Original article

Novel vein closure procedure using a proprietary cyanoacrylate adhesive: 30-day swine model results

Robert J Min*, Jose I Almeida†, Derek J McLean‡, Monte Madsen§ and Rodney Raabe**

*Department of Radiology, Weill Cornell Medical College, New York, New York, USA; †Voluntary Associate Professor of Surgery, University of Miami School of Medicine, University of Miami, Miami, Florida, USA; ‡Department of Animal Sciences, Washington State University, Pullman, Washington, USA; §Inland Imaging, Spokane, Washington, USA; **Department of Radiology, Sacred Heart Medical Center, Spokane, Washington, USA

Abstract

***Purpose*:** To conduct a pilot study to demonstrate a novel method of using a proprietary cyanoacrylate (CA) for closure of superficial veins.

***Materials and methods*:** Right and left superficial epigastric veins from two swine models were utilized due to the vein's similarities with the human great saphenous vein. Under ultrasound guidance, access was gained and a 5-F delivery catheter was advanced to the junction of the superficial epigastric and abdominus rectus veins. A dispenser gun was then utilized to inject 0.16 mL of CA while compression was applied cephalad to the end of the catheter. Immediately after delivery, the catheter was pulled back 3 cm and manual compression was employed for 30 seconds. After this first injection, the ultrasound probe was repositioned caudad to the injection and cephalad to the catheter tip and another 0.16 mL injection was delivered with immediate 3 cm pullback of the delivery system. Manual compression was applied at the caudad end of the treated vein for 30 seconds. This process was repeated until the entire target segment was treated.

***Results*:** At 30 days postimplantation, the treated veins were occluded with no evidence of recanalization or migration. Histological findings revealed that the lumen was dilated by coalescing, arborizing clear spaces with entrapped lytic erythrocytes, demarcated by a thin band of granular eosinophilic material. Spindle cells with dense eosinophilic matrix replaced the tunica intima and disrupted the tunica media.

***Conclusion*:** Results of this initial study demonstrated that intravascular injection of CA is feasible for closure of superficial veins in animal models. These findings warrant further animal studies of this proprietary CA to assess efficacy, safety and its effects on perivenous structures.

Keywords: endovenous technique; varicose veins; venous disease; venous reflux

Introduction

The use of cyanoacrylate (CA) for medical applications dates back to the 1960s, most notably when a specialized surgical team began using the adhesive to stop bleeding and seal wounds during the Vietnam War.[1] Over the past 50 years this compound has been utilized extensively in the medical field, including ophthalmic surgery, cosmetic procedures, dental applications, tissue adhesion and haemostasis of acute bleeding, to name a few. In particular, CA injection has been used extensively for endoscopic sclerotherapy of gastric variceal bleeding with high safety profiles reported in patients followed for up to 10 years.[2] More recently, variations of CA have been employed intravascularly with great success to treat conditions such as type I and

Correspondence: **Robert J Min MD MBA,** Department of Radiology, Weill Cornell Medical College, 525 East 68th Street, Starr 8a–37 New York, NY 10065, USA.
Email: rjm2002@med.cornell.edu

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II endoleaks of abdominal aortic aneurysm repair procedure, varicoceles, pelvic congestion syndrome and arteriovenous malformations (AVM). CAs have been permitted for use in endovascular procedures in Europe for several decades, but were not approved in the USA until 2000 when Trufill cyanoacrylate (Cordis, Miami Lakes, FL, USA) gained Food and Drug administration clearance for the devascularization of cerebral AVMs.[3] Although its use is off-label for other peripheral applications, the properties of CA make it ideal for a number of vascular closure procedures.[4]

The introduction of CA within a vessel triggers an acute inflammatory reaction in the wall and surrounding tissues.[3] On contact with anionic substances such as blood cells, endothelium or plasma, the adhesive begins to polymerize.[5] This polymerization damages the vascular intima and induces immunological responses.[6] Gradual resorption of the occlusive polymer occurs after polymerization is complete. After approximately one month, the response progresses to a granulomatous process with foreign body giant cells and fibrosis.[7,8] Effective injection into a target vessel is dependent upon controlling the polymerization of CA. Factors that affect this process include the dilution of CA, flow of blood within the target vessel, the size of the vessel and velocity of injection by the user.[5] A polymerization rate which is too rapid may result in the catheter becoming glued to the vessel, whereas an over-diluted solution may delay polymerization for too long and result in migration of the CA into unwanted areas.[5] Another rare complication is embolization of polymerized CA fragments.

