





Cyanoacrylate closure for peripheral veins: Consensus document of the Australasian College of Phlebology

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Abstract

Background: Cyanoacrylates are fast-acting adhesives used in procedural medicine including closure of superficial wounds, embolization of truncal vessels pre-operatively, vascular anomalies, visceral false aneurysms, endoleaks, gastrointestinal varices and gastrointestinal bleeding. More recently, catheter-directed cyanoacrylate adhesive closure was introduced as an alternative to endovenous thermal ablation (ETA) to occlude superficial veins of the lower limbs.

Objectives: To formulate policies for the safe and effective delivery of cyanoacrylate adhesive closure procedures in Australasia, based on current experience and evidence.

Methods: A panel of phlebologists including vascular surgeons, interventional radiologists, dermatologists and research scientists systematically reviewed the available data on cyanoacrylate products used in medicine and shared personal experience with the procedure. The reviewed material included bibliographic and biomedical data, material safety data sheets and data requested and received from manufacturers.

Results and recommendations: Cyanoacrylate adhesive closure appears to be an effective treatment for saphenous reflux with occlusion rates at 36 months of 90–95%. We recommend a maximum dose of 10 mL of cyanoacrylate per treatment session. Serious complications are rare, but significant. Hypersensitivity to acrylates is reported in 2.4% of the population and is an important absolute contraindication to cyanoacrylate adhesive closure.¹ Post-procedural inflammatory reactions, including hypersensitivity-type phlebitis, occur in 10–20% of patients.² In the long term, cyanoacrylate adhesive closure results in foreign-body granuloma formation within 2–12 months of the procedure. We recommend

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against the use of cyanoacrylate adhesive closure in patients with uncontrolled inflammatory, autoimmune or granulomatous disorders (e.g. sarcoidosis). Caution should be exercised in patients with significant active systemic disease or infection and alternative therapies such as thermal ablation and foam sclerotherapy should be considered.

Conclusions: Cyanoacrylate adhesive closure appears to be an effective endovenous procedure, with short-term closure rates comparable to ETA and therefore greater efficacy than traditional surgery for treating superficial veins of the lower limbs. Ongoing data collection is required to establish the long-term safety.

Keywords

n-Butyl cyanoacrylate, glue, cyanoacrylate, saphenous vein, endovascular

Introduction

Cyanoacrylate (CA) adhesives were first patented in 1949 and are well-known fast-acting strong adhesives commonly used for domestic and industrial purposes under brand names such as 'Super Glue'. These adhesives are administered as liquid monomers that polymerize on contact with free radicals and anions such as those found in water with variable flexibility depending on constituents.

CA differs depending on the length of the carbonyl group of the molecule. *n*-Butyl cyanoacrylate (*n*-BCA) is the most common adhesive used in medicine and was introduced in the late 1960s for closure of minimum tension wounds and as a substitute for suturing.³ Since then, the regulatory authorities including the United States of America (USA) Food and Drug Administration (FDA) have granted approval for a range of products and several medical indications.^{4,5} Histoacryl® was the first medical-grade adhesive introduced in 1968. The Trufill® preparation was approved by the FDA for treating cerebral arteriovenous malformations (AVMs) in 2000.⁶ In 2012, VenaSeal™ was registered in Australia as the first *n*-BCA designed for peripheral venous interventions providing a non-thermal alternative to endovenous thermal ablation (ETA) of the great saphenous veins (GSV) and small saphenous veins (SSV). Since then, other similar products such as VenaBlock™ have gained registration in Australia. In all cases, the CA products have been approved by the Australian Therapeutic Goods Administration (TGA) as medical devices and not as drugs for use in humans. This means there is no safety data, phase 1 safety trials or TGA approved product information (PI) document for their use in a clinical setting. In addition, clinicians have used the drug without full disclosure of its constituent ingredients and in particular the additives and solvents used, which may be associated with immune-mediated reactions.

Given the popularity of endovenous procedures, standardization of techniques and cross-specialty

procedural training have become necessary. The Australasian College of Phlebology (ACP) has previously released training and procedural standards for other endovenous procedures including endovenous laser ablation (EVLA) and ultrasound-guided sclerotherapy (UGS).⁷ The current document reviews the clinical applications of cyanoacrylate adhesive closure (CAC) for lower limb veins in Australasia. We outline the relevant protocols for the assessment, treatment and post-treatment follow-up of superficial venous disease management using CAC.

Methods

Literature search and data collection

The published scientific, biomedical and regulatory literature was reviewed including MEDLINE and EMBASE, journal articles, PI sheets, material safety data sheets, Australian TGA, Australian Register of Therapeutic Goods (ARTG), National Institute for Health and Excellence interventional procedural guidelines and National Industrial Chemical Notification and Assessment Organization (16 December 2018). Manufacturers of VenaBlock™ and VenaSeal™, Invamed and Medtronic, respectively, were contacted to provide information on the physiochemical, safety and regulatory data of each product through a standard set of questions (Appendix 1).

Panel members

The document was written by the primary authors (KP, SR, MK). A panel from Australia and New Zealand was invited to review the paper and make evidence-based recommendations. This occurred via an initial face-to-face meeting followed by digital communication. The panel had 22 members which included phlebologists, endovascular surgeons, interventional radiologists, dermatologists, research scientists and independent research fellows. The clinician members of the panel all had experience in using CA and significant personal

experience in endovenous thermal and non-thermal ablation. None of the panel members had a current conflict of interest to declare. One panel member had served as consultant for Medtronic previously.

Product review

Preparations containing medical-grade CAs have been used as venous occlusive agents, embolic agents and for closure of minimum tension superficial wounds. In this paper, we focus on the use of medical-grade CAs as occlusive agents to treat peripheral veins and review their established use as embolic and adhesive agents. All products discussed here are *n*-BCA with the exception of Dermabond® which is an octyl-CA and Onyx® which is not a CA. We also briefly review the use of other acrylates as adhesives in wound dressings. Technical considerations are discussed under the ‘Treatment protocols’ section.

1. Occlusive agents to treat peripheral veins
2. Embolic agents to treat vascular anomalies
3. Adhesive agents for closure of superficial wounds
4. Adhesive agents in dressing and bandages.

Cyanoacrylates as venous occlusive agents

Several CAC systems for treatment of peripheral veins are available but only three products, VenaSeal™, VenaBlock™ and Veinoff™ are registered in Australia on the ARTG⁸ (Figure 1, Table 1).

VenaSeal™. VenaSeal™ was initially developed by Dr Rodney Raabe, the original founder of *Sapheon Inc.*, along with several co-founders Don Crawford, Monte Madsen, Bruce Choi and Nate Raabe. *Sapheon Inc.* was later acquired by *Covidien* in 2014, itself subsequently acquired by *Medtronic* (Minnesota, USA). This product obtained CE (Conformité Européenne) marking in 2011 and then received registration with the TGA in 2012 as a medical device (Table 2). The FDA approved the VenaSeal™ system in 2015 and approval was granted in the Russian Federation in 2017.⁹ The product is currently in clinical use across most continents.¹⁰

The VenaSeal™ system is a catheter-assisted endovenous method to deliver *n*-BCA. The *n*-BCA is delivered via a dispensing gun that is attached to the delivery catheter. The sheath and dilator are high-density polyethylene, and the delivery catheter is a polytetrafluoroethylene (PTFE) product.

