From the Western Vascular Society

Safety and feasibility of adjunctive dexamethasone infusion into the adventitia of the femoropopliteal artery following endovascular revascularization

Christopher D. Owens, MD, MSc, Warren J. Gasper, MD, Joy P. Walker, MD, Hugh F. Alley, BA, Michael S. Conte, MD, and **S. Marlene Grenon, MD,** *San Francisco, Calif*

Objective: **Restenosis following endovascular treatment of the femoropopliteal segment is associated with the inflammatory response produced in the artery wall at the time of the procedure. Although local drug delivery to the superficial femoral and popliteal arteries promises improved patency, data are currently limited. We hypothesized that improved percutaneous delivery of an anti-inflammatory compound into the adventitia of the femoropopliteal at the time of endovascular treatment would be safe, feasible, and decrease the inflammatory response.**

Methods: **This was a prospective, investigator-initiated, phase I, first-in-man study testing the safety and feasibility of percutaneous adventitial delivery of dexamethasone. Following successful intervention, an adventitial microinfusion catheter was advanced over a 0.014-inch wire to the treated segment. Its microneedle (0.9 mm long × 140-μm diameter) was deployed into the adventitia to deliver dexamethasone (4 mg/mL) mixed with contrast agent (80:20 ratio), providing fluoroscopic visualization. The primary safety outcome measure was freedom from vessel dissection, thrombosis, or extravasation while the primary efficacy outcome was duplex-determined binary restenosis defined as a peak systolic velocity ratio >2.5.**

Results: **Twenty patients with Rutherford clinical category 2-5 enrolled in this study. The mean age was 66, and 55% had diabetes mellitus. Treated lesion length was 8.9 ± 5.3 cm, and 50% were chronic total occlusions. Eighty percent of treated lesions were in the distal superficial femoral or popliteal arteries. All lesions were treated by balloon angioplasty with provisional stenting (n = 6) for suboptimal result. Three patients were treated with atherectomy as well. A mean of 1.6 ± 1.1 mg (0.5 ± 0.3 mL) of dexamethasone sodium phosphate was injected per centimeter of lesion length. In total, a mean of 12.1 ± 6.1 mg of dexamethasone was injected per patient. The mean number of injections required per lesion was 3.0 ± 1.3 cm, minimum one and maximum six injections. There was 100% technical success of drug delivery and no procedural or drug-related adverse events. The mean Rutherford score decreased from 3.1 ± .7 (median, 3.0) preoperatively to .5 ± .7 at 6 months (median, 0.0; $P < .00001$). Over this same time interval, the index leg ankle-brachial index increased from .68 ± .15 to .89 ± .19 ($P = .0003$). The preoperative C-reactive protein in this study was 6.9 ± 8.5 indicating severe baseline inflammation, which increased to 14.0 ± 23.1 mg/L (103% increase) at 24 hours following the procedure. However, this increase did not reach statistical significance of $P = .14$. Two patients met the primary efficacy end point of loss of primary patency by reoccluding their treated segment of the index lesion during the follow-up period.**

Conclusions: **Adventitial drug delivery via a microinfusion catheter is a safe and feasible alternative to intimal-based methods for adjunctive treatment in the femoropopliteal segment. The 6-month preliminary results suggest perivascular dexamethasone treatment may improve outcomes following angioplasty to the femoral and popliteal arteries, and support further clinical investigation of this approach. (J Vasc Surg 2014;59:1016-24.)**

From the Division of Vascular and Endovascular Surgery, University of California San Francisco Medical Center.

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Reprint requests: Christopher D. Owens, MD, MSc, Division of Vascular and Endovascular Surgery, University of California San Francisco, 400 Parnassus Ave, San Francisco, CA 94143 (e-mail: christopher.owens@ucsfmedctr.org).

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Balloon angioplasty superimposes an acute barotraumatic injury on a chronically inflamed artery, resulting in the recruitment of neutrophils and macrophages into the site of injury.[1-3] These cells, in concert with intrinsic vascular cells, participate in injury-induced stress responses, which ultimately determine the fate of the revascularization procedure.[4,5] Vascular injury programs, mediated in part by the coordinated activity of the inflammatory transcription factors, nuclear factor κB and activated protein-1, lead to the expression of a broad spectrum of inflammatory proteins resulting in cellular proliferation, fibrous protein production, and remodeling of the vascular wall.[6] The magnitude of the inflammatory response has been linked to subsequent restenosis in the femoropopliteal artery suggesting that therapies, which mitigate the initial inflammatory cascade, might improve patency.[7]

