VenaSeal closure despite allergic reaction to n-butyl cyanoacrylate

Leslie Fiengo, PhD, FRCS,1 Adam Gwozdz, MSc, MRCS,a Laura Tincknell, BSc, MBBS,1 Vanessa Harvey, BA, BN,a Timothy Watts, MSc, MRCP,1 and Stephen Black, MD, MBBCh, FRCS(Ed), FEBVS,a London, United Kingdom

ABSTRACT
The VenaSeal closure system (Medtronic, Minneapolis, Minn) is a nonthermal, minimally invasive method for the treatment of superficial venous insufficiency using a proprietary n-butyl cyanoacrylate. We report the case of a 45-year-old woman who underwent right great saphenous vein closure with VenaSeal and subsequently had a biphasic reaction to n-butyl cyanoacrylate, confirmed on patch testing that had negative results for other cyanoacrylates. Despite the initial allergic response, which settled with antihistamines, follow-up duplex ultrasound imaging confirmed successful great saphenous vein closure, and the affected vein remained in situ without further complication. (J Vasc Surg Cases and Innovative Techniques 2020;6:269-71.)

Keywords: VenaSeal; Varicose vein; Allergic reaction; Superficial venous insufficiency

Superficial venous insufficiency is a common disease, and its treatment has evolved substantially during the last several years to include a number of minimally invasive technologies.1 Cyanoacrylate-based closure (CAC) with the VenaSeal closure system (Medtronic, Minneapolis, Minn) is a new technique approved by the Food and Drug Administration2 in 2015 and by the Conformité Européenne in 2011.

The cyanoacrylate compounds were originally synthesized in the 1940s for military use as they possess a strong cohesive force, high strength, rapid polymerization, and hemostatic and bacteriostatic properties. Three types of n-butyl cyanoacrylate (NBCA) are currently available on the market for superficial vein incompetence: VariClose (Bilas, Ankara, Turkey), VenaBlock (Invamed, Ankara, Turkey), and VenaSeal. We report a case, with consent, of a 45-year-old woman receiving great saphenous vein (GSV) closure using VenaSeal.

CASE REPORT
A 45-year-old woman presented to our venous clinic in December 2016 with a past medical history of right popliteal deep venous thrombosis secondary to a long flight and combined oral contraceptive pill use. The patient had a past medical history of asthma, allergic rhinitis, and penicillin allergy.

She presented complaining of significant discomfort in her right leg including the upper thigh associated with swelling, for which she had trialed compression hosiery with little improvement. Duplex ultrasound showed an incompetent GSV with saphenofemoral junction reflux and incompetent communicating varicosities 15 cm above the knee. The GSV had a caliber of 5 mm, and the femoral and popliteal veins were incompetent. Magnetic resonance venography and intra-vascular ultrasound were performed to exclude significant iliac outflow obstruction, which was suspected on the basis of her history of deep venous thrombosis. After deep venous assessment, it was concluded that the superficial refluxing vein was not contributing to drainage of her leg, a concept previously demonstrated by Labropoulos et al.3

She underwent a right GSV closure procedure under local anesthesia as a day case with VenaSeal under the supervision of a proctor experienced in this procedure. The procedure itself was uneventful. Nine days later, bright red erythema developed over the right knee in association with swelling and itchiness. These symptoms settled after a few days of treatment with antihistamines. At approximately 20 days postoperatively, further erythema developed around her groin, followed by the development of a generalized macular rash that involved the arms, abdomen, thorax, neck, shoulders, and scalp. There was no mucosal involvement, blistering, or peeling of the skin. No other medications or triggers were implicated at the time. She had no history of reacting to acrylate or other contact allergens.

The presentation suggested that this could have been a delayed hypersensitivity to the acrylates contained within VenaSeal, given the biphasic nature of the reaction, with the initial local reaction over the right leg resolving before the more generalized macular eruption appeared. A patch test was therefore performed, which demonstrated a strong positive response to
the VenaSeal adhesive (NBCA) and negative results for all other acrylates in our series (ethyl cyanoacrylate alongside 2-hydroxyethyl methacrylate), which were performed to exclude cross-reactivity. These investigations confirmed a diagnosis of allergic contact dermatitis potentially to a single agent.

