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Jacobs Journal of Experimental Cardiology and Research

Research Article

Efficacy and Safety of the Novel Sirolimus-Eluting, Biodegradable Polymer Coated Stent in Human Coronary Lesions

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Received: 07-08-2014

Accepted: 07-30-2014

Published: 09-05-2014

Abstract

The postulated relationship between nonbiodegradable polymers and LST has led to a concerted effort to seek alternative biodegradable polymers for drug delivery. Bioabsorbable coatings with a degradation period matched to that of the drug elution may be a better alternative, clinically and economically. The purpose of this study was to evaluate the safety and the efficacy of the novel sirolimus-eluting stent (SES) with biodegradable polylactic-co-glycolic acid (PLGA) polymeric matrix (Tivoli™, Essen Technology, Beijing, China) implantation in human atherosclerotic coronary. Seventeen patients with angina pectoris were enrolled in the study. The primary end points included the percentage of in-stent restenosis of the luminal diameter and in-stent late luminal loss at 8 months, as determined by quantitative angiography. The secondary end point was the major adverse cardiac events (MACE) 30 days and 9 months after stenting procedure. A total of 27 Tivoli™ SESs were implanted successfully in 23 lesions (22 de novo lesions and 1 ISR lesion), and all patients were discharged without clinical complications and completed 9-month clinical follow-up. Except for target vessel revascularization, no other major adverse cardiac events developed during clinical follow-up period. Thirteen patients (18 lesions, 22 stents) completed 8 months of angiographic follow-up. No in-sent or in-segment diameter restenosis was observed. The median of in-stent/in-segment late loss is 0.1mm. Target vessel initial narrow (not target lesion restenosis) was occured in only one patient (5.9%), who underwent repeated PCI. Thus, both total MACE rate and the target vessel revascularization rate per patient were 5.9%.This study showed that Tivoli™ sirolimus-eluting cobalt-chromium stent coated with bioabsorbable PLGA polymer demonstrated a safe and efficacious clinical alternative to reduce restenosis.

Keywords: Bioabsorbable Polymer; PLGA; Percutaneous Coronary Intervention; Sirolimus-Eluting Stents; Restenosis

Abbreviations

SES: Sirolimus-Eluting Stent;
PLGA: Polylactic-Co-Glycolic Acid;
MACE: Major Adverse Cardiac Events;
ACEI: Angiotensin Converting Enzyme Inhibitors;
ISR: In-Stent Restenosis;
LLL: Late Luminal Loss;
PCI: Percutaneous Coronary Intervention

Introduction

The first generation Cypher™ sirolimus-eluting stent (SES) is more effective than bare-metal stents in reducing restenosis and related target vessel revascularization mainly by limiting intimal hyperplasia [1,2]. Thereby, these stent devices coated with permanent polymeric materials quickly became the standard of care for the percutaneous treatment of symptomatic coronary artery disease. However, the concern of adverse effects secondary to the durable polymer coating of CYPHER SES has not been eliminated completely yet. Polylactic-co-glycolic acid (PLGA), a synthesis degradable polymer, can be fully metabolized to water and carbon dioxide in vivo, and thus is a rational approach to avoid the persistent toxicity of permanent polymer matrix. Our animal study [3] demonstrated the feasibility, the better biocompatibility and the efficacy of PLGA-coated SES. However, the effects of the novel SES in humans have not been reported.

The aims of this study were to evaluate [1] the safety and efficacy of implanting sirolimus-eluting stent coated by a PLGA polymer (Tivoli™, Essen Technology, Beijing, China) in atherosclerotic human coronary arteries and [2] the effect of the stent on neointimal proliferation.

Materials and Methods

Description of the Stent

Tivoli™ (Essen Technology, Beijing, China) stent is a laser-cut, cobalt-chromium metal, open-cell designed sirolimus-eluting stent. The novel SES uses biodegradable polymer polylactic-co-glycolic acid (PLGA) as coating film (10μm thickness) being loaded with or without 8μg/mm sirolimus per stent. EXCEL stent is available in lengths of 10, 15, 20, 25, and 30mm and in diameters of 2.25, 2.5, 2.75, 3.0, 3.5, and 4.0mm.

Selection of Patients

Patients were eligible for the study if they were 18–75 years old and were diagnosed with stable or unstable angina. Additional eligibility criteria were the presence of a primary target lesion in a native or restenosis coronary artery that was 2.5–3.5 mm in diameter and stenosis of 51–100% of the luminal diameter, as estimated visually. Patients were excluded from the study if they had left main trunk stenosis, acute myocardial infarction, congestive heart failure(LVEF<40%), or renal insufficiency with baseline serum creatinine >2.0 mg/dl.

All patients received loading dose of dual antiplatelet therapy (300mg of aspirin and a-300mg oral dose of clopidogrel) at least 1 day before undergoing catheterization, and then received 100 mg of aspirin daily indefinitely and 75mg of clopidogrel daily after stenting for at least 12 months. Other medications such as b-blockers, ACEI, statins, calcium-antagnoists or nitrates were taken as clinically indicated.

