**Interventional Cardiology**

**Phosphorylcholine-coated Dexamethasone Eluting Stent in the Prevention of Restenosis: A Randomized Trial in a Single Hospital**

Ai-Hsien Li,1,2 Chiau-Suong Liau,2 Wen-Po Chuang, Dong-Feng Yeih1 and Shu-Hsun Chu1

**Background/Purpose:** In-stent restenosis (ISR) occurs in approximately 20% of the patients undergoing coronary stenting. Post-stenting inflammation may be among the major pathogenetic mechanisms in which vascular reactions produce intimal hyperplasia and smooth muscle cell migration. The objective of this open-label randomized controlled study was to evaluate the effect of phosphorylcholine-coated stents treated with dexamethasone to prevent ISR.

**Method:** We evaluated 17 discrete coronary lesions with a stenosis diameter > 70% from 13 patients. The diameter of the reference vessels ranged from 2.7 mm to 3.7 mm (mean 3.18 ± 0.31 mm). Using open-label randomization, 9 lesions were assigned to the control group and implanted with un-coated bare-metal stents. The remaining lesions were treated with dexamethasone-treated phosphorylcholine-coated stents. All patients were followed clinically and/or angiographically.

**Result:** One patient died from a nontreatment-related event one week after the procedure. Four patients, two each in the dexamethasone group and the control group, refused to have a follow-up coronary angiography (CAG), however, three of those patients refusing CAG had a thallium myocardial perfusion study. Of these patients, 2 in control group showed myocardial perfusion impairment. In the remaining 12 lesions in 7 patients, the diameter of the stenosis was smaller in the dexamethasone group versus the control group, although the difference was not significant statistically (0.33 ± 0.22 versus 0.22 ± 0.06 mm, \( p = 0.352 \)). There was a tendency toward a higher binary restenosis rate in the control group versus the dexamethasone group (33% vs. 0%, \( p = 0.202 \)). When the angiographic and clinical restenosis rates were combined, the control group had a significantly higher restenosis rate than the dexamethasone group (44.4% vs. 0%, \( p = 0.042 \)). One patient from the control group underwent target lesion revascularization.

**Conclusion:** Results of this study suggest that dexamethasone-eluting stents may have a potential role in the prevention of ISR in patients with coronary artery stents implanted.

**Key Words:** In-stent restenosis • Drug eluting stents • Dexamethasone

**INTRODUCTION**

In-stent restenosis (ISR) occurs in 15% to 30% of patients treated with coronary stenting.1–7 Although brachytherapy is effective in preventing ISR, its role has recently been replaced by the drug-eluting stents (DES).4 Studies have shown that both the rapamycin (Sirolimus)-eluting stent (SES) and the paclitaxel-eluting stent (PES) can significantly reduce the rate of ISR.2–14 Stents coated with a variety of agents (e.g., angiopeptin, antisense DNA, and vascular endothelial growth factor [VEGF]) are currently being tested in both animals and humans and show promising results.15–26 Evidence indicates that the inflammatory process may contribute to subsequent intimal hyperplasia in the...
early stages after stent implantation. Phosphorylcholine (PC) is a synthetic mimic of the outer wall of the red blood cell and PC-coated stents can be used as a delivery platform for biologically active entities. Dexamethasone is a corticosteroid with strong anti-inflammatory effects. In this study, we tested the ability of PC-coated stents treated with dexamethasone to prevent ISR.

STUDY SUBJECTS AND METHODS

Patients

We evaluated the coronary angiography of 1210 consecutive patients between November, 2004 and April, 2005. Patients with de novo lesions of >70% stenosis diameter in coronary arteries with diameter between 2.5 and 4.0 mm were eligible for inclusion. Patients with severe comorbidity including: chronic renal failure, previous myocardial infarction, unstable angina, and hemodynamic instability were excluded. Thirteen (13) patients with 17 discrete coronary lesions with stenosis diameter >70% were randomly assigned in an open label fashion to receive either uncoated bare metal stents (9 lesions) or dexamethasone-eluting stents (8 lesions). The diameter of the reference vessels ranged from 2.7 mm to 3.7 mm (mean 3.18 ± 0.31 mm). Informed consent was obtained from all patients and the study protocol was approved by the Institutional Review Board.

