The treatment of peripheral arterial disease (PAD) costs the United States roughly $21 billion annually and affects more than 5,000,000 people. Percutaneous transluminal angioplasty (PTA) is the most common mode of endovascular treatment for PAD and its most severe manifestation, critical limb ischemia (CLI). CLI, associated with extensive atherosclerotic disease of below-the-knee (BTK) vessels, is burdened by high morbidity and mortality. Treatment of these vessels presents a great challenge to endovascular interventionist due to the high incidence of long chronic total occlusions and calcified lesions; it has historically been associated with high restenosis rates and poor long-term clinical patency.

The recent advent of drug-coated balloons (DCBs) was designed to overcome the limitations of stents and balloon angioplasty in the treatment of PAD. Clinical DCB trials have shown promising results in the treatment of femoropopliteal disease; however, in the BTK arteries, results have been limited and long-term success has yet to be determined. DCBs were designed similar to drug-eluting stents, as antiproliferative agents are stored in the intima. Mechanistically, this concept is flawed since the deposition of drugs on the intima leads to delayed healing and incomplete endothelialization, prolonging thrombosis. Novel catheters that can deliver therapeutic agents directly to the medial wall, treat multiple lesions, and minimize any drug loss during the process offer clear advantages over DCBs.

The Occlusion Perfusion catheter (OPC; Advanced Catheter Therapies) is a universal delivery catheter capable of delivering paclitaxel to the medial layer. The OPC delivers therapeutic agents by creating a treatment chamber between two occlusion balloons through which the agent is delivered. The delivery of the therapeutic agent is mechanically driven, using pressure that can be measured inside the treatment chamber (Figure 1). It was hypothesized that using this approach, paclitaxel could be delivered uniformly both circumferentially and longitudinally into the vessel wall, which has been confirmed in preclinical studies.
TECHNICAL/ENGINEERING ASPECTS OF THE OPC DESIGN

The OPC, a multilumen balloon catheter, is designed to temporarily occlude the target lesion from blood flow, flush the blood from the treatment chamber, and then locally deliver the therapeutic agents into the artery (Figure 2). A built-in pressure sensor continuously monitors the chamber during delivery. Unlike DCBs, the OPC is designed to deliver an agent to the media of the vessel wall, circumferentially and longitudinally.

The design of the OPC arrived from years of clinical practice and the realization of the limitations and potential complications of balloon angioplasty, stents, and DCBs. These limitations included the inability to treat multiple lesions with a single device, drug loss, minimal flexibility in agent delivery, etc. The solution to overcome these limitations seemed to be a universal drug-delivery device. Based on the simple idea of a universal drug delivery system, a set of requirements was developed to guide the design and ultimately provide an effective drug-delivery system to treat peripheral disease (Table 1). In 2008, Advanced Catheter Therapies was established and the OPC became a reality.

BENCH-TOP & PRECLINICAL ASSESSMENT OF THE OPC

The initial feasibility and safety assessment of the OPC was performed using a set of bench-top and preclinical studies to visualize
the distribution and retention of paclitaxel within the arterial wall and measure quantitatively the uptake of paclitaxel and vascular response. For these studies, paclitaxel was selected as the antiproliferative agent due to its proven clinical effectiveness.

Bench-top experiments to evaluate the OPC were conducted in a novel ex vivo system capable of rapidly evaluating arterial drug levels and visualizing drug penetration. Figure 3 shows a representative image of a porcine carotid artery being treated by a perfusion catheter within the ex vivo bioreactor system. Confocal analysis demonstrated that fluorescent paclitaxel (Flutax-1) was delivered to the artery in a uniform pattern. Additionally, ex vivo results demonstrated variable drug penetration based on treatment chamber pressure, which can be monitored and measured with the OPC.

Following ex vivo studies, in vivo studies were performed using the rabbit ilio-femoral injury model to determine the impact of excipient on arterial paclitaxel retention. Arteries were treated with either paclitaxel alone or paclitaxel with an excipient using the OPC. An angiogram of the OPC within the ilio-femoral artery is shown in Figure 4. In comparing initial paclitaxel loading at 1 hour to 3 days, a significant decrease in the non-excipient group was observed (1 hr: 246.9 ± 120.3 ng vs 3 days: 2.92 ±2.91 ng; \(P=0.01\)), whereas no significant decrease was observed with the excipient group (1 hr: 107.7 ± 62.1 ng vs 3 days: 40 ± 23.0 ng; \(P=0.82\)). Results from the bench-top and animal models demonstrated our capability to deliver paclitaxel in a uniform manner and at therapeutic levels into the medial layer wall.

