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SURGICAL TECHNIQUES

Morphological Changes during Creation of a Neo-Bile Duct Using a Vein and a Biodegradable Endoluminal Stent

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ABSTRACT

Major bile duct lesions are usually treated by a hepaticojejunostomy which is often complicated by cholangitis and liver fibrosis. The aim of this study was to investigate the morphologic features of a neo-bile duct created from a vein and a biodegradable endoluminal stent. The neo-bile duct was created using a segment of the external jugular vein which was endoluminally stented by a biodegradable poly-lactate-acid stent. In 18 pigs, the common bile duct was resected and replaced by the vein with ($n = 12$) or without endoluminal stent ($n = 6$). Six animals served as controls. Survival, liver function and morphological changes of the neo-bile duct and the liver were observed for six months. After six months, the neo-bile duct morphologically resembled the native bile duct showing Ck7-positive columnar epithelium and newly formed capillaries in the bile duct wall. The biodegradable stent disappeared after four months. All animals survived and showed normal liver function and no cholestasis. In contrast, after sole vein reconstruction of the bile duct, four animals died due to biliary peritonitis and cholangitis. Creation of a neo-bile duct which morphologically resembles the native bile duct is feasible by using a body's own vein and a biodegradable endoluminal stent.

Keywords: neo-bile duct, vein, biodegradable stent, pig

INTRODUCTION

Major bile duct defects, e.g., in case of treatment of bile duct stenosis, bile duct cancer, or even complications after cholecystectomy, usually require reconstruction by a hepaticojejunostomy [1–4]. In many cases, however, a biliodigestive anastomosis is complicated by retrograde infections via the intestine or stenosis and a secondary biliary cirrhosis will develop when no re-anastomosis will be performed.

In face of this unsatisfying long-term outcome after hepaticojejunostomy, alternative methods for reconstruction of major bile duct injuries are desirable.

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Replacement by a small bowel segment is feasible but represents a complex procedure which has not become favored over the biliodigestive method [5, 6]. Reconstruction using autologous vein or rectus sheath grafts has led to a collapse and biliary tract obstruction when no endoluminal stent was applied [7–10]. In this context, biodegradable biliary stents, e.g., bioabsorbable polymers or small intestine submucosa, have been implemented representing a temporary scaffold [8, 11–13].

In a recent study, we developed a neo-bile duct in pigs using an autologous venous interponate which is easily available and applicable, e.g., in contrast to autologous bone marrow cells which have also been successfully used [12, 14]. By endoluminally supporting this vein graft using a biodegradable poly-lactate-acid-(PLA) stent, we showed that this artificial bile duct functions indentically to the natural organ [8]. In the present study we investigated morphologic changes by correlating the artificial and native bile duct.

MATERIALS AND METHODS

Animals and Study Design

All operations and handling procedures were performed after approval by the veterinary district administration of Muenster and were in accordance with the Animal Protection Law of Germany.

Twenty-four female pigs (German Landrace, 20–25 kg) were randomized and divided into four experimental groups. First, in all animals, a segment of the external jugular vein was resected and harvested in heparinized isotonic saline solution at room temperature for replacing a part of the common bile duct. In group I (sham operation, $n = 6$), a median laparotomy was performed and the common bile duct was mobilized. In group II ($n = 6$), a 2-cm long segment of the common bile duct was resected and replaced by the venous interponate which has been sutured continuously end-to-end with 6-0 PDS (Ethicon, Norderstedt, Germany). In group III ($n = 6$), the same procedure has been carried out and additionally the venous interponate was endoluminally stented by a biodegradable PLA stent (Institute of Textile Technology and Process Engineering, Denkendorf, Germany). In group IV ($n = 6$), the same surgical procedure than in group III has been carried out but the animals were earlier sacrificed for investigation of the degradation of the stent.

All procedures were carried out under intubation anaesthesia (nitrous oxide/oxygen = 2:1) and continuous intravenous application of ketanest and etomidate. Preoperatively, the pigs were fasted for 24 hr but had free access to water. Postoperatively, animals received water and feed ad libitum. Survival, general condition, and weight have been observed up to six months. In group IV (degradation group), animals were sacrificed at earlier time points with two animals each after three, four, and five months. Blood samples have been drawn preoperatively, immediately, and seven days after surgery as well as during sacrifice of the animals. After sacrifice of the animals, the diameter of the bile duct was measured and tissue samples of the venous interponate respectively the bile duct and liver were dissected and histologically evaluated.

Surgical Technique

All surgery has been carried out under sterile conditions and in supine position of the animals. Thirty minutes prior surgery, 1.5 g cefuroxime were intravenously applied.

