ABSTRACT

OBJECTIVES This study provides preliminary data on the safety and feasibility of the use of a novel focal implant for managing post-percutaneous transluminal balloon angioplasty (post-PTA) dissection.

BACKGROUND Post-PTA dissection of the lower extremity arteries is managed with stent placement. This provides an acceptable post-intervention result but has long-term disadvantages, such as in-stent restenosis. Focal treatment of post-PTA dissection and avoidance of stents are the objectives of the Tack-It (Intact Vascular, Inc., Wayne, Pennsylvania) device.

METHODS A preclinical study and first-in-human data are presented. Seven swine underwent superficial femoral artery device placement, with a self-expanding nitinol stent on 1 side and a series of 4 Tack-It devices on the other side. Specimens were harvested at 28 days. The clinical study included 15 limbs that underwent revascularization for critical limb ischemia (n = 9) or claudication (n = 6). Twenty-five lesions were treated in the superficial femoral (n = 8), popliteal (n = 7), and tibial (n = 10) arteries.

RESULTS The preclinical study demonstrated a reduction in stenosis with the Tack-It (16.8 ± 2.6%) compared with stents (46.4 ± 9.8%). Neointimal thickness and injury score decreased with the Tack-It. Clinically, Tack-It placement resulted in acute technical success with resolution of the post-PTA dissection in 100% of lesions. There were no device-related complications or major amputations. Eighteen of the 25 lesions were available for angiographic follow-up at 1-year, and patency was 83.3%.

CONCLUSIONS Preclinical data suggest that the Tack-It device causes minimal vessel injury. Clinical use of the Tack-It to manage post-PTA dissection was safe and feasible in this early study and resulted in apposition of dissection flaps without stent placement. (J Am Coll Cardiol Intv 2015;8:347–54) © 2015 by the American College of Cardiology Foundation.

The existing paradigm for managing lower extremity occlusive lesions is severely limited by currently available tools. Balloon angioplasty (percutaneous transluminal balloon angioplasty [PTA]) functions by inducing dissection and causes excessive acute vascular injury (1–4). Post-PTA results are often suboptimal, and stents are the only practical solution available to manage this problem. Challenging morphologies such as longer lesions and occlusions are more likely to
require mechanical support with stent placement. Unfortunately, stents induce chronic injury and underlying inflammation, leading to intimal hyperplasia formation and in-stent restenosis (5–7). Stent fracture is the consequence of implanting relatively rigid metal scaffolds in areas exposed to complex biomechanical forces, leading to the continuous and unremitting deformation of the stent within the vessel (8,9).

These untoward clinical outcomes have motivated investigators to seek alternative solutions that provide the benefits of scaffolding but aim to induce low levels of inflammation and neointimal hyperplasia. It has been proposed that treatment with a minimal implant aimed at providing focal tissue apposition and fixation of dissection flaps would provide a smooth arterial flow surface without the long-term disadvantages imposed by a stent. The Tack-It device (Intact Vascular, Inc., Wayne, Pennsylvania) provides focal mechanical support only where needed after PTA. This is an opportunity to achieve an acute stentlike angiographic result without a stent. The technology functions on the basis of less metal, less outward force, minimal scaffolding, spot treatment, and an opportunity for more natural remodeling of the treated lesion while maintaining arterial flexibility.

METHODS

EXPERIMENTAL PROTOCOL. A total of 7 healthy swine received bilateral superficial femoral artery (SFA) implants and were kept alive for 28 days. At the time of the implantation, 1 SFA underwent deployment of a series of 4 (each 6 mm in length) nitinol self-expanding Tack-It devices. The contralateral artery received a self-expanding nitinol stent (40 mm long SMART stent [Cordis Corporation, Fremont, California] as a control. Fourteen vessels were explanted at 28 days and submitted for light microscopy and morphometric analysis. Animal investigation included animal care and use by qualified individuals, supervised by veterinarians, and facilities and transportation complying with legal requirements and guidelines; anesthesia was used for all interventions, and animal facilities met the standards of the American Association for Accreditation of Laboratory Animal Care.

LIGHT MICROSCOPY PROTOCOL. Explanted vessels were dehydrated in a graded series of ethanol solutions and embedded in methyl methacrylate plastic. After polymerization, each Tack-It device was sawed at 3 levels, and each stent was sawed at 4 levels. All segments were glued onto plastic slides and ground to a thickness of 17 to 70 μm using Exakt Linear Grinding technology (EXAKT Technologies, Inc., Oklahoma City, Oklahoma). All sections were examined by light microscopy for the presence of inflammation, thrombus, neointimal formation, and vessel wall injury. Histologic sections were analyzed using digital planimetry with a calibrated microscope system (IP Lab Software, Rockville, Maryland). Cross-sectional areas of the vessel, stent, and lumen were analyzed using conventional and previously published formulas. In addition, vessel healing was analyzed by quantifying strut apposition, fibrin deposition, granuloma and giant cell reactions, hemorrhage around the device struts, and total number of uncovered struts.