The protocol was approved by the Medical Ethics Committee of Peking University First Hospital, and informed consent was obtained from every patient.

Stenting Procedure

All the procedures were performed by the standard Judkins techniques using the GE INNOVA 2000 system (GE Medical Systems, USA). During the procedure, intravenous bolus injection of unfractional heparin (100U/kg) was administered. Lesions were treated with the use of standard interventional techniques, including predilation before the placement of the stent. After predilation, an appropriate-sized stent (2–4mm longer than the lesion and the stent-to-vessel diameter ratio of 1:1) was implanted at a pressure of at least 12 atm. If more than one stent was needed in the same lesion, additional stent was allowed to be implanted with 2–3mm overlapping of the two stents.

Quantitative Coronary Angiography Analysis

Coronary angiograms of the stented segment, performed before, immediately after, and 8 months after the procedure were quantitatively analyzed using the Cardiovascular Measurement System (Medical Imaging Systems). Baseline and follow-up cine angiograms were evaluated in the same view. Angiographic "binary" in-stent restenosis (ISR) was defined as a follow-up diameter stenosis ≥50% in the target lesion. In-stent late luminal loss (LLL) was defined as the difference between the minimal luminal diameter at the completion of the stenting procedure and that measured during follow-up.

Study End Points

The primary end points of the study included the percentage of ISR and LLL at the 8-month follow-up, as determined by quantitative angiography. The secondary end points were defined as the incidence of major adverse cardiac events, including death, myocardial infarction with or without ST elevation, stent thrombosis and revascularization of the target lesion or vessel 30 days and 6 months after the index procedure.

Statistical Analysis

Continuous variables were expressed as mean±SD or median with 25th and 75th percentiles and were compared by Student's t test or the Wilcoxon rank-sum test. A 2-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics and Procedural Results

Between September 2007 and January 2008, a total of 17 patients were enrolled in this study. Baseline clinical and angiographic characteristics of patients and lesions are shown in Table 1. Their mean age was 57.9±12.1; 58.8% (10/17) of these patients were male. All patients were discharged without complications after stent implantation.

Baseline lesion characteristics are also listed in Table 1. Twenty-seven biodegradable-coated Tivoli™ sirolimus-eluting stents were implanted successfully in 23 lesions (22 de novo lesions and 1 ISR lesion): Ten stents were implanted in 9 left anterior descending coronary arteries, ten stents in 7 circumflex coronary arteries, and seven stents in 7 right coronary arteries. A single stent was implanted in 20 lesions, double stents in 2 lesions, and triple stents in one lesion. Nearly all the treated lesions were class B or C according to the American College of Cardiology/American Heart Association classification [4].

Table1. Baseline Demographic and Clinical Characteristics

characteristic	n
age, y	57.9±12.1
male (%)	10 (58.8)
hypercholesterolemia (%)	7 (41.2)
hypertension (%)	10 (58.8)
diabetes mellitus (%)	11 (64.7)
current smoker (%)	9 (52.9)
prior myocardial infarction (%)	6 (35.3)
prior CABG (%)	0 (0)
unstable angina (%)	10 (58.8)
major coronary stenosis (>50% stenosis)	
1	7 (41.2)
2	2 (11.8)
3	8 (47.1)
Target vessel	23
LAD	9 (39.1)
LCX	7 (30.4)
RCA	7 (30.4)
Target lesion type	
ACC/AHA type A/B/C	4/13/6
de novo/restenosis	22/1

The mean reference vessel diameter was 2.97±0.53 mm by QCA (Table 2). The percent diameter stenosis decreased from 60.7% before stenting to 9.7% after stenting. The MLD increased from 1.17 mm before stenting to 2.60 mm after stenting.

Table 2. Results of QCA Analysis (n=18)

	before stenting	after stenting	8-month follow-up
reference vessel diameter, mm	2.97±0.53	2.91±0.53	2.86±0.48 †
MLD, mm	1.17±0.72	2.60±0.37	2.38±0.52 †
percent diameter stenosis, %	60.7±23.6	9.7±9.9	15.7±17.7 †
in-stent LLL, mm	-	-	0.10 (0.075-0.30)
in-stent restenosis, n	-	-	0
in-segment LLL, mm	-	-	0.10 (0.10-0.475)
in-segment restenosis, n	-	-	0

Angiographic Outcomes At 8 months

Thirteen patients (18 lesions, 22 stents) completed 8-months angiographic follow-up. No target lesions of these patients approached to 50% vessel narrowing by QCA. Angiographic data are presented in Table 2. The abnormal distribution of LLL (the median, 0.1 mm) is presented in Figure 1.