Glucocorticoids are powerful anti-inflammatory, immune-suppressive, and anti-proliferative compounds used to treat a variety of immune-mediated diseases.[8]

Dexamethasone is a long-acting synthetic glucocorticoid approved by the Food and Drug Administration to treat inflammatory conditions and is 25 times more potent than hydrocortisone (cortisol) and has no mineralocorticoid crossover activity.[8] While systemic delivery of steroids[9,10] following percutaneous coronary intervention has had mixed results in part related to systemic side effects, dexamethasone-coated stents have been more successful demonstrating a reduction in binary restenosis and clinical events.[11-13] However, widespread adoption has been limited given the older generation stent platforms and the propensity for crystallization on the stent surface.

Endovascular adventitial delivery, through a microinfusion syringe is an attractive alternative for local drug delivery because the drug can be injected directly into the artery at the site of injury without the need for a permanent implanted stent or partitioning from a balloon surface. Adventitial delivery also establishes an outside-in concentration gradient with the majority of the drug distributed in the adventitia and media but relative sparing of endothelial cells. Specifically targeting the adventitia is also of interest as this outer vessel layer actively participates in inflammatory cell recruitment, arterial remodeling, and contribution of cells to neointima formation.[1,14-16] Animal studies have demonstrated that adventitial micro-infusion is one of the most efficient means of local drug delivery by maximizing tissue concentration and minimizing plasma levels and nontarget organ distribution of drug.[17] Consequently, pilot clinical trials have utilized this approach in the coronary arteries to deliver bone marrow-derived stem cells.[18] However, this approach has not been utilized in peripheral arteries. We hypothesized that percutaneous delivery of dexamethasone with a microinfusion catheter to the adventitia of symptomatic patients with peripheral artery disease would be safe and feasible.

METHODS

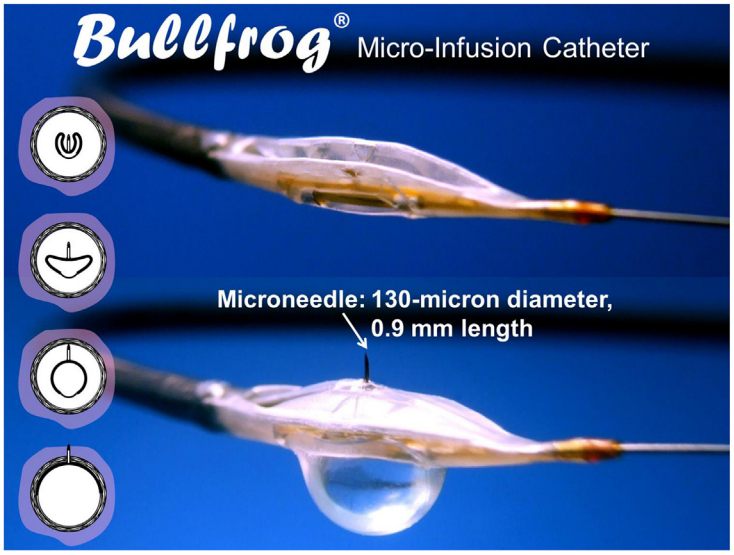
Study design and patient population. This was a first-in-human study to test the safety and feasibility of dexamethasone administration through a microinfusion catheter (Bullfrog, Mercator MedSystems, Inc, San Leandro, Calif) into the superficial femoral and popliteal artery (http://www.clinicaltrials.gov). Unique identifier: NCT 01507558). The study design was a prospective, single-center, investigator-initiated study that enrolled consecutive patients who met eligibility requirements from the San Francisco Veteran Affairs Medical Center. This study was approved by the Committee for Human Research and the University of California Clinical and Translational Science Institute. Safety data and outcomes were monitored by a Data Safety and Monitoring Committee that convened on a quarterly basis or as needed.

The primary inclusion criteria were patients suffering from moderate to severe disabling claudication, ischemic rest pain, or minor tissue loss secondary to atherosclerotic lower extremity occlusive disease with TransAtlantic Inter-Society Consensus II A-D lesions of the superficial femoral artery (SFA) or popliteal arteries. The minimal reference vessel lumen diameter was required to be 3 to 6 mm, and the patient was required to have at least one infrapopliteal runoff vessel. Exclusion criteria included serum creatinine ≥2.5 mg/dL, prior revascularization of the target limb, known allergy to contrast agents or dexamethasone, estimated life expectancy less than 1 year, or other concurrent illness in which the investigators thought would limit the patient's ability to follow the schedule of assessments.

