Literature Spider

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Web bots and spiders commonly scan the Internet to find and store relevant information, following in depth the detected links on the visited pages.
By analogy, this section is devoted to the selection of interesting vascular papers, providing an extended summary (more than an abstract) and a very personal comment.
Following the spirit of the journal, readers' opinion is welcome, especially if different. Colleagues are invited to collaborate, suggesting valuable articles and hopefully reviewing them.
Practical instructions are available at the address http://www.vasculab.eu/jtavr/literatureSpiderInstructionsForAuthors.pdf

Chronicles of "Glue"

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Abstract Glue is new, is easy, is effective, it does not need anaesthesia nor require compression: glue is trendy. However, few but important drawbacks may be encountered (material persistence, inflammation, granuloma). Analysis of 4 recent articles may help to clear some doubts.

Keywords Glue, Cyanoacrylate, Saphenous closure, Hypersensitivity reaction, Foreign body granuloma

Detailed summary

Cyanoacrylate closure for peripheral veins: Consensus document of the Australasian College of Phlebology[1].
K Parsi et al.

The Consensus panel had 22 members which included phlebologists, endovascular surgeons, interventional radiologists, dermatologists, research scientists and independent research fellows. all had experience in using CA and significant personal experience Cyanoacrylates (CA) have been used as embolic agents for wounds closure and superficial and venous occlusive agents. The Consensus focuses on the use of CAs as occlusive agents to treat peripheral veins.

Three products are currently used:

- **VenaSeal™**: The product is currently in clinical use in many countries; it has the highest viscosity and longest polymerization time, beginning approximately 5 seconds after contact with a liquid containing water (such as blood), and hence is the slowest to act, needing to 3 min for nearly complete polymerization. The product packaging provides 5mL of n-BCA allowing for treating 90 cm of vein length if the vein diameter is less than 6mm (see below) and hence to treat two legs would require 10mL.
- **VenaBlock™**: It is available for both catheter-directed administration (6F PTFE catheter with an atraumatic tip with a laser light guiding precise placement of the tip) as well as direct percutaneous injections. This product is at least 60 times less viscous than VenaSeal but 20 times more viscous than water.
- **Veinoff™**: It was developed for percutaneous injections is the least viscous and comparatively most flexible material after polymerization

Acrylates are plastic compounds commonly found in artificial nail products, paints, varnishes and adhesives. CAs are produced as liquid monomers that when exposed to ionic surfaces readily join to polymerize and form long-chain polymers. The polymers form strong resins and effectively adhere closely spaced surfaces including plastic, metal, glass and biological materials. The polymerization process is an exothermic reaction releasing heat during the process. Temperatures can reach 40–45 C in the peri-venous space causing mild discomfort, but the heat is not sufficient to damage any adjacent structures. Following entry into the target vessel, the product delivered into the vessel forms a cast which may adjust to the shape of the vessel lumen resulting in vessel closure and interruption of flow.

Mast cell degranulation is reported in the peri-vascular space within 10 min of exposure to glue. A study showed that by weeks 2–3, there was a granulocytic infiltration of vessel walls and the peri-vascular tissue, patchy loss of intima, medial necrosis as well as early foreign body giant cell formation and round-cell infiltration by six weeks. One-year biopsy revealed a lack of endothelial lining in the treated vessels, but there was lymphoid hyperplasia and fibrosis of the surrounding tissue with extrusion to the peri-vascular space and extra-vascular cavitated foreign body granulomas with foreign body-type giant cells.

Acrylates, due to their ubiquity in the modern-day environment may cause **sensitization** directly related to duration of exposure as the CA is intravenously injected as a permanent implant. Several studies have shown that CA closure (CAC) is clinically safe and effective with occlusion rates comparable to those for endovascular thermal methods with **occlusion rates** at 36 months of 90–95%. No differences were observed in occlusion rates between the three modalities, CAC with RFA and EVLA, but CAC appeared superior with respect to periprocedural pain, return to work and decreased VCSS.

Phlebitis is the most common adverse event following CAC, reported in up to 20% of cases, while, in comparison, phlebitis following EVLA is reported in 7.7% to 7.9% and following RFA in 14%2 of patients. It is a **hypersensitivity-type phlebitis** (characterized by erythema, oedema, urticaria, pruritus and histological finding of mast cell degranulation and systemic eosinophilia.), a separate entity to conventional phlebitis driven by a cell-mediated reaction to foreign body material. However, **true phlebitis** may occur at a rate of 3-4%.