Coronary Angiography

Patients with definite or suspected coronary artery disease were studied with coronary angiography (CAG). Significant coronary artery stenosis was defined as stenosis diameter >50%. Quantification coronary analysis software (Quancor, Siemens Corp, or QCA CAAS II v4.0, Pie Medical Imaging BV or Philips manual analysis online) was used for coronary lesion measurements. Angiographic parameters are listed in Table 1.

Drug-eluting stent preparation

The dexamethasone-eluting stents were prepared us-

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Table 1. Patient/lesion data

<table>
<thead>
<tr>
<th>Lesion no.</th>
<th>Patient serial no.</th>
<th>Stent used</th>
<th>Location</th>
<th>Ref. (mm)</th>
<th>Minimal lumen diameter (mm)</th>
<th>F/U time (days)</th>
<th>Stenosis at F/U</th>
<th>Binary stenosis</th>
<th>RNA</th>
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<tbody>
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<td>1</td>
<td>A</td>
<td>B</td>
<td>LCX-M</td>
<td>3.30</td>
<td>1.50</td>
<td>146</td>
<td>20%</td>
<td>n</td>
<td></td>
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<tr>
<td>2</td>
<td>A</td>
<td>B</td>
<td>LAD-M</td>
<td>2.80</td>
<td>1.20</td>
<td>146</td>
<td>25%</td>
<td>n</td>
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<tr>
<td>3</td>
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<td>A</td>
<td>LAD-M</td>
<td>2.78</td>
<td>0.61</td>
<td>154</td>
<td>62%</td>
<td>r</td>
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<tr>
<td>4</td>
<td>C</td>
<td>A</td>
<td>LAD-M</td>
<td>3.24</td>
<td>1.24</td>
<td>167</td>
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<tr>
<td>5</td>
<td>D</td>
<td>A</td>
<td>RCA-M</td>
<td>3.00</td>
<td>1.00</td>
<td>139</td>
<td>9%</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>D</td>
<td>B</td>
<td>LAD-M</td>
<td>3.60</td>
<td>1.40</td>
<td>139</td>
<td>25%</td>
<td>n</td>
<td></td>
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<tr>
<td>7</td>
<td>E</td>
<td>A</td>
<td>LAD-M</td>
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<td>0.70</td>
<td>116</td>
<td>53%</td>
<td>r</td>
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<td>B</td>
<td>LCX-M</td>
<td>2.70</td>
<td>0.80</td>
<td>7</td>
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<td></td>
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<tr>
<td>9</td>
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<td>A</td>
<td>LAD-M</td>
<td>3.70</td>
<td>1.60</td>
<td>433</td>
<td>21%</td>
<td>n</td>
<td></td>
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<tr>
<td>10</td>
<td>H</td>
<td>B</td>
<td>LAD-M</td>
<td>3.05</td>
<td>0.30</td>
<td>348</td>
<td>13%</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>11</td>
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<td>n</td>
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<td>12</td>
<td>I</td>
<td>B</td>
<td>LAD-M</td>
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<td>0.84</td>
<td>405</td>
<td>0</td>
<td>n</td>
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<tr>
<td>13</td>
<td>I</td>
<td>A</td>
<td>LAD-P</td>
<td>3.10</td>
<td>1.15</td>
<td>405</td>
<td>13%</td>
<td>n</td>
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</tr>
<tr>
<td>14</td>
<td>J</td>
<td>A</td>
<td>LAD-P</td>
<td>3.30</td>
<td>1.01</td>
<td>60</td>
<td></td>
<td></td>
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<tr>
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<td></td>
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<tr>
<td>16</td>
<td>L</td>
<td>B</td>
<td>LAD-P</td>
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<td>1.20</td>
<td>310</td>
<td>32%</td>
<td>n</td>
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<tr>
<td>17</td>
<td>M</td>
<td>A</td>
<td>RCA-P</td>
<td>3.50</td>
<td>0.00</td>
<td>375</td>
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</table>