The ability of the operator to control the rate of reaction makes CA an ideal candidate to be used for occlusion of veins. One such potential application is vein closure in the superficial venous system. Venous insufficiency of the great saphenous vein, small saphenous vein, accessory saphenous veins, perforators and tributaries are highly prevalent peripheral venous conditions. Venous reflux of the lower extremities occurs in an estimated 15% of all men and 28% of all women.[9] Treatment for this disease has evolved greatly over the past 10 years from traditional surgical stripping with the advent of minimally invasive radiofrequency ablation and endovenous laser ablation procedures. Radiofrequency employs an electrode which delivers heat via direct contact with the vein wall, producing initial collagen denaturation and eventual fibrosis to achieve vein closure.[10] Endovenous laser ablation utilizes a laser fibre to deliver heat intravascularly, which results in vein wall damage and ultimately fibrosis.[11,12] Both radiofrequency and endovenous laser ablation require large amounts of tumescent anaesthesia to create external compression to the target vein and provide a thermal barrier to protect surrounding tissues from heat that is generated during the procedure. The tumescence is administered to the patient via needle punctures into the perivenous space. While thermal ablation technologies have demonstrated efficacy rates greater than 90%,[13,14] postoperative pain and bruising continue to be common side-effects that cause patient discomfort.[15,16]

Alternative minimally invasive treatments for varicose veins are continually evolving to increase patient comfort, reduce risk and improve cost efficiencies. Based on the success and safety of CAs in the closure of other vessels, this agent may have potential to be a viable treatment for venous insufficiency in the lower extremities. The aim of this study was to assess the use of CA in vein closure, including its efficacy and effect on the vein wall in an animal model.

Materials and methods

Equipment

All imaging during the procedure was performed with a MicroMaxx (SonoSite, Bothell, WA, USA) high-resolution ultrasound system with a 7.5 MHz transducer and image archive capability. A 5-F micropuncture set was used to gain venous access and included a 21-gauge needle, 0.018′ SS wire and a 5-F sheath/dilator (Vascular Solutions, Minneapolis, MN, USA). A 5-F introducer sheath/dilator (Vascular Solutions) was utilized for insertion of the delivery catheter. The closure system consisted of a 5-F delivery catheter, a 3 mL syringe, a dispenser tip and a custom-designed dispenser gun (Sapheon, Santa Rosa, CA, USA). The dispenser gun was operated by depressing a trigger to deliver a set amount of adhesive through the connected syringe and catheter into the target vessel. CA adhesive (Sapheon) was utilized as the adhesive. The CA was a proprietary formulation which was mixed with a curing retardant and a thickening agent to attain optimal viscosity and polymerization rate for intravascular injection in a vein.

Description of technique

The right and left superficial epigastric veins (SEVs) were harvested from two swine, weighing 160 and 175 lb, respectively. Swine SEVs were utilized due

to the vein's ideal structure and likeness to the human great saphenous vein. The veins course along the ventral portion of the abdomen, emptying into the abdominus rectus vein (ARV) in the deep system. Preprocedural ultrasound evaluation revealed the SEV to be suprafascial with a consistent diameter ranging from 2.4 to 4.5 mm.

The live pigs were housed in accordance with USDA regulations and care complied with the 'Guide for the Care and Use of Laboratory Animals' (National Institutes of Health). The pigs were administered general anaesthesia and monitored by a veterinarian. The abdomen of the swine were shaved with electric clippers and prepped with Betadine solution. Sterile technique was observed throughout the entire procedure.

Under ultrasound guidance, the SEV was located to determine a site for access. Compression of the vein was performed at a location adjacent to the swine elbow to observe its maximum diameter and viability for access. A position at the level of the third nipple cephalad from the groin revealed junctions of both medial and lateral venous branches. This site exhibited excellent compressibility and a consistent diameter and length making it ideal for access.

After selecting an insertion site, ultrasound guidance was used to access the SEV with a 21-gauge needle from a 5-F Micro Introducer Kit. A 0.018′ wire was advanced into the vein and access was confirmed under ultrasound. The needle was removed and the 5-F micropuncture sheath/dilator was advanced over the wire. The wire and dilator were removed and a double-ended 0.035′ J guide wire, 80 cm (Vascular Solutions) was advanced through the sheath and into the lumen of the vein. Under realtime ultrasound, the guide wire was positioned just caudad to the junction of the SEV and ARV. After confirmation, the 5-F micropuncture sheath was removed and a 5-F introducer sheath/dilator was threaded over the guide wire to the junction of the SEV and ARV.