Compared to other products in this category, VenaSeal™ has the highest viscosity and longest polymerization time and hence is the slowest to act. Polymerization begins approximately 5 s after contact with a liquid containing water (such as blood) and extends to 3 min for nearly complete polymerization (Table 1). The high viscosity of the agent works to prevent extension of the adhesive process to adjoining non-target vessels.

VenaBlock™. This product was developed by Invamed (Ankara, Turkey) and obtained registration with the

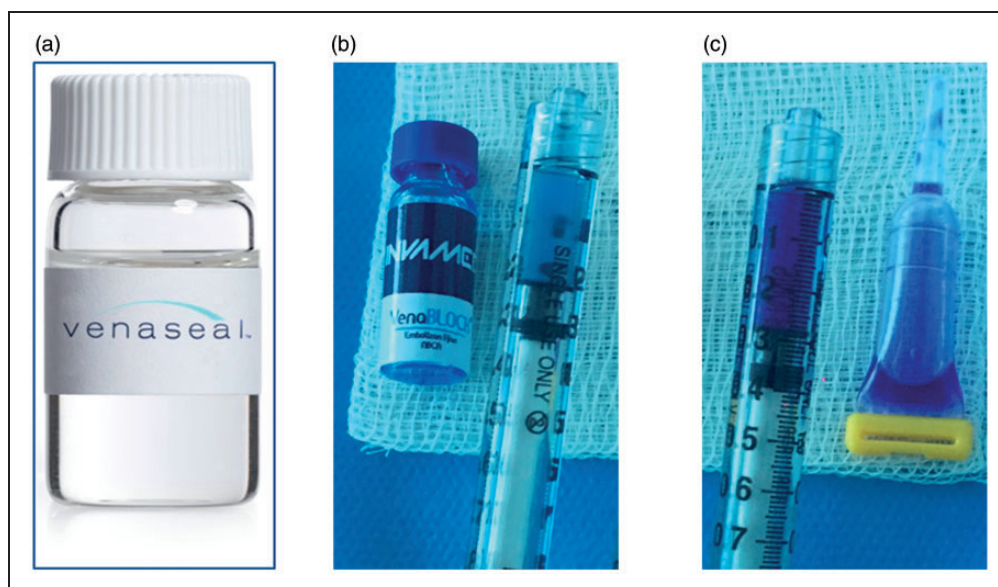


Figure 1. Product appearance in its packaging. Note the colourlessness of VenaSeal™, while VenaBlock™ and Histoacryl Blue® have a clear blue colour. (a) VenaSeal™. (b) Left, VenaBlock™; Right, VenaBlock™ drawn up in syringe. (c) Left, Histoacryl Blue® drawn up in syringe; Right, Histoacryl Blue® in tube.

Table 1. Comparison of physiochemical properties of cyanoacrylate adhesive agents used in the treatment of peripheral veins.

Properties	VenaBlock™	Veinoff™	VenaSeal™
Polymer length (alkyl group)	Short chain	Medium chain ^a	Long chain
Polymerization time	Fastest, 5 s	Medium, 15 s ^b	Slowest, 30–180 s
Action	Fastest	Slower	Slowest
Viscosity at 37°C (cP)	20	18	>1200
Rigidity	Relatively firm	Soft and malleable	Soft and flexible
Biodegradability	Permanent implants		

Note: Data obtained from manufacturers (Medtronic and Invamed). Viscosity values are expressed in cP (centipoise). The viscosity of water is 1 cP at 20°C. The VenaSeal™ preparation has the highest, while Veinoff™ has the lowest viscosity.

VenaSeal™ has the slowest, while VenaBlock™ has the fastest polymerization time. cP: centipoise.

^a20–30% larger than Venoblock.

^bVeinoff™ with 5% dextrose has a longer polymerization time of 60 s.

Table 2. Registration details of VenaSeal™ with Australian Therapeutic Goods Administration (TGA).

Product	VenaSeal™
Registered title	Venous adhesive occlusion system
ARTG entry	194201
ARTG entry for	Medical Device Included Class IIb
Sponsor	Medtronic Australasia Pty Ltd
ARTG start date	30 January 2012
Product category	Medical Device Class IIb
Approval area	Medical Devices
Manufacturer	Sapheon Inc.
Manufacturer address	951 Aviation Parkway Suite 900, Morrisville, NC 27560, USA
Intended purpose	Intended for the permanent, complete, endovascular adhesive closure of the great saphenous vein (GSV) and associated varicosities in the treatment of venous reflux disease

Table 3. Registration details of VenaBlock™ with Australian Therapeutic Goods Administration (TGA).

Product	VenaBlock™
Registered title	Venous adhesive occlusion system
ARTG entry	283020
ARTG entry for	Medical Device Included Class IIb
Sponsor	Diverse Devices Pty Ltd
ARTG start date	29 November 2016
Product category	Medical Device Class IIb
Approval area	Medical Devices
Manufacturer	Invamed Saglik Ilac San ve Tic AS
Manufacturer address	Anadolu OSB 30 Agustos Cad No. 13 Malikoy, Ankara, Turkey
Intended purpose	Intended for the permanent, complete, endovascular adhesive closure of the great saphenous vein (GSV) and associated varicosities in the treatment of venous reflux disease

TGA in 2016 as a medical device (Table 3). VenaBlock™ is available for both catheter-directed administration as well as direct percutaneous injections. This product is at least 60 times less viscous than VenaSeal™ but 20 times more viscous than water. It has a very short polymerization time, and compared to Venaseal™ and Veinoff™, it is the fastest *n*-BCA to act (Table 1). These properties have the theoretical advantage of reducing the possibility of migration and extension but yet to be demonstrated in randomized trials.

Veinoff™. This product was developed by Invamed for percutaneous injections and was registered with the TGA in 2017. Veinoff™ is the least viscous and comparatively most flexible material after polymerization with a slightly longer polymerization time and hence slower action than VenaBlock™ but still faster than VenaSeal™ (Table 1).

Other products. There are new products entering the international market currently not available in Australasia, and therefore not specifically reviewed in this document. VariClose™ was developed by Biolas Health Inc. (Ankara, Turkey) and is currently not registered in Australasia. Another Turkish product, Venex™ has been developed by Vesta Medical (Ankara, Turkey) is yet to be available in Australia. Other similar products have appeared in Russian Federation and India.

Cyanoacrylates as embolic agents

n-BCA products have been used as embolic agents in interventional radiology (IR), interventional neuroradiology (INR) and endovascular surgery in the treatment of AVMs, portal vein system disease, e.g. gastric varices and aneurysms amongst others. Several products are available internationally but only two,

Glubran 2[®] and Histoacryl[®], are registered with the TGA. Onyx[®] is also registered with TGA for some of the above applications but is not a CA.

