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PERIPHERAL

# Local Ultrasound to Enhance Paclitaxel Delivery After Femoral-Popliteal Treatment in Critical Limb Ischemia

## The PACUS Trial

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**ABSTRACT**

**OBJECTIVES** The aim of this study was to evaluate the safety and efficacy of percutaneous catheter-delivered ultrasound energy to improve local paclitaxel delivery effects in patients with critical limb ischemia (CLI) treated for femoral-popliteal arterial disease.

**BACKGROUND** Treatment of patients with CLI continues to be the greatest challenge in peripheral artery disease; in particular, treatment of femoral-popliteal chronic total occlusion is characterized by poor primary patency.

**METHODS** This single-center, single-blind, randomized trial included 56 patients with CLI randomly assigned to treatment in 2 groups: 28 patients (the control group) were treated with drug-eluting balloons, and 28 patients (the study group) were treated with intravascular ultrasound using the CardioProlific Genesis System followed by local administration of a liquid mixture of iopromide 370 and paclitaxel 1.0 μg/mm$^3$. In the study group, mean lesion length was 168.8 mm, and 21 patients had calcifications. In the control group, mean lesion length was 164 mm, and 23 patients had calcifications.

**RESULTS** No adverse procedural events were observed; all 56 patients tolerated the procedure well. At 6-month follow-up, no myocardial infarction, deaths, or amputations were observed in either group. In the study group, the rate of restenosis at 6 months was 3.6% (1 of 28), and the rate of target lesion revascularization (TLR) was 0% (0 of 28); at 12 months, the rate of TLR was 3.8% (1 of 26), and the rate of amputation was 0% (0 of 26). In the control group, the rate of restenosis at 6 months was 21.4% (6 of 28), and the rate of TLR was 10.7% (3 of 28); at 12 months, the rate of TLR was 36% (9 of 25), and the rate of amputation was 16% (4 of 25).

**CONCLUSIONS** This study demonstrates encouraging results at 6- and 12-month follow-up in patients treated with ultrasound and paclitaxel compared with drug-eluting balloons. Larger multicenter studies are required to validate this approach. (J Am Coll Cardiol Intv 2016;9:2147–53) © 2016 by the American College of Cardiology Foundation.

Critical limb ischemia (CLI) secondary to superficial femoral or popliteal artery disease is among the greatest challenges for endovascular interventionists (1). Long chronic total occlusions and calcific lesions are associated with high restenosis rates and poor long-term clinical patency (2). Drug-eluting balloons (DEBs) have shown promise in decreasing restenosis rates but have not been extensively evaluated in CLI (3). Patients with CLI have a worse prognosis than those with claudication (4). Lesion characteristics such as Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease classification, calcification, lesion length, and run-off affect primary patency rates of percutaneous interventions in these patients (5). Local delivery of paclitaxel has been demonstrated to decrease the rate of restenosis in multiple DEB trials (3,6) and the ZILVER PTX stent trial (7). The THUNDER

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**ABBREVIATIONS AND ACRONYMS**

**BTK** = below-the-knee

**CLI** = critical limb ischemia

**DEB** = drug-eluting balloon

**DSA** = digital subtraction angiography

**DUS** = duplex ultrasonography

**FU** = follow-up

**MI** = myocardial infarction

**PTA** = percutaneous transluminal angioplasty

**SFA** = superficial femoral artery

**TLR** = target lesion revascularization

(Local Taxane With Short Exposure for Reduction of Restenosis in Distal Arteries) trial demonstrated unsatisfactory results with local paclitaxel injection compared with DEBs (8). In DEB trials, a 10% to 20% rate of restenosis still persists in patients with claudication, and none of these trials have focused on CLI (3,6,9), in which results with other treatment modalities have been associated with worse clinical outcomes and higher rates of restenosis.

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Basic scientific studies have demonstrated that an ultrasound frequency of 20 kHz enhances vascular permeability and can modify medial calcification, making a vessel more compliant and therefore distensible (10,11). Ultrasound energy has been shown to create microchannels in the medial/intimal calcium, enhancing drug penetration and migration from the intima to the adventitia (12).