After a lateral neck incision, the external jugular vein was mobilized and a 2-cm long segment resected and harvested in heparinized saline solution until its interposition between the common bile duct. Successively, a median laparotomy was performed. The serosa of the hepatoduodenal ligament was cut and the common bile duct between the insertion of the cystic duct and the superior margin of the pancreas was dissected.

In the sham operation group (group I), surgery was finished at this point after closing the serosa of the hepatoduodenal ligament and the abdominal wall in two layers.

In groups II—IV, bile duct replacement by a vein graft was carried out as previously described (13). A 2-cm long segment of the common bile duct was resected and replaced by the venous interponat which was sutured end-to-end using 6-0 PDS (Ethicon, Germany) between the bile duct stumps (Figure 1). A leak-proofed sealing was reached by the continuous suture of the venous interponate to the bile duct stumps. In group III and IV, the venous interponate has been stented by the biodegradable stent before suturing the venous interponate between the stumps of the bile duct (Figure 2). The stent diameter was chosen according to the previously measured intraluminal diameter of the bile duct (7.0 ± 1.1 mm). For endoluminal stenting of the venous interponate, a split cannula has been used with the biodegradable stent inside and the venous interponate outside. First, the split cannula was inserted into the proximal bile duct stump and pulled back in a way that the biodegradable stent was inserted and spread out at a length of 1 cm into the proximal bile duct stump (Figures 2c–e). The proximal anastomosis between venous interponate and proximal bile

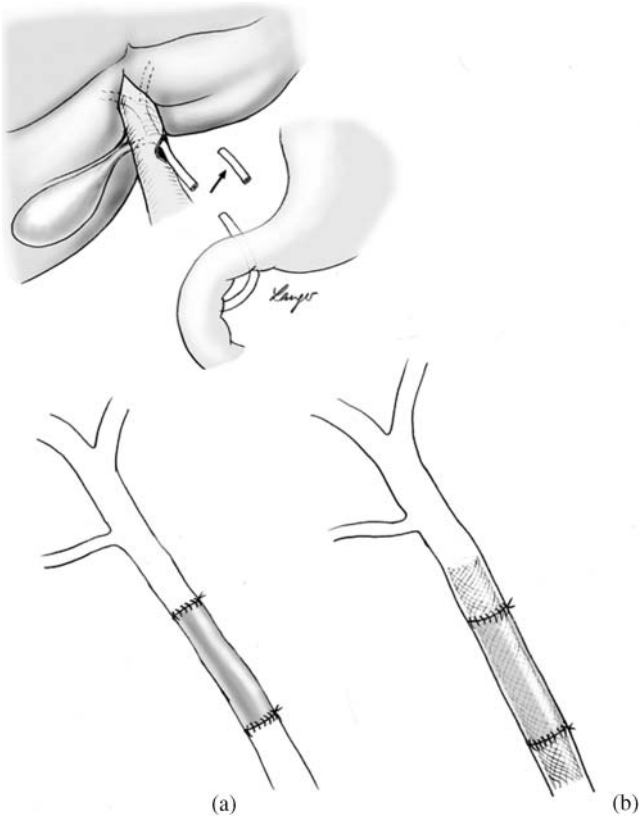

Figure 1. Surgical technique. A 2-cm long segment of the bile duct was resected and replaced either by a venous interponate (a) or by a venous interponate which has been endoluminally stented by a biodegradable PLLA-stent (b)

duct stump was carried out with additional transmural stitches for fixing the position of the stent. After that, the split cannula was inserted in the distal bile duct stump and removed in a way that the biodegradable stent was spread out at a length of 1 cm into the distal bile duct stump. The distal anastomosis was carried out in the same fashion as the proximal anastomosis (Figure 2f). Surgery was finished after reconstruction of the serosa of the hepatoduodenal ligament, abdominal lavage, and closure in two layers.

Postoperatively, no abdominal drain was kept and no postoperative antibiotics were given.

Biochemistry

Preoperatively, and again at the end of surgery and seven days and six months after operation, blood samples (500 μl, micromethod, Ektachem-Kodak) were drawn via an ear vein for determination of AST, bilirubin, alkaline phosphatase, and γ-GT at 37°C by standard enzymatic techniques

Table 1. Semiquantitative bile duct score

Criteria	Points	Morphologic findings
Inflammation	0	Single inflammatory cells
	1	Sparse infiltration of inflammatory cells
	2	Alternating close infiltration of inflammatory cells
	3	Close infiltration of inflammatory cells
Fibrosis	0	No fibrosis
	1	Minimal fibrosis
	2	Moderate fibrosis
	3	Strong fibrosis
Foreign body	0	No foreign body
	1	Sparse areas of foreign bodies
	2	Distinct areas of foreign bodies
	3	Coherent areas of foreign bodies

Morphologic Investigations

For light microscopy evalutation, specimens of the bile duct and of the liver were fixed for 2 days in 4% formaldehyde solution and were subsequently dehydrated and embedded in paraffin wax by routine procedures to be sectioned at a thickness of 5 μm. Sections were stained with *Ehrlich's* haematoxylin/eosin and semiquantitatively scored (0–3 points) for the degree of inflammation and fibrosis as well as the presence of foreign body material in the bile duct (Table 1), and for the presence of cholangitis, fibrosis, and periportal inflammation in the liver (Table 2).