Cross-reactivity to other cyanoacrylate skin and soft tissue adhesives, such as 2-ocetyl cyanoacrylate—found commonly in Dermabond (Ethicon, Somerville, NJ)—was also tested, and the response was negative. The patient did however test positive to Histoacryl (B. Braun Medical, Bethlehem, Pa), which also contains NBCA.

Follow-up duplex ultrasound at 3 months after the procedure reported no untoward features or fluid around the vein. The patient made a full clinical recovery and has been followed up for 24 months. Her residual deep venous reflux remains with no evidence of any further deep venous changes since presentation.

DISCUSSION

CAC is widely used in the vascular system to embolize arteriovenous malformations and arterial aneurysms. The high viscosity and rapid polymerization of NBCA are preferred in the venous system to ensure that the glue placed in the veins achieves sealing without washout. Once it is in the venous lumen, NBCA induces inflammation and long-term fibrotic occlusion.4,5

Almeida et al10 published the first-in-human use of CAC for treatment of saphenous vein incompetence in a series of 38 patients, demonstrating complete closure of the GSV in 100% at 48 hours and 92% at 12 months. Furthermore, CAC was shown in the VenaSeal Saphenous Closure System vs Radiofrequency Ablation for incompetent Great Saphenous Vein (VeClose) randomized trial to be an effective and noninferior alternative in terms of safety and effectiveness to radiofrequency ablation in the treatment of incompetent veins. The VeClose study reported similar intraprocedural pain ratings, quality of life improvement, and adverse events in comparing VenaSeal and radiofrequency ablation.6

However, despite promising early outcomes, adverse reactions to CAC have been recognized. The first-in-human study of Almeida et al10 reported the development of phlebitis requiring oral nonsteroidal anti-inflammatory drug treatment in six (15.8%) patients. A study by Park7 analyzed the outcomes of 34 patients (63 legs) treated with VenaSeal, reporting development of an “abnormal skin reaction” described as erythema, itchiness, edema, pain, and tenderness over the treated area in 8 (23.5%) patients, all recovering fully within 2 weeks.

Almeida et al10 later reported in their 2-year follow-up paper a 16% rate of phlebitis after VenaSeal treatment of 38 patients; the phlebitis lasted an average of 5.2 days and resolved with oral nonsteroidal anti-inflammatory drug treatment only. A multicenter prospective European cohort study of CAC of refluxing GSV reported by Proebstle et al8 described 70 patients undergoing VenaSeal GSV closure with adverse events also including an 11.4% rate of phlebitis and 8.6% rate of pain without phlebitic reaction.

Similar outcomes have been reported in other studies. A recent review by Bissacco et al11 analyzing a total of 918 patients who underwent GSV treatment with NBCA reported the major complications as postoperative pain (4.8%) and superficial vein thrombosis (2.1%).

Hypersensitivity reactions to intravenous cyanoacrylate have been described. Full-body urticaria developed in a single patient in the Lake Washington Vascular VenaSeal Post-Market Evaluation (WAVES) trial 1 week after CAC treatment; it resolved with the use of oral steroids.11

A recent case report by Jones et al12 detailed GSV treatment with VenaSeal in which worsening leg pain and erythema developed 13 days postoperatively despite treatment with oral diphenhydramine and topical diclofenac 1% cream. The patient had a positive patch test response for cyanoacrylate and continued to experience leg pain, erythema, and swelling up to 124 days postoperatively and eventually decided to have the affected vein endoscopically excised. The excised vein was histologically examined, showing the majority of mononuclear cells as T4 subset lymphocytes, as would be expected in a type IV hypersensitivity reaction. Furthermore, other uses of cyanoacrylate, such as the topical skin closure product Dermabond (Ethicon) and cosmetic eyelash and nail adhesives, have been known to cause type IV hypersensitivity reactions.13

More recently, Navarro-Tivino et al14 reported a case of allergic reaction to VenaSeal, confirmed on patch testing. However, unlike our experience, they reported evidence of fluid surrounding the vein on ultrasound imaging. A complication using VenaBlock was reported by Parsi et al,15 who identified extravascular foreign body granulomas containing lymphoid aggregates, fibrosis, and spicules of cyanoacrylate 1 year after vein closure with NBCA. Phlebitis remains the most commonly reported complication of VenaSeal in the literature, ranging from 4% to 20%.16 More substantial hypersensitivity reactions can occur, and it is important to consider hypersensitivity in cases in which CAC is used. Anaphylactic shock is rare and has not yet been reported with VenaSeal.