The purpose of the PACUS (Ultrasound to Enhance Paclitaxel Uptake in Critical Limb Ischemia) trial was to evaluate the safety and effectiveness of intravascular percutaneous catheter-delivered high-intensity, low-frequency ultrasound energy in connection with local paclitaxel drug delivery in the treatment of patients with CLI.

## METHODS

**STUDY DESIGN.** The PACUS trial was a single-center, single-blind, randomized trial designed to evaluate the safety and efficacy of intravascular percutaneous catheter-delivered high-intensity, low-frequency ultrasound to improve local paclitaxel delivery in patients with CLI due to femoral-popliteal lesions and occlusions. The protocol was approved by a local review board and the institutional ethics committee. All patients provided written informed consent before enrollment. The trial was conducted in accordance with the Declaration of Helsinki.

**PATIENT POPULATION.** Patients were eligible for enrollment if they had CLI (Rutherford class 4 to 6) associated with femoral-popliteal lesions ≥10 cm in length with or without concomitant below-the-knee (BTK) disease. Major inclusion criteria included Rutherford category ≥4, femoral-popliteal lesion length ≥10 cm, successful intraluminal recanalization without need for a stent to obtain a satisfactory angiographic result, at least 1 patent BTK vessel, and age >18 years. Major exclusion criteria included Rutherford category <4, pregnancy, known allergies to study medications and materials, need for a subintimal approach to perform the recanalization, and target vessel stent release.

**RANDOMIZATION.** Randomization occurred after successful crossing and pre-dilation of the target lesion with a standard percutaneous transluminal angioplasty (PTA) balloon. If residual stenosis was <30% without a subintimal approach and/or flow-limiting dissections, patients were assigned and treated on the basis of randomization. Subjects were randomly assigned by a computer-generated random sequence (in a 1:1 ratio). Randomization was done in advance for all patients and without any stratification.

The patients and physicians involved in the follow-up (FU) control were blinded to treatment assignment through the completion of all 6-month FU evaluations. Operators were not blinded, because of differences in treatment protocol. Twenty-eight patients were treated with intravascular percutaneous catheter-delivered high-intensity, low-frequency ultrasound and local paclitaxel delivery with temporary blood flow occlusion created by a distal occlusion PTA balloon (the study group), and 28 patients were treated with DEBs with conventional methods (the control group).

**PROCEDURE.** All patients underwent endovascular treatment performed in dedicated angiographic suites under local anesthesia (lidocaine 2%). Mild sedation was administered. All cases were approached from an antegrade puncture of the ipsilateral common femoral artery using a 6- or 25-cm (depending on target superficial femoral artery [SFA] lesion localization), 6-F Radifocus Introducer II sheath (Terumo, Tokyo, Japan). After positioning the femoral sheath, an initial intra-arterial heparin bolus (3,000 to 5,000 U) was administered, followed by 750 to 1,000 U/h infusion during the procedure to maintain an activated clotting time of 250 s. Moreover, all patients received as pre-medication dual-antiplatelet therapy (100 mg/day aspirin and 75 mg/day clopidogrel) at the time of the procedure.

Pre-procedural biplane angiography with quantitative analysis of the target vessel was performed to identify the target lesion. Angiographic measurements of the vessel and lesion diameters were performed using the automated contour detection program of the angiography unit (Philips Healthcare, Best, the Netherlands).

Stenosis and occlusions were crossed using a 0.035-inch J-tip and occlusion with a straight-tip hydrophilic guidewire supported by a diagnostic catheter using an intraluminal approach. After crossing the lesion, angioplasty was performed using a 0.035-inch standard PTA Admiral balloon catheter