Immunohistochemistry for labeling bile duct epithelium and vessel endothelium was performed on cryostat sections using the LSAB/HRP-method with DAB as chromogen. A monoclonal antibody specific for Cytokeratin-7 (Ck7, diluted 1:800), and Factor VIII (FVIII)-related protein (diluted 1:1000) were purchased from Dako Cytomation, Hamburg Germany. The slides were semiquantitatively evaluated for the presence of specifically labelled cells by scanning approximately 50 square high power fields using an eyepiece integration grid.

Statistics

All data are presented as means ± SD. Statistical analysis was performed by the Kruskal-Wallis test

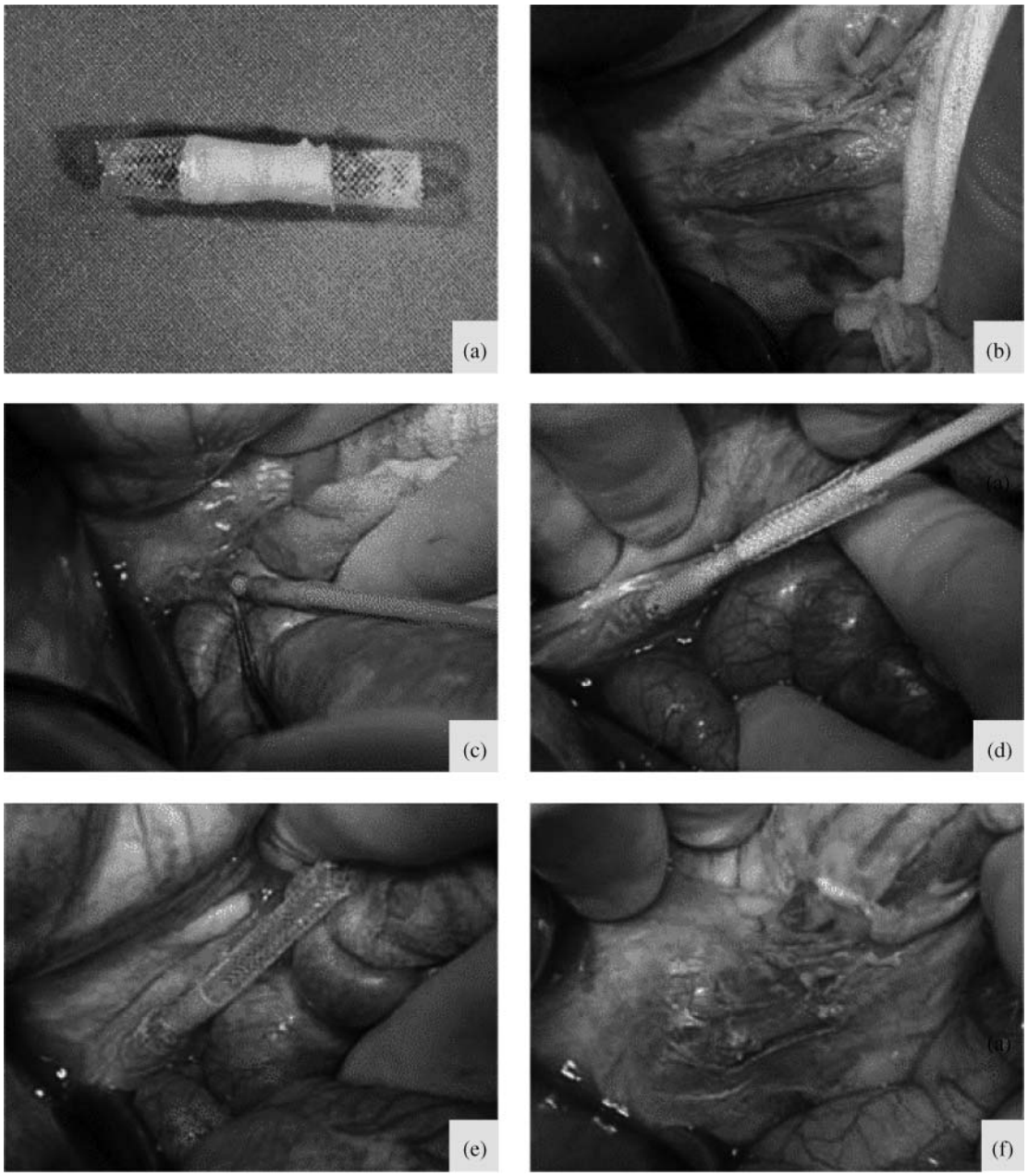

Figure 2. Creation of a neo-bile duct. The neo-bile duct consists of a vein segment which was endoluminally stented by a biodegradable stent (a). The native bile duct was dissected (b) and a 2-cm long segment was resected. Implantation of the vein graft with its endoluminal stent was performed using a split cannula with the vein having been drawn over its outer surface (c). After removing the split cannula, the biodegradable stent was released (d) and the proximal anastomosis was performed (e). After introducing the stent into the distal stump of the native bile duct, the distal anastomosis was performed (f).

using SPSS-software. A level of significance of $p < .05$ was considered as sufficient in all experimental groups.

RESULTS

All operations had been carried out without complications within 86 ± 15 min (group II) and 102 ± 15 min (groups III and IV).

SURVIVAL AND BIOCHEMISTRY

After sham operation (group I) and bile duct replacement by vein and biodegradable stent (group III), all animals survived until sacrifice after six months in a good general condition with a weight of 117.8 ± 9.4 kg respectively 121 ± 17.3 kg. However, using a sole vein for bile duct replacement (group II) led to death of three animals within the first three weeks and

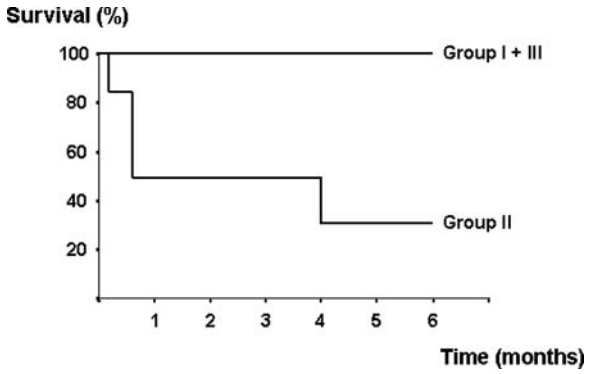

Figure 3. Survival rates. All animals in group I and III survived until their sacrifice after six months. In group II, three animals died within the first three weeks and one animal died after four months.

of one animal after four months. The remaining two animals of this group survived until their sacrifice after six months (Figure 3).

In group I and III, all animals showed biochemical parameters laying within the normal range (Table 3). In contrast using a sole vein for bile duct replacement (group II) led to significant elevated cholestatic parameters which already appeared after seven days. After six months, the degree of liver damage in the still surviving animals of group II was significantly increased combined with an impairment of the synthetic capability of the liver. Additionally the number of leukocytes was significantly increased (Table 3).

Table 2. Semiquantitative liver score

Criteria	Points	Morphologic findings
Cholangitis	0	Single inflammatory cells
	1	Sparse infiltration of inflammatory cells
	2	Alternating close infiltration of inflammatory cells
	3	Close infiltration of inflammatory cells
Fibrosis	0	No fibrosis
	1	Minimal fibrosis
	2	Moderate fibrosis
	3	Strong fibrosis
Periportal infiltration	0	Single inflammatory cells
	1	Sparse infiltration of inflammatory cells
	2	Alternating close infiltration of inflammatory cells
	3	Close infiltration of inflammatory cells