Microinfusion catheter. The Bullfrog Micro-Infusion Catheter (Mercator MedSystems, San Leandro, Calif) is a rapid-exchange, wire-guided catheter with a balloon-sheathed 0.9-mm-long, 35-gauge (140 μm diameter) needle that delivers infusions to adventitial and perivascular tissues (Fig 1). It is Food and Drug Administration 510(k)-cleared for use in coronary and peripheral arteries. It is advanced through a 6F sheath over a 0.014-inch wire and can treat vessels from 3 to 6 mm in diameter (Fig 2). Three radio-opaque markers on the catheter allow for proper orientation of the needle. Using standard angioplasty inflation equipment, the balloon is inflated exposing the needle. When the balloon contacts the arterial wall opposite the needle tip, contact pressure forces the needle through the vessel wall and into the adventitia and perivascular tissues. The contact pressure of the balloon against the artery wall is limited to 2 atmospheres by a pressure release valve, which prevents damage to the artery wall. A mixture of infusate and contrast (4:1) is then delivered under fluoroscopic guidance into the adventitia. A test injection of 0.1 mL is made to confirm proper adventitial placement of the microinfusion needle tip. If resistance is met, or the test injection enters the blood stream, the balloon is deflated and the injection is attempted in another location by moving the catheter a few millimeters proximally or distally or rotating the catheter a few degrees. Once adventitia placement is confirmed, the remainder of the infusate is delivered at a rate of 1 mL/min. When the infusion is complete, the balloon is deflated, sheathing the needle, and allowing the catheter to be withdrawn (Fig 2). Injections were administered approximately every 3 cm along the length of the treated arterial segment. Because the drug:contrast admixture can be visualized on both sides of the arterial wall, only one fluoroscopic view is necessary to confirm circumferential arterial coverage in the majority of cases.

Procedure. Patients not taking aspirin or clopidogrel before study enrollment received 325 mg of aspirin 12 hours prior the procedure. Postprocedure, patients were prescribed 81 mg/d of aspirin to be taken indefinitely and 75 mg/d of clopidogrel daily for 12 weeks. Vascular access was accomplished by either the contralateral or ipsilateral (anterograde) approach. Patients received a bolus of 5000 IU of heparin after insertion of the sheath in the common femoral artery, and their activated clotting time was kept above 250 seconds with additional heparin as needed. In the case of chronic total occlusions, all lesions were crossed subintimally with a glide wire and glide catheter (Terumo, Somerset, NJ). After securing access across the lesion with a guidewire, the target lesion was treated

A



B

Diffusion Grade	Characteristics	Appearance relative to target (X)	Diffusion Grade	Characteristics	Appearance relative to target (X)
A	*complete* circumferential, *complete* longitudinal coverage of target		C	*partial* circumferential, *partial* longitudinal coverage	
B1	*complete* circumferential, *partial* longitudinal coverage		D	perivascular, but no target overlap	
B2	*partial* circumferential, *complete* longitudinal coverage		F	No detectable perivascular infusion	

Fig 1. The Bullfrog microinfusion catheter **(A)**. Diffusion grading scale **(B)**. **A** is supplied courtesy of Mercator Medsystems (San Leandro, Calif).

according to physician preference. All patients were treated with balloon angioplasty. If a flow-limiting dissection or residual stenosis was determined to require a stent, the protocol specified for treatment with dexamethasone prior to stent placement. In all cases, the microinfusion catheter was advanced to the treatment site following angioplasty to deliver dexamethasone into the arterial adventitia.

Following the procedure, all patients were admitted for a 23-hour observation period for access site, adverse event, and revascularization monitoring. Prior to discharge, ankle-brachial indexes (ABIs) and arterial duplex ultrasound studies were performed in the vascular laboratory. Blood was drawn at baseline and at 24 hours following the procedure to assess the inflammatory response.