(Medtronic, Minneapolis, Minnesota) with a lesion length/balloon length ratio of 1:1. After the angioplasty, angiography was performed to confirm successful recanalization with residual restenosis ≤30% and no flow-limiting dissections, and the patient was enrolled in the study. Recanalization and angioplasty of BTK lesions were performed to obtain better angiographic results. Distal runoff was evaluated using the Society for Vascular Surgery runoff score (13). In the study group, patients were treated using the Genesis System (CardioProlific, Hayward, California), comprising a generator that converts alternating-current line power into high-frequency current and a transducer equipped with piezoelectric crystals that convert high-frequency current into ultrasonic energy at a frequency of 20 kHz. The transducer is connected with a 5-F, 200-cm-long intravascular percutaneous catheter that propagates high-intensity, low-frequency ultrasound to the treatment site. The catheter is equipped with an active probe covering treatment lengths between 10 and 100 mm. The catheter is advanced over any 0.014-inch guidewire. The intended treatment segment was exposed to 60 s of ultrasound energy. Lesions longer than 10 cm required sequential 60-s treatments to cover the entire lesion length. The Genesis catheter was removed from the treatment area following placement of a 2-cm-long PTA Admiral balloon catheter, distal to the treatment area and inflated to create flow cessation. Paclitaxel in a mixture with contrast medium at a concentration of 1.0 μg/mm$^3$ was delivered to the treatment area for 60 s. The column of the paclitaxel mixture filling the vessel was observed under fluoroscopy and sustained for 60 s. The additional amount of paclitaxel mixture with contrast was limited to a maximum of 15 ml. A small distal PTA balloon occlusion prevented the paclitaxel mixture with contrast from flowing outside the treatment area. The mixture of paclitaxel and contrast medium was then aspirated with a 50-ml syringe, and the distal PTA balloon was deflated. A final angiographic control was performed and compared with the pre-procedural one.

In the control group, angioplasty was performed using the IN.PACT Admiral DEB (Medtronic). The IN.PACT Admiral DEB includes paclitaxel as the antiproliferative agent at a dose of 3.5 μg/mm$^2$, with urea as the excipient. To avoid geographic miss, DEB length was chosen to exceed the target lesion length by 10 mm at the proximal and distal edges. If the treatment required multiple balloons, an overlap of 10 mm was applied for contiguous balloon inflations. A minimum balloon inflation time of 180 s was adopted. A final angiographic control was performed as previously described for the study group.

In both groups, post-procedural medical therapy included aspirin 100 mg/day and clopidogrel 75 mg/day for a minimum of 3 months. After 3 months, clopidogrel was discontinued; aspirin therapy was continued for life.

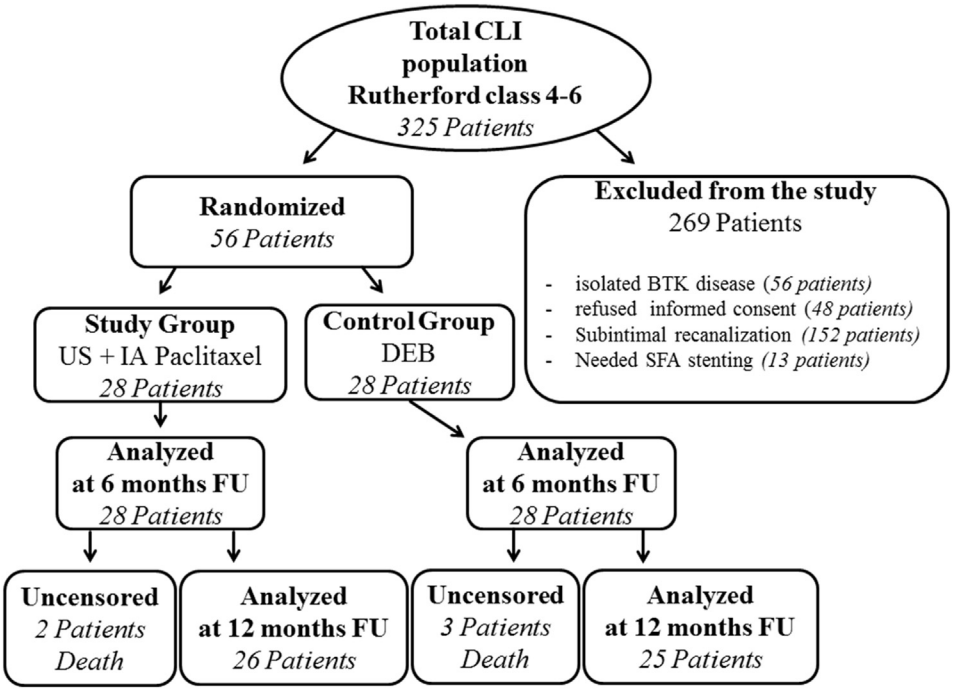
**FU.** Patients were followed up at 30 days, 6 months, and 12 months by the treating physician. Office visits included duplex ultrasonography (DUS). If the peak systolic velocity ratio was higher than 2.5, the patient was classified as having restenosis >50%. Planned 6-month digital subtraction angiography (DSA) was performed in all patients to evaluate primary patency. Any required reinterventions were performed according to standard practice by using PTA balloons and stenting if needed. No core laboratory was used in this study. The localization of the treated segment during 6-month FU with DSA was performed by measuring the distance of the lesions location from the femoral head.

