Application of Paclitaxel-Eluting Metal Stents in Renal Artery of Pig Model

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ABSTRACT

Background and Purpose: Recent reports concerning coronary, carotid, and femoral vasculature have proposed the use of drug-eluting metal stents (MS) to improve clinical and angiographic outcomes. Based on these reports, we used paclitaxel-eluting MS within an animal renal artery lumen and compared the results with those using a bare-metal stent.

Materials and Methods: The experimental model in this study was the female pig renal artery. Ten pigs with weights ranging from 25 to 30 kg were used. Twenty stents were placed, two in each animal. The MS placement was randomly performed in either the right or left renal artery of each animal. In 10 arteries, a 3.5 × 18 mm R-stent (group A) was placed; in the remaining 10 arteries, a 3 × 32 mm paclitaxel-eluting coronary stent (T-stent, group B) was inserted. Patency was estimated with the use of digital subtraction angiography, CT angiography, and virtual endoscopy at 24 hours and 1 month poststent placement.

Results: The positioning of the MS was successful in all cases. The initial angiographic result was maintained 24 hours after the intervention. No stent migration was seen, except for one paclitaxel stent that was acutely occluded. The one-month patency rate, as demonstrated by angiography, CT angiography, and virtual endoscopy, was 70% (8 arteries) in group A and 90% (9 arteries) in group B. The thickness of the endothelium and of the muscular coat was statistically significantly less in group B compared with group A (P = 0.0352 and P = 0.0046, respectively).

Conclusion: These preliminary experimental study results suggest that the paclitaxel-eluting MS is more efficient than the bare-metal stent when used within the pig renal artery. Further experimental and clinical studies are necessary to validate our preliminary encouraging results.

INTRODUCTION

Renal artery stenosis is a pathologic entity that leads primarily to renovascular hypertension. If the condition is left untreated, renal function impairment may occur.

Atherosclerosis, the most common cause, usually involves the proximal 2 cm of the renal artery. The result can be narrowing of the arterial lumen and destruction of the intimal layer.1 2

The advent of percutaneous transluminal angioplasty and stenting has revolutionized the management of renal artery stenosis. The use of metal stents (MS) has become common practice for the management of renal artery stenosis. Most investigators concur that stent implantation has produced good results in the management of ostial stenosis. Nevertheless, treatment outcomes are still far from ideal.1 3

Recent reports related to the coronary, carotid, and femoral vasculature have proposed the use of drug-eluting MS, ame-
lorating the final clinical and angiographic outcome. Various eluting agents have been used to inhibit thrombus formation (such as heparin), inflammation (such as dexamethasone), and/or cellular proliferation (such as paclitaxel).4–12 Drug-eluting stents are advantageous when compared with systemic drug administration; they provide a higher drug concentration in tissue adjacent to the stent, with minimal systemic side effects.13–20 In a recent study by our group, drug-eluting MS have been used in pig ureters with encouraging results.21

Based on a previous encouraging coronary experience, we initiated the use of paclitaxel-eluting MS within the animal renal artery lumen and compared results with those in which a bare-metal stent was used.

MATERIALS AND METHODS

The experimental model used in this study was the renal artery of female pigs. The protocol was approved by the Institutional Animal Care Committee of our academic institution.

The animals were allowed a minimum of 72 hours before the procedure to recover from the stress of transportation. Food was withheld for 12 hours before administration of anesthesia. All interventions were performed under general anesthesia in a standard operating room, equipped with a C-arm fluoroscope. At the beginning of surgery, ketamine (20 mg/kg body weight) in combination with xylazine (2 mg/kg body weight) were used; thereafter, anesthesia was maintained with inhaled isofluorothane (3%–4%). Intramuscular administration of morphine sulfate (0.1 mg/kg body weight) was used postoperatively to ensure the animals’ comfort.

For the study, 10 pigs with weights between 25 and 30 kg were used. Twenty stents were placed; two in each animal. MS were randomly placed in either the right or left renal artery of each animal. In 10 arteries, a 3.5 × 18 mm R-stent (Orbus Medical Technologies, The Netherlands) (group A) was placed; in the rest of the 10 arteries, a 3 × 32 mm paclitaxel-eluting coronary stent (Taxus®, Boston Scientific, Natick, MA) (T-stent, group B) was inserted.