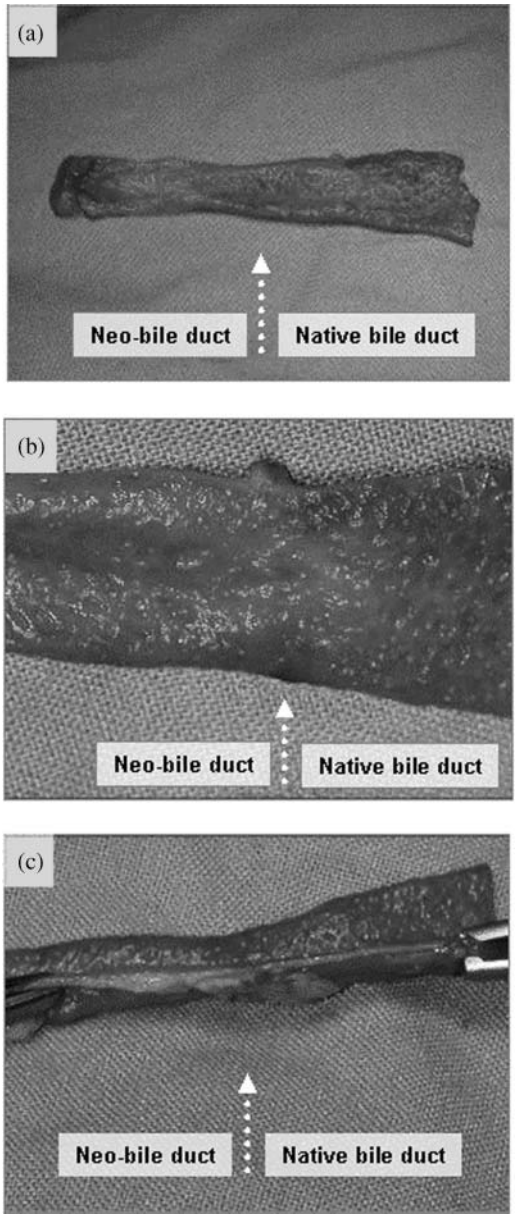

Figure 4. Macroscopic results. After four months, the biodegradable stent disappeared. The neo-bile duct was already covered with bile duct epithelium (a + b) but still showed a thickened surface and developed the diameter of the endoluminal stent (c).

Table 3. Biochemical results. Group I: Sham operation, Group II: bile duct reconstruction using a sole vein, Group III: Bile duct reconstruction using a vein and biodegradable stent

Parameter	Group	Preoperative	60 min postoperative	7 days postoperative	6 months postoperative
AST	I	13.7 ± 3.3	16.5 ± 6.3	9.0 ± 3.0	12.2 ± 2.0
(U/l)	II	20.3 ± 5.1	$35.0 \pm 13.2^{a,c}$	$115.3 \pm 8.6^{a,c}$	$12.3 + 3.4$
	III	15.5 ± 4.7	16.0 ± 3.7	18.0 ± 5.4^{b}	$45.0 \pm 47.6^{b,c}$
Bilirubin	I	0.3 ± 0.2	0.3 ± 0.2	0.1 ± 0.0	0.1 ± 0.0
(mg/dl)	II	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.1	0.1 ± 0.0
	III	0.2 ± 0.1	0.2 ± 0.1	$1.0 \pm 1.0^{b,c}$	$1.5 \pm 1.6^{b,c}$
γ-GT	I	18.7 ± 5.3	19.0 ± 5.6	15.0 ± 4.6	19.3 ± 6.5
(U/l)	II	17.8 ± 4.5	19.0 ± 8.7	16.0 ± 3.7	17.5 ± 6.3
	III	18.2 ± 4.4	22.5 ± 13.7	19.3 ± 3.6	21.7 ± 7.4
AP	I	166.2 ± 59.4	170.8 ± 61.3	107.5 ± 22.1	159.3 ± 68.6
(U/l)	II	171.7 ± 63.2	177.0 ± 67.6	144.7 ± 69.9^{a}	129.5 ± 43.5
	III	208.0 ± 53.1	233.5 ± 62.4	248.7 ± 92.1^{b}	151.3 ± 38.6
Albumin	I	2466.7 ± 377.7	2433.3 ± 403.3	2333.3 ± 280.5	3333.3 ± 233.8
(g/l)	II	2866.0 ± 280.5	2633.3 ± 294.4	2616.7 ± 75.3	3083.3 ± 365.6
	III	2366.7 ± 307.7	2250.0 ± 258.8	2416.7 ± 278.7	$2233.3 \pm 1011.6^{b,c}$
Leukocytes	I	17.1 ± 6.0	17.7 ± 4.7	22.1 ± 2.4	13.9 ± 2.7
($10^3/\mu$l)	II	11.8 ± 3.7	13.9 ± 7.8	19.1 ± 2.6	13.1 ± 2.4
	III	12.7 ± 3.5	14.0 ± 4.5	20.7 ± 7.3	$14.9 \pm 3.7^{b,c}$

[a] $p < .05$: group II vs. III; [b] $p < .05$: group II vs. I; [c] $p < .05$: group III vs. I.

Macroscopic Results

Using a sole vein for bile duct replacement (group II) led either to necrosis of the venous interponate and biliary peritonitis in three animals which died within the first three weeks. The both surviving animals of this group developed a high-grade stenosis of the complete neo-bile duct with secondary biliary cirrhosis of the liver after six months. The animal which died after four months showed an high-grade stenosis of the neo-bile duct accompanied by a purulent cholangitis.

When bile duct replacement by a vein and a biodegradable stent was performed, the PLA stent was macroscopically disappeared after four months (Figure 4). The neo-bile duct showed a bright and thickened surface after three and four months and developed the diameter (7.0 ± 0.9 mm) of the biodegradable stent (7 mm). At these time points the neo-bile duct was already covered with bile duct epithelium. After six months, the macroscopic findings of the neo-bile duct were comparable to the bile duct in the sham-operated animals.