Dexamethasone dosing and rationale. The dosage utilized in this protocol was an off-the-shelf concentration of dexamethasone sodium phosphate for injection USP, 4 mg/mL, which is approved for reducing soft tissue inflammation. Specifically, dexamethasone is indicated for soft tissue injection of 0.4 to 6 mg to treat acute exacerbations in a variety of inflammatory conditions. Based on these similar uses of the drug to treat localized inflammation, it was postulated that a similar dose (2-6 mg) should be used to treat each 3 cm of lesion (0.7-2 mg/cm), allowing for multiple infusions in the case of long lesions. The 3-cm benchmark was chosen based on typical longitudinal perivascular diffusion patterns in preclinical ex vivo cadaveric femoral artery studies (unpublished data). The dexamethasone sodium phosphate for injection USP, which contains 4.0 mg dexamethasone phosphate per milliliter, was mixed 80%:20% with an iso-osmolar iodinated contrast medium (iodixanol 320 mg I/mL; GE HealthCare, Cork, Ireland) resulting in a final concentration of 3.2 mg dexamethasone phoshate and 60 to 74 mg of iodine in each milliliter of solution. The final dosing target was, therefore, determined to be approximately 0.5 mL of the diluted drug per centimeter of lesion or 1.6 mg/cm.

The coinfusion of contrast medium with the drug allowed the X-ray fluoroscopic visualization required to positively assess infusion success (Figs 2 and 3). All infusions were graded based on the circumferential and longitudinal distribution of the drug/contrast infusate and the coverage of the target lesion (Fig 1). For example, an infusion that was completely circumferential and extended 3 cm in either direction from the point of injection would be considered a diffusion grade A. If infusions were only partially circumferential or partially longitudinal, then a grade of B was given and so on according to Fig 1.

Patient assessment and end point definitions. Medical history was obtained before the procedure, including concomitant medication use, Rutherford clinical category, resting ABI, and laboratory results for baseline C-reactive protein (CRP), serum creatinine, and lipids.

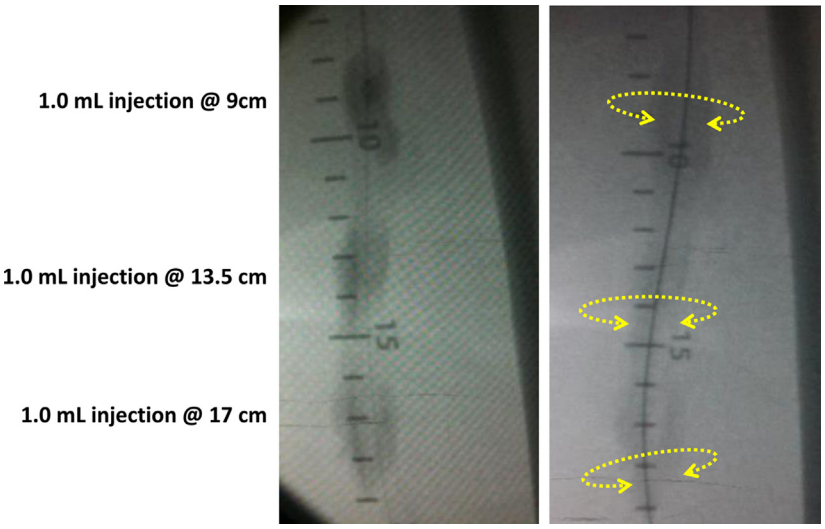


Fig 2. Endovascular treatment with adjunctive dexamethasone. This is a 49-year-old man with severe disabling claudication and a 16-cm superficial femoral artery (SFA) occlusion. Following securing access across the lesion with a glide wire, the lesion was treated with balloon angioplasty. Following successful angioplasty, four 1.0-mL injections were performed along the length of the lesion (only three shown). In the left panel, there is a discreet contrast blush seen at each injection site. Note that the contrast appears circumferentially at each injection site. Three minutes later, the drug-contrast admixture can be seen to have diffused longitudinally to fully cover the treated segment. The patient is now 2 years from his index procedure and remains patent and complains of only mild claudication with heavy exertion. He has an ankle-brachial index (ABI) of 1.09 and a peak systolic velocity ratio of less than 2.5.

