Hypersensitivity Reaction With Cyanoacrylate Glue: Patient Selection, Technical Considerations, and Management

Approach to hypersensitivity management after endovenous ablation.

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The first use of cyanoacrylate glue as a nontumescent, nonthermal treatment for great saphenous vein reflux in humans was reported in 2012.[1] After FDA approval in 2015, the VenaSeal Closure System™ (VenaSeal, Medtronic) became the most widely used form of cyanoacrylate ablation.[1] VenaSeal offers several advantages, including avoiding the risk of thermal nerve injury, eliminating the need for tumescence, and removing the traditional requirement for compression postprocedure, while still having a high rate of long-term closure, comparable to surgical stripping and thermal ablation.[2-4] However, cyanoacrylate polymerizes in the vein, acting as a foreign body and carrying the risks unique to this technique. These include foreign body granuloma (0.7%-1.6%; not discussed in this article)[4,5] and hypersensitivity reactions (HSR; 5.6%-13.3%).[4-7]

HSRs after VenaSeal treatment may be categorized as either type I or type IV, or a combination of both. Type I hypersensitivity is a mast cell–activated reaction that occurs shortly after exposure (usually within minutes to days) due to excessive histamine release. Common symptoms include erythematous rash and itching. In contrast, type IV hypersensitivity is a T-cell–mediated, delayed immune reaction that can occur when the immune system is in prolonged contact with the allergen.[8] The distinction between the two reactions is rarely made in the literature, and the reported hypersensitivity rates are likely a combination of the two.

O'Banion et al reported a 13.3% (n = 79/595) incidence of HSRs in their case series. Of these, 18 patients required oral steroid treatment. All cases resolved without further sequelae.[7] Gibson et al reported that 6.3% (n = 18/286) of patients in their study developed a HSR, with 13 patients classified as mild, four classified as moderate, and one case requiring a vein excision due to a severe HSR.[6] Despite multiple case reports describing HSRs requiring vein excision,[9,10]

Pre-procedure: Patient considerations

Patient selection†,1

If any of the following conditions exist, consider alternative treatment modalities:

1. Significant autoimmune or systemic inflammatory disorder
2. Prior adverse reaction to cyanoacrylate
3. Known intolerance to adhesives (eg, skin glue, acrylic nails, eyelash glue, adhesive bandages, tape)
4. History of numerous food and/or drug allergies

Patient education

Discuss hypersensitivity reaction, risk, and treatment options. Discuss different vein closure treatment options. Educate patients on symptom recognition and when to seek help.

†The authors of this document view these factors as being potentially related to, or predictive of, whether or not a patient develops a hypersensitivity reaction to VenaSeal.

1. Vasquez MA, et al. *Phlebology*. 2024;39:245-250.

the true incidence remains unknown, but it is likely rare. A nationwide survey done in Japan, which included 24,209 patients, found that glue resection was performed in only four patients due to HSR.[5]

Although widely regarded as a safe and effective procedure, the unique properties of VenaSeal that may trigger HSRs underscore the necessity for establishing clinical recommendations pertaining to patient selection, procedural techniques, and treatment options. In light of these considerations, this article's authors convened for a 2-day meeting in December 2024 to address this issue in detail.

PATIENT SELECTION AND COUNSELING

Proper patient selection is a critical first step to minimize the risk of HSRs. Contraindications for VenaSeal are listed in the instructions for use.[11]

1. **Patients with adhesive allergy.** A prior adverse reaction to adhesives and cyanoacrylate is considered a contraindication to the use of VenaSeal.[11] Although patients may not know if they have specifically reacted to cyanoacrylate, they can often recall past reactions to common adhesives. Therefore, it is necessary to ask about sensitivity to products such as skin glue (eg, Dermabond; Ethicon, a Johnson & Johnson company), acrylic nails, eyelash glue, adhesive bandages, and tape. Patch testing alone is inadequate to definitively exclude the possibility of developing a HSR.[12] While individuals with a positive patch test should not be treated with VenaSeal, a negative result does not guarantee that a reaction will not occur.
2. **Patients with significant autoimmune or systemic inflammatory disorders.** These patients may be at a higher risk of developing a HSR; therefore, caution should be exercised when determining whether they are appropriate candidates for VenaSeal. Additionally, a history of multiple food, environmental, and/or medication allergies may be an indicator for a predisposition to allergic reactions, and this should be carefully considered when selecting the best ablation modality.

