Catheterization and Cardiovascular Interventions 72:294–298 (2008)

Successful Revascularization of Re-Stenosis of Lower Extremity Arteries With Localized Delivery of Paclitaxel

Faisal Latif, MD and Thomas A. Hennebry,* MB BCH BAO, FSCAI, FACC

Restenosis after percutaneous revascularization techniques is a challenging issue in patients with severe peripheral arterial disease. We report two cases where multiple revascularization techniques had been used previously, but restenosis occurred. We used an irrigation balloon to deliver paclitaxel locally into the tissues to obtain better results. © 2008 Wiley-Liss, Inc.

Key words: paclitaxel; drug delivery; restenosis; peripheral vascular disease

INTRODUCTION

Percutaneous revascularization procedures lead to significant improvement in quality of life and claudication distance [1]. Restenosis remains a challenging issue after percutaneous revascularization procedures for peripheral arterial disease. Anti-coagulants including low-molecular weight heparin have not yielded any significant improvement in results [2].

Newer techniques continue to emerge now and then to bring about improvement in short- and long-term outcomes. Various interventions including endovascular brachytherapy, arterial gene therapy and photo-angioplasty have shown somewhat favorable results, however, have not proved to be very convincing [3]. Drug-eluting stents (DES) using sirolimus have been tested in the peripheral vasculature, however, the results have not been encouraging [4]. We report a novel technique utilized in two patients for localized delivery of paclitaxel as treatment for restenosis in peripheral arterial disease.

Case 1

A 60-year-old male with history of peripheral arterial disease who had a long-standing right common iliac artery occlusion and underwent femoral–femoral (fem–fem) crossover grafting 6 years ago. Subsequently, he developed left common iliac artery stenosis and over the years, underwent multiple repeat revascularization procedures including angioplasty and stenting at an outside facility. The patient reported mild improvement in claudication symptoms for a few months only after each of these procedures. He was referred to our hospital and had severe symptoms with claudication distance being only 25 yards. He had a past medical history of hypertension and dyslipidemia in addition to a 60 pack year smoking history. On physical examination, he had a faintly palpable dorsalis pedis (DP) pulse in right foot and 1+ DP and posterior tibial pulse in left foot.

Arterial access was obtained in left common femoral artery (CFA) below the level of fem–fem crossover graft using ultrasound guidance. Angiography showed that left common iliac artery had multiple sandwiched stents with a focal 80% lesion with a 60 mm Hg pressure gradient (Fig. 1). Right common iliac was known to be completely occluded from before. Left external and internal iliac, superficial femoral and profunda femoris arteries were patent. Fem–fem crossover graft was also patent. Intravascular ultrasound (IVUS) of the stenosed portion of the left common iliac artery showed a luminal area of 34 mm^2 (diameter 2.7 mm, Fig. 2A) compared with a reference vessel area of 134 mm^2 (diameter 11 mm). The original stent was 8 mm in diameter. Laser atherectomy of left common iliac artery was performed which increased minimal lumen area from 34 to 80 mm (Fig. 2B) and reduced the pressure gradient from 80 to 20 mm Hg. Then, an 8 × 10 mm Vascular Clearway™ irrigation balloon

Cardiovascular Section, Department of Internal Medicine, University of Oklahoma Health Sciences Center, Oklahoma, Oklahoma

Conflict of interest: Nothing to report.

*Correspondence to: Thomas A. Hennebry, 920 Stanton L. Young Blvd., WP# 3010, Oklahoma City, OK 73104.
E-mail: thomas-hennebry@ouhsc.edu

Received 24 February 2008; Revision accepted 18 March 2008

DOI 10.1002/ccd.21598
Published online 21 July 2008 in Wiley InterScience (www.interscience.wiley.com).

© 2008 Wiley-Liss, Inc.

(Atrium, Hudson, NH) was used to infuse 1.7 mg of paclitaxel diluted in 10 cc of normal saline at the lesion site along with angioplasty at 3 atm. IVUS, at this stage revealed a luminal area of 90 mm^2 with no pressure gradient across the lesion (Fig. 2C). Figure 3 shows the final angiographic image of the left common iliac artery. His claudication distance improved significantly. Four months post-procedure, the patient continues to report a significantly improved quality of life with claudication distance of 500 yards. At this point, his ankle brachial index on the right is 1.1, whereas 0.73 on the left.

Fig. 1. AP fluoroscopic projection demonstrating in-stent restenosis in the left common iliac artery.