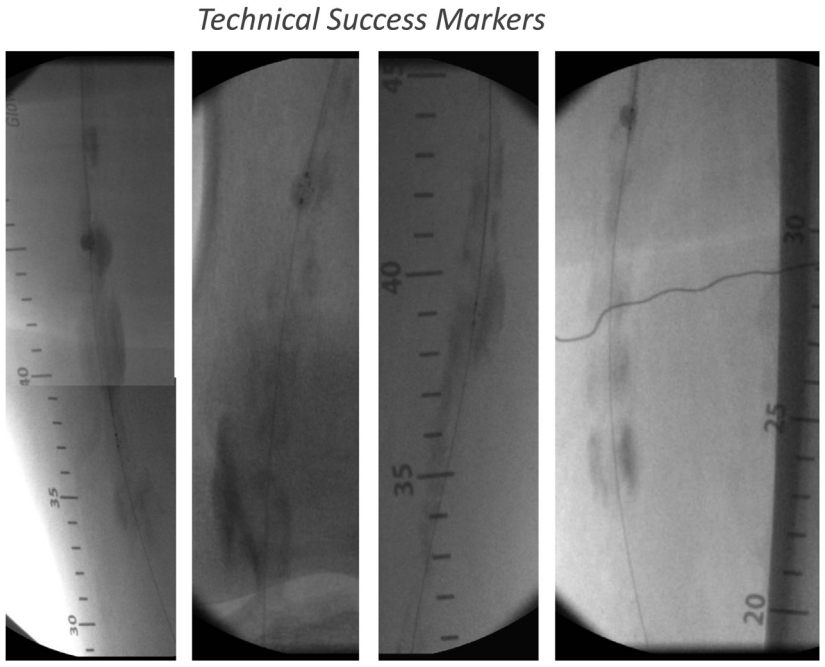


Fig 3. Examples of typical dexamethasone-contrast diffusion patterns in patients treated in this study.

Adverse event evaluation was performed at the end of the index procedure and at each follow-up visit. Patients were then reassessed with vascular history and physical examination, ABIs, and duplex arterial ultrasound examinations at 1, 3, and 6 months. The primary safety end point was freedom from death, vessel perforation, dissection, thrombosis, or pseudoaneurysm formation within 30 days following the procedure. The primary feasibility end

point was procedural success for adventitial infusion of dexamethasone and contrast at the target lesion as determined by the relationship of the fluoroscopic blush to the treatment segment. While not powered for an efficacy signal, the primary efficacy end point was a primary patency rate defined as freedom from the combined end points of target lesion revascularization, occlusion, or >50% restenosis in the treated lesion. Duplex ultrasonography was performed to assess restenosis and >50% restenosis was defined by a peak systolic velocity ratio >2.5. Rates of target lesion revascularization, death, and amputation end points were also analyzed. Secondary end points were change in Rutherford classification and ABI from baseline to 6 months.

Inflammation as detected by plasma CRP has been linked to restenosis following peripheral intervention. As one of our intended goals was to reduce inflammation following vascular intervention, serum CRP was measured at baseline and 24 hours following the procedure.

Statistical analysis. This study was not powered for clinical outcomes. Normally distributed continuous variables were expressed as mean and standard deviation and were evaluated with the Student *t*-test or one-way analysis of variance where appropriate. Proportions were evaluated by the χ^2 test. Rutherford classification and categorical variables were assessed by the Kruskal-Wallis test. Safety parameters were collected and assessed qualitatively or summarized quantitatively by descriptive statistics. Statistical significance was set at the two-tailed .05 level.

RESULTS

Patient profile and lesion characteristics. Demographic and lesion characteristics are presented in Table I. In brief, 20 male patients were enrolled in this study with 35% African American and 50% Caucasian. The mean age of this cohort was 66.5 ± 9.8 years, and 55% had diabetes mellitus. Eighty percent of the patients had claudication, the majority had a preoperative Rutherford score of 3 (65%), and the mean preoperative ABI index was .68 ± .15. Lesion characteristics treated in this study are presented in Table II. The mean lesion length was 8.9 ± 5.3 cm (2.3-25.2 cm), and 50% of treated lesions were chronic total occlusions. Eighty percent of lesions were located in the distal SFA and/or popliteal artery. The mean reference vessel diameter was 4.8 ± .1 mm. Six patients (30%) required the placement of a self-expanding stent because of residual stenosis or flow-limiting dissection following balloon angioplasty. The lesion characteristics of the patients who received stents including percentage occlusions or lesion length were not different than those who were not stented.

Safety of adventitial delivery of dexamethasone. There were no device-related adverse events in this study. There were no amputations or deaths at 30 days or during follow-up. There were no dissections, pseudoaneurysm formation, or 30-day thrombosis. There was one case of hyperglycemia following dexamethasone treatment in a long-standing diabetic patient who did not receive his hypoglycemic medications.