1. A = Bare metal stent, B = Dexamethasone PC coated stent; 2. Diameter of reference segments; 3. *counted from first catheterization to the date of second catheterization or the date of final Thallium scan; 4. Angiographic follow-up stenosis percentage; 5. Binary stenosis (r => 50%, n <= 50%); 6. Dipyridamole-Thallium201 scan (‘+’ = reversible perfusion defect in target vessel area)

Abbreviations: LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery. M = middle portion, P = proximal portion, D = distal portion.
ing the BiodivYsio Matrix LO stent (Biocompatibles, UK), which is coated with a 2-μm-thickness of PC. The stent was then bathed in a dexamethasone solution (Abbott Vascular Devices), 15 mg/mL in concentration at room temperature for 5 minutes in order to effect a loading dose density of dexamethasone of 2.2 μg/mm² to the surface of the stent and to achieve a dexamethasone load of 225 μg to an 18-mm stent. The dose of dexamethasone used in this study was the same as that recommended by the stent manufacturer and that used in previous studies that demonstrated the safety of the dosage and formula. Stents were deployed according to usual procedure.

**Patient follow-up**

After discharge from the hospital, the patients received oral clopidogrel and aspirin for at least 3 months and were followed at the out-patient clinic. Thallium myocardial perfusion scanning with dipyridamole stress was scheduled for 4 months after coronary stenting, but could be performed earlier in the event that angina-like chest pain occurred before the predetermined time. Follow-up angiography was suggested at 6 months after stenting for all patients. Angiographic restenosis was defined as > 50% stenosis diameter of the culprit vessel at the follow-up coronary angiogram. In this study, both angiographic restenosis and myocardial ischemia as shown on myocardial perfusion scanning are considered indicators of coronary restenosis, and summarized in Table 2.

**Statistical analysis**

Uni-variate analysis was conducted for angiographic parameters for comparison between the dexamethasone group and the control group, the Chi-square test was used for the nominal variables (e.g., binary restenosis rate), and an independent t-test was used for the rational variables (e.g., stenosis diameter, reference segment diameter, and follow-up duration). Kaplan-Meier survival curves were used to depict the restenosis-free survival curves for the two groups. All the statistical analyses were conducted with SPSS 11th edition (SPSS Inc. Chicago, Illinois, USA). A p-value of < 0.05 was considered statistically significant.

**RESULTS**

**Clinical events**

All of the stenting procedures were successfully performed. The mean follow-up duration was 255.2 ± 130.7 days. One patient in the dexamethasone stent-group died of a non treatment related event (septicemia) one week after the procedure. Cause of death was reviewed and confirmed as not related by our institutional review board. There were no other significant clinical events. Four patients (2 each from the dexamethasone and the control groups) declined to have a follow-up CAG. Among these, three received a follow-up thallium myocardial perfusion scan, which revealed myocardial perfusion defects in the areas supplied by the study arteries in two patients from the control group (Table 1).

**Angiographic studies**

A total of 12 lesions were studied among the 7 patients who underwent follow-up CAG. The dexamethasone group had a smaller stenosis diameter than the control group (0.33 ± 0.22 versus 0.22 ± 0.06, p = 0.352). The binary restenosis rate of control group was higher, but not significantly, than that of the dexamethasone group (33% vs 0%, p = 0.202) (Table 2). However, when the angiographic results were combined with the clinical

<table>
<thead>
<tr>
<th>Table 2. Angiographic parameters</th>
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<tr>
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<tr>
<td>Reference diameter (mm)</td>
</tr>
<tr>
<td>MLD (mm)</td>
</tr>
<tr>
<td>Follow-up duration (days)</td>
</tr>
<tr>
<td>Angiographic stenosis (%)</td>
</tr>
<tr>
<td>Binary restenosis rate</td>
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<tr>
<td>Combined restenosis*</td>
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</table>

MLD: minimal luminal diameter. *Angiographic and the clinical restenosis rates (Nuclear medicine).
restenosis cases, the control group had a significantly higher restenosis rate than the dexamethasone group (44.4% vs. 0% $p = 0.042$). The Kaplan-Meier Survival curve demonstrated a trend of higher restenosis-free survival rate for the dexamethasone group (Figure 1). Of all the study patients, only one from the control group underwent target lesion revascularization.