PATIENT POPULATION AND STUDY DESIGN. The clinical study was a prospective, nonrandomized, first-in-human safety and feasibility study with 1-year follow-up, registered at ClinicalTrials.gov (NCT02044003). Patients were treated at 2 sites in Asunción, Paraguay (Santa Clara Hospital and The Italian Hospital). Eleven patients were enrolled (15 lower extremities treated). Seven patients underwent treatment of 1 lower extremity, and 4 patients underwent treatment in both legs. The protocol was approved by the Human Subjects and Ethics Committee of each hospital. Major adverse events (MAEs) were reviewed by an independent clinical events committee. The subjects’ written informed consent was obtained. Baseline clinical data were collected on case report forms by a clinical research coordinator at the study sites. A database of patients and dissections was maintained. Data management was performed by Northwest Clinical Research Group, Inc. (Woodinville, Washington). The database was built on Microsoft Excel, and the data were audited by Databent (Seattle, Washington). The safety endpoint was the MAE rate, defined as the composite of death, device embolization, the occurrence of surgery related to the device, device-related occlusion of the artery, or major unplanned amputation of the ipsilateral lower extremity at 30 days. The feasibility endpoint was the ability to secure vascular dissection flaps with the device at the time of implantation. The technical success endpoint was defined as acute luminal patency at the conclusion of the revascularization procedure, with angiography demonstrating that the lumen of the artery at the location of implant remains patent. Patients were followed at 1 month, 6 months, and 12 months with clinical examination. One-year angiographic follow-up was obtained. Restenosis was defined as ≥50% by angiography.

TACK-IT DEVICE AND PLACEMENT PROCEDURE. Each patient underwent angiography to assess lower
extremity lesions. Heparin was administered, and transfemoral sheath placement was performed, using either up-and-over or antegrade approach using a 6-French access sheath. Heavily calcified lesions were excluded from the study (defined as circumferential calcification or contiguous calcification of ≥4 cm along the length of the lesion). The lesion was crossed using a standard guidewire technique. Each patient underwent balloon angioplasty with the balloon inflated to nominal pressure to match the reference vessel diameter. Post-PTA angiograms were obtained in multiple views. Any significant residual stenosis (≥30%) was treated with repeat PTA. Post-PTA dissection flaps were identified. The Tack-It delivery catheter was loaded onto the same guidewire and advanced to the site of the post-PTA dissection. The tacks were deployed separately at intervals of ≥6 mm from each other across the lesion. Each tack has an axial length of 6 mm (Figure 1) (10). The Tack-It is a self-expanding nitinol device that is specifically designed for tissue apposition and focal pressure application. Tack-It device features include low outward force, paired anchor fixation bars in the center of the implants, and variable pressure application, with more pressure exerted by the middle section of the device than by the wings. The device has a relatively flat outward force curve, so there is minimal change in outward force when implanted in vessels over range of diameters of several millimeters. The unconstrained diameter of the device is 7.3 mm. It is indicated for vessels with a reference diameter ranging from 2.5 to 5.5 mm. This permits serial implantation of the devices into a tapering artery without significant change in the mechanism and function of the device and without exerting increased outward force. The outward force exerted by the tack is lower than that observed in commercially available lower extremity stents. After deployment across the dissected segment, post-placement balloon angioplasty is performed to secure the device and the anchor fixation bars. Follow-up catheter-based angiography was performed in all available patients after 12 months or sooner if repeat revascularization was required.

RESULTS

EXPERIMENTAL STUDY. All implanted animals survived the entire in-life duration. Both devices matched vessel anatomy with good apposition (<5% malapposed struts in both groups). The percent of diameter stenosis was reduced (16.82 ± 2.64%) in the Tack-It group compared with the stent group (46.37 ± 9.75%). Neointimal growth consisted of organizing smooth muscle cells in a proteoglycan matrix, and it was higher in the stent group (Figure 2).

FIGURE 1 The Tack-It Device Is Indicated for the Focal Treatment of Post-PTA Dissection

The Tack-It device is a self-expanding nitinol design that is 6 mm in length and is able to treat arteries over a 3-mm range of diameters, from 2.5 mm to 5.5 mm. The device is secured by 6 pairs of anchor fixation features that are located in the center of the Tack-It, each with a radiopaque (RO) marker for radiographic visualization of the device.
Peristrut fibrin deposits were minimal in the Tack-It group and occurred in 11.01 ± 11.10% of the struts, whereas they were greater and more frequently seen (48.14 ± 14.61%) in the stent group. The Tack-It group demonstrated lower injury scores, less inflammation, and more endothelialization than the stent group. Histological parameters are summarized in Table 1.