Histological studies have demonstrated **a granulomatous phlebitis reaction** developing within two months and evident at 12 months after injection. This reaction commonly remains asymptomatic but may progress to suppuration, necrosis and ulceration.

Extension of CA from the saphenofemoral junction into the common femoral vein has been reported on several occasions (21% in earlier studies) likely due to the catheter being positioned 3 cm from the SFJ; increasing the distance to 5 cm, thread-like thrombus seems having reduced the problem. **Hyperpigmentation** has a reported incidence of 1.3 to 11.8%, either transient or still visible at one year. **Palpable nodules** along the length of the treated vein have been reported, some nodules requiring excision or phlebectomy.

History of immediate (urticarial) or delayed hypersensitivity reactions to acrylates (household 'Super Glue' preparations, glue used for eyelash extensions or glue used in acrylic, signature nail systems and shellac nail preparations) should be considered as a **specific contraindication**

Catheter-directed CAC should be performed in operating theatres, hybrid theatres or appropriately equipped and staffed outpatient procedure rooms with access to appropriate resuscitation equipment with use of **full sterile surgical technique**

Peri-venous tumescent anaesthesia is usually not required; it should be considered when treating large diameter veins, particularly for limited use at sites of vein dilatation and at the saphenous junctions, to ensure vein closure, reduce the risk of embolization and to reduce the volume of n-BCA required

Graduated compression stockings are not recommended by the manufacturers but should be prescribed if there is an increased risk of phlebitis, inflammation, pigmentation or DVT, if there are other endovenous procedures performed concurrently or if the patient prefers to wear compression for comfort reasons.

Venous tributaries can be dealt with at the same time as treatmentof saphenous trunks or at a later date. Only VenaBlock and Veinoff are registered for direct percutaneous injection of tributaries, located at least 5mm deep to the skin.

The postoperative course, usually benign, may register mild tightness and discomfort for up to two weeks but not sufficient to limit normal activities. Some patients develop a moderate to severe inflammatory reaction treated by applying compression and oral NSAIDs.

The patient should be mobilized immediately after treatment and should walk regularly each day for the next week or two, but heavy physical activities should be avoided for at least 7–14 days.

Postoperative ultrasound surveillance shows an echogenic material with a strong shadow artefact in the vein, lasting to three years.

Granuloma formation following cyanoacrylate glue injection in peripheral veins and arteriovenous malformation[2]. K Parsi et al.

The late pathological reaction that follows CAC treatment of peripheral veins has not been investigated in humans. Histopathological studies in pig arteries and veins, as well as arteriovenous malformations in humans have consistently demonstrated chronic granulomatous reactions. A case report described suppurative granulomas with extrusion of the CA four months after bilateral treatment of great saphenous veins indicating a probable immunological tissue response rather than a local technical complication.

VenaBlock™ glue was percutaneously delivered using a 25G needle in aliquots of 0.2 mL under ultrasound-guidance. The injected target vessel was compressed with the ultrasound probe for 10 s after each injection.

Patient 1: A 28-year-old underwent treatment for incompetent peripheral veins (right medial calf and left lateral calf tributary of the GSV) in two procedures. Incisional biopsies to include skin, subcutaneous fat and the target vessels were obtained at one week, six weeks and one year post-glue injection.

Patient 2: A 27-year-old male with a peripheral arteriovenous malformation of the right anterior shin. Venablock was delivered percutaneously into the lateral shin feeding artery that communicated with the anterior tibial artery. Ultrasound-guided incisional biopsy was performed 12 months later. Clinically, there were no systemic or local adverse events on all follow-up.

Patient 1, peripheral vein

- **one week**: The glue was seen in the vein lumen presenting as a homogenous eosinophilic crystallised material.
- **six weeks**: Glue and fibrillary spicules were observed in the sampled vein lumen. Fibrinous material and erythrocytes were adherent to the glue. No granulomatous reaction was seen.
- **one year**: In the deep tissue, there were multiple granulomas with multinucleated foreign body giant cells lining empty spaces with matted fibrillary borders of spicules of glue and surrounding fibrosis; All granulomas were extra-vascular and none were observed in the vessel walls or within the lumen of the treated vessels.

