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Evaluation of the small intestinal submucosa covered stent in preventing restenosis after percutaneous transluminal angioplasty in the swine

Xiaobai Wang*, Jinglei Li[1], Hong Zhang[2], Yan Zhang[3]

Department of Interventional Radiology and Vascular Surgery, The First Affiliated Hospital of Jinan University, Guangzhou, 510630, China

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ABSTRACT

Objective: To compare the performance of small intestinal submucosa (SIS)-covered endografts (SCEs) to bare nitinol stents (BSs) in injured swine iliac arteries.
Materials and methods: Twenty-eight nitinol stents were used: 14 externally SCEs and 14 BSs. Devices were implanted in each side of balloon-injured external iliac arteries of 14 swine via carotid approach. Arteriograms were obtained before and after implantation and before animal sacrifice at 4, 8, and 12 weeks. Histopathological and electron microscopy studies of explanted specimens were performed.
Results: Implantation of all SCEs and BSs was technically successful, but one SCE and one BS were obstructed at 8 weeks after implantation. At sacrifice, the other 26 stents were patent, with angiogram showing no significant different luminal narrowing between SCEs and BSs. Proliferating cell nuclear antigen (PCNA) immunohistochemistry examination revealed that the percentage of PCNA(+) cells were lower in SCEs ($p < 0.05$). Additionally, histomorphological analysis indicated that the neointima area and percentage of narrowing area were greater in SCEs, but there was no statistical significance. Greater endothelial cell count in SCEs than in BSs per visual field at 4000 times magnification by scanning electron microscope ($p < 0.05$).
Conclusion: Compared to BSs, no definite decrease of neointima and restenosis was found in SCEs in the present study. However, it is effective in promoting endothelial regeneration and strengthening endothelial function.

1. Introduction

Compared to percutaneous transluminal balloon angioplasty (PTA) alone, percutaneous transluminal stenting (PTS) has been an important method in the management of vascular stenosis and occlusion. However, for peripheral arterial diseases patients, stent studies to date still show dissatisfied long-term patency due to the development of chronic in-stent restenosis [1] and drug-eluting stents have not yielded statistically significant improvements over uncoated stents [2].

Two main components contribute to the development of restenosis after PTA. The first mechanism is the proliferation of smooth muscle cells and matrix formation resulting in neointima formation [3,4]. The second mechanism is the negative remodeling. This leads to constriction of the entire vessel [5]. Negative remodeling can be avoided by stent placement. However, stents do not reduce the occurrence of restenosis by intima hyperplasia as was demonstrated in peripheral arteries [6,7].

Over the past decade, the treatment of many different vascular diseases has become more reliant on "covered stent" technology. Covered stents are able to open vessels and provide a circumferentially occlusive boundary between the stent and the vessel. Covered stents may also be used for reestablishing the integrity of vessels that are at risk for rupturing (or have already ruptured) as in aortic aneurysms or are located in areas of severe stenosis such as coarctation of the aorta. To date, dacron, nitinol, polyester terephthalate, polyurethane, polytetrafluorethylene (PTFE), small intestine submucosa (SIS), and silicone have all been used to cover stents with varying degrees of success.

Small intestinal submucosa is a natural, collagen-rich, acellular biomaterial derived from the submucosal layer of porcine small intestine. It serves as a temporary scaffold for tissue in growth, leads to a strong tissue matrix [8]. What's more, it is considered as an attractive graft for the regeneration of native tissues in blood vessels [9]. Evidence reveals that SIS has a greater propensity for endothelialization and incorporation into the vascular wall when placed in arterial structures [10]. The purpose of the present study is to compare the performance of small intestinal submucosa

* Corresponding author. Tel.: +86 13392692251.
E-mail addresses: xiaobaiwang@163.com (X. Wang), lijinglei80@126.com (J. Li), zhangdongda@hotmail.com (H. Zhang), dsazy@163.com (Y. Zhang).
[1] Tel.: +86 13560042246.
[2] Tel.: +86 13711526778.
[3] Tel.: +86 13922206007.

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Fig. 1. Side views of a bare stent and endografts with SIS attached to the external surfaces of the bare stents. SIS has covered the whole bare stent.

(SIS)-covered nitinol endografts (BCEs) with bare nitinol stents (BSs) in injured swine iliac arteries.

2. Materials and methods

2.1. Animals

This study was approved by the Institutional Animal Care and Use Committee of our university. A total of 14 adult domestic swine (seven female and seven male, Shima experiment animal center, Guangzhou City, China) weighing 25–28 kg (mean, 26.9 kg) were used in this study. Using the right common carotid artery approach, each swine received first balloon injury of iliac artery bilaterally. Different devices, one on each side, were then placed in the injured iliac artery sites. All animals received SCE and BS.