**DISCUSSION**

**Drug Eluting Stent and In-stent Restenosis**

In-stent restenosis is still a major problem in interventional cardiology and may occur in > 20% of the treated lesions.\(^1\)\(^-\)\(^4\) The restenosis rates are especially higher for small vessels and for the diabetic patients.\(^5\)\(^-\)\(^7\) Intracoronary brachytherapy has been demonstrated to be effective in the prevention of ISR, but its effectiveness is limited by several factors such as geographic miss, delayed endothelial healing, late thrombosis, and edge effect.\(^3\) With the emergence of DES, interventional cardiologists are now equipped with a new user-friendly and highly effective device to combat ISR. There are 2 DES’s with extensive clinical experience: the SES from Cordis Company and the PES from Boston Scientific. Both stents have been demonstrated to be highly effective in the long-term prevention of ISR.\(^4\)\(^-\)\(^12\) Compared with the bare-metal stents, SES can reduce ISR by > 80% as demonstrated in angiographic and intravascular ultrasound studies.\(^4\) Even in diabetic patients, small vessels, and complex lesions, SES still proves superior to bare-metal stents.\(^5\)\(^-\)\(^7\) Stone et al. has demonstrated that PES was better than intra-coronary brachytherapy in the treatment of ISR.\(^13\)

**PC-coated stent in the prevention of in-stent restenosis**

Encouraged by the successful experiences of the coated stents eluting sirolimus or paclitaxol, investigators are looking for other possible effective materials with which to coat stents. PC coated stents can absorb chemicals with a molecular weight between 390 and 1150 daltons and, after vascular implantation, can slowly release the absorbed materials.\(^14\) The PC-coated stent as a drug delivery vehicle has been assessed in “in vivo models” using a radio-labeled analog of a relatively rapidly eluting drug, angiopeptin.\(^15\)\(^-\)\(^16\) Autoradiography showed that the drug was released locally into the vascular wall of the stented vessel and could be detected up to 28 days after implantation.\(^16\)

Results of several animal studies have shown successful prevention of neointimal hyperplasia after vascular injury and ISR after stenting using a PC-coated stent as a platform for drug delivery. The molecules that have been demonstrated capable of being absorbed and gradually released by PC-coated stents include angiopeptin,\(^15\) paclitaxel,\(^17\) estrogen,\(^18\) antisense oligodeoxy-nucleotides,\(^19\)\(^,\)\(^20\) anti-oxidants,\(^21\) and Zotalrolimus.\(^22\) All have been shown to be effective in inhibiting intimal hyperplasia in porcine or other animal models. It has also been found that PC stents coated with ph-VEGF plasmids can reduce ISR in rabbit vessels, although by a different mechanism — facilitation of epithelialization.\(^23\) Although PC-coated stents without additional coating have not been found to be superior to bare-metal stents in the prevention of ISR,\(^24\)\(^-\)\(^25\) Kwo and colleagues recently reported exciting results in a small-scale human study on the angiopeptin-absorbed PC-coated stents.\(^26\) In their study, no binary angiographic restenosis was noted among 16 lesions from 14 patients treated with PC-coated angiopeptin eluting stents.