Glubran 2[®]. This product was developed by GEM (Viareggio, Italy) in 1998 and was registered with the TGA in 2009 for internal use in open and laparoscopic surgery and in digestive tract endoscopy, IR and INR.¹¹

Glubran 2[®] is composed of *n*-BCA in addition with the metacryloxysulpholane monomer, which makes its polymer more pliable and stable. The polymerization reaction is a milder exothermic reaction at 45°C which results in decreased inflammation and histotoxicity compared to Histoacryl[®] or Trufill[®].¹²

Histoacryl[®]. Histoacryl[®] was developed in 1968 and is distributed by B-Braun Surgical (Ruby, Barcelona). It obtained re-registration with the TGA in 2013 for embolization of large oesophageal or fundal varices and fixation of reinforcement material on soft tissue.¹³ Histoacryl[®] is available in both blue and clear colours. Clear colour should be used for embolization of superficial lesions.

Trufill[®]. This product was developed by Cordis (Miami Lakes, USA) and was approved by FDA in 2000.⁶ It is indicated for the embolization of cerebral AVMs when presurgical devascularization is desired. Trufill[®] is not registered with the TGA.

Onyx[®]. Onyx[®] is not a CA but a non-adhesive liquid embolic agent comprised of ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. It was developed by ev3 Endovascular, Inc. (Plymouth, USA) and is used to treat AVMs and to occlude vessels where other mechanical agents such as coils and plugs may not be suitable or available. Onyx[®] is registered with the TGA.

Co-administration of contrast agents. Contrast agents are used when the embolization is performed under fluoroscopic guidance. Contrast agents are mixed with adhesives at the time of the procedure to achieve radio-opacity, alter viscosity and delay polymerization within the delivery catheter. Powdered metals such as tantalum and tungsten, and iodized oils such as lipiodol (Vilpinte, France) are used to make the glue radiopaque and to delay polymerization time. The iodized oils are mixed in various ratios with *n*-BCA varying from 1:1 to 1:4 (oil-to-glue ratio) before delivery. Warming Histoacryl[®] and lipiodol mixtures to

temperatures close to 40°C decreases the viscosity and makes the injection easier to manage.¹⁴

Cyanoacrylates as skin adhesive agents

n-BCA has been used as a wound adhesive agent for the closure of surgical wounds as well as trauma-induced lacerations in areas of low skin tension that are simple, thoroughly cleansed and have easily approximated skin edges. Histoacryl[®] and Indermil[®] are registered with the TGA in Australia for this purpose.

Histoacryl[®]. Histoacryl[®] was registered as a wound adhesive by the FDA in 2007.¹⁵ It is indicated for closure of minimum tension wounds from clean surgical incisions and simple, trauma-induced lacerations.

Indermil[®]. This product was developed by Henkel (Dublin, Ireland) and is registered with the TGA.¹⁶

LiquiBand[®]. This product was developed by Medlogix (Plymouth, UK) and was approved by the Medicines and Healthcare Products Regulatory Agency of the United Kingdom (UK) in 2005. It is indicated for the use in laparoscopic surgical repair of inguinal hernia.

PeriAcryl[®]. PeriAcryl[®] was developed by GluStitch Inc. (Delta, Canada) and was approved by FDA in 2007 to assist in securing periodontal dressings.

GluStitch[®]. This product was also developed by GluStitch Inc. (Delta, Canada) and was approved by the FDA in 2015 for closure of skin incisions and trauma-induced lacerations.

Dermabond[®]. This is not an *n*-BCA, rather, an octyl-CA manufactured by Ethicon (Somerville, USA) and not registered in Australasia. The rate of contact dermatitis has been suggested to be the highest of all CAs used in medicine reaching up to 2%.¹⁷

Acrylates as adhesives in tapes and dressings

Two groups of compounds are used as adhesives in dressings and bandages including acrylates and epoxies. CAs in general are not used in dressings but other acrylates such as methacrylates are. The potential for cross-reactivity between CAs and other acrylates is discussed under Cross-reactivity of Acrylates and Cyanoacrylates.

Basic sciences

Basic physiochemistry

Acrylates are plastic compounds commonly found in artificial nail products, paints, varnishes and adhesives. They have numerous applications in medicine, dentistry and in the printing industry. CAs are ester derivatives of acrylates produced as low-viscosity liquids that can spread rapidly and polymerize quickly on contact with anions. The liquids are typically clear and colourless, although some CAs used to treat peripheral veins have a blue or purple colour. CAs are stable at body core temperatures but degrade at temperatures higher than 165°C.⁴

Molecular structure. Acrylic acid contains the vinyl group $\text{CH}_2=\text{CH}-$ connected to a carboxylic acid $-\text{COOH}$ terminus forming the molecule $\text{CH}_2=\text{CH}-\text{COOH}$. Acrylates are salts, esters or base conjugates of acrylic acid. CA is an ester $-\text{COO}-$ derivative of acrylic acid. The ester group is called carbonyl. The carbonyl group $-\text{COO}-$ connects to an alkyl group $-\text{R}$ that can be of various lengths ($-\text{COOR}$). One carbon atom would create a methyl-CA $-\text{COO}-\text{CH}_2$ derivative. Increasing the length of the carbonyl produces ethyl ($-\text{COO}-\text{CH}_2-\text{CH}_2$) and butyl $-\text{COO}-(\text{CH}_2)_4$ derivatives. The molecule also contains a cyano-group (nitrile; $-\text{C}\equiv\text{N}$) (Figure 2(a)).

Hence, the general formula of CA is $\text{CH}_2=\text{C}(\text{CN})-\text{COOR}$.

The non-medical adhesive, ‘Super Glue’ is ethyl 2-CA. All commercial systems currently used in Australasia for venous closure are *n*-BCA containing the butyl group ($-\text{C}_4\text{H}_9$) (Figure 2(b)). *n*-Butyl stands for normal butyl or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$ and implies the butyl group is organized in a linear hydrocarbon chain of four carbon atoms.

Antigenicity and the molecular structure. The antigenic component of acrylates is thought to be the carboxyl ethyl ($-\text{COOH}-\text{CH}_2-\text{CH}_2$) functional group. The molecule is less likely to be allergenic if the hydrocarbon chain is longer than an ethyl group. The extra length results in the masking of the antigenic group. Hence, an acrylate containing a carboxyl butyl group such as *n*-BCA has less potential for allergenicity than one containing an ethyl group.