Microscopic Results

Bile duct replacement using a sole vein (group II) led microscopically to strong fibrosis of the neo-bile duct without detection of bile duct epithelium respectively CK-7 and FVIII-related protein expression after six months (pictures not shown). In contrast, the additional use of a biodegradable stent led to a complete covering with bile duct epithelium. After three months, the wall of the neo-bile duct still showed residues of the PLA-stent and an accompanying inflammation and fibrosis (Figure 6). The histological investigation of the liver revealed a high degree of fibrosis, cholangitis, and periportal infiltrations (Figure 7). After four months, the stent material was completely degraded. The neo-bile duct showed an increased inflammation reaction. Simultaneously the cholangitis had decreased (Figures 6 and 7). After six months, the neo-bile duct showed a regular bile duct histoarchitecture with a single layered columnar epithelium, a strong de novo expression of Ck-7, and expression of FVIII-related protein without indications for remnant stent material (Figure 5). In comparison to the bile duct of sham-operated animals, the neo-bile duct showed a similar epithelialization and vascular supply, but still a thicker subendothelial connective tissue layer (Figures 5c and 6b). The bile duct and liver score revealed a regular histoarchitecture with only a low degree of bile duct inflammation and fibrosis compared to the native bile duct and liver in sham-operated animals (Figures 6 and 7).