**POST-REVASCULARIZATION CARE.** Medical wound care was performed by a group of diabetologists not involved in the study and not informed about techniques used for recanalization. To facilitate ulcer healing, surgical debridement was routinely performed at each examination according to the progression of the ulcer. If required, broad-spectrum antibiotic therapy was administered in case of an infected ulcer and adapted to culture results during FU. In the acute phase, adequate post-operative shoes were prescribed according to ulcer localization.

**ENDPOINTS.** The primary efficacy endpoints in this study were primary patency at 6-month FU, defined as freedom from clinically driven target lesion revascularization (TLR) and significant restenosis as determined by DSA. Restenosis was defined as a reduction in luminal diameter of more than 50% in any angiographic view. Target lesions with >50% late luminal loss were considered to have lost primary patency.

Safety endpoints included 30-day device- and procedure-related death, all-cause death, major target limb amputation, and target vessel acute occlusion. Secondary endpoints were technical success and freedom from clinically driven TLR, clinical improvement, and major adverse clinical events at 12-month FU. Technical success was defined as successful recanalization of the target vessel with <30% residual stenosis after the procedure. TLR was defined as any repeat surgical or percutaneous interventions of the target lesion due to loss of patency as evaluated by DSA. Clinical improvement was defined as freedom from target limb amputation, TLR, and increase in Rutherford class at 6 and 12 months. Major adverse clinical events included stroke, myocardial infarction, need of surgical revascularization, distal embolization, and recurrence of CLI.

**FIGURE 1 Study Flowchart**




Overall number of subjects recruited and number of subjects lost at 6-month and 12-month follow-up (FU) or missing because of death. BTK = below-the-knee; CLI = critical limb ischemia; DEB = drug-eluting balloon; IA = intra-arterial; SFA = superficial femoral artery; US = ultrasound.

**STATISTICAL ANALYSIS.** Because the objective of the study was to evaluate safety and efficacy, no statistical powering requirements were specified.

However, with 25 subjects per treatment group, the PACUS trial will be able to detect a 36 percentage point difference between the treatment groups in the incidence of superficial femoral or popliteal artery restenosis, using a chi-square test with a 2-sided $\alpha$ level of statistical significance of 0.05 and a level of statistical power of $1 - \beta = 0.80$. The 95% confidence interval around the difference would be no larger than ±29%. Considering a 10% rate of attrition, a sample size of 28 patients per group was recruited. All analyses were based on the intention-to-treat principle.

Continuous variables are described as mean ± SD and were compared using Student *t* tests. Categorical variables are described as proportions and percentages and were compared using chi-square tests. Freedom from clinically driven TLR was analyzed using the Kaplan-Meier method during the 6- and 12-month FU periods. The difference in the survival curves between groups was assessed by using log-rank statistics. Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, New York).