Case 2

A 67-year-old female with a history of coronary artery bypass grafting and severe peripheral arterial disease of lower extremities presented with Rutherford category 4 ischemia in her left lower extremity. Her left superficial femoral artery (SFA) was known to be occluded for almost 10 years and she had left femoro-popliteal bypass grafting, which was also known to be occluded for many years. She had had angioplasty and stenting as well as cryoplasty of left SFA on different occasions within the previous year. On duplex scanning, she was found to have restenosis in the left SFA. Right common femoral artery (CFA) was accessed and in addition to a 70% lesion in left CFA, a 90% ostial lesion was found in SFA (Fig. 4). A 0.035-inch guidewire (Rosen wire; Cook Critical Care) was passed into the left SFA and a 30 cm long sheath (Cook Critical Care) was passed up and over the aortic bifurcation. Laser atherectomy was performed using turbo booster 2.0 mm over-the-wire laser system (Spectranetics, Colorado Springs, CO) in left CFA as well as SFA. A 6 × 10 mm Vascular Clearway™ irrigation balloon (Atrium, Hudson, NH) was used to deliver a total of 3 mg of paclitaxel locally into the most significant lesion sites performing two inflations each in CFA and SFA. Less than 20% residual stenosis was present at the end of the procedure in left SFA (Fig. 5), whereas a 20% residual stenosis in left CFA remained. Her symptoms improved significantly and a repeat angiogram, which was performed via access sheath during a follow up procedure to revascularize the right lower extremity, demonstrated no recurrence of stenosis in the left SFA, 3 months later (Fig. 6).

Vascular Clearway™ irrigation balloon (Atrium, Hudson, NH) is an irrigating, micro-porous PTFE balloon catheter which creates a low-pressure fluid layer

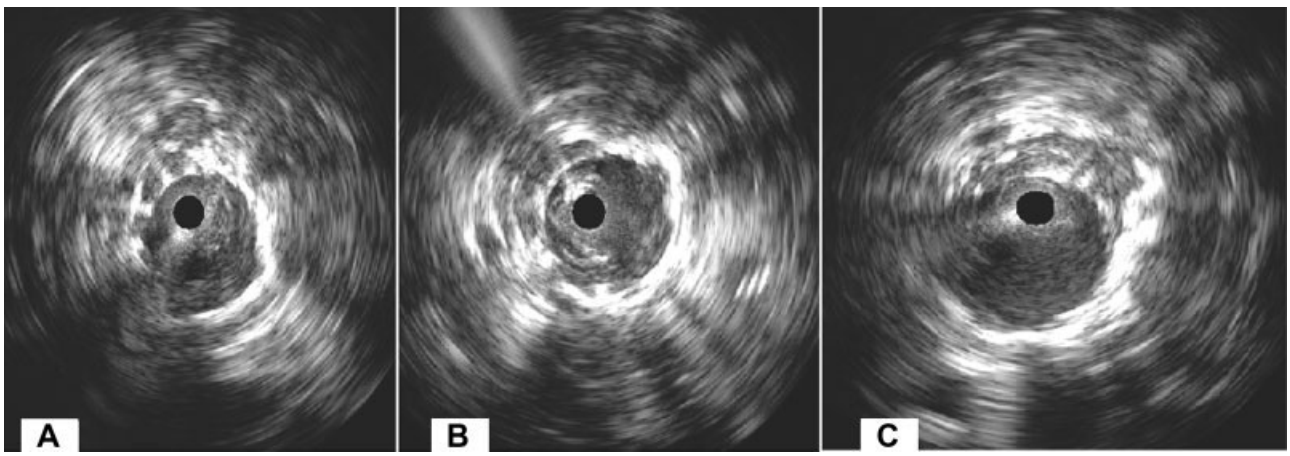

Fig. 2. (A) IVUS showing the in-stent restenosis in left common iliac artery. (B) IVUS showing the result after laser atherectomy. (C) IVUS showing the final result following local delivery of paclitaxel.

Fig. 3. Left anterior oblique projection of the left common iliac artery showing a good runoff with no significant lesion after localized delivery of paclitaxel.

Fig. 4. AP fluoroscopic projection showing the 90% ostial lesion in left superficial femoral artery.

over the balloon which allows for local delivery of thrombolytic, or, as in our case, chemotherapeutic agents to reduce neo-intima formation (Fig. 7). The PTFE surface along with the low pressure of the balloon reduces the chance of rupture of the vessel and damage to the intima when used in and around a deployed stent.

Fig. 5. Left anterior oblique projection demonstrating a mild residual stenosis in the ostial left superficial femoral artery.