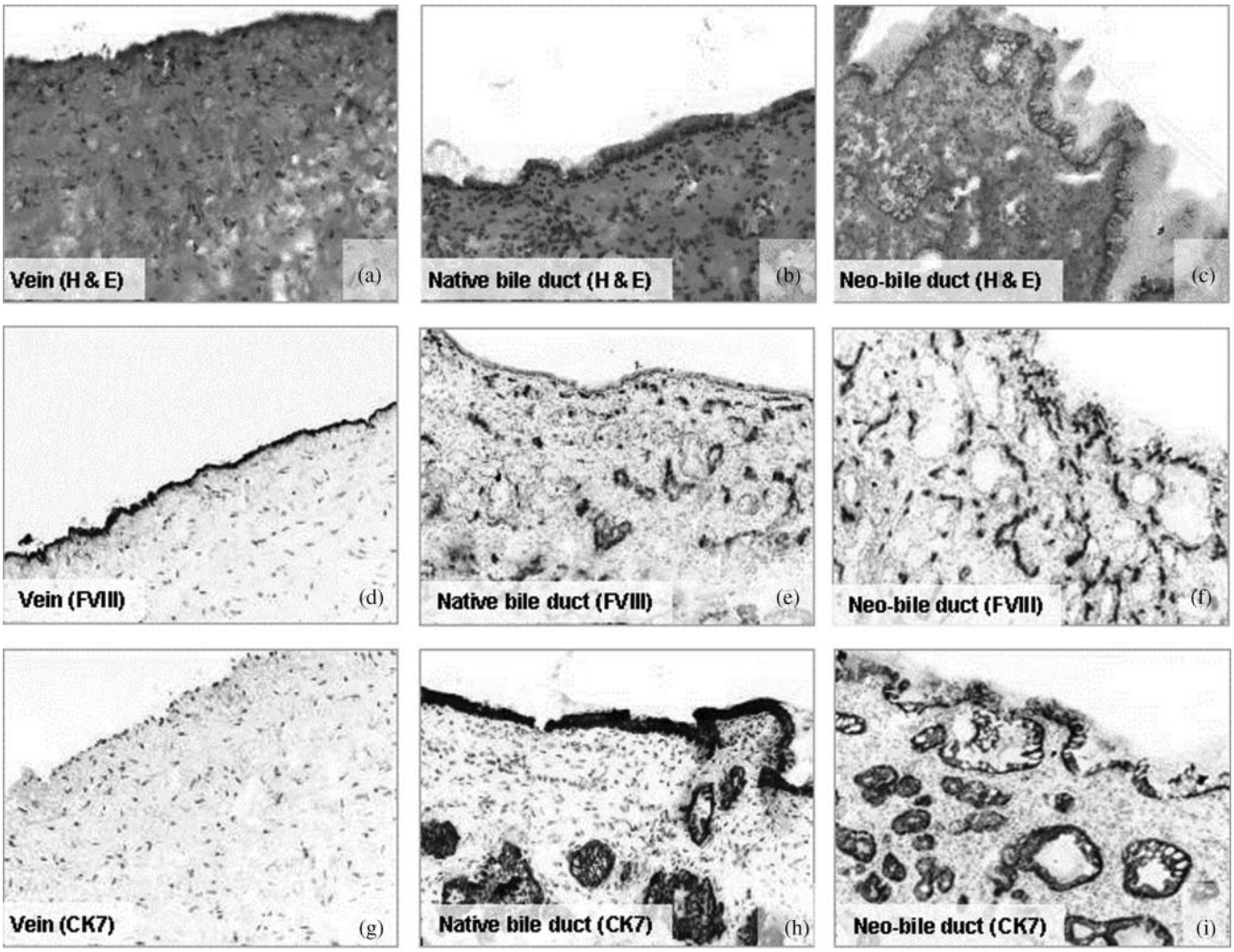

Figure 5. Immunohistochemical findings. The venous interponate (left column) displayed a normal vein histoarchitecture with a continuous, single-layered endothelium (a), strong expression of F VIII-related protein along the entire lining (d) and without expression of Ck-7 (g). After six months, the native bile duct of the sham-operated animals (group I, middle column) showed the typical histoarchitecture with a single layered columnar epithelium (b) and a strong expression of Ck7 (h) and F VIII (e). The neo-bile duct (group III, right column) displayed a lining by columnar epithelium (c) with expression of Ck7 (i), whereas expression of F VIII-related protein was restricted to newly formed capillaries (f) after 6 months. H&E staining = a–c, F VIII-immunostaining = d–f; bile duct epithelium labelling with Ck-7- antibody = g–i; original magnification ×100.

DISCUSSION

Roux-en-Y-hepaticojejunostomy currently represents the standard procedure in the treatment of major bile duct lesions, bile duct stenosis, or bile duct cancer. However, this method is associated with unsatisfying rates of immediate and long-term complications up to 30% [15, 16]. Therefore, new biliary reconstruction procedures are required that ideally should provide a sufficient biliary drainage with long-term patency, avoidance of biliary leaks and ascending cholangitis, and, finally, represent a simple surgical procedure.