**EARLY HUMAN CLINICAL STUDY.** The mean age of the 11 enrolled patients was 66 years (range 47 to 85 years). Five of the 11 (45%) were male. All patients had a history of hypertension (11 of 11), hyperlipidemia was present in 72.7% (8 of 11), and coronary artery disease was present in 72.7% (8 of 11). The indication for revascularization in the 15 limbs according to the Rutherford classification was gangrene (stage 5) in 5 patients, rest pain (stage 4) in 4, and claudication (stage 3) in 6. Of the 15 limbs, there were 25 treated lesions of the SFA (n = 8), popliteal artery (n = 7), and tibial artery (n = 10). Six of the 25 lesions (24%) were occlusions, and 19 were stenoses. Among the 6 occlusions, 5 were crossed using a looped subintimal wire, and 1 was crossed transluminally. The mean lesion length was 5.6 ± 4.2 cm. Acute technical success was achieved with Tack-It placement and tissue apposition/flap management in 25 of 25 treated arteries (100%), as determined by completion angiography (Figure 3). In each case, the area of dissection was successfully tacked down, and no dissection flaps persisted. The safety, feasibility, and technical endpoints are summarized in Table 2. The number of Tack-It devices placed per patient ranged from 1 to 12 (mean 3.4). Forty-eight of 50 devices were placed accurately (96%). In 1 case, 2 Tack-It devices were placed imprecisely near, but not at, the intended target (reference vessel diameter, 5.2 mm). Additional
Tack-It devices were implanted, and there were no untoward consequences. Of the 15 lesions of the superficial femoral and popliteal arteries, there were 5 occlusions (33%), and of the 10 lesions of the tibial arteries, there was 1 occlusion (10%). The number of Tack-It devices implanted in the femoral-popliteal lesions ranged from 1 to 5, and in the tibial lesions, it ranged from 1 to 3. The mean procedure time was 51 min (range 10 to 128 min). The mean fluoroscopy time was 13 min (range 5 to 30 min).

One patient had an intraprocedure puncture site thrombosis (contralateral femoral area using up-and-over approach) that required thrombus aspiration. One patient died of a myocardial infarction in the perioperative period. The MAE rate was 9.1% (1/11) due to the death in the perioperative period. Two patients were lost to follow-up before 1 year. There was no occurrence of device embolization, surgery related to the device, device-related occlusion of the artery, or major amputation. Eighteen of the 25 lesions were available for follow-up at 1 year, and angiographic patency was 83.3%. There was recurrent stenosis (≥50%) in 3 of 18 (16.7%). One patient with a popliteal artery occlusion and toe gangrene underwent recanalization, balloon angioplasty, and Tack-It placement but returned with a recurrent stenosis as seen on duplex ultrasonography at 3 months and required repeat angioplasty and Tack-It placement for a target lesion revascularization rate of 4%. The 1-year patency rate for the femoral and popliteal artery lesions was 87.5%. Recurrent stenosis developed in 2 patients with tibial artery lesions, for a 1-year tibial artery patency rate of 80%. One lesion recurred after treatment of an occluded tibioperoneal trunk, and 1 occurred after treatment of a stenosis. Both patients initially had healed ischemic foot ulcers that healed and neither required repeat intervention. The 1-year patency rate for tibial artery lesions was 80%.

**DISCUSSION**

These preliminary results suggest that use of the Tack-It device is safe and that this alternative nonstent method of securing post-PTA dissection flaps is feasible. The experimental evaluation of the Tack-It device at 28 days demonstrated less neointimal formation, degree of injury, inflammation, and stenosis than an SFA-approved self-expanding nitinol stent. In addition, overall vascular healing was superior with the Tack-It device as reflected by the lower amounts of peristrut fibrin and red blood cell deposits. The anchor fixation segment of the Tack-It device did not induce additional degrees of inflammation.

The first-in-human study demonstrated the feasibility and safety of focal treatment of post-PTA dissection in the lower extremity using a novel implant designed to achieve tissue apposition but maintaining the natural configuration and qualities of the artery. Multiple post-PTA dissections were managed in a range of arteries and lesion morphologies without bailout stent placement. The 1-year angiographic patency was acceptable in this small preliminary study comprising all-comers: lesions of the superficial femoral, popliteal, and tibial arteries and in limbs with gangrene, rest pain, or claudication. The principles used in the construction of the Tack-It device (less outward force, less metal, and spot treatment) are specifically intended to address areas in which currently available devices have failed (Table 3). A much larger study is required to understand the overall patency implications of this approach.