Patient 2, peripheral arteriovenous malformation

- **one year**: There was fibrosis and lymphoid aggregates in the subcutaneous fat and its septa that extended into the deep tissue and surrounded a nerve. Focal empty cavities were associated with a fibrillar outline surrounded by foreign body histiocytes with surrounding fibrosis and lymphocytic inflammation.
- **The one-year follow-up biopsies** demonstrated lymphoid hyperplasia and surrounding tissue fibrosis. The glue appeared to be mostly extruded from the treated vessels and was contained within extra-vascular granulomas.

The extra-vascular location of the granulomas containing glue implies extrusion of some of the glue material with lymphoid hyperplasia indicating a possible reactive immunological response to the injected glue. Histological findings are consistent with the published literature demonstrating foreign body granuloma formation as a late tissue reaction to CA. Foreign body granuloma formation may progress to

necrosis, ulceration, foreign body extrusion or immunological reaction to the foreign material with sarcoid features or lymphoid hyperplasia. A case is reported (Zernovicky F. Fast progressive devastating granulomatic reaction after VenaSeal procedure. In: XVIII UIP world congress, Melbourne, Australia, 2018, pp. 168–169) that developed spontaneous skin perforations with extrusion of glue pieces from the treated sites bilaterally four months after a bilateral CAC procedure on GSVs.

Saphenous vein histopathology 5.5 years after cyanoacrylate closure[3].
JI Almeida et al.

Findings from the histopathologic analysis of a great saphenous vein segment that was excised 5.5 years after cyanoacrylate implantation are described. A 65-year-old man seen for follow-up 5.5 years agreed to have excised a segment of the left GSV, previously treated with 1.4 mL of cyanoacrylate: the treated GSV was still occluded, contained polymer remnants, and had characteristics typical of a foreign body reaction. Focal areas of granulomatous inflammation were present in the vein wall extending to the adventitia. The presence of multinucleated giant cells and granulomatous inflammation was consistent with the prolonged course of a foreign body reaction that will continue as long as the implanted material stays in the tissue. Immunohistochemistry results from this case study showed that the treated GSV had high levels of cells that expressed the macrophage markers CD68 and CD163, specific markers for those macrophages with anti-inflammatory properties. As an implanted device, questions remain about how long cyanoacrylate persists in the vein after closure and the effects therein.

Frequency and severity of hypersensitivity reactions in patients after VenaSeal™ cyanoacrylate treatment of superficial venous insufficiency[4].
K Gibson et al.

This study tries evaluate the frequency, severity, and clinical characteristics of hypersensitivity reaction (HSR) in CAC-treated patients as it was noted that in post-treatment some developed a erythematous cutaneous/dermal reaction within the first few weeks after great saphenous vein (GSV) closure, usually in the skin overlying the treated vein.

The study is a single-centre, review conducted from April 2013 to December 2018 of all patients (286 patients, 379 limb), undergoing CAC of incompetent saphenous veins. CAC HSR is defined as a red, itchy dermal reaction that is sometimes painless, but sometimes associated with discomfort and/or localized swelling. The HSR severity was defined as **mild** if the patient required **no treatment, moderate** if the patient required prescription **medications** (oral steroids), and severe if the reaction was prolonged >**30 days** or required vein excision.

Eighteen HSRs occurred (6% patients, 5.8% treated limbs). Twenty patients (7% patients, 6.4% limbs) had pain, tenderness, and swelling without erythema or itching consistent with treated vein phlebitis without evidence of HSR. Twenty-one patients (7.3% of patients, 6.7% limbs) had pain and tenderness over thrombosed tributaries. Of the HSRs, **13 were mild (4.3%), 4 were moderate (1.3%), and 1 was severe (0.3%)**. This case was a 36-year-old female that developed symptoms within the first two weeks in addition to a rash over the treated area resolved with oral steroids but recurring several months later and after one year. A skin patch testing suggested topical allergy to cyanoacrylates and her treated GSV was removed small incisions under a general anaesthetic. Histology revealed a giant cell foreign body reaction within the specimen with dense intramural chronic inflammation and dense lymphoid follicles. There were no patient or procedural factors (treatment length, dose of cyanoacrylate, vein treated (GSV, SSV, or AASV), vein diameter) identified when comparing the cases with and without HSR, other than a trend towards decreased HSR in patients with more advanced CEAP clinical classes. The mean duration of symptoms was 8.2 days in the mild group and 19.0 days in the moderate group. Data suggest that HSR appears within the first three weeks of treatment.