Bile duct reconstruction via an isoperistaltic interposed jejunal segment has been proposed as a successful alternative to biliodigestive anastomosis [6, 17]. This method offers the possibility to preserve the physiologic biliary drainage via the Papilla vateri. Therefore, the risk of ascending cholangitis is minimized and additionally endoscopic retrograde choledochography (ERC) imaging as well as endoscopic interventions are still feasible. However, this procedure is technically demanding and requires in contrast to the standard Y-Roux reconstruction two possibly critical biliary anastomoses [6, 17]. Experiments of *Cushieri* et al. who used an autologous vein segment for subtotal and total

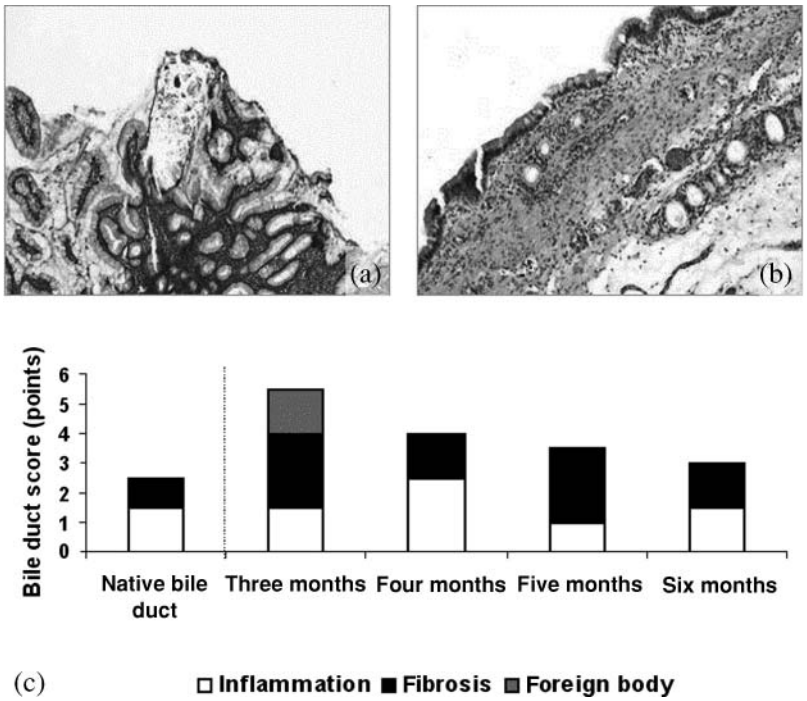

Figure 6. Neo-bile duct formation. After three months, the neo-bile duct still shows residuals of stent material (a). After four months, the stent material has been completely degraded accompanied by an increased inflammatory reaction (c). After six months the neo-bile duct shows a regular histoarchitecture (b) similar to the native bile duct (c). (a + b: H&E staining; original magnification ×100).