**Dexamethasone in the prevention of in-stent restenosis**

Dexamethasone is well absorbed onto PC-coated stents and released slowly after intravascular stent implantation with an inflammatory reaction peak between 3
and 7 days.\(^27\) As a potent anti-inflammatory agent, dexamethasone is potentially a promising agent for ISR prevention after stent implantation. Sheerder and colleagues demonstrated that implantation of corticosteroid-loaded stents could reduce the inflammatory reaction as well as the intimal hyperplasia in porcine coronary arteries.\(^28\) Results of another in vitro study showed that corticosteroids can inhibit proliferation of smooth muscle cells derived from human atherosclerotic arteries.\(^29\) Although canine studies demonstrated similar inhibitory effects of corticosteroids on intimal hyperplasia,\(^30\) there are 2 human studies in which corticosteroids were found not to be effective in the prevention of ISR.\(^31,32\) We believe these results may be due to the method and duration of corticosteroid delivery. As shown in our study and in another European study using PC-coated stents to elute dexamethasone, only slow, continuous, and local eluting of the dexamethasone from a gradually releasing platform such as PC coated stent can achieve optimal inhibition of ISR.\(^33\)

The results of our study, although limited in size, provide evidence of inhibition of ISR using a PC-coated dexamethasone eluting stent in the Chinese population. Further, our experience could also facilitate the application of this convenient platform, the PC-coated stent, to other agents capable of inhibiting ISR.

In conclusion, the preliminary results of our small-scale study demonstrate an exciting effect of PC-coated stents with dexamethasone elution on ISR in coronary artery intervention in Chinese population. Larger scale studies are needed.

**LIMITATIONS OF THIS STUDY**

Because of its small sample size, the statistical power of this study is limited. In addition, ischemic change shown on a Thallium scan has been used in this study to represent evidence of restenosis; this is controversial in terms of an angiography-based study.

**REFERENCES**


Edelman ER, Rogers C. Pathobiologic response to stenting. Am J Cardiol 1998;81:4-6E.


用 phosphorylcholine 塗覆 dexamethasone 釋放支架
預防再狹窄：某醫學中心隨機研究

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目的 大約有五分之一的病人在接受冠狀動脈支架放置手術之後可能會出現支架內再狹窄的現象。造成這種現象的主要病理機轉之一可能是血管在支架放置後出現了發炎反應，繼而出現內皮增生和平滑肌細胞位移的情形。我們嘗試研究以 dexamethasone 處理已塗有 phosphorylcholine 的支架對於預防支架內再狹窄的效果。

方法 我們的研究共納入了十二個病人，其中包含了十七個直徑狹窄程度大於 70% 的冠狀動脈病兆。參照血管的直徑介於 2.7 mm 到 3.7 mm 之間 (平均值為 3.18 +/- 0.31 mm)。在開放標籤的隨機化後，有 9 個病灶被分配到對照組，也就是以未塗藥支架來處理這些病灶； 其餘的病灶則以用 dexamethasone 處理已塗有 phosphorylcholine 的支架來治療。所有的病人都接受了臨床追蹤，部分則加上血管攝影的追蹤。

結果 有一個病人在接受手術後的一個星期，因為非手術相關的原因死亡。而有四個病人 (包含 dexamethasone 組和對照組各二個) 拒絕接受血管攝影追蹤。但這四個病人中有三個人 (包括對照組的兩位及 dexamethasone 組的其中一位) 的 thallium 灌流攝影有心肌灌流不足的現象。剩下的七個病人 (共 12 個病灶) 中，dexamethasone 組直徑的狹窄程度比對照組較少，雖然沒有達到統計學上的意義 (0.33 +/- 0.22 比 0.22 +/- 0.06 mm, p = 0.352)。而對照組的再狹窄率也有較高的傾向 (33% 比 0, p = 0.202)。當我們同時考慮血管攝影和臨床上的再狹窄率後，我們發現對照組的再狹窄率比 dexamethasone 組要高 (44% vs. 0%, p = 0.042)。在全部的病人中，只有一個對照組的病人針對目標病灶再進行處理。

結論 從我們的初步結果可以得知對於要放置冠狀動脈支架的病人而言，塗有 dexamethasone 的支架可能對於預防支架內再狹窄扮演潛在的角色。

關鍵詞：支架內再狹窄、藥物釋放型支架、類固醇。