Polymerization of cyanoacrylates. CAs are produced as liquid monomers that when exposed to ionic surfaces readily join to polymerize and form long-chain polymers. Exposure of CA monomers to an anion, such as the hydroxyl ($-\text{OH}$) group in water, initiates the polymerization process with bonding of the ethylene units (Figure 2(c)). The polymers form strong resins and effectively adhere closely spaced surfaces.¹⁵ CA

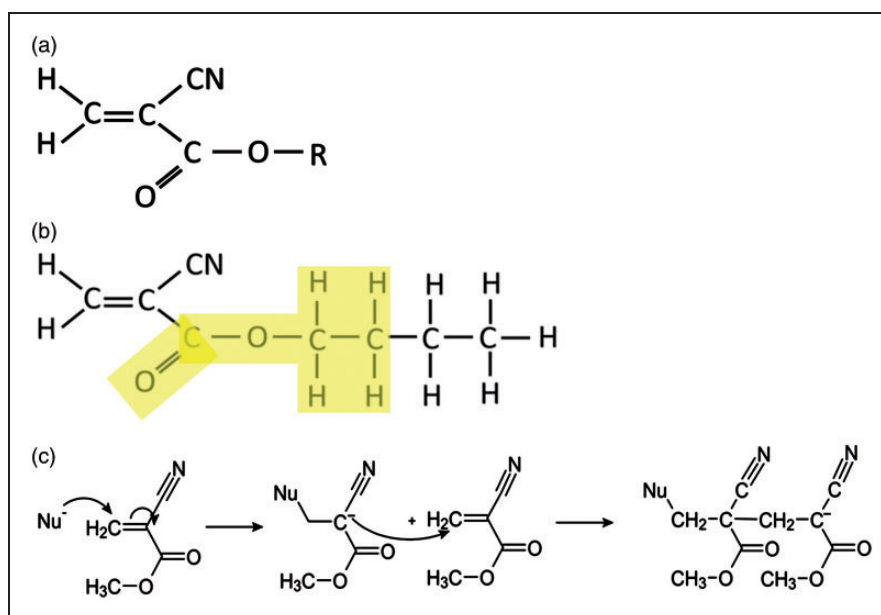


Figure 2. Molecular structure of cyanoacrylate and the polymerization process (adapted from Pollak and White¹⁸). (a) Monomeric cyanoacrylate $\text{CH}_2=\text{C}(\text{CN})-\text{COOR}$. The R represents an alkyl group. (b) *n*-Butyl-2-cyanoacrylate (*n*-BCA). The carboxyl ethyl ($-\text{COOH}-\text{CH}_2-\text{CH}_2$) group is the antigenic component of the molecule. (c) Polymerization process of cyanoacrylate (CA). Exposure of CA monomers to an anion, such as the hydroxyl ($-\text{OH}$) group in water initiates the polymerization process with bonding of the ethylene units.

polymers bond almost instantly to a variety of 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. A longer hydrocarbon length results in a slower rate of polymerization and less exothermic reaction.¹⁸

Production. There are several known methods of synthesizing CA monomers. The following sequence is usually followed in the industrial production of CA:

1. Reaction of formaldehyde with a cyanoacetate ester to produce the 2-cyanoacrylate ester, which spontaneously polymerizes.
2. Thermal depolymerization into a liquid monomer. This is typically done under acidic conditions and in the presence of an inhibitor such as sulphur dioxide, phosphorous pentoxide or nitric oxide to generate the monomer.
3. Modification of the monomer by altering the carbonyl (–COOR) group to obtain compounds with different chain lengths.
4. Addition of additives, stabilizers and thickeners to modify viscosity, polymerization time and performance properties such as the bond strength. The additives play a major role in determining the final physiochemical properties of these products.

Proprietary information. Commercially available medical-grade CAs are defined by their composition, viscosity, polymerization, pliability, tensile strength and adhesion strength. These physiochemical properties are determined by the concentration of the *n*-BCA in addition to solvents, additives and excipients that make up the composition of the final product. For instance, Trufill® used as an embolic agent contains tantalum powder for radiopacity and iodized oil for radiopacity and viscosity. With *n*-BCA products used in treatment of peripheral veins, much of this information is classified as confidential and not available to the public or the practicing physicians. The additives may play a role in the observed hypersensitivity reactions and other complications associated with the products. This information was requested by the panel from both manufacturers of endovenous glues registered with the TGA (Appendix 1), but the data were considered proprietary information and withheld.

Mechanism of action

n-BCA is delivered intravascularly to induce a mechanical occlusion of the target vessel or lesion, resulting in

obstruction to flow. Following entry into the target vessel, the delivered product forms a cast which may adjust to the shape of the vessel lumen. With direct percutaneous injections into smaller calibre vessels using faster polymerizing agents, adjusting to the shape of vessel may not happen unless significant compression is applied at time of injection. Under low shear conditions, such as that found in veins, the formation of the cast is sufficient to induce obstruction, resulting in vessel closure and interruption of flow. It has been argued that in high shear conditions such as in an AVM or arterial aneurysm, the introduction of the *n*-BCA is insufficient to cause permanent occlusion unless additional products such as metal coils or detergent sclerosants are co-administered.¹⁹ The *n*-BCA is then thought to induce necrosis of the intimal layer, resulting in an inflammatory process that ultimately leads to vascular fibrosis. Vascular endothelial damage is caused by chemical and/or heat-based reactions resulting in acute necrotizing vasculitis.²⁰ In low shear conditions as in veins or venous malformations, intravascular thrombus formation may also contribute to endothelial damage.

Tissue response to cyanoacrylate

The histopathological response that follows the introduction of *n*-BCA in blood vessels has been investigated in multiple studies, mostly involving AV malformations and oesophageal varices. In these studies, *n*-BCA was shown to induce a local inflammatory response within one month of use, likely due to generation of heat and formaldehyde during polymerization.⁴

Currently, there are only two studies describing the histology of a truncal vein following its treatment with *n*-BCA. The first is a Russian study where the vein was dissected after 10 min of exposure to Venaseal™.²¹ The second is an Australian study where serial biopsies were taken at one week, six weeks and one year after Venablock™ treatment of peripheral veins.²²

The Russian study reported mast cell degranulation in the peri-vascular space within 10 min of exposure to glue.²¹ In AVM studies, acute inflammation consisting mainly of polymorphonuclear cells was observed with foci of intramural haemorrhage within 24–48 h of *n*-BCA injection.^{23,24}

In the Australian study using Venablock™, the first week biopsy revealed the injected *n*-BCA in the vein lumen to be coated with erythrocytes. No histiocytes or granulomas were present at this stage.²² The AVM studies showed that by weeks 2–3, there was a granulocytic infiltration of vessel walls and the peri-vascular tissue. The vessel wall showed patchy loss of intima, medial necrosis as well as early foreign body giant cell formation and round-cell infiltration.^{23–25} An

eosinophilic vasculitis representing a hypersensitivity reaction was reported in three patients treated with *n*-BCA for cerebral AVMs associated with clinical bleeding in one case.²⁶

In the Australian study, by six weeks, the *n*-BCA was still present in the vein lumen, adherent to fibrous material and erythrocytes. No granulomatous reaction was seen at this stage, but small luminal foci of isolated foreign body histiocytes were present.²² The AVM studies showed that by week 8, mural angioneurosis was completely replaced by fibrosis with segmental wall thickening, achieving venous closure. Foreign body giant cells were present.^{27,28} The one-year biopsy in the Australian study revealed a lack of endothelial lining in the treated vessels, but there was lymphoid hyperplasia and fibrosis of the surrounding tissue. Significantly, there was extrusion of *n*-BCA to the peri-vascular space and extra-vascular cavitated foreign body granulomas with foreign body-type giant cells. These features were not present in the one-week and six-week biopsies from the same patient implying that the glue extrusion is a long-term finding. In the Australian study, all granulomas were found to be extra-vascular and not observed in the vessel walls or within the lumen of the treated vessels, and hence there was no evidence of a granulomatous phlebitis.²² The foreign body granulomas were observed for as long as 52–60 months.