In general, shared decision-making (SDM) between the patient and treatment provider should be standard practice when discussing the potential risks, benefits, and alternative treatment options. The authors recommend that, when considering treatment with VenaSeal, an additional discussion should be held to inform patients about the nature of the product, including its role as a foreign-body implant and the associated risk of developing HSRs. Patients should receive clear instructions on symptom recognition and when to seek medical attention as a part of the informed consent process. Several studies and consensus documents have supported that SDM between patients and providers leads to improved patient outcomes and satisfaction.[13]

TECHNICAL CONSIDERATIONS

VenaSeal is a permanent implant, and therefore full sterile technique is a requirement. The triggers for the HSR are not completely known. However, it is critical to minimize risk through the use of the following procedural best practices.

1. **Atraumatic catheter placement.** Assessing the target vein's diameter along the course of the targeted treatment pathway is essential for ensuring atraumatic catheter placement and determining the appropriate volume of adhesive for effective vein closure. Gentle manipulation of the wire and catheter is best to avoid any unintended trauma or perforation that may lead to adhesive extravasation beyond the vein wall.
2. **Adequate compression.** The instructions for use recommend applying sufficient pressure to collapse

Procedural best practices (Follow VenaSeal instructions for use)

Sterile technique
VenaSeal is an implanted device. Full sterile technique is mandatory.

Atraumatic wire and catheter placement
Assess target vein diameter to ensure atraumatic catheter placement. Gentle manipulation of wire and catheter is recommended to minimize tissue trauma.

Glue deployment
Modify adhesive volume based on vein diameter. Apply sufficient pressure to coapt the vein, avoiding excessive pressure.

Ultrasound
Use real-time ultrasound to confirm catheter position and immediate vein closure.

Exposure control
Recapture glue catheter into sheath prior to removing sheath from vein. Prevent adhesive contact with extravascular tissues to avoid inflammation and granulomatous reactions.