**EARLY CLINICAL RESULTS**

Clinical testing of the OPC was initiated in 2015. A prospective, multicenter, first-in-human registry of a novel delivery catheter delivering liquid paclitaxel was conducted in 10 patients. The primary efficacy endpoint at 6 months was freedom from clinically driven target-lesion revascularization (CD-TLR) and the primary safety endpoint at 1, 3, and 6 months was thrombosis, major amputation in the target limb, and target-limb related death.

All patients tolerated the procedure well, with no reports of adverse procedural events. Twelve lesions in 10 patients were treated (mean lesion length, 83.3 ± 49.2 mm; range, 30–182 mm). At 6-month follow-up, the CD-TLR rate was 30% (3 out of 10 patients). Zero out of 10 patients demonstrated thrombosis, major amputation in the target limb, and target-limb related death at the 1-month, 3-month, and 6-month follow-up intervals. An example of a lesion angiogram before and after treatment is shown in Figure 5.

This first-in-human experience obtained in a multicenter study of real-world de novo and restenotic lesions demonstrates a favorable safety and efficacy profile at 6 months. A randomized comparison to current DCBs should be performed to further validate this approach and positive experience.
DISCUSSION

The initial experimental and clinical studies provide the first evidence of the capability of the OPC to deliver liquid paclitaxel uniformly into the medial wall, as well as the feasibility, safety, and initial efficacy of paclitaxel administered using a universal delivery catheter for the prevention of restenosis in infrapopliteal de novo and restenotic lesions. Device success, defined as the ability to deliver paclitaxel to the interventional treatment area as intended, was 93% in the initial clinical study. The primary safety outcome demonstrated no treatment-related deaths, thrombosis, or major amputation. The CD-TLR rate was 30% in lesions with a mean length of 83.3 ± 49.2 mm. Together, these initial clinical results show the promise of such technology to treat heavy peripheral atherosclerotic disease, particularly for BTK applications.

The safety and utility profile of the OPC offers a promising option to utilize this device for the treatment of infrapopliteal lesions in CLI patients. The design of the OPC system ensures no loss of paclitaxel during tracking of the device to the lesion, as the drug is not infused at the treatment location until the treatment chamber has been established by inflation of the occlusion balloons. The absence of drug coatings and the use of liquid paclitaxel minimizes the risk of embolization, as observed in DCB studies. In comparison to a DCB, there is minimal barotrauma during drug delivery by the OPC, as balloon sizing is not a factor. The drug is delivered directly to the medial layer and multiple lesions can be treated with one device. This single-dose approach works well due to the potency and hydrophobicity of paclitaxel, facilitating a rapid cellular uptake and long-lasting effect on smooth muscle cell proliferation and migration.

FUTURE PERSPECTIVE

The experience obtained from a combination of bench-top and multicenter clinical studies treating de novo and restenotic lesions has demonstrated OPC safety and efficacy. The delivery of liquid paclitaxel using the OPC under controlled pressure has been shown to be technically achievable without procedural complications. The feasibility and initial efficacy of this device provide encouragement for this new technique, with the potential to be an alternative approach for peripheral occlusive disease revascularization. In particular, the ability to treat very long or multiple lesions with a single device can provide a more economical option. Although only a small cohort of clinical studies has been published, the safety profile is particularly favorable in view of recent concerns regarding adverse events with DCB for BTK applications. Longer-term follow-up and larger clinical studies will be needed and is currently ongoing to support the recent clinical findings of this technology with head-to-head comparisons between DCB and balloon angioplasty.

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Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Teeslink holds a patent for the Occlusion Perfusion catheter and reports personal fees from Advanced Catheter Therapies from his roles as Inventor/Co-Founder/Scientific Advisor. Dr Yazdani is on the Scientific Advisory Board of Advanced Catheter Therapies and Toray Industries and reports grants from Toray and Bard-Lutonix.


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