Utilizing a dispenser tip, a 3-mL syringe was used to extract the CA adhesive from its glass vial. Once the syringe was filled, the dispenser tip was removed and the syringe was attached to a 5-F delivery catheter. The combined syringe and catheter were then connected to a dispenser gun. Prior to insertion, the catheter was primed using the dispenser gun to advance the adhesive to within 3 cm of the catheter tip. Caution was taken to avoid advancing the adhesive to the catheter tip during priming.

Next, the dilator and 0.035′ wire were removed, leaving the 5-F introducer sheath in place. A saline-filled syringe was then attached and utilized to flush the introducer. Under realtime ultrasound guidance, the tip of the sheath was pulled back and positioned 1.5–2.0 cm caudad from the junction of the SEV and abdominus rectus. The saline-filled syringe was removed and the primed 5-F delivery catheter was inserted into the sheath and advanced to the level of the 5 cm peel-away spacer on the catheter. Removing the spacer, the sheath was then pulled onto the catheter and locked into place with a spin-lock mechanism, exposing the catheter tip and positioning it 1.5–2.0 cm from the junction (Figure 1).

The ultrasound transducer was positioned just cephalad to the catheter tip and pressure was applied with the ultrasound probe in the transverse plane, compressing the SEV and the SEV–ARV junction. While applying manual compression, 0.16 mL of CA was delivered by depressing the trigger of the dispenser gun and holding it for three seconds. Following this initial injection, the delivery system (sheath and catheter) was immediately pulled back 3 cm and transverse compression was held for an additional 30 seconds.

The ultrasound probe was then positioned to relocate the catheter tip. Upon confirmation, compression of the vein caudad to the initial injection and cephalad to the catheter tip was applied with the ultrasound probe. One three-second trigger depression was used to deliver 0.16 mL into the vein. The delivery system was pulled back another 3 cm and compression was applied by hand at the injection site while the ultrasound probe was simultaneously compressing the caudad end of the treated vein. This process was repeated until the entire length of the target vein segment was treated to the level of the access site (Figure 2). After the final CA injection, the delivery system was removed and vein closure

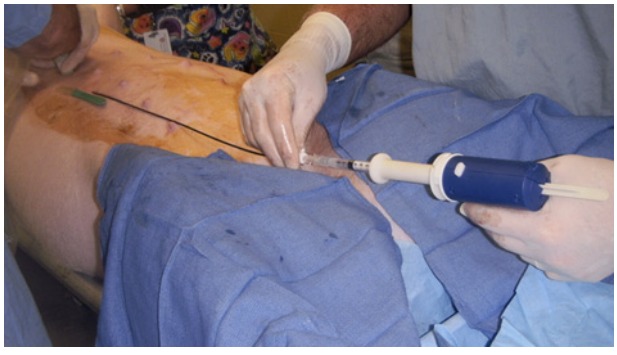

Figure 1 The 5-F sheath is pulled onto the 5-F delivery catheter and locked in place on the catheter. Tip position is confirmed under ultrasound

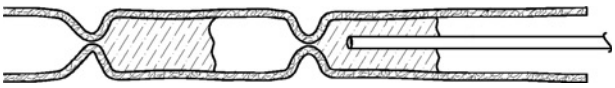

Figure 2 The ultrasound probe is repositioned caudad to the previous injection site and cephalad to the catheter tip. While applying transverse compression with the ultrasound probe, another injection of cyanoacrylate is delivered

along the treated segment was confirmed under ultrasound.

Both the right and left SEVs of each pig were injected, for a total of four treated veins. The swine remained healthy after the procedure and were sacrificed 30 days postimplantation. Tissue specimens were harvested from the left and right epigastric veins of the model and histological evaluation of the treated SEV was conducted by an independent pathologist. The treated SEV was evaluated in cross-sections, with six in total. Both the cephalad and caudad ends of the SEV were studied, as well as side branches arising from the treated SEV. Microscopic assessment was performed to determine effects in the epithelium caused by the adhesive, the presence or adherence of the adhesive within the lumen, and the degree of inflammatory process.

Results

Both the right and left SEV of each swine model were successfully accessed with no complications. The injection of the CA into each target vein was achieved without difficulty, using the outlined protocol. Acute ultrasound assessment of the four treated veins revealed successful occlusion postinjection.