Hypersensitivity and immune response to cyanoacrylate

Type I hypersensitivity. Type I hypersensitivity, also known as immediate-type hypersensitivity, is an IgE-mediated immune response typically occurring within minutes after the antigen interacts with the IgE molecule attached to the mast cell surface. There is an immediate release of vasoactive amines such as histamine, and other mediators such as heparin and trypsin followed by a later recruitment of inflammatory cells. Prototypical disorders include anaphylaxis, urticaria and bronchial asthma. Type I reaction can be clinically detected by skin prick testing and measurement of serum IgE and serum and urinary trypsin.²⁹

Histopathologically, Shaidakov et al. demonstrated active mast cell degranulation in the removed extra-fascial segment of the GSV within 10 min of VenaSeal™ *n*-BCA injection.²¹ Additionally, Korkmaz et al.³⁰ found eosinophilia 2 h after the CAC procedure.

To date, there have been no clinical reports of anaphylaxis to *n*-BCA, and only a few documented allergic reactions exist in the English literature of transient total body urticaria^{31,32} and asthma.³³

Type IV hypersensitivity. Type IV hypersensitivity, also known as delayed-type hypersensitivity, is a T-cell mediated immune response occurring within 24–48 h. Allergic contact dermatitis (ACD) is a prime example of a type IV hypersensitivity reaction.²⁹ Type IV reactions can be clinically detected by skin patch testing (see the ‘Prick and patch testing’ section).

Acrylates were named ‘Contact Allergen of the Year’ in 2012 by the American Contact Dermatitis Society due to their ubiquity in the modern-day environment.³⁴ ACD to CA-based medical adhesives has been frequently described in the literature, with Dermabond (2-octyl CA) being commonly implicated in numerous cases of tissue adhesive contact hypersensitivity.³⁵ In addition to CA, extensive reports of occupational and non-occupational ACD to acrylates, including methacrylates, ethyl acrylates, ethylene glycol dimethacrylate, have been published in dentists, dental technicians, printers, fibreglass workers, beauticians and women who are in contact with manicured/sculptured artificial nails.³⁶ ACD caused by acrylates is common in dental personnel and may present with respiratory or conjunctival symptoms.³⁷

It is strongly recommended that professionals using acrylates avoid touching the product to prevent sensitization.

Irritant contact dermatitis. Other than ACD, acrylates can cause irritant contact dermatitis (ICD). The skin reaction to most medical adhesive tapes, dressings and bandages is primarily an ICD.³⁸ The adhesive used in medical tapes is in general either an acrylate or an epoxy. ICD is more frequent with the use of reactive-type acrylates containing methacrylate monomers and oligomers and polymerization initiators and additives. Acrylate monomers are strong irritants and are responsible for most of the documented cutaneous reactions.³⁶ In general, monomers with polarity and lower molecular weights tend to present a greater potential for skin irritation. By contrast, completely cured acrylic polymers are relatively inert.

ICD from medical personnel manipulating *n*-BCA is rare; however, it is quite likely that some of the reported cases of ‘phlebitis’ following the use of *n*-BCA in peripheral veins may be due to ICD. In such cases, the presenting sign of ‘phlebitis’ has been erythema in the absence of venous inflammation. Further studies are required to investigate this finding.

Prick and patch testing. Although rare, acrylates may trigger an immediate hypersensitivity reaction. Acrylates are not part of the standard skin prick test panels. Prick testing can be performed using an appropriately low but optimal concentration of the product itself by an experienced allergist.

A negative prick test would not exclude a delayed type hypersensitivity, which is the more common reaction to acrylates. Patch testing is used to detect delayed-type hypersensitivity reactions. Commercially available patch test series for acrylates include multiple compounds including methyl methacrylates, ethyl methacrylate and ethyl CA but currently do not include *n*-BCA.²¹ When patch tested, acrylate-allergic patients often display multiple positive tests. These reactions may represent cross-reactivity or a reaction to a concomitant product or impurity that is not disclosed in the material safety data sheet.³⁹

Patch testing is performed using a carefully selected concentration of the allergen. If the concentration is too high, it can result in an ICD and a false-positive result. A high concentration can even cause sensitization and induce a true allergy. If the concentration is too low, it can result in a false-negative result. Commercially available patch test panels do not include *n*-BCA. The concentration of *n*-BCA in the commercially available products is not disclosed (correspondence with manufacturers) making estimation of an appropriate dilution very difficult. Patch testing using the actual product without dilution may either result in sensitization or a false-positive ICD.

Given the lack of standardized prick and patch test panels for *n*-BCA, we recommend against routine screening of patients prior to CAC and testing by inexperienced practitioners. If attempted, testing should be performed by an experienced allergist and contact dermatologist familiar with selection of the optimal dilution of the allergens, the use and significance of positive and negative controls, contraindications to testing and other factors that might affect the results.⁴⁰ *n*-BCA and other acrylate monomers should not be deliberately applied to the skin for patch testing and all those handling acrylate monomers should avoid direct skin contact with them. Direct contact with the product monomer especially when applied under occlusion may sensitize the individual. If sensitization occurs, further exposures will result in type IV hypersensitivity reactions manifested by erythema and itch. Many cases of non-specific 'phlebitis' presenting with erythema and itch reported in clinical studies may have been a type IV hypersensitivity ACD (see the 'Phlebitis and hypersensitivity-type phlebitis' section).

Cross-reactivity of acrylates and cyanoacrylates. Acrylate cross-reactivity is thought to be due to the carboxyl ethyl $-\text{COOH}-\text{CH}_2-\text{CH}_2$ functional group (Figure 2 (b)). The carboxyl ethyl group is the requisite for antigenicity as it reacts with receptors on antigen presenting cells (APC).⁴¹ Further, this functional group needs to be exposed on the end of the molecule for it to be detectable

by APCs. Molecules with a carboxyl group where the alkyl component is longer than ethyl (two carbon atoms) will not cross-react. For example, if the side group is carboxyl butyl ($-\text{COOH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2$), despite it containing the antigenic carboxyl ethyl group ($-\text{COOH}-\text{CH}_2-\text{CH}_2$) within it, the additional ethyl group at the end makes the functional group too large and hydrophobic, concealing it from the APCs. In other words, ethyl-CA is much more likely to be antigenic and cross-react with other acrylates compared with butyl-CA. Nonetheless, *n*-BCA may cross-react with other acrylates as it contains the antigenic carboxyl ethyl group. The cross-reactivity potential should not be underestimated in the clinical setting as the *n*-BCA is intravenously injected as a 'permanent implant' with a potential life-time of exposure and risk of sensitization is directly related to duration of exposure. Manufacturers of medical-grade *n*-BCA, in particular VenaSealTM and VenaBlockTM, recommend against the use of this product if the patient has a known allergy to an acrylate.

