo* model, as can be seen in Fig. 9, although statistical difference was not obtained. SEM images in the *in vitro* model at 4 weeks showed the stents began losing the top coating layer, suggesting that biofilm formation might have started afterward, only inhibited by the remaining base coating layer. We could infer a correlation of biofilm formation is negatively associated with the hydrophilic coating presence and the base coating presence.

This report is likely the first proof-of-concept study using an endoscopic biliary dilation porcine model with realistic ERC stent insertion. The fact that the durability of stents could be prolonged to 8 weeks by using our model, not a surgical model, is academically of great significance. This mode of investigation into experimental biliary devices may hold great promise for future studies. Another significance of the current study is that we demonstrated with the bilaminar coating enhanced the biodurability of the stents, inhibiting biofilm formation and thus improving stent patency, unlike previous reports which suggest-

ed that hydrophilic coating layer lasts only for a short period of time and may not provide a long-term inhibition of biofilm formation. Although our study could not observe the superiority of the hydrophilic coating stent than other conventional stents, this study looked into the technical features of the hydrophilic coating stent with bilaminar coating method, and is deemed meaningful as a noninferiority test.

Our study has the following limitations; being an *in vitro* and *in vivo* animal model, not an *in vivo* human study, the difference of bile acid composition and hydrophilicity (hydrophobic-hydrophilic balance) between human and swine, and the inner diameter of the prototype stents may not be identical to the inner diameter of commercially available stents. Nevertheless, we could conclude that advanced hydrophilic coating technology led to less forming of biofilm in PS than uncoated PS. Further studies are needed to demonstrate the beneficial effect of hydrophilic coating on biofilm formation more accurately and in a more quantitative way. Thereafter, human studies would be essential to support superior effects of advanced hydrophilic coat-

ing technology prior to general acceptance. Also, in addition to bile flow phantom model, swine bile duct dilation model made by endoscopic procedure can be useful for PS evaluation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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