Technical considerations and feasibility of femoropopliteal adventitial delivery. In all cases, dexamethasone was able to be delivered to the adventitia of the target lesion. The mean number of injections required per lesion was 3.0 ± 1.3 cm, minimum one and maximum six injections. Each injection was graded on an ordinal descriptive scale as depicted in Fig 1. In 19 out of 20 subjects, there was complete circumferential coverage of

Table I. Baseline patient demographics and clinical characteristics

Age, years	66 ± 10
Male sex	20 (100)
Race	
Caucasian	10 (50)
African American	7 (35)
Hispanic	2 (10)
Asian	1 (5)
Diabetes mellitus	11 (55)
Coronary artery disease	11 (55)
Hypertension	19 (95)
Hyperlipidemia	20 (100)
Body mass index, kg/m^2	27.4 ± 4.5
Creatinine, mg/dL	1.0 ± .34
CRP, mg/dL	6.9 ± 8.5
Total cholesterol, mg/dL	149.1 ± 37.5
Rutherford classification	3 = Moderate claudication 13 = Severe claudication 3 = Ischemic rest pain 1 = Minor tissue loss
Index limb ABI	.68 ± .15

ABI, Ankle-brachial index; *CRP*, C-reactive protein.
Continuous data are presented as mean ± standard deviation and categoric data as number (%).

Table II. Baseline lesion characteristics

SFA location	Proximal SFA, 2 (10) Mid-SFA, 2 (10) Distal SFA, 8 (40) Popliteal, 8 (40)
Lesion length,[a] cm	8.9 ± 5.3
Reference vessel diameter, mm	4.8 ± .1
Diameter stenosis (%)	78.5
Occlusion	10 (50)
% Occlusion	88 ± 12
TASC II classification	A = 5 B = 11 C = 2 D = 2
Revascularization method	PTA in 20 patients (100%) + atherectomy in three patients (15%) + provisional stent in six patients (30%)

PTA, Percutaneous transluminal angioplasty; *SFA*, superficial femoral artery; *TASC*, TransAtlantic Inter-Society Consensus.
Continuous data are presented as mean ± standard deviation and categoric data as number (%).
[a]Normal-to-normal lesion length as assessed by principal investigator.

the lesion with the infusate as assessed immediately after the infusion (grade = A). In one patient, there was only partial coverage noted by contrast distribution (grade = B). The mean volume injected was 3.8 ± 1.9 mL, which contained a mean of 12.1 ± 6.1 mg of dexamethasone sodium phosphate and .80 ± .4 mL of contrast. This equated to a mean of 1.6 ± 1.1 mg of dexamethasone sodium phosphate per centimeter of lesion length. The minimal dose was 3.2 mg, and the maximal dose a patient received was 24 mg of dexamethasone sodium phosphate. Accordingly, there was a positive linear correlation between the amount of dexamethasone received and length of lesion treated ($R^2 = .27$; $P = .019$).

Inflammatory response. The postintervention immune response following femoropopliteal intervention has been shown to be independently associated with subsequent restenosis. The preoperative CRP for subjects in this study was 6.9 ± 8.5 indicating severe baseline inflammation, which increased to 14.0 ± 23.1 mg/L (103% increase) at 24 hours following the procedure indicating that there was an inflammatory response following peripheral intervention. However, this increase did not reach statistical significance ($P = .14$).

Effectiveness. Two patients in this study reached the primary end point of loss of primary patency by duplex ultrasound-determined binary restenosis by 6 months. The first, a 77-year-old man who had an 11.9 cm chronic total occlusion involving the distal SFA extending into the popliteal artery treated with balloon angioplasty and a 7- by 100-mm Everflex stent (Covidien, Plymouth Minn) was found to have reoccluded his lesion at 172 days following the procedure. The second patient is a 63-year-old man that had a 10-cm popliteal artery occlusion, which was treated by angioplasty and was found to have reoccluded 182 days following his procedure. The mean preoperative Rutherford score decreased from 3.1 ± .71 (median, 3.0) preoperatively to .5 ± .70 (median, 0) at 6 months; $P < .00001$. Over this same time interval, the preoperative index leg ABI increased from .68 ± .15 (range, .22-.89) to .89 ± .19 (range, .49-1.2; $P = .0003$; Fig 4).

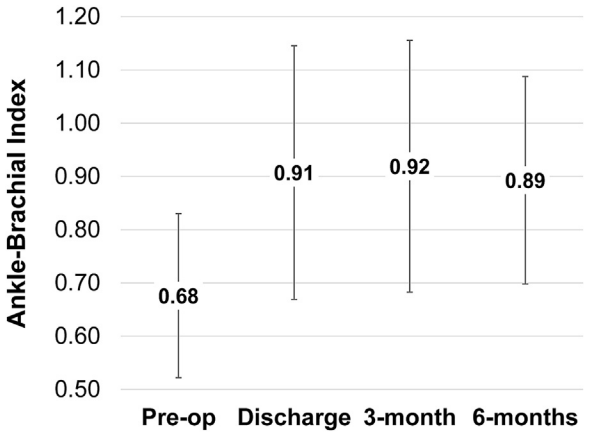


Fig 4. The mean ankle-brachial index (ABI) is significantly improved from baseline across all time points postprocedure.