Toxicology and antimicrobial properties

Toxicology. All occlusive agents licensed for peripheral venous applications are registered with regulatory bodies as *devices* and not as drugs and hence have undergone a different pathway of registration compared with that required for new drug licensing. Changes to the preparations made by the companies to make them commercially acceptable remain confidential and hence the additives and excipients that define the viscosity and the physicochemical properties of each product are not disclosed. Given the reports of *n*-BCA migration and pulmonary embolism (PE) following their use in gastric varices, the modifications of CA products have mostly been aimed at viscosity and polymerization time and have mostly focused on modifications in the composition of the additives.⁴²

Toxicology of all registered endovenous glues was established on unpublished in-house studies, required as a part of the submission to notified bodies and regulatory agencies. The US National Toxicology programme has extensively studied ethyl-cyanoacrylate and methyl 2-CA, particularly for potential mutagenic and carcinogenic effects⁴³ and these compounds are not considered to be a problem for use in humans. Isobutyl CA was withdrawn from the market by the manufacturer after reports of sarcomas in laboratory animals and has been replaced by *n*-BCA since the late 1980s.⁴

Antimicrobial properties. The bacteriostatic and bactericidal properties of *n*-BCA have been documented extensively in the ophthalmic literature in the context

of sealing corneal incisions, both in vivo and in vitro.^{44–48} The *n*-BCA inhibited the growth of Gram-positive organisms including *Staphylococcus aureus*, *Streptococcus pyogenes* and *S. pneumoniae*⁴⁷ but had less effect on Gram-negative organisms including *Pseudomonas aeruginosa* and *Escherichia coli*.⁴⁴

Clinical studies

Observational studies

Several studies have shown that CAC is clinically safe and effective with cumulative occlusion rates comparable to those for ETA. The initial study by Almeida et al.^{49,50} reported a 36-month cumulative occlusion rate of 94.7% in 29 of 38 patients with GSV reflux treated by CAC. This study showed no more than mild to moderate adverse effects. No peri-venous tumescent anaesthesia (TA) or graduated compression stockings (GCS) were used. A multicentre European trial presented by Proebstle et al.⁵¹ reported a cumulative 12-month occlusion rate of 92.9% in 70 GSVs. No GCS or TA was used and a phlebotic reaction occurred in 11.4% with a median duration of 6.5 days. Two independent Turkish studies showed similar results with different techniques. One study with 62 patients with GSV reflux showed a six-month total occlusion in 90.3% and subtotal occlusion (flow in a 5–10 cm segment of treated vein) in 6.5%.⁵² Another study of 180 patients with GSV reflux treated by VariClose™ showed a 30-month cumulative occlusion rate of 94.1%.⁵³

An American study reported early outcome for 70 veins treated including GSV, SSV and anterior accessory tributary of GSV (AAGSV) measuring up to 20 mm diameter.³¹ GCS were not used, and phlebitis in the treatment area or tributaries occurred in 20% but completely resolved in all but one patient by one month. All veins were occluded at one month and adjunctive procedures for tributaries decreased from a predicted 96% to an actual 74%. Mean time to return to work and normal activities was less than three days.

A single-centre study of 57 legs treated for GSV reflux in Hong Kong showed a 78.5% closure rate at one year.⁵⁴ Mean vein diameter ≥ 8 mm was a significant predictor for recanalization. A study from the Netherlands showed that it is feasible to use CAC to treat incompetent perforators.⁵⁵

Randomized trials

A collaborative trial involving 10 centres in the USA treated 222 patients with GSV reflux in veins up to 12 mm diameter randomized to CAC or radiofrequency ablation (RFA).² There were identical occlusion rates

at 12 months (CAC 97.2%: RFA 97.0%). There was comparable improvement of symptoms and quality-of-life in both groups and adverse effects for CAC were mild to moderate.

A single centre Turkish trial studied 310 patients with GSV reflux treated with CAC or EVLA. The one-year closure rate for CAC was 95.8%. Operative time was shorter (15 ± 2.5 vs. 33.2 ± 5.7 min, respectively) and periprocedural pain was less (3.1 ± 1.6 vs. 6.5 ± 2.3 , respectively) for CAC.⁵⁶ Both groups had significant improvement in their quality-of-life scores and there was no difference in Venous Clinical Severity Score (VCSS) and Aberdeen Varicose Vein Questionnaire score between the groups in the first year. Another larger single-centre Turkish trial with 456 patients, with a two-year follow-up compared CAC with RFA and EVLA with treatment of superficial venous incompetence. No differences were observed in occlusion rates between the three modalities, but CAC appeared superior with respect to periprocedural pain, return to work and decreased VCSS. They did not use any specific quality of life measures beyond the reported pain pre- and post-procedures.⁵⁷

Complications

Medical uses of CA have been associated with a wide range of complications when used in different settings and for various applications. Some of the reported complications are due to mixing the agent with contrast agents such as lipiodol and not due to the CA itself. Some of the complications may also be due to the additives but there is insufficient data to discern the effect of the additive as against the compound itself. Here, we focus on complications of CAC for treatment of peripheral veins and briefly review complications associated with their use as embolic and adhesive agents.

Complications of CAC

CAC in general is a safe procedure with relatively low rates of complications (Table 4). Immediate and delayed hypersensitivity reactions, granuloma formation, phlebitis and glue extension are the most feared and significant complications.

Hypersensitivity reaction. Anaphylactic reactions to CA and death from anaphylaxis have not been reported. Allergic reactions to CA are rare and although true incidence is not known, there has only been a few documented cases in the English literature of transient total body urticaria,^{31,32} contact dermatitis^{35,58,59} and asthma.³³ The authors of the current consensus have reported incidences of pruritus without a rash

Table 4. Summary of CAC procedure for peripheral veins complications reported in the literature.

References	Year	Subjects	Follow-up (months)	Glue migration	PE	DVT	STP	Phlebitis	Hyper-sensitivity	Injection site complication	Pigmentation	Paraesthesia	Other
Almeida et al. ⁶⁵	2015	38	24	21.1%	0	0	NR	16% ^a	NR	NR	2.6% ^b	NR	NR
Almeida et al. ⁵⁰	2017	38	36	21.1%	0	0	7.9%	16%	NR	27.3% ^c	NR	NR	NR
Proebstle et al. ⁷⁰	2015	70	12	1.4%	0	0	NR	11.4%	NR	1.4% infection	NR	NR	NR
Morrison et al. ²	2015	108	3	NR	0	0	4%	20%	NR	1% Infection	NR	3%	3% ^d
Tekin et al. ⁵²	2016	62	6	0	0	0	3.2%	NR	NR	NR	NR	NR	1.6% haematoma
Bozkurt and Yilmaz ⁵⁶	2016	310	12	0	0	0	NR	4.5%	NR	14.3% ecchymosis	1.3%	0	NR
Gibson and Ferris ³¹	2017	(50)	1	2.0%	0	0	NR	20%	2.0% ^e	2.0% local reaction	NR	NR	2.0%
Kolluri et al. ^{66g}	2016	108	12	NR	Unspecified.	Unspecified.	20.4% mild, 5.6% moderate, 0% severe	NR	NR	NR	NR	NR	NR
Chan et al. ⁵⁴	2017	29	12	NR	Unspecified.	Unspecified.	25.0% mild, 6.1% moderate, 5% severe	NR	NR	NR	NR	3.4% ^h	NR
Koramaz et al. ⁶⁷	2017	150	12	6.9%	0	0	NR	NR	NR	3.4% infection	NR	0	NR
Parç ⁶⁸	2017	34	1	NR	0	0	NR	2.1% ^h	NR	NR	0	0	NR
Yasim et al. ⁵³	2017	180	3 to 7	0	0	0	NR	NR	11.4% ⁱ	NR	11.8%	0	NR
Yavuz et al. ⁶⁹	2018	538	12	0	0	0	NR	NR	NR	0 ecchymosis	NR	NR	NR
				0	0	0	NR	1.2%	NR	1% ecchymosis	0	0	70% Burning sensation