Swine model #1

The left SEV of this model measured 4.3 mm in diameter and was injected with a total of 1.2 mL of CA. The vein was pale in colour, with CA present in the lumen. Upon explantation, the vein was completely occluded with no evidence of patency in the vein or its side branches. The lumen was dilated by coalescing, arborizing clear spaces with entrapped lytic erythrocytes (Figure 3a). A well demarcated, thin band of granular eosinophilic material outlined the spaces. Spindle cells with dense eosinophilic matrix replaced the tunica intima and disrupted the tunica media. Additionally, the tunica intima was disrupted by numerous aggregates of histiocytes with fewer multinucleated giant cells, lymphocytes, plasma cells and eosinophils. This inflammation extended in a less severe manner into the tunica media and tunica adventitia. A healthy, untreated segment of the left SEV was utilized as a control. Histological evaluation revealed normal appearance for the tissue and lack of significant changes (Figure 3b).

Similarly, the right SEV of this model measured 4.5 mm in diameter and was injected with 1.5 mL of CA. As observed with the left SEV, no bulge or discolouration was found near the treated veins prior to dissection. Evaluation of its cross-sections demonstrated histology analogous to that of the left SEV.

Swine model #2

The diameter of the left SEV from this model was recorded at 3.2 mm, with a total CA injection of 1.1 mL. This vein was completely occluded with no visible patency in the vein or its side branches. CA was present throughout the segment, with most of the vein exhibiting a pale colour. Although not

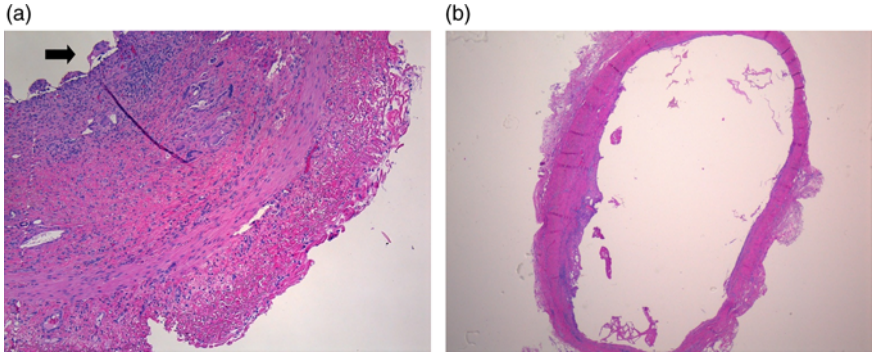

Figure 3 (a) Photomicrograph of epigastric vein injected with cyanoacrylate showing disruption of the tunica intima with histiocytes forming projections into the lumen (arrow). Tissue appearance consisted mainly of minimal degeneration of the wall. Disruption extends into the tunica media with inflammation in the tunica mucosa and tunica adventitia consistent with chronic foreign-body type inflammatory response (×100). (b) Photomicrograph of control epigastric vein showing typical tissue layers and normal tunica intima, tunica media and tunica adventitia. This epigastric vein sample was removed from the same animal as in (a) at a site caudad to the injection (×40)

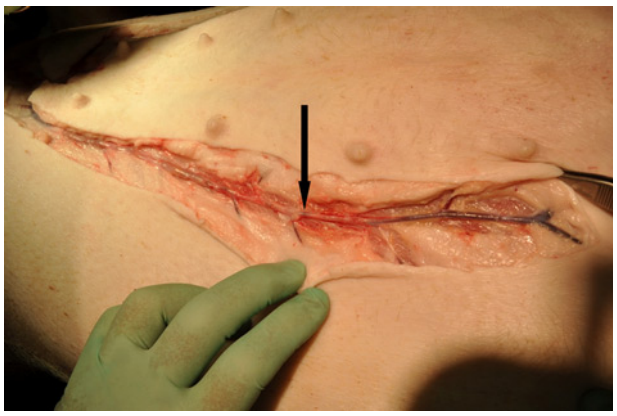

Figure 4 Left swine epigastric vein dissected to reveal vein and surrounding tissue. The vein appearance varies with segments that are white, where the lumen is filled predominantly with cyanoacrylate (CA), and areas that are dark (arrow) resulting from the mixing of CA with blood during the injection. No leakage or migration of the CA was observed in surrounding tissue

visible on the skin, a dark colour was apparent in some areas of the vein as a result of CA mixing with blood during injection (Figure 4). Histologically, this left SEV is similar to that observed in the left and right SEV of model #1, with the exception that the lumen is narrowed in three of the six cross-sections due to profuse inflammation and fibrosis.