Balloon angioplasty plays a major role in lower extremity revascularization and will likely be an essential technique in the foreseeable future. Drug-coated balloons have shown promise and will prompt renewed interest in the angioplasty mechanism and how it may be optimized (11–13). In arteries that are obstructed by atherosclerotic plaque, balloon angioplasty increases the vessel lumen diameter by causing dissection. Post-PTA dissections are uncontrolled arterial injuries that are usually manifested by longitudinal tears creating tissue flaps of varying degrees of

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<th>Table 1: Comparison of Self-Expanding Nitinol Stent and Tack-It Device</th>
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<tr>
<td><strong>Tack-It Implant Group</strong></td>
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<tr>
<td>(n = 28)</td>
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<tr>
<td>EEL area, mm²</td>
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<td>Strut malapposition, %</td>
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Values are mean ± SD. *Animal 16-106D (CV29819) RSFA Tack 1 mid-section excluded from analysis due to processing artifacts, and a section was unavailable from the proximal region of animal 16-117D (CV29821) RSFA, Tack 4. EEL = external elastic lamina; IEL = internal elastic lamina; RBCs = red blood cells.
severity that are visible angiographically. When post-PTA dissection produces a suboptimal result in current practice, the only reasonable option available is stent placement to secure the dissection flap and ensure the integrity of the lumen. Contemporary SFA stent trials conducted primarily in TASC A and B lesions have a stent bailout rate of 35% to 50% in patients randomized to balloon angioplasty (14,15). The more challenging lesions (TASC C and D, longer lesions, occlusions) are even more likely to require mechanical support, and a stent is often deployed to achieve an acceptable result (16-18). One major unsolved challenge is that it remains unclear which dissections require treatment and which do not.

Almost every important aspect of stent design and construction is associated in some way with stent failure. For example, the stent material, degree of outward force, wall pattern, rigidity, stent length, and

FIGURE 3 A 65-Year-Old Man With Short-Distance Right Leg Claudication

(A) Angiogram of right superficial femoral artery before treatment. (B) Post-angioplasty dissection (arrows). (C) Three Tack-It devices (arrows) deployed in right superficial femoral artery to treat post-angioplasty dissection. (D) Completion angiogram after Tack-It device placement. (E) Angiogram performed in follow-up at 1 year.
strut thickness are all associated with in-stent restenosis (16,19–24). It is apparent that the longer the lesion is, the lower the long-term patency. This is typically attributed to lesion length; however, it may also be due to stent length, which becomes correspondingly longer with lesion length. It is generally agreed that a “full metal jacket” is not a durable or desirable solution (25). This suggests that when mechanical support is required at the treatment site, one consideration may be to minimize the implant.

The current treatment paradigm with balloon angioplasty and stenting is somewhat in flexible and indicates stent placement even when much less mechanical support and less metal may actually be required. A stent is generally able to provide a smooth post-intervention surface but may also provide too much scaffolding, causing increased stiffening of a highly mobile and flexible artery. Stents may also cover too much surface area with metal, apply too much chronic outward force against the artery wall, and allow too much friction between the metal implant and the artery wall. In the interest of managing post-PTA dissection, the function of a stent in the current treatment paradigm is to force the artery into a configuration that it would not otherwise naturally assume. Newer stents of various configurations or that exert varying forces or are coated with medication have been introduced, with each design intended to minimize the impact of the implant on the recipient artery (26). However, it is possible that these constructs cause injury that exceeds the acceptable threshold that might avoid the previously mentioned stent-related failure modes. Substantial arterial scaffolding with a stent permanently alters the conformational quality of the artery. When in-stent restenosis occurs, there is no durable treatment (27,28). When the continuum of care is assessed over the patient’s life span, the patient may be better off without a stent in the lower extremity. When a stent is placed, a bridge is burned along that care continuum. Perhaps a stentlike acute angiographic result could be achieved without the late complications of a stent. In addition, the availability of an accurate method of spot treatment returns control of the procedure to the operator. This increases precision, provides only as much mechanical support as is needed, and is more akin to a dose-response approach to optimizing balloon angioplasty.

Use of the Tack-It is a highly versatile solution to a complex problem. This approach provides the ability to treat a broad range of artery diameters with a single device and to treat multiple locations with a single catheter. Use of the Tack-It Endovascular Stapler to manage post-PTA dissection is safe and feasible. It resulted in less injury, inflammation, and stenosis than standard control SFA stents in the pre-clinical study and permanent securement of dissection flaps without stent placement and with reasonable angiographic patency at 1 year in this first-in-human study. This device provides focal treatment of post-PTA dissections, allowing the artery to maintain its natural configuration, avoid overscaffolding with stents, and potentially avoid the long-term failure modes of in-stent restenosis and stent fracture.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Peter A. Schneider, Division of Vascular Therapy, Kaiser Foundation Hospital, 3288 Moanalua Road, Honolulu, Hawaii 96819. E-mail: peterschneidermd@aol.com.

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