2.2. Devices

The bare metal self-expanding stents (GRIKIN Advanced Materials Co., Ltd., Beijing) used in this study were made of braiding-lattice nickel-titanium with a 6 mm diameter and 30 mm long. The stainless-steel wire of the stents has a round profile and a diameter of 0.012-in. Twenty-eight such bare stents were used: 14 stents were used to make SCEs by suturing SIS to the BSs externally. (Fig. 1) One end of the SIS sheet was sutured to one end of the stent with the other end dissociated, and the overlapping parts of the SIS was sutured to every stent wire juncture by interrupted sutures using 10-0 vascular monofilament. The hydrated porcine SIS sheet (Institute of Stem Cell and Tissue Engineering, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, China) was 80 μm thick, 20 mm wide and 30 mm long. The other 14 bare stents with no elaboration were used as control group in this study. For delivery of the SCEs and the BSs, a 9-Fr delivery system (Bard; New Jersey; USA) (Fig. 2) was used. After the SCEs and BSs were preloaded into the delivery system, they were gas-sterilized.

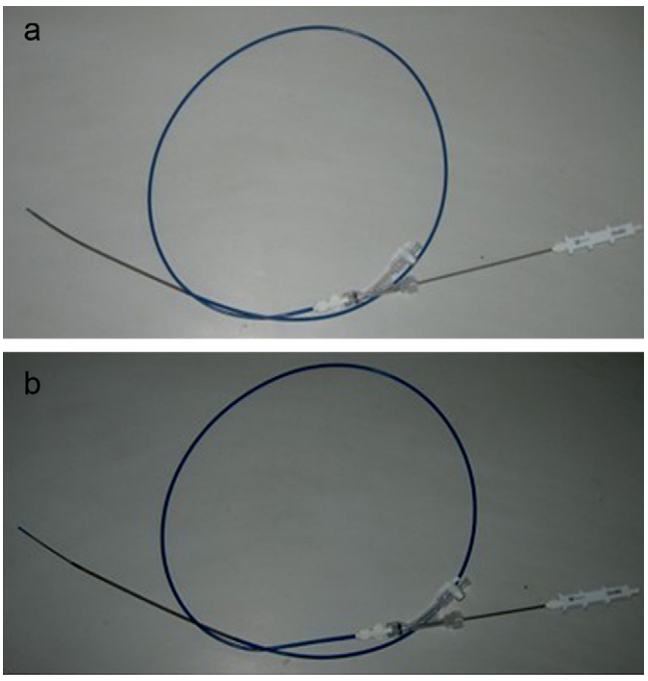

Fig. 2. Delivery systems (Bard; New Jersey; USA) before (a) and after (b) stents deploying were photographed. The 9 Fr system used in this study were 135 cm long. Before deploying, BS and SCE were put into the delivery system manually.

2.3. Procedure

Preoperative fasting and water deprivation were applied for 24 h and 12 h respectively to all the swine before the procedure. After intramuscular administration of Atropine Sulfate Injection (2.0 mg) and Cefazolin Sodium Injection (20 mg), the swine were tranquilized with intramuscular Diazepam Injection (20 mg), Ketamine Hydrochloride Injection (300 mg) and then intubated. Intravenous anesthesia was maintained with 3% sodium pentobarbital (initial dose 5 ml, then 3 ml/0.5 h according to anesthesia depth; total quantity <20–30 mg/kg) via ear vein. An LCV-PLUS system (GE, Salt lake city, UT, USA) and Dash 3000 monitor (GE, Salt lake city, UT, USA) were used for the procedure.

Using a sterile technique, the right carotid artery was surgically exposed and a 23 cm long 5 Fr short vascular sheath (Cordis, Co.) was introduced under direct vision after intraveneous application of Heparin Sodium Injection (4000 units). A 5 French graduated sizing side-hole angiographic catheter (Cordis, Co.) was advanced through the sheath over a 0.035 in. guide-wire (Terumo, Cor.), and positioned at the distal aorta to perform arteriograms. Diameters of each iliac artery were measured using GE ADW4.3 workstation software measuring tool. Then the 5 Fr sheath was replaced with a 9 Fr sheath (Cordis, Cor.) through a 260 cm 0.035 in. guide-wire (Terumo, Cor.) to accommodate the balloon catheter and stent delivery system. A 6 mm × 40 mm balloon (ev3, Inc.) catheter was advanced into each side of iliac arteries, inflated for twice to create an experimental injury.

After creation of the injury and intraarterial administration of Heparin Sodium Injection (1000 units), the pre-louded SCEs or BSs were sequentially inserted into the injured portions. Follow-up arteriograms were then obtained. After vascular sheath removal, the right carotid artery was surgically repaired with 10-0 silk threads and the skin wound was closed. The animals were monitored until they regained consciousness and then returned to the