## RESULTS

**PROCEDURAL OUTCOMES.** Between November 2013 and February 2015, 325 patients were admitted to our

**TABLE 1 Demographic Variables**

| | Study Group (n = 28) | Control Group (n = 28) | p Value |
|---|---|---|---|
| Age, yrs | 74.2 ± 7 | 75.5 ± 9.1 | 0.86 |
| Hypertension | 27 (96.4) | 26 (92.9) | 0.55 |
| Diabetes | 13 (46.4) | 12 (42.9) | 0.79 |
| Smoker | 18 (64.3) | 16 (57.1) | 0.58 |
| Current smoker | 5 (17.9) | 5 (17.9) | |
| Previous smoker | 13 (46.4) | 12 (42.9) | 0.79 |
| Dyslipidemia | 17 (60.7) | 15 (53.6) | 0.59 |
| Family history of CAD | 12 (42.9) | 13 (46.4) | 0.79 |
| Previous CAD | 12 (42.9) | 14 (50) | 0.59 |
| Previous neurological disease | 9 (31.1) | 7 (25) | 0.55 |
| Renal failure | 5 (17.9) | 9 (32.1) | 0.22 |
| Rutherford scale | | | |
| Class 4 | 13 (46.4) | 12 (42.9) | 0.79 |
| Class 5 | 14 (50) | 13 (46.4) | 0.79 |
| Class 6 | 1 (3.6) | 3 (10.7) | 0.30 |

Values are mean ± SD or n (%).
CAD = coronary artery disease.

foot care unit for foot ulcers or pain at rest due to CLI; 269 patients were excluded from the study, and 56 patients were prospectively randomized to the study group and the control group. The study flowchart is shown in Figure 1. Pre-procedural patient demographics are shown in Table 1. No significant differences were observed between the groups in baseline characteristics. All patients were treated through an ipsilateral antegrade common SFA approach.

The mean length of the treated SFA/popliteal stenosis was 168.8 ± 54.4 mm in the study group and 164 ± 14.4 mm in the control group (p = 0.1). SFA/popliteal total occlusions were present in 20 patients (71%) in the study group and 15 patients (53.6%) in the control group. Calcification was observed in 21 patients (75%) in the study group and 23 patients (82%) in the control group. In the control group, a mean of 1.6 ± 0.5 DEBs per patient were used to treat SFA lesions. The imaging surveillance of BTK arteries was performed during FU by DSA and DUS. No significant difference was reported in BTK patency at FU as reported in Table 2. Associated angioplasty of the BTK lesions was achieved in both groups with at least 1 patent BTK vessel in each patient, without any difference in the runoff score (2.43 ± 0.5 in the study group vs. 2.39 ± 0.5 in the control group, p = 0.1). Baseline lesion characteristics are reported in Table 2.

**SAFETY OUTCOMES.** No procedure-related deaths were observed within 30 days. No procedural and post-procedural paclitaxel-related adverse effects were reported during the study. No acute vessel occlusion was observed at 1-month DUS. Two deaths (7.1%) were reported in the study group (1 myocardial infarction and 1 sudden death), and 3 deaths (10.7%) were reported in the control group (2 myocardial infarctions and 1 sudden death) during 12-month FU.

**TABLE 2 Baseline Lesion Characteristics**

| | Study Group (n = 28) | Control Group (n = 28) | p Value |
|---|---|---|---|
| Isolated SFA location | 19 (67.9) | 20 (71.4) | 0.77 |
| Proximal popliteal involvement | 9 (32.1) | 8 (28.6) | 0.77 |
| Lesion length, mm | 168.8 ± 54.4 | 164 ± 14.4 | 0.10 |
| CTOs | 20 (71.4) | 15 (53.6) | 0.17 |
| Severe calcifications lesion | 21 (75) | 23 (82) | 0.5 |
| Associated BTK interventions | | | |
| Anterior tibial artery | 7 (25) | 6 (21.4) | 0.75 |
| Posterior tibial artery | 10 (35.7) | 9 (32.1) | 0.78 |
| Peroneal artery | 3 (10.7) | 7 (25) | 0.16 |
| Post-procedural runoff score | 2.43 ± 0.5 | 2.39 ± 0.5 | 0.10 |
| Technical success | 28 (100) | 28 (100) | |

Values are n (%) or mean ± SD.
BTK = below-the-knee; CTO = chronic total occlusion; SFA = superficial femoral artery.