CONCLUSIONS

Several studies have shown that VenaSeal is safe and effective; however, hypersensitivity and later allergic responses as demonstrated by our case report need further mechanistic evaluation. CAC and NBCA-based treatments should be avoided in patients with known hypersensitivity, and clinicians should include this complication in patient information leaflets and during the consent process. Most adverse effects are self-limited without clear long-term sequelae. This case demonstrates formally reported patch testing and defined
sensitivity to the specific NBCA found in VenaSeal, indicating the potential for development of sensitivity in patients without any prior exposure, with the outcome including the reaction's resolving and the successfully closed vein being left in situ.

REFERENCES
1. Rabe E, Guex JJ, Puskas A, Scuderi A, Fernandez Quesada F; VCP Coordinators. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. J Angiol 2012;31:105-15.
2. U.S. Food and Drug Administration. Approval order: VenaSeal closure system P140018. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140018A.pdf. Accessed May 7, 2020.
3. Labropoulos N, Volteas N, Leon M, Sowade O, Rulo A, Giannoukas AD, et al. The role of venous outflow obstruction in patients with chronic venous dysfunction. Arch Surg 1997;132:46-51.
4. Min RJ, Almeida JJ, McLean DJ, Madsen M, Raabe R. Novel vein closure procedure using a proprietary cyanoacrylate adhesive: 30-day swine model results. Phlebology 2012;27:398-403.
5. Almeida JJ, Javier JJ, Mackay E, Bautista C, Proebstle TM. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. J Vasc Surg Venous Lymphat Disord 2013;3:174-80.
6. Morrison N, Gibson K, McEnroe S, Goldman M, King T, Weiss R, et al. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). J Vasc Surg 2015;61:985-94.
7. Park I. Initial outcomes of cyanoacrylate closure. VenaSeal System, for the treatment of the incompetent great and small saphenous veins. Vasc Endovascular Surg 2017;51:545-9.
8. Almeida JJ, Javier JJ, Mackay EG, Bautista C, Cher DJ, Proebstle TM. Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. Phlebology 2014;30:397-406.
9. Proebstle TM, Alm J, Dimitri S, Rasmussen L, Whiteley M, Lawson J, et al. The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins. J Vasc Surg Venous Lymphat Disord 2015;3:2-7.
10. Bissacco D, Stegher S, Calliari FM, Viani MP. Saphenous vein ablation with a new cyanoacrylate glue device: a systematic review on 1000 cases. Minim Invasive Ther Allied Technol 2019;28:6-14.
11. Gibson K, Ferris B. Cyanoacrylate closure of incompetent great, small and accessory saphenous veins without the use of post-procedure compression: initial outcomes of a post-market evaluation of the VenaSeal System (the WAVES Study). Vascular 2017;25:149-56.
12. Jones AD, Boyle EM, Woltjer R, Jundt JP, Williams AN. Persistent type IV hypersensitivity after cyanoacrylate closure of the great saphenous vein. J Vasc Surg Cases Innov Tech 2019;5:37-24.
13. Shanmugam S, Wilkinson M. Allergic contact dermatitis caused by a cyanoacrylate-containing false eyelash glue. Contact Dermatitis 2012;67:309-10.
14. Navarro-Triviño FJ, Cuenca-Manteca J, Ruiz-Villaverde R. Allergic contact dermatitis with systemic symptoms caused by VenaSeal. Contact Dermatitis 2019;82:185-7.
15. Parsi K, Kang M, Yang A, Kossard S. Granuloma formation following cyanoacrylate glue injection in peripheral veins and arteriovenous malformation. Phlebology 2020;35:115-23.
16. Lam YL, De Maeseneer M, Lawson J, de Borst GJ, Boersma D. Expert review on the VenaSeal system for endovenous cyano-acrylate adhesive ablation of incompetent saphenous trunks in patients with varicose veins. Expert Rev Med Devices 2017;14:755-62.

Submitted Jan 16, 2020; accepted Mar 23, 2020.