Note: Adapted from Lam et al.,⁷⁴ with recent updates. PE, pulmonary embolism; DVT, deep vein thrombosis; STP, superficial thrombophlebitis; NR, not reported.

^aResolved with non-steroidal anti-inflammatory drugs.

^bPersistent after one-year follow-up.

^c10.5% inflammation, 2.6% vesicles, 2.6% ulcer, 2.6% swelling, 2.6% skin irritation, 1% infection.

^d1% light-headedness post-procedure 2% stocking irritation.

^eTotal body hives for one week resolved with antihistamines and short oral steroids.

^fIntraoperative nausea/light headedness.

^gStudy of two groups undergoing cyanoacrylate closure, one group was extended follow-up of Morrison et al.²

^hResolved.

ⁱAbnormal skin reaction: erythema, itching, pain, oedema and tenderness possibly classified as 'non-specific phlebitis' in other studies.

following VenaSeal™ and Venablock™ treatment. Systemic hypersensitivity reactions to *n*-BCA are exceedingly rare. In a recent report, a 26-year-old male developed an intermittent systemic urticarial reaction four weeks after *n*-BCA embolization of an orbital AVM.⁶⁰ Subsequent skin allergy testing confirmed hypersensitivity to *n*-BCA glue and the patient has since been successfully managed with daily oral antihistamines. Further exposure to *n*-BCA was avoided.

Sensitization to other acrylates has been extensively reported in beauticians and dental workers and even recreational users with frequent exposure to false acrylic nail or eyelash glues, gel nail polishes or dental fillings.^{37,61–63} Contact dermatitis is the most common manifestation (80–93%),⁶² followed by dyshidrotic eczema (pompholyx) (9.1%)⁶² and very rarely asthma and rhinoconjunctivitis.^{37,64} A UK and Irish audit of 4931 patients found a patch test positive rate of 2.4% to at least one type of (meth)acrylate. In the audit, 60% of people developed their allergy through recreational exposure, 33% through occupational and 7% through medical adhesives.¹ A history of hypersensitivity reaction to acrylic nails and the glue used for eyelash extensions is an absolute contraindication to CAC. However, there is a paucity of information on possible cross-reactivity between medical adhesives used in dressings and cyanoacrylate products.

Phlebitis and hypersensitivity-type phlebitis. Phlebitis is consistently the most common adverse event following CAC, reported in up to 20% of cases^{2,31,49,50,54,56,65–70} (Table 4).

In comparison, phlebitis following EVLA is reported in 7.7%^{56,69} to 7.9%⁶⁷ and following RFA in 14%² of patients. CAC is heavily marketed with a claim that it does not require the concomitant use of GCS or TA.⁷¹ By contrast, the treatment protocols of both EVLA and RFA require the use of GCS and TA. The high rates of phlebitis following CAC cannot be attributed to the lack of postoperative external compression. This was demonstrated in the VeClose trial where all subjects undergoing CAC were mandated to wear GCS in order to have their postoperative regimen identical to the RFA group. Despite the use of stockings, the rate of ‘phlebitis’ was as high as that seen in studies of CAC closure where stockings were not mandated.

The literature is not very specific on the nature of the reported phlebitis and whether these reported complications are true phlebotic reactions (inflammation of the vein wall) or immune skin reactions resembling phlebitis. This is highlighted by the fact that ‘phlebitis’ may be noticed at the site of the treated vein or at distant untreated sites. When the phlebitis has involved treated veins, it has been responsive to non-steroidal

anti-inflammatory drugs (NSAIDs) whereas some of the phlebitis-like reactions clinically presenting with erythema, oedema, pruritus and tenderness have been unresponsive to NSAIDs but responded to antihistamines. In a study by Morrison et al., the phlebitis post-VenaSeal™ CAC was classified as phlebitis occurring in the treated site as against those occurring over untreated sites. One-third of all phlebotic reactions occurred in untreated sites. In a study by Gibson et al., phlebitis was classified as those occurring at the treated vein, those occurring at adjoining tributaries and a non-specific erythematous skin reaction occurring at other sites. Similarly, one-third of the reported phlebotic reactions had the non-specific erythematous reaction.^{31,65,68} In a report by Zierau, unspecified, inflammatory reddening of the skin was observed approximately five to eight days post-surgery in 11.7% of cases.⁷² Park et al.³² recently identified such reactions as a separate entity from true phlebitis. He postulated that it is a type IV delayed hypersensitivity reaction due to a foreign material, rather than localized inflammation and named it phlebitis-like abnormal reaction. The reaction he described was bilateral, pruritic and was alleviated by antihistamines and steroids in over 85% of patients. It occurred more commonly following CAC treatment of extra-fascial veins than sub-fascial veins. The fact that this reaction responded to antihistamines suggests a more immediate-type hypersensitivity response rather than a delayed type. Consistent with this finding, Shaidakov et al.²¹ found active degranulation of mast cells in the removed extra-fascial segment of the *n*-BCA-treated vein. Further, Korkmaz et al.³⁰ found eosinophilia 2 h after the CAC procedure.

In summary, it is likely that hypersensitivity-type phlebitis (HTP) is a separate entity to conventional phlebitis driven by a cell-mediated reaction to foreign body material. Given the timing of pruritus and its responsiveness to anti-histamines, it is possible that the hypersensitivity reaction is a combined type I and type IV response which would explain the constellation of erythema, oedema, urticaria, pruritus and histological finding of mast cell degranulation and systemic eosinophilia. This combined pattern of immune reaction is not uncommon and is seen in atopic dermatitis where the patient can exhibit both an immediate type hypersensitivity manifested by an urticarial reaction driven by mast-cell degranulation combined with a dermatitis which is a T-cell driven hypersensitivity. Therefore, the treatment of such hypersensitivity type reaction should include the combined use of NSAIDs and oral antihistamines, as well as systemic immunosuppressants such as oral or IV steroids in severe cases. As with other venous interventional procedures, CAC must be performed in controlled environments where

resuscitation equipment is readily available, and the staff are trained and well equipped in dealing with anaphylaxis and hypersensitivity reactions.