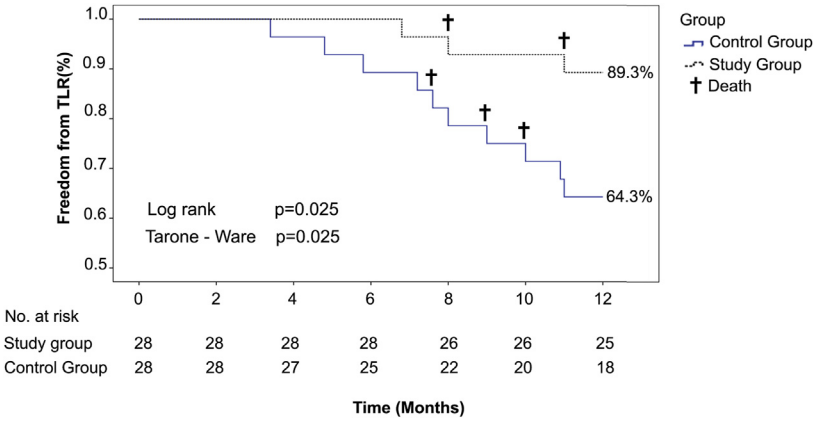
No major or minor amputations were noted during FU in study group, and 4 major amputations (16%) were reported in the control group (p = 0.03).

**EFFICACY OUTCOMES.** Acute successful angiographic results were obtained in all cases (100%). DUS control at 1-month FU showed 100% patency rates in both groups. Primary patency at 6-month FU evaluated with DSA was 96.4% in the study group and 78.5% in the control group (p = 0.04). One significant restenosis (3.6%) was observed in the study group, and 6 significant restenoses (21.4%) were observed in the control group at 6-month FU. DUS control at 12-month FU showed primary patency rates of 96.2% (25 of 26 lesions) in the study group and 68% (17 of 25 lesions) in the control group (p = 0.008). Higher freedom from TLR was observed in the study group, at 89.3% compared with 64.3% in the control group at 12-month FU (p = 0.025), as shown in Figure 2. Stenting was necessary during reintervention in 3 patients in the control group to manage flow-limiting dissections. Angiographic and clinical results are reported in Table 3.

## DISCUSSION

In this study, the use of high-intensity, low-frequency ultrasound before infusion of a mixture of paclitaxel and contrast medium with a distal occlusion balloon resulted in superior efficacy in comparison with angioplasty using DEBs in this cohort of patients with CLI with femoral-popliteal disease. Improved primary patency was obtained at 6- and 12-month FU in the study group. These reductions in restenosis led to a reduction in TLR and to clinical improvements. In previous trials, Tepe et al. (6,8) demonstrated the efficacy of paclitaxel to reduce restenosis in patients with SFA lesions and claudication. There are few studies of DEBs in patients with CLI. Listro et al. (14), in a single-center randomized study, evaluated the efficacy of DEB to treat SFA lesions (14). In this study, 79.2% of patients had CLI. Even without a specific analysis of patients with CLI, the investigators highlighted the efficacy and safety of DEBs with concomitant stenting, with a lower restenosis rate (17%) compared with patients treated with conventional PTA with concomitant stenting (26%). The result was more evident in patients with long occlusions (>100 mm). The DEBELLUM (Drug-Eluting Balloon Evaluation for Lower Limb Multilevel Treatment) randomized study in patients with SFA disease reached the same conclusions: the overall rate of TLR was 12.2% for DEBs and 35.3% for PTA (9). Unfortunately, that trial also lacked an analysis of the results of patients with CLI and multilevel disease in comparison with patients with claudication.

**FIGURE 2 Kaplan-Meier Curves Comparing Freedom From Target Lesion Revascularization Between the Groups**




There was a significant advantage in 1-year freedom from target lesion revascularization (TLR) in the study group (p = 0.025). Standard error is shown in Table 3.

