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ORIGINAL ARTICLE

Colchicine Reduces Restenosis after Balloon Angioplasty Treatment for In-Stent Restenosis

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Background and Aims. Treatment of coronary in-stent restenosis (ISR) is hampered by a high incidence of recurrent ISR. Colchicine is an old drug with known anti-inflammatory and antiproliferative actions. We evaluated the strategy of colchicine combined with conventional balloon angioplasty for the treatment of ISR.

Methods and Results. Sixty coronary arteries of 60 mini-pigs underwent oversized bare-metal stent implantation to induce ISR. After 28 days, vessels with ISR (≥50% diameter stenosis) were randomly divided into three groups: control (conventional balloon angioplasty combined with placebo), colchicine (conventional balloon angioplasty combined with colchicine) and drug-eluting balloon (DEB). Restenosis and neointima formation were elevated with angiography and histological and morphometric analysis at 28 days after different interventions. Late lumen loss and percent area stenosis at follow-up were lower in colchicine group compared to control group but were similar to those of DEB group. There was no significant difference in proliferating cell nuclear antigen-positive vascular smooth muscle cells and inflammatory score between the colchicine group and the DEB group.

Conclusions. The efficacy of colchicine combined with conventional balloon angioplasty for treatment of ISR was comparable to that of DEB. Treatment of ISR might not require a second stent implantation, and colchicine combined with conventional balloon angioplasty seemed to be another consideration.

Key Words: Colchicine, Balloon angioplasty, Stent, Restenosis.

Introduction

Although the incidence of in-stent restenosis (ISR) has significantly decreased with the introduction of drug-eluting stents, it still occurs in 10–20% of cases (1–4). Various interventions have been used to treat ISR, which include conventional balloon angioplasty, cutting balloon angioplasty, (5) drug-eluting stent implantation (1,6), intracoronary irradiation (2,7) and drug-eluting balloon (DEB) angioplasty. Preclinical trials demonstrated that the efficacy of paclitaxol eluting balloon angioplasty in the treatment of ISR is superior to that of conventional balloon angioplasty and not inferior to drug-eluting stent implantation (8,9). DEB is a conventional balloon coated with antiproliferative agent and the antiproliferative agent is the key to inhibit neointimal proliferation (10). Oral antiproliferative agent combined with conventional balloon angioplasty may be another consideration for treatment of ISR.

Colchicine is an old drug with known anti-inflammatory and antiproliferative actions. Intimal inflammatory hyperplasia is the main reason for restenosis following coronary stent implantation. In experimental animal models this agent has prevented or reduced the formation of atherosclerotic plaques (11,12), and *in vitro* studies with human smooth muscle cells (SMCs) from arteriosclerotic lesions suggest that colchicine may be useful in producing anti-arteriosclerotic effects by inhibit SMC proliferative, migratory, and secretory processes (13). Colchicine has also been effective in preventing intimal proliferation following

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balloon angioplasty in dogs through downregulation of leukocyte vascular endothelial growth factors expression and without apparent toxicity (14). Deftereos et al. (15) found oral colchicine may be yet another consideration to limit restenosis rates in diabetic patients treated with bare-metal stents. However, there is lack of related research to further explore its superiority to other strategies widely accepted by clinicians for treatment of ISR, such as DEB.

The aim of this study is to compare 28-day imaging and pathology outcomes between oral colchicine combined with conventional balloon angioplasty and DEB for ISR in pig models.

Materials and Methods

All animal care and procedures conformed to the Guidelines for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication No. 85−23, revised 1996) and were approved by the Institutional Animal Care and Use Committee of the Second Affiliated Hospital of Harbin Medical University (2009−X023).

Establishment of the ISR Model and Grouping

Sixty mini-pigs (20−25 kg) were pretreated with aspirin (300 mg) and clopidogrel (75 mg) once a day starting 3 days prior to the procedure. Animals were intubated after sedation with ketamine (20 mg/kg, i.m.) and diazepam (0.4 mg/kg, i.m.) followed by 3% sodium pentobarbital through the marginal ear vein (25 mg/kg, i.v.). A 6-F guiding catheter was used. Continuous hemodynamic and surface electrocardiographic monitoring was maintained throughout the procedure. After intravenous heparin (150 U/kg) and intracoronary injection of nitroglycerin (100 μg), baseline angiography of the target vessel was performed. The methods of stent implantation have been published previously (16). One bare metal stent (BMSs, 3.0−3.5 × 18 mm; Lepu Medical Company, Beijing, China) was placed in the left anterior descending artery of each pig at 12−14 atm for 30 sec. The stent-to-artery ratio was maintained at 1.2:1. After the equipment was removed, all mini-pigs were fed a normal diet and received aspirin (300 mg, p.o.) and clopidogrel (75 mg, p.o.) daily.

At 28 days after BMSs implantation, repeated angiography was performed. The segments with ISR ≥50% diameter stenosis by quantitative coronary angiography were randomly assigned to one of the three treatment groups: control (conventional balloon angioplasty combined with placebo), colchicine (conventional balloon angioplasty combined with colchicine, 0.5 mg/kg daily for 28 days) and DEB (paclitaxel-eluting balloon, 3.0−3.5 × 20 mm; Dior, Eurocor, Bonn, Germany). Conventional balloon angioplasty procedure was done using noncompliant or semi-compliant balloons that matched the size of the final balloon used at the time of stent implantation. Single or multiple high-pressure balloon inflations (≥12 atm) were generally performed with the goal of achieving a near 0% residual stenosis. After the target lesion was pre-dilated with a non-study balloon catheter, DEB was inflated in the same fashion as a conventional balloon catheter for 60 sec. Restenosis and neointima formation were studied with angiography and histological and morphometric analysis at 28 days after different interventions.

Quantitative Coronary Analysis (QCA)

Angiograms were performed during the initial procedure, on day 28 after BMS implantation and at another 28 days after three different strategies for the treatment of ISR. A computerized coronary angiography analysis system (GE Co., Germany) was used for quantitative coronary analyses by two experienced cardiologists blinded to the treatment protocol. Discrepancies were resolved by mutual consensus. The minimal luminal diameter (MLD), reference vessel diameter (RVD) and percent diameter stenosis (DS%) were measured. The acute lumen diameter gain (MLD immediately after interventional procedure—the MLD before the interventional procedure) and late lumen loss (MLD immediately after interventional procedure—the MLD at follow-up) were calculated.

Morphometry

For the morphometric analysis, stented arteries were harvested and fixed in 10% buffered formalin and embedded in glycol methacrylate. Stented segments were cut into three parts (proximal, mid, distal). Thin sections from each artery block were stained with hematoxylin and eosin (H&E) for measurement of the stent area (SA), lumen area (LA), and for histological analyses. Intimal area (IA) was calculated using the equation: IA = SA − LA. The percent of lumen area stenosis (AS%) was calculated using the equation AS% = IA/SA × 100%. Injury score at each strut site was assessed as described by Schwartz et al. (17) where 0 = no injury; 1 = break in the internal elastic membrane; 2 = perforation of the media; and 3 = perforation of the external elastic membrane to the adventitia. Assessment of the pathological score for strut-associated inflammation was graded as follows: (18) 0, none; 1, scattered inflammatory cells; 2, inflammatory cells encompassing 50% of a strut in at least 25−50% of the circumference of the artery; and 3, inflammatory cells surrounding a strut in at least 25−50% of the circumference of the artery. To determine the cellularity of the vessel wall, the total number of nuclei in the IA per cross-sections was counted.

Immunohistochemistry

For immunohistochemistry, the stent sites were dissected into blocks, and the stent wires were carefully removed.