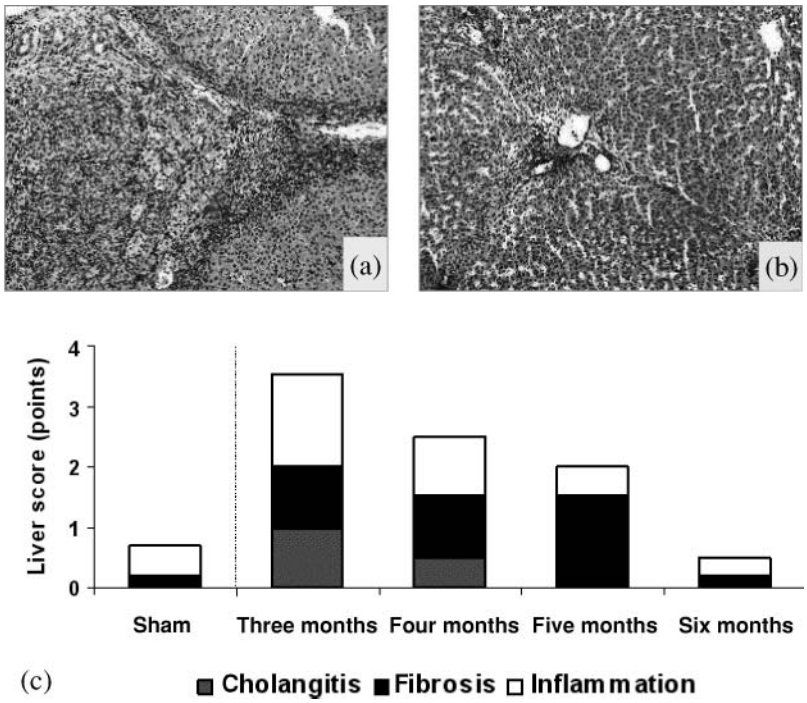

Figure 7. 7 Liver morphology. The neo-bile duct formation was accompanied by a temporary cholangitis and liver fibrosis showing its maximum after three months (c). Bile duct replacement by using a sole vein (group II) led to a secondary biliary cirrhosis of the liver (a). All animals with endoluminally stented neo-bile duct showed a regular histoarchitecture similar to the sham group after six months (b, c). (a+b: H&E staining; original magnification ×100).

replacement of the bile duct failed due to the development of bile duct strictures [18]. These authors advocated the use of silicon tubes as stents [18]. However, the plastic or metal stents commonly used in reconstructive biliary surgery have also shown considerable problems, e.g., bile duct lesions by stent insertion, foreign body reaction, fistula formation, stent occlusion, or migration [19–21].

We therefore developed a new technique of bile duct reconstruction by combining an autologous venous interponate with a biodegradable PLA-stent which functions as a temporary scaffold. In contrast to a recent study using autologous bone marrow cells to create a neo-bile duct we used a body's own vein which is always available and easily to obtain [12]. In this study, we showed that it is possible to create a neo-bile duct by using a body's own vein which is morphologically similar to the native bile duct. After four months, the neo-bile duct was already covered with bile duct epithelium, probably by growing in from the native bile duct's stumps. At this time the stent material was completely degraded and the neo-bile duct showed a thickened wall diameter accompanied by an inflammatory reaction. After six months, the neo-bile duct nearly completely resembled the native bile duct showing Ck7-positive columnar epithelium and newly formed capillaries in the bile duct wall.

On the other hand, bile duct reconstruction using a sole vein without endoluminal stent has either resulted in necrosis of the venous interponate with consecutive biliary peritonitis or bile duct stenosis with consecutive secondary fibrosis of the liver. Apparently the biodegradable stent has avoided a collapse of the venous interponate and protected it against the alkaline bile and therefore met the precondition for the ingrowth of capillaries and bile duct epithelium. In this context, the size of the biodegradable stent is of crucial importance. When the chosen stent size is too large, kinking complications with consecutive bile duct stenosis can occur. In case of an insufficient stent length, an insufficiency of the anastomosis can happen endangering the remodelling of the venous interponate. In this study, an overlap of the stent over 1 cm into the proximal and the distal bile duct stumps has been proven of value.

In summary, it is possible to create an artificial bile duct using a body's own vein and a biodegradable endoluminal stent which morphologically resembles the native bile duct. In the treatment of major bile duct lesions, the new method represents an attractive alternative to a hepaticojejunostomy. Furthermore, because of the simple technique and the availability of the vein, this new procedure shows potential for clinical application in patients with major bile duct defect lesions.

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