Previous studies have evaluated the efficacy of high-intensity, low-frequency ultrasound to improve outcomes of PTA in patients with coronary and peripheral disease. Siegel et al. (10) demonstrated that catheter-delivered high-intensity, low-frequency ultrasound may be useful for lesion debulking and enhancing arterial distensibility by changing lesion compliance and allowing balloon dilation at relatively low pressures. In 19 patients with coronary artery disease, successful PTA after ultrasound exposure was achieved at lower mean balloon pressures. This finding could have 2 potential implications. After ultrasound ablation, heavy calcific lesions became treatable with low-pressure balloon dilation. Moreover, the possibility to perform successful PTA at lower pressure reduces the risk for barotrauma, which may often be responsible for acute dissections or promote subsequent restenosis. Ultrasound energy has been shown to cause endothelium-independent smooth muscle relaxation, often referred to as arterial vasodilation, in both animals and humans.

The mechanism of vasodilation induced by low-frequency, high-intensity ultrasound is due to a local vasodilator effect related to the stimulation of endothelial cells obtained by local vibrations of sound waves (15,16).

This activation also opens intercellular junctions of endothelial cells, enhancing permeability and potentially increasing drug uptake (12). Mitragotri et al. (17) revealed that high-intensity, low-frequency ultrasound can deliver and control therapeutic doses of proteins across human skin. In our study, these properties of high-intensity, low-frequency ultrasound have shown beneficial effects in combination with paclitaxel. Patients treated with high-intensity, low-frequency ultrasound and paclitaxel infusion with a distal occlusion balloon showed improved angiographic and clinical outcomes in comparison with DEB. Ultrasound might act in 2 ways: causing calcific and atheromatous plaque remodeling and changes in lesion compliance that allow more efficient drug delivery to the vessel wall, at the same time causing the activation of the endothelial cells to increase vessel permeability, allowing a higher concentration of paclitaxel to penetrate into the vessel wall to promote reduction of the inflammatory response. Although published research indicates that ultrasound may

**TABLE 3 Efficacy and Safety Outcomes**

| | Study Group (n = 28) | Control Group (n = 28) | p Value |
|---|---|---|---|
| Patency at 1-mo FU (DUS) | 28/28 (100) | 28/28 (100) | |
| Angiographic patency at 6-mo FU | 27/28 (96.4) | 22/28 (78.5) | 0.04 |
| Patency at 12-mo FU (DUS/PSV ratio >2.5) | 25/26 (96.2) | 17/25 (68) | 0.008 |
| TLR at 6-mo FU | 0/28 (0) | 3/28 (10.7) | 0.08 |
| TLR at 12-mo FU | 1/26 (3.8) | 9/25 (36) | 0.004 |
| Freedom from TLR at 6-mo FU* | 100 | 89.3 | 0.025 |
| Standard error | 0 | 0.06 | |
| Freedom from TLR at 12-mo FU* | 89.3 | 64.3 | 0.025 |
| Standard error | 0.035 | 0.09 | |
| Clinical improvement at 12-mo FU | 24/26 (92.3) | 17/25 (68) | 0.03 |
| Procedure-related death during 12-month FU | 0/28 (0) | 0/28 (0) | |
| Non-procedure-related death during 12-mo FU | 2/28 (7.1) | 3/28 (10.7) | 0.64 |
| Recurrence of CLI at 12-mo FU | 1/26 (3.8) | 9/25 (36) | 0.004 |
| Major amputations at 12-mo FU | 0/26 (0) | 4/25 (16) | 0.03 |

Values are n/N(%) or n. *Evaluated using the Kaplan-Meier method.

CLI = critical limb ischemia; DUS = duplex ultrasonography; FU = follow-up; PSV = peak systolic velocity; TLR = target lesion revascularization.

change lesion compliance and improve vessel permeability, these hypotheses are also corroborated by the improved patency rate, the lower amputation rate, and the lower rate of TLR at 6- and 12-month FU in the study group. Moreover, the paclitaxel dose used in the study group, a mixture with contrast medium at a concentration of 1.0 μg/mm$^3$, is significantly lower compared with the dose delivered by the DEB used in the control group, which has a paclitaxel dose of 3.5 μg/mm$^2$ (6).