The right SEV was the smallest of the treated veins with a diameter of 2.4 mm and a resultant 0.9 mL of injected CA. As was observed in the left SEV of this model, a dark colour was present in some areas due to the adhesive mixing with blood. Congruent to the other treated veins, this vein was totally occluded with no visible patency. Histological observations were comparable to findings in the veins of model #1.

In all treated veins, unwanted migration of CA was not found nor was recanalization observed.

Discussion

This study demonstrated that the use of CA for closure of a swine SEV was feasible and well tolerated in an animal model 30 days after the procedure. Given that this is the first use of our proprietary formulation of CA, its specific mechanism and reactions with endothelium are not known in their entirety. Comparable to our use of CA, Kailasnath and Chaloupka[17] performed a detailed assessment of CA polymerization-binding mechanics using an explanted common carotid artery of a swine and a plastic model vessel, each approximately 3.0 mm in diameter. They identified a multiphasic pattern of binding forces consisting of three phases: an initial rapid, incomplete polymerization phase with increasing tensile forces lasting approximately 10 seconds; a second phase of incomplete polymerization which displayed a constant tensile force and spanned up to one minute in length; and a final phase characterized by a rapid, exponential rise of tensile force that completed polymerization.[17] The polymerization times and binding forces varied based on the formulation and type of CA used.[17] The procedural technique utilized in our study appears to coincide with their multiphasic conjecture. We injected 0.16 mL into the vein and retracted the catheter 3 cm before completion of polymerization. Compression was applied for 30 seconds to ensure coaptation of the vein walls, allowing polymerization to advance well into the second phase or possibly to completion before administering the next injection.

Our method is unique in that typical intravascular injection of CA has been reported using a continuous pullback method.[17–19] One of the primary concerns in the endovascular delivery of CA is adhesion of the catheter tip to the CA and potentially to the intima.[19] Since our technique incorporated immediate catheter pullback from the injection site combined with a proprietary formulation of CA to prevent premature curing, catheter tip adhesion was not an issue. In addition, the delivery catheter design was optimized for hydrophobicity and ease of use, with 1 cm markings to aid in precise pullback after each injection.

One of the limitations of this pilot study is that the tissue adjacent to the treated vein was not evaluated. Others have studied the effects on surrounding tissues using a varied formulation of CA. Freeny *et al.*[20] performed postmortem examinations of patients whom had undergone successful transcatheter embolization of various visceral arteries or veins with isobutyl 2-cyanoacrylate. Upon studying these treated vessels, the investigators observed that the inflammatory reaction was contained entirely within the vessel lumen and did not extend into the vessel walls or contiguous tissues.[20] Furthermore, there was no evidence of tissue damage or vasculitis in time frames ranging from two days to six months postembolization.[20] These findings present a viable justification for future animal testing of our CA formulation to evaluate its effect on surrounding tissue.

Current technologies used for the closure of superficial veins present the possibility of adjacent structure damage. Radiofrequency and laser ablation emit heat directly or indirectly to the target vessel which may damage perivenous tissue, resulting in complications such as skin burns or paresthesia.[21,22] Injury to surrounding structures is largely avoided

in these procedures by administering perivenous tumescent anaesthesia, which compresses the vein and creates a heat sink to dissipate generated heat.[23] While tumescence is highly successful in preventing damage from heat, it incorporates an additional procedural step, in that delivery of perivenous tumescence requires numerous needle sticks around the target vein. Inadvertently, needle puncture of the vein wall can cause vessel perforation, leading to postprocedure bruising and pain.[12,24] The use of CA for vein closure does not require tumescence, but further studies are needed to assess its effects on perivenous tissue.

Conclusions

This pilot study successfully demonstrated that the use of CA for superficial vein closure is feasible in animal vessels. The procedure proved to be uncomplicated, predictable, and repeatable, requiring only basic endovascular skills. To further define the role of CA in vein closure, a more detailed evaluation is warranted which should include an in-depth look at safety and the effects of CA on bordering tissues. Longer-term animal studies are underway to assess this novel procedure's efficacy and tolerability.

Conflicts of interest: RJM: Sapheon, Medical Advisory Board; Sapheon, Stockholder. JIA: Sapheon, Research Grant. MM: Sapheon, Stockholder. RR: Sapheon, Stockholder.

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