# VenaSeal closure despite allergic reaction to *n*-butyl cyanoacrylate

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## 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 Administration[2] 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 (Biolas, 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 intravascular 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 previous 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

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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-octyl 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 al[5] 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 Sapheon 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 al[5] reported the development of phlebitis requiring oral nonsteroidal anti-inflammatory drug treatment in six (15.8%) patients. A study by Park[7] 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 al[8] 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 al[9] 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 al[10] 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 al[12] 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 T 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-Tiviño et al[14] 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.

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