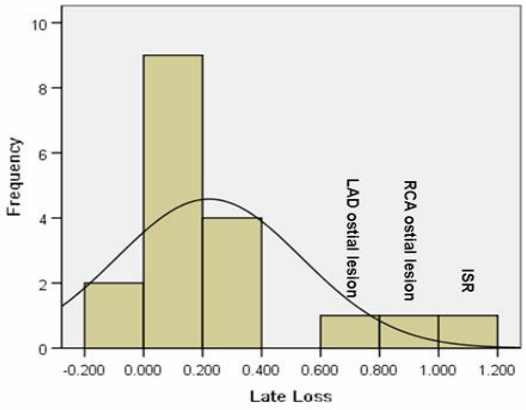

Fig 1: The distribution of late luminal loss

Clinical Outcomes

All patients completed 9-months clinical follow-up. No stent thrombosis and major cardiac events developed within 30 days after stenting procedures. Within 9 months, no deaths, myocardial infarctions, or CABGs occurred in any of these 17 patients. Because of target vessel initial narrowing (not target lesion restenosis), only one patient (5.9%) underwent repeated PCI. Thus, both MACE rate and the target vessel revascularization rate per patient were 5.9% (Table 3).

Table 3. Clinical Events in 9-Months Observation (n=13)

Event	N (%)
Death	0
Myocardial infarction	0
Stent thrombosis	0
Target lesion revascularization	0
Target vessel revascularization	1 (5.9)
Major adverse cardiac events	1 (5.9)

Discussion

The current study is the first human experience with the implantation of novel biodegradable polymer PLGA coated SESs, which demonstrated the feasibility and safety of PLGA serving as stent coating. Neither definite stent thrombosis nor restenosis in the 22 novel SESs was observed by angiography. The 9-month clinical follow-up of 17 patients with 27 stents in 23 lesions showed no deaths, myocardial infarctions, CABGs or target lesion revascularization rates, were recorded. Although the number of patients was limited and the follow-up period was relatively short, the initial and 9-month results were quite encouraging.

It has been proven beyond doubt that the first generation SESs are more effective than bare-metal stents in reducing restenosis and related target vessel revascularization mainly by limiting intimal hyperplasia [1,5]. However, there are more and more concerns regarding the long-term safety of the current SESs using 'permanent-polymer' technology. The potential relationship between permanent polymer and stent thrombosis has led to a concerted effort to seek alternative biocompatible and biodegradable polymers for drug delivery. For the reason, the hot field of the 'temporary' biodegradable polymer coatings is rapidly evolving.

Among these biodegradable polymers, polyesters are the widely used and most attractive alternatives to serve as the temporary SESs coatings, which comprise polylactides (PLA), polyglycolides (PGA) and polylactic-co-glycolic acid (PLGA) [6]. Because they can be fully metabolized to water and carbon dioxide through hydrolysis of the ester-linkage, the bioabsorbable polymeric coatings would leave in situ a bare-metal stent after all the drugs being released, and have the theoretical advantage of producing less toxicity. Lincoff et al. [7] have demonstrated no evidence of acute or chronic inflammation after implantation of high monocular PLA coated stent in porcine coronary arteries. Stents coated with PLA incorporating sirolimus [8] or everolimus [9] have also shown encouraging clinical results. PLGA, a copolymer comprising hydrophilic PGA and hydrophobic PLA, is more preferable to hydrolysis than PLA. Namely, the degradation and clearance process of PLGA maybe faster than PLA. Thus, theoretically,the use of PLGA coating has the theoretical advantage of accelerating the restoration of neointima.

Our animal study [3] has documented the feasibility, the efficacy and the safety of the new-generation SES with PLGA polymers. In the porcine coronary model, PLGA may offer good biocompatibility and long-term safety when used as a passive surface coating on stents. Besides vascular biocompatibility, the stent coatings can serve as drug reservoir and permit controlled drug release. Our data even show the drug release kinetics of PLGA-coated SES is similar to permanent-polymer coated Cypher SES in vitro [3]. Being consistent with the result, the present trail indicates the novel SES has remarkable anti-proliferation effect like Cypher stent in human. At 8-month angiography follow-up, the late losses for Cypher stents and for PLGA-coated SESs were separately 0.17mm in the SIRIUS trail [1] and 0.10mm in our study. A 0.1mm late loss for PLGA-coated SESs was observed in the present trail. Thus, it is feasible that PLGA serves as a stent-coating for drug delivery.

In summary, the novel thin-strut, PLGA polymer-coated, sirolimus-eluting stent seems to be safe and effective in preventing neointimal formation at 9 months after stent implantation in atherosclerotic human coronary arteries. It appears to be a potentially viable clinical alternative to the first generation SES. But further large, randomized, placebo-controlled, multicenter trails are necessary to confirm our observations and can provide more information about the safety and efficacy of PLGA polymer based SES.

Study Limitations

The present study was a single-center, single-blind, no controlled trial, including only 17 patients with 23 lesions. Moreover,the observational period(only 8 months) is short.

Conclusion

In present clinical experience, Tivoli™ sirolimus-eluting cobalt-chromium stent coated with bioabsorbable PLGA polymer demonstrated a safe and efficacious clinical alternative to reduce restenosis. Subsequent randomized controlled trial is needed to determine these remarkable and promising findings.

Acknowledgments

This study was sponsored by Essen Technology Company.

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