DISCUSSION

This first-in-human study establishes the safety and feasibility of adventitial delivery of dexamethasone into the femoropopliteal artery to augment patency after therapeutic interventions. An additional novel feature of this methodology is that the drug-contrast admixture can be seen "staining" the area of interest thereby providing visual confirmation of drug delivery. Because the Bullfrog catheter is a microinfusion device, the dose applied can be titrated to deliver a desired concentration of drug and scaled to the length of artery treated rather than relying on passive elution from a fixed-length stent or balloon surface. Therefore, this represents a significant departure from intimal-based drug delivery methods and is the first application of this technology to the peripheral vasculature.

Additional novelty is found in the ability to percutaneously deliver the anti-inflammatory drug dexamethasone to the adventitia, hence establishing a reverse concentration gradient with maximal drug concentration located in the adventitia and outer media with relatively sparing of the endothelial cell layer. This outside-in approach of drug delivery specifically targets the adventitia, which has been shown to be an active participant in vascular remodeling after angioplasty.[1,2] Once thought to be a passive layer within the arterial wall, the tunica adventitia is now known to be extremely metabolically active and capable of regulating vascular homeostasis.[15] Following vascular injury, resident adventitial fibroblasts undergo transformation into myofibroblasts, which have been shown to contribute to neointimal growth and vessel contraction. In porcine models of balloon angioplasty, injections with 5-bromo-2-deoxyuridine have identified the majority of the first wave of proliferating cells to be located in the adventitia as early as 2 days following injury.[19,20] Further, Shi et al demonstrated that adventitial myofibroblasts both contribute to synthesis of extracellular matrix including collagen and migrate into the developing neointima following balloon injury.[21,22] Finally, utilizing in vivo reporter gene transfer studies into adventitial cells, Siow et al demonstrated adventitial myofibroblast migration into the media and neointima following balloon injury.[16] Collectively, these studies provide important biological rationale supporting the targeting the adventitia to reduce the rate of restenosis.

The hypothesis that restenosis principally occurs in those whose inflammation associated with vascular healing is excessive or is not appropriately turned off is intriguing but has not been clinically confirmed. However, it has been known for over 25 years that inflammation is involved in nearly every step in restenosis and that the adventitia harbors a rich array of inflammatory cells including macrophages, dendritic cells, lymphocytes, neutrophils and mast cells.[23] Within hours following vascular wall injury, additional inflammatory cells home to the site of injury and liberate cytokines, growth factors and reactive oxygen species that contribute to the proliferation of smooth

muscle cells and adventitial cells.[24] There is increasing evidence that the magnitude of inflammation at baseline as well as the spike in inflammation following vascular intervention is correlated with the subsequent restenosis.[25] In this regard, Schillinger et al demonstrated that plasma CRP increased in patients without restenosis by 113%, whereas CRP increased by 155% at 24 hours in patients who subsequently developed restenosis of their treated lesions.[25] Accordingly, therapies specifically targeting inflammation may inhibit or dampen the proliferative response.

Glucocorticoids are ideal candidates to repress angioplasty-induced immune response programs by inhibiting inflammatory transcription factors, nuclear factor κB and activated protein-1, and their downstream mediators.[6,26] Preclinical studies have demonstrated that dexamethasone downregulates monocyte chemoattractant protein-1, tumor necrosis factor α and interleukin 1β in nano- and micromolar concentrations in vascular smooth muscle cells.[27,28] In the specific context of neointimal hyperplasia and vascular restenosis, dexamethasone has been shown to inhibit the proliferation and migration of smooth muscle and inflammatory cells as well as adventitial myofibroblasts through effects on thymidine kinase, matrix metalloproteinases, and retinoblastoma protein.[29-31] Clincally, dexamethasone has been shown to reduce soluble inflammatory proteins following vascular intervention. For example, patients with unstable angina treated with dexamethasone-eluting stents had lower plasma concentrations of CRP, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 postintervention compared with patients treated with a bare metal stent.[32,33] Dexamethasone induces the anti-inflammatory proteins annexin 1 and mitogen-activated kinase phosphatase 1 while repressing the transcription of proinflammatory molecules such as cyclooxygenase 2.[34] Dexamethasone also markedly inhibits the production of reactive oxygen species by mononuclear cells and polymorphonuclear leukocytes in vivo. Dexamethasone increases the immunemodulatory cytokine interleukin 10 which is known to inhibit the proinflammatory TH1 cells.[35] Finally, by delivering an anti-inflammatory drug shown to improve endothelial cell migration, the need for dual antiplatelet therapy required after a limus or taxol-eluting stent or balloon may not be necessary.