Since the recognition of HSR the Authors made several changes in the clinical practice: patients selection excluding those with allergy or skin reaction to adhesives, those with medical history of skin conditions such as active psoriasis or atopic dermatitis; waiting a full 30 s to allow full cyanoacrylate polymerization before removing the delivery system; advancing the sheath forward over the catheter prior to removal while still inside the vein to diminish the chance of leaving adhesive in the subcutaneous tissues and dermis.

Comments

These four papers concerning “glue” GSV embolization appear nearly contemporarily in Phlebology Journals to signify the importance that this method is gaining in the most evolved countries, either because its objective advantages or by the pression of business.

The first paper, the Consensus of the Australasian college of Phlebology, is a very complete survey about all that have been published about the clinical use of cyanoacrylate products, with particular reference to GSV closure; treatment of tributaries is briefly mentioned. Chemical, biological, commercial, technical, and finally clinical details are described, with particular concern to complications and adverse effect described in current literature. The impression is that “Glue” era is only at the beginning, with several Companies ready to enter the market from Turkey, India, Russia, and by the way, several products already exist as embolic agents and skin adhesive agents that could easily change their destination. Every physician involved in GSV closure (not necessarily by CAC) could find important data in reading this paper either for reinforce their CAC use or, at the opposite, to refuse it.

The second, about granuloma formation after one year follow up, is particularly interesting as it is based on biopsies of treated veins in two patients, moreover taken in progressive sessions in one. Interestingly, the one- and six-weeks samples did not demonstrate granuloma tissue reactions while the one years did, with still presence of glue, extruded from the veins causing extra-vascular foreign body granulomas. A similar extrusion of glue was histological described after treatment of oesophageal varices. According to Author: “Foreign body granuloma formation may progress to necrosis, ulceration, foreign body extrusion or immunological reaction to the foreign material Whether granuloma formation can progress to ulceration and abscess formation may depend on the size and depth of the vessels treated and glue extrusion to the surrounding tissue.”

The case presented at 2018 UIP Congress (Zernovicky F. Fast progressive devastating granulomatic reaction after VenaSeal procedure. In: XVIII UIP world

congress, Melbourne, Australia, 2018) cited by the Author seems an extreme example of these possible events, but a new recent case (PS Lew, YK Tan, TT Chong, TY Tang. Venaseal™ Cyanoacrylate Glue Rejection Following Endovenous Ablation - Another New Complication. BiomedJ Sci & Tech Res 17(4)-2019. BJSTR.MS.ID.003040) suggest that probably some type of hypersensitivity reaction to cyanoacrylates may be hidden and not yet recognised, however difficult to manage from the clinical and insurance point of view. Will patients give consent when informed about these (rare but on the rise) complications?

The third, resumes the problem of material persistence with an exceptional check at 5,5 years after implantation, confirming the foreign body immunological reaction. **The fourth**, concerning frequency and severity of hypersensitivity reactions, tries to answer to some question just posed. Over 286 patients 18 had reactions but only one was serious requiring a general anaesthesia and saphenectomy. The method seems very satisfying and effective but when a strong reaction is present, the complication may be heavy: will the patient accept the risk?

In conclusion, a new interesting and effective GSV occlusion method is available with rare but consistent complications. No mention is usually done about varices treatment (usually the reason for consultation). Some initial trial for treating varices by specific more fluid injectable glue are still not published, but the superficial site of varices will probably be followed by more evident reactions. The presence of the glue material after more than 5 years, possibly permanent, should be a concern, due to some immunologic still not well identified reactions.

Patients and physicians are particularly attracted by avoiding tumescent anaesthesia and post-operative need of compression garments, but if varices phlebectomies are needed local anaesthesia is anyway necessary, if sclerotherapy is needed, compression treatment is requested. Elastic stockings are the true symbol of phlebology; they are essential for, curing, maintaining, preventing, healing in all the stages of CEAP classification. They are poorly appreciated by patients and “feared” by physicians that must prescribe them; consequently, both try to avoid them making a macroscopic mistake.

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