DISCUSSION

Curtailing restenosis after percutaneous angioplasty in the peripheral vascular beds is a challenging avenue and often requires thoughtful combination of various available technologies. Both of our patients had received multiple treatments utilizing different modalities, yet had not experienced much relief with prompt restenosis. Localized delivery of Paclitaxel using this newly available irrigation balloon (Vascular Clearway™, Atrium) presents as a newer technique available for restenotic lesions in peripheral vasculature, with good results, at least in the short term. The dose of paclitaxel that we delivered was an extrapolation of the dosage used in paclitaxel-eluting coronary DES (Taxus, Boston Scientific), calculating the volume of the vessel to which it was to be delivered. The dose used is very small compared with the chemotherapeutic dose of paclitaxel, and therefore, no systemic side effects were observed in our patients.

After percutaneous transluminal angioplasty (PTA), there is disruption of the atherosclerotic plaques and an extensive remodeling process of the arterial wall. Luminal loss after PTA is due to inward vessel remodeling and neo-intimal proliferation [5]. Additionally, inflammation has also been shown to play a critical role in vascular response to injury and has been implicated as a major factor in restenosis after angioplasty in peripheral vasculature, as depicted by an increase in C-reactive protein, D-dimer and P-selectin after angioplasty [6]. Paclitaxel has been shown to stabilize

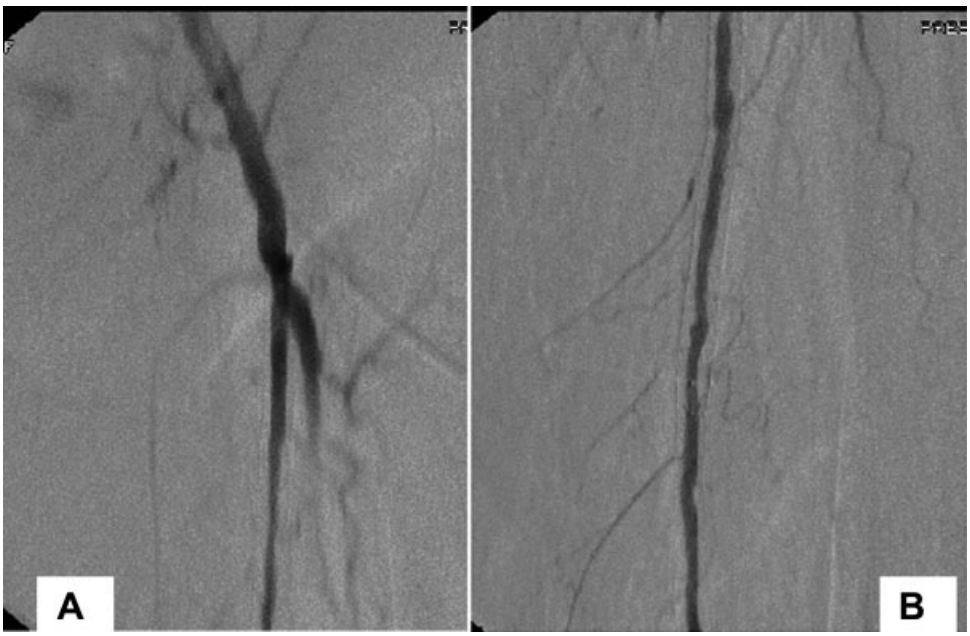

Fig. 6. Three-month follow up angiogram showing (A) patency of the ostium of the superficial femoral artery and (B) patency of the superficial femoral artery.

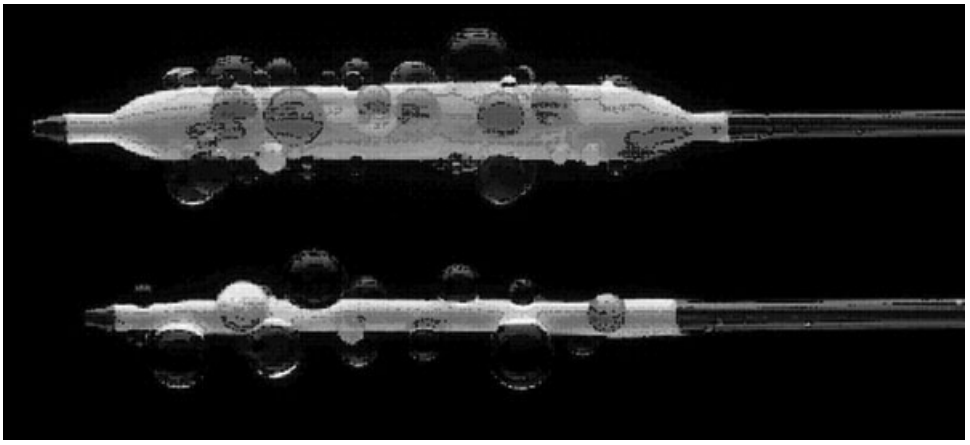

Fig. 7. Image of the Vascular Clearway™ balloon catheter demonstrating the infusion of paclitaxel through its micro-porous PTFE surface.