Limitations. This was a pilot safety and feasibility study with short follow-up of a heterogeneous group of symptomatic patients with peripheral artery disease. The lesions were distributed in the SFA and popliteal artery and treated with a variety of interventions including angioplasty and atherectomy. Provisional stenting was applied when necessary. The intent of the study was to determine the safety and feasibility of adventitial steroid delivery in the periphery. Nevertheless, this was an extremely morbid cohort reflected by a mean CRP >6 mg/L with challenging lesion characteristics. The treated lesion was over 8 cm, and 50% of lesions were chronic total occlusions. Further, 80% of treated lesions included the distal SFA and popliteal arteries, which have traditionally been considered no-stent zones. No core facility was employed to either adjudicate duplex ultrasound or angiographic results in this study. Although the 6-month patency results were considered to be excellent, no conclusions about efficacy can be drawn from a pilot trial design.

CONCLUSIONS

This pilot study establishes that adventitial delivery of dexamethasone using a microinfusion catheter following femoropopliteal intervention is safe and feasible. This method of local drug delivery represents an alternative to intimal-based delivery platforms and may have unique advantages. Further study is required to determine the efficacy of this approach to improve vessel patency.

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AUTHOR CONTRIBUTIONS

Conception and design: CO, WG
Analysis and interpretation: CO, WG, JW, MC, SG
Data collection: CO, WG, JW, HA, SG
Writing the article: CO, WG, HA, MC
Critical revision of the article: CO, WG, JW, HA, MC, SG
Final approval of the article: CO, WG
Statistical analysis: CO, WG, JW
Obtained funding: CO
Overall responsibility: CO

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DISCUSSION

Dr Gregory J. Landry (*Portland, Ore*). This is mainly a safety and feasibility trial. As such, there is not much data to discuss in this paper. The 20 patients treated did reasonably well, but without a control group, it is hard to say whether or not this technology was helpful. But, it is clear that localized drug delivery is the next big thing in endovascular therapy. Whether this will involve drug elution or, as in this case, localized drug injection, whether this will involve treating the intima, media, or adventitia, what the proper medication or perhaps gene product will be remains to be seen, but this area is moving forward at immense speed. My questions are primarily technical:

1. Are there vessel characteristics or issues, such as calcification, thrombus, or subintimal wire passage, that limit the use of this technology?
2. Why is there only one needle in the catheter? While it seems to be able to circumferentially deliver the drug in most cases, is there a technical reason that the multiple needles could not be placed helically on the balloon to deliver the drug more uniformly?
3. Since this does treat a different vessel layer than the drug eluting balloons, do you see this as complementary or as competitive technology?
4. This balloon was proposed for use in renal denervation. Is this still being investigated?

I look forward to seeing your ongoing progress in this work.

Dr Christopher D. Owens. I would like to thank Dr Landry for his comments on our paper. He is correct that this is only a safety and feasibility trial and was not designed or powered to

assess efficacy. This was a first in-human study, and we had no prior knowledge of whether therapeutic agents could be delivered to peripheral arteries in this manner. In this sense, it was entirely proof of concept.

These were all pretty challenging cases. There were 50% occlusions, and the average lesion was about 9 cm. In addition, most of the lesions involved the popliteal artery, which has been a problematic area for stents. We were able to deliver dexamethasone to the perivascular tissue in all cases. We did not choose to treat anyone with fresh thrombus. I think that circumferential calcification would be a limitation of the technology going forward, because it is simply a physical barrier for needle or drug penetration. Circumferential calcification is problematic for any drug delivery platform. However, we found that if you can get the needle through the vessel wall, then drugs will diffuse circumferentially, 360 degrees, around the vessel in most cases despite partial calcification.

Regarding whether this is complementary or competitive to intimal-based drug delivery platforms such as balloons or stents, I believe this to be complementary. Further, we are targeting inflammation rather than proliferation.

Finally, we have presented our preclinical renal denervation studies at the Society for Vascular Surgery meeting, whereby we used the bullfrog catheter to deliver guanethidine to the adventitia of renal arteries to chemically destroy the sympathetic nerve fibers. Regulatory work is ongoing so that we can move into early phase human studies.