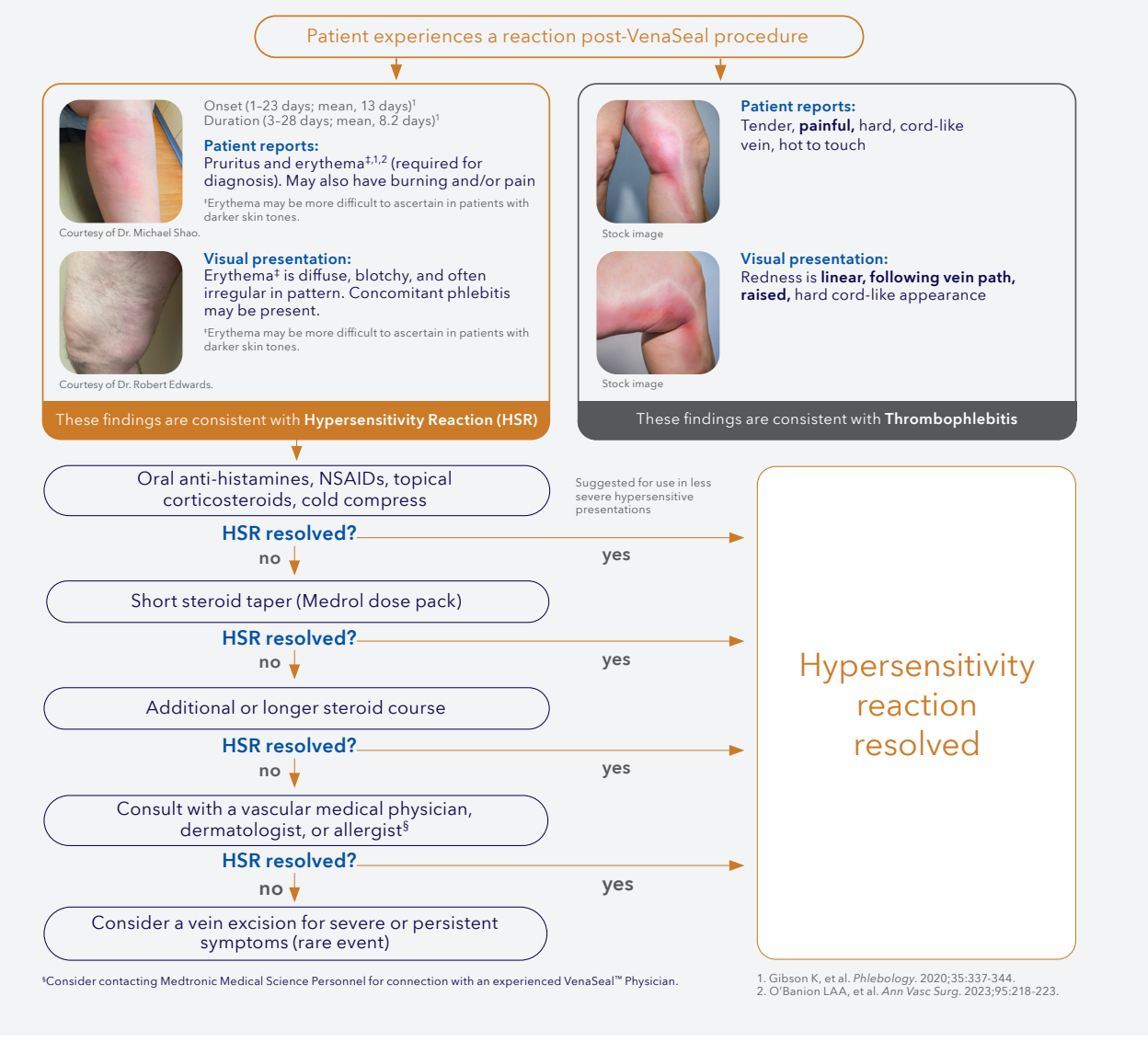

Figure 1. Differential diagnosis and treatment algorithm for HSR after VenaSeal treatment. NSAID, nonsteroidal anti-inflammatory drug.

the vein during closure; however, it is important to avoid excessive pressure in order to prevent trauma to diseased, thin-walled veins leading to glue extravasation. The concomitant use of real-time ultrasound during the procedure allows the treating physician to confirm catheter position and immediate vein closure.

3. **Avoiding subdermal glue exposure.** Finally, recapturing the adhesive delivery catheter into the sheath prior to removing the sheath from the vein is a critical step. This prevents any adhesive from contacting with extravascular tissue, reducing the risk of developing inflammation and/or a granuloma at the exit site.

HYPERSENSITIVITY MANAGEMENT

Diagnosis

Type I hypersensitivity. This can present in a biphasic manner with the immediate stage occurring rapidly (within minutes of exposure) and the late phase developing 4 to 12 hours after exposure.[8] Pruritus and erythema are required for diagnosis. The patient may also report burning, pain, or systemic symptoms.

Type IV hypersensitivity. This typically presents 1 to 3 days after exposure,[8] but initial onset has been reported as late as 23 days after exposure.[6] Pruritus and erythema are required for diagnosis. The patient may also report burning or pain.

Initial reports of safety outcomes from studies with VenaSeal likely combined the cases of phlebitis with HSR due to their similar clinical presentation.[6] Classic phlebitis presents as a tenderness and painful erythema often with a hard or cord-like vein and can be hot to the touch, with an absence of any pruritus. In contrast, the most specific symptoms of HSRs are pruritus and erythema. It is important to understand that it is possible for patients to present with concomitant hypersensitivity and phlebitis, and appropriate diagnosis is critical to treat effectively.

Treatment

The treatment algorithm developed by the authors is detailed in Figure 1. Initial treatment options will depend on the severity of patient presentation. Most HSRs can be managed with oral and/or topical antihistamines with the option to prescribe nonsteroidal anti-inflammatory drugs and cold compress to alleviate any associated pain or swelling.

In cases with prolonged or more severe symptoms including those with systemic manifestations, a short steroid taper (ie, Medrol Dosepak; Pfizer, Inc.) can be used either as a single treatment or in multiple rounds of treatment. Some patients may require higher-dose steroids or an extended course of steroids. If a HSR is persistent through multiple rounds of treatment, it may be beneficial to consult with a local physician with expertise in treating hypersensitivity cases (dermatologist, allergist, and/or vascular medicine specialist). In rare cases that are refractory to maximal medical therapy, where hypersensitivity persists despite steroid treatment and despite subspecialist consultation, complete excision of the treated vein may be required to fully alleviate symptoms; however, this option should be carefully considered in a multidisciplinary discussion and in conjunction with SDM.

DISCUSSION AND CONCLUSION

Various thermal and nonthermal modalities are available to treat axial venous reflux. The appropriate treatment plan for the patient should be guided by physician discretion and in collaboration with the patient through SDM. When VenaSeal is selected as the procedure of choice, consideration of unique complications should be discussed. While VenaSeal is a safe and effective treatment, there is a paucity of high-quality data on how to best prevent and manage HSRs. In 2022, the American Vein and Lymphatic Society published a report on the current practice of cyanoacrylate, including a potential screening tool to help determine which patients to treat with VenaSeal.[12] The goal of this publication is to expand upon this foundation by providing additional considerations to mitigate HSRs and offer a treatment algorithm for managing cases when they do occur.

Overall, VenaSeal is a valuable option in the repertoire of available modalities for the treatment of superficial venous disease. High rates of long-term closure along with the ability to avoid surgical complications, nerve damage, tumescent anesthesia, and the requirement of compression postprocedure make it an attractive choice for patients and physicians alike. With proper technique and appropriate patient selection, the potential for development of a HSR is low and the vast majority of HSR cases after VenaSeal treatment are self-limited and resolve without further sequelae. ■

This article does not discuss foreign body granuloma, which is a unique complication from hypersensitivity but can occur either independently or concomitantly with HSR.

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