The technique of stent insertion has been previously described.2 Briefly, under sterile conditions and after palpating the femoral artery, a 21-gauge needle was inserted in the vessel. Under fluoroscopy, a 0.018-inch guide wire was advanced to the abdominal aorta. A long 5F sheath was then placed, a hydrophilic 4F Cobra catheter (Cook Medical, Bloomington, IN) was advanced to the renal artery, and a 0.014-inch guide wire was positioned. The stents were then introduced, and proper implantation was confirmed angiographically (Fig. 1). The Taxus device consists of a stainless steel stent coated with the taxane paclitaxel and a polymer carrier premounted on a balloon catheter. The TransLute™ polymer is a proprietary polymer carrier that protects the drug and maintains coating integrity during preparation, delivery, and stent expansion. The polymer controls the release of paclitaxel, allowing consistent drug release and more uniform drug distribution. The taxanes

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**TABLE 1. MEASUREMENTS OF HYPERPLASIA FORMATION**

<table>
<thead>
<tr>
<th>Pig</th>
<th>Endothelium (cm)</th>
<th>Muscular coat (cm)</th>
<th>Connective tissue coat (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig 1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.25</td>
</tr>
<tr>
<td>Pig 2</td>
<td>0.1</td>
<td>0.15</td>
<td>0.12</td>
</tr>
<tr>
<td>Pig 3</td>
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<td>0.14</td>
<td>0.2</td>
</tr>
<tr>
<td>Pig 4</td>
<td>0.0</td>
<td>0.1</td>
<td>0.20</td>
</tr>
<tr>
<td>Pig 5</td>
<td>0.15</td>
<td>0.18</td>
<td>0.21</td>
</tr>
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<td>0.05</td>
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<td>0.2</td>
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<tr>
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<td>0.17</td>
<td>0.21</td>
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<td>Pig 10</td>
<td>0.0*</td>
<td>0.15*</td>
<td>0.20*</td>
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<table>
<thead>
<tr>
<th>Pig</th>
<th>Endothelium (cm)</th>
<th>Muscular coat (cm)</th>
<th>Connective tissue coat (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig 1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.28</td>
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<tr>
<td>Pig 2</td>
<td>0.18</td>
<td>0.24</td>
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<td>0.19</td>
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</tr>
<tr>
<td>Pig 4</td>
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<td>Pig 9</td>
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<td>Pig 10</td>
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<td>0.24*</td>
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*The last one of the T-stents and the last two of the R-stents were completely acutely occluded.

FIG. 1. Intra-arterial angiography demonstrates both right (T-stent) and left (R-stent) patent stented renal arteries.
are widely used in cancer treatment as potent antiproliferatives. Paclitaxel induces almost complete growth inhibition within a dose range of 1.0 to 10.0 mmol/L even after a short single-dose application; the agent is cytotoxic, however, at higher concentrations.

The R-stent is a balloon expandable stainless steel vascular prosthesis. It has two radio-opaque marker bands that delimit the working length of the balloon, and it is supplied mounted on a low profile monorail dilation balloon catheter with a lumen diameter of 0.014 inch.

Patency of stented arteries was estimated with the use of digital subtraction angiography, CT angiography, and consequently, virtual endoscopy at 24 hours and 1 month after the procedure. Euthanasia and harvesting took place thereafter. All the renal arteries and their interconnecting aortic segment were extracted and examined histopathologically.

RESULTS

No perioperative or postoperative complications were observed except 2 minor hematomas at the area of the sheath insertion. All animals survived the follow-up period. The positioning of the endoprostheses was successful in all 20 procedures. Preoperatively and postoperatively, 100 mg aspirin and 500 mg cefprozil were added in the food of the animals until the end of the study.

All stents were dilated at the end of the procedure to obtain good expansion and good anchorage to the arterial wall. We did not observe any immediate stent migration.

The initial angiograms at 24 hours after stent insertion did not reveal any stent migration, with the exception of one paclitaxel stent that was acutely occluded. The 1-month patency rate, as depicted by angiography, CT angiography, and virtual
endoscopy, was 70% (8 arteries) in group A and 90% (9 arteries) in group B (Fig. 2).