**STUDY LIMITATIONS.** Although this study was structured as a single-blind randomized study, operators could identify patients receiving ultrasound-enhanced paclitaxel delivery simply because it involves several additional steps in the procedure in comparison with DEB angioplasty. Furthermore, a patient cohort of 56 patients, even if sufficient to reach 80% power, is far too small to obtain definitive results, and larger multicenter randomized studies are needed.

## CONCLUSIONS

Ultrasound-enhanced delivery of paclitaxel in this small study involving patients with CLI secondary to femoral-popliteal disease was associated with improved patency and less need for TLR. This approach is associated with less cost, particularly in long-segment disease. The ability to treat any lesion length and any vessel diameter with 1 device is possible.

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## PERSPECTIVES

**WHAT IS KNOWN?** Patients with CLI are fragile and characterized by several associated comorbidities. Major amputations and morbidity and mortality rates are correlated with poor clinical outcomes of CLI.

**WHAT IS NEW?** Reduced primary patency is among the major limitations of percutaneous femoral-popliteal treatment in patients with CLI. Combined use of local delivery of low-frequency, high-intensity ultrasound and paclitaxel may improve clinical outcomes by increasing primary patency, reducing TLR and amputations.

**WHAT IS NEXT?** Additional research and larger multicenter studies are needed to validate this combined approach in patients with peripheral artery disease.

## REFERENCES

**1.** Soga Y, Iida O, Hirano K, Yokoi H, Nanto S, Nobuyoshi M. Mid-term clinical outcome and predictors of vessel patency after femoropopliteal stenting with self-expandable nitinol stent. J Vasc Surg 2010;52:608–15.

**2.** Capek P, McLean GK, Berkowitz HD. Factors influencing long-term success. Circulation 1991;83:I70–80.

**3.** Rosenfield K, Jaff MR, White CJ, et al., for the LEVANT 2 Investigators. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med 2015;373:145–53.

**4.** Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. J Vasc Surg 2007;45:751–61.

**5.** DeRubertis BG, Pierce M, Chaer RA, et al. Lesion severity and treatment complexity are associated with outcome after percutaneous infrainguinal intervention. J Vasc Surg 2007;46:709–16.

**6.** Tepe G, Laird J, Schneider P, et al., for the IN.PACT SFA Trial Investigators. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation 2015;131:495–502.

**7.** Dake MD, Ansel GM, Jaff MR, et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. J Am Coll Cardiol 2013;61:2417–27.

**8.** Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med 2008;358:689–99.

**9.** Fanelli F, Cannavale A, Corona M, Lucatelli P, Wlderk A, Salvatori FM. The "DEBELLUM"—lower limb multilevel treatment with drug eluting balloon—randomized trial: 1-year results. J Cardiovasc Surg (Torino) 2014;55:207–16.

**10.** Siegel RJ, Gunn J, Ahsan A, et al. Use of therapeutic ultrasound in percutaneous coronary angioplasty. Experimental in vitro studies and initial clinical experience. Circulation 1994;89:1587–92.

**11.** Sundaram J, Mellein BR, Mitragotri S. An experimental and theoretical analysis of ultrasound-induced permeabilization of cell membranes. Biophys J 2003;84:3087–101.

**12.** Goertz DE. An overview of the influence of therapeutic ultrasound exposures on the vasculature: high intensity ultrasound and microbubble-mediated bioeffects. Int J Hyperthermia 2015;31:134–44.

**13.** Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26:517–38.

**14.** Listro F, Grotti S, Porto I, et al. Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (Drug Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery). J Am Coll Cardiol Intv 2013;6:1295–302.

**15.** Siegel RJ, Gaines P, Procter A, Fischell TA, Cumberland DC. Clinical demonstration that catheter-delivered ultrasound energy reverses arterial vasoconstriction. J Am Coll Cardiol 1992;20:732–5.

**16.** Iida K, Luo H, Hagisawa K, Akima T, et al. Noninvasive low-frequency ultrasound energy causes vasodilation in humans. J Am Coll Cardiol 2006;48:532–7.

**17.** Mitragotri S, Blankschtein D, Langer R. Ultrasound-mediated transdermal protein delivery. Science 1995;269:850–3.

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