microtubules in fibroblast cells and therefore, inhibits smooth muscle proliferation after angioplasty [7,8]. With paclitaxel, the idea is to instill the drug deeply into the local tissues and therefore, inhibit neo-intimal hyperplasia and decrease the inflammatory reaction. In contrast to other anti-proliferative drugs, Paclitaxel has properties which make it a better choice for local delivery and prevent smooth muscle proliferation in restenosis after angioplasty or stent implantation. These include a lipophilic character which promotes rapid cellular uptake and its unique mode of action supports a long-lasting anti-proliferative action even after a brief, single dose application at very low concentrations [9,10]. Localized delivery of paclitaxel has been tested in animal models and has been shown to reduce neo-intima formation [11]. Prosthetic graft models have also demonstrated paclitaxel's anti-inflammatory effects as depicted by the presence of fewer macrophages around the grafts [12]. A recent study has reported localized delivery of paclitaxel using a different technique [13].

CONCLUSION

Ours is the first report of the use of localized delivery of paclitaxel in humans in the peripheral arterial

bed using an irrigation balloon and has yielded good short term results. Further large-scale evaluation will be necessary to validate long term outcomes.

REFERENCES

1. Deutschmann HA, Schoellnast H, Temmel W, Deutschmann M, Schwantzer G, Fritz GA, Brodmann M, Hausegger KA. Endoluminal therapy in patients with peripheral arterial disease: Prospective assessment of quality of life in 190 patients. Am J Roentgenol 2007;188:169–175.
2. Koppensteiner R, Spring S, Amann-Vesti BR, Meier T, Pfammatter T, Rousson V, Banyai M, van der Loo B. Low-molecular-weight heparin for prevention of restenosis after femoropopliteal percutaneous transluminal angioplasty: A randomized controlled trial. J Vasc Surg 2006;44:1247–1253.
3. Schainfeld RM. Potential emerging therapeutic strategies to prevent restenosis in the peripheral vasculature. Catheter Cardiovasc Interv 2002;56:421–431.
4. Ellozy SH, Carroccio A. Drug-eluting stents in peripheral vascular disease: Eliminating restenosis. Mount Sinai J Med 2003;70: 417–419.
5. Wyttenbach R, Gallino A, Alerci M, Mahler F, Cozzi L, Di Valentino M, Badimon JJ, Fuster V, Corti R. Effects of percutaneous transluminal angioplasty and endovascular brachytherapy on vascular remodeling of human femoropopliteal artery by noninvasive magnetic resonance imaging. Circulation 2004;110:1156–1161.
6. Wahlgren CM, Sten-Linder M, Egberg N, Kalin B, Blohme L, Swedenborg J. The role of coagulation and inflammation after angioplasty in patients with peripheral arterial disease. Cardiovasc Intervent Radiol 2006;29:530–535.
7. Schiff PB, Horwitz SB. Taxol stabilizes microtubules in mouse fibroblast cells. Proc Natl Acad Sci USA 1980;77:1561–1565.
8. Sollott SJ, Cheng L, Pauly RR, Jenkins GM, Monticone RE, Kuzuya M, Froehlich JP, Crow MT, Lakatta EG, Rowinsky EK, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. J Clin Invest 1995;95:1869–1876.
9. Straubinger RM, Sharma A, Murray M, Mayhew E. Novel Taxol formulations: Taxol-containing liposomes. Monogr Natl Cancer Inst 1993;15:69–78.
10. Jordan MA, Toso RJ, Thrower D, Wilson L. Mechansim of mitotic block and inhibition of cell proliferation by Taxol at low concentrations. Proc Natl Acad Sci USA 1993;90:9552–9556.
11. Kohler TR, Toleikis PM, Gravett DM, Avelar RL. Inhibition of neointimal hyperplasia in a sheep model of dialysis access failure with the bioabsorbable Vascular Wrap paclitaxel-eluting mesh. J Vasc Surg 2007;45:1029–1038.
12. Axel DI, Kunert W, Göggelmann C, Oberhoff M, Herdeg C, Küttner A, Wild DH, Brehm BR, Riessen R, Köveker G, Karsch KR. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation 1997;96:636–645.
13. Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwälder U, Beregi JP, Claussen CD, Oldenburg A, Scheller B, Speck U. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med 2008;358:689–699.