Pathologic examination of the stents was conducted after the 1-month imaging follow-up (Fig. 3). The differences in hyperplasia formation between the renal arteries managed with R-stents and T-stents were compared with the application of the paired t-test. More specifically, for each pig we measured the thickness of the endothelium, the muscular coat, and the connective tissue coat in the two renal arteries (one with the R-stent and the other with the T-stent, respectively). The measurements of hyperplasia formation are shown in Table 1.

All statistical tests were two-sided, and the threshold of sta-

FIG. 3. Macroscopic images display obstructed endothelium in group A (R-stent) (a) and patent endothelium in group B (T-stent) (b).

FIG. 4. When the hyperplastic endothelial and muscular layers in group A (R-stent) (a) are compared with those in group B (T-stent) (b), the endothelial layer in group B is clearly thinner and smoother and the lamina propria is clearly seen between the endothelium and the muscular layer.
tical significance was set at 5%. The SPSS v.11 statistical software package was used for all data analysis and statistical calculations.

The thickness of the endothelium was lower in group B compared with group A ($P = 0.0352$), and the thickness of the muscular coat was lower in group B compared with group A ($P = 0.0046$). The differences were statistically significant. The thickness of the connective tissue coat did not differ statistically significantly in group B compared with group A ($P = 0.0721$). There was more hyperplasia related to R-stents (group A) compared with T-stents (group B) (Fig. 4).

**DISCUSSION**

The introduction of drug-eluting stents represents a major advantage in the battle against vascular restenosis. Stent restenosis is caused primarily by neointimal hyperplasia. Postangioplasty injury leads to an uncontrolled proliferation of smooth muscle cells around the vessel intima and the deposition of extracellular matrix material, hindering luminal patency.13–20

Drug-eluting stents have proved their effectiveness in constraining the restenosis rate after coronary intervention. Various drugs that were bound on polymers offered different pharmacokinetic properties and biocompatibility to promote prevention of restenosis were tested. One of the first was paclitaxel, with promising results.4–12

Paclitaxel is a new anticancer agent that promotes the polymerization of tubulins, inhibits the disassembly of microtubules, and induces the expression of tumor necrosis factor $\alpha$ (TNF-$\alpha$) gene. The microtubule dynamics required for normal cell division are interrupted, thus causing the death of the cell. This characteristic of the drug led to the hypothesis that it may inhibit neointimal hyperplasia, leading to restenosis prevention. Using this concept, many trials in coronary artery models have been conducted.4–12

Heldman and coworkers4 and Hong and associates5 showed that paclitaxel reduces intimal and medial proliferation threefold 7 days after stenting and eliminates later intimal restenosis in a porcine coronary model. Liatsikos and colleagues21 have recently checked the efficacy of paclitaxel-eluting stents in the pig model ureter with encouraging results.

In humans, the experience with paclitaxel-eluting stents has been positive, reducing intimal hyperplasia and thus the restenosis rate. Granillo and associates22 reported the case of a 48-year-old man with bilateral renal artery stenosis who was treated with paclitaxel-eluting stents. These investigators showed a patent arterial lumen at 3-month follow-up.

To our knowledge, ours is the first experimental study evaluating the use of drug-eluting stents within the renal vasculature. We used the porcine animal injury model, which is a widely used animal model for the study of restenosis. Porcine arteries have a similar structure and physiology to that of human arteries. Particularly in peripheral arteries, previous experiments have shown that neointimal hyperplasia is generated 4 weeks after overstretch injury and the degree of hyperplasia is strongly connected to the degree of damage induced in the arterial wall. Healing stages are reported to be surprisingly sim-

The present study has two main drawbacks. The relatively short follow-up period of 1 month did not allow us to prove the long-lasting effectiveness of these stents. Nevertheless, inflammatory processes were generated with higher rates in the bare-metal stents, and more hyperplasia developed in animals with R-stents when compared with animals with T-stents. In addition, we did not have an actual stenosis to treat.

**CONCLUSION**

Drug-eluting MS are an innovation that will soon prove itself within the renal artery lumen. Further clinical studies are necessary before there is a clear indication to use these stents for the management of arterial restenosis.

**ACKNOWLEDGMENT**

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**REFERENCES**


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ABBREVIATIONS USED

CT = computed tomography; MS = metal stents.