Granulomatous phlebitis. Histological studies have consistently demonstrated a granulomatous phlebitic reaction developing within two months and evident at 12 months after injection of *n*-BCA. This reaction commonly remains asymptomatic but may progress to suppuration, necrosis and ulceration. Extrusion of the glue from the vein lumen is another important consideration. A case report by Zernovicky described a 54-year-old female treated with VenaSeal™ who developed spontaneous skin perforations with spontaneous evacuation of fragments of *n*-BCA from the treated sites on both legs four months postoperation.⁷³ Ultrasound demonstrated movement of the glue in the terminal part of both GSVs. The progression continued despite the use of steroids and excision of the initial granuloma and the patient eventually required bilateral saphenectomy. After dissection of the vein, glue was observed to be mobile within the treated vein. Ten days after saphenectomy, the pain and erythema were reduced, but there was long-term residual lymphoedema.

Superficial thrombophlebitis. Despite 'phlebitis' being the most commonly reported complication of CAC, a range of skin complications such as ICD as well as true phlebitis appear to have been grouped together and labelled as 'phlebitis' in the published literature. These include HTP, granulomatous-type phlebitis (GTP) as well as superficial thrombophlebitis (STP). Three of the 11 studies identified STP as a complication distinct from the non-specific 'phlebitis', occurring at a rate of 3–4%.^{2,52,65} Future studies need to clearly differentiate between ICD, ACD, HTP, STP and GTP.

Glue migration, deep vein thrombosis and PE. PE following CAC has not been reported, but there have been reports of PE following *n*-BCA embolization of gastric varices.^{42,74} Deep vein thrombosis (DVT) remains an uncommon complication of the CAC procedure, but extension of *n*-BCA from the saphenofemoral junction (SFJ) into the common femoral vein (CFV) has been reported on several occasions (Table 4). Earlier studies reported higher rates^{51,65} (21%) of *n*-BCA extension observed at the 48-h follow-up on duplex ultrasound (DUS) that resolved at three-month follow-up with anticoagulation.⁶⁵ This was likely due to the catheter being positioned 3 cm from the SFJ, thereby not providing adequate room for glue propagation along the GSV.⁷⁵ With recent technique modifications of increasing the distance to 5 cm, thread-like thrombus/CAC extension is less likely.⁵² However, extension of *n*-

BCA from the target saphenous vein into the adjoining deep veins, i.e. the CFV or the popliteal vein remains a concern. This is most likely influenced by several physiochemical factors and in particular the product's viscosity and polymerization time. Glue migration and extension would be more likely with less viscosity and longer polymerization time. Higher viscosity and shorter polymerization time would anchor the glue at the injection site preventing migration. Randomized clinical trials comparing various *n*-BCAs are required to investigate the effect of these physiochemical properties on glue migration and extension. Caution with perforator treatment is required due to the potential risk of deep venous extension but slow careful injection under real time guidance may reduce the risk.

The published studies have referred to the observed extension as 'thrombus extension', 'thread-like thrombus', 'glue extension' or a combination of these descriptions.^{31,65,76} More recently, 'endovenous glue-induced thrombosis' was proposed to closely parallel 'endovenous heat-induced thrombosis' described previously in association with EVLA.⁷⁷ Currently, there is no histological or biochemical data to demonstrate a thrombotic element in the observed glue extension. Chronic inflammatory changes alter the composition and structure of the injected *n*-BCA,²² and a thrombo-inflammatory component may develop in time. However, in the absence of data and for the purpose of describing the acute ultrasonic finding, '*n*-BCA extension' is probably the best description.

Injection site complications. Injection site infections are rare (~1%). Other reported injection site complications include localized bruising, pruritus, inflammation, vesicles, ischaemic ulcer, skin irritation and swelling.⁵⁰ Extrusion of a small plug of glue with both VenaSeal™ and VenaBlock™ has been reported by two doctors on the consensus leading to delayed healing of the access point.

Hyperpigmentation. Hyperpigmentation has a reported incidence of 1.3⁵⁶ to 11.8%,⁶⁸ resulting from treatment of a vein coursing close to the skin surface such as the epifascial GSV.⁶⁵ Some hyperpigmentation has been transient,⁵⁶ while others were still visible one year post-treatment.⁶⁵

Paraesthesia. Two studies have reported paraesthesia with rates of 0–3%.^{2,70} In both studies, the paraesthesia was mild and transient.

Oedema and lymphoedema. Members of the panel have reported incidences of oedema following VenaSeal™ treatment in the absence of deep vein occlusion or

HTP. This may be due to an exaggerated inflammatory response to CA. Lymphoedema was reported following the case of suppurative granulomas by Zernovicky.⁷³

Palpable nodules. Members of the panel have reported palpable nodules along the length of the treated vein following VenaSealTM, VenaBlockTM and VeinoffTM treatments with some nodules requiring excision or phlebectomy. This could be due to the proximity of the vein to the skin surface. Palpable nodules have also been reported due to extension of the glue into superficial tributaries when injecting perforators and truncal veins.

Skin discolouration. There are no reports of skin 'tattooing' from the use of *n*-BCA in the setting of endovenous injection. However, there have been reports of tattooing of the skin from when Histoacryl Blue was used as an embolic agent close to the skin.⁷⁸ An advantage of VenaSealTM over VenaBlockTM or VeinoffTM is its clearer colour, whereas the other two products are blue (Figure 1). It is worth noting that Histoacryl is also available in clear form.

Complications in embolic use

Reported complications of CAC in its use as an embolic agent have included tissue ischaemia, end-organ infarction,²⁰ PE,⁴² cerebral infarction,⁷⁹ haemorrhage⁸ and rupture of AVMs due to increased intranidal pressure. Systemic reactions have included nausea, vomiting²⁰ and fever, while other local complications include regional pain, catheter retention,⁸⁰ reflux, blockage or adhesion to vascular walls.²⁰ When used to treat superficial vascular malformations, *n*-BCA has been associated with suppuration, palpable cast formation and tattooing of the skin with blue Histoacryl[®]. It should be noted that when used with fluoroscopic guidance, *n*-BCA is mixed with lipiodol and some of the above reactions may be due to the contrast agent.

Complications in adhesive use

Reported complication of CAC in its use as an adhesive for wound closure has been limited to contact dermatitis and allergic reactions.^{81,82}

Treatment protocols

Preoperative assessment

Initial consultation

- A complete medical history and physical examination (with specific reference to the 'Indications and contraindications' section) should be performed before treatment is offered.

- Clinical-Etiological-Anatomical-Pathophysiological (CEAP) classification should be recorded.
- Photographs of lower limbs and other relevant photographs should be obtained.

Preoperative duplex mapping

- Comprehensive DUS venous incompetence studies should be undertaken to map out the pathway of venous incompetence, exclude venous thrombosis and confirm suitability for intervention.
- DUS should be performed within one year of proposed treatment and repeated if the lapsed period is longer than 12 months.
- Copies of the diagnostic findings and proposed treatment plan should be sent to the referring practitioner.

Prick and patch testing

- Referral to an allergist and a contact dermatologist should be considered for assessment of possible allergies and to organize testing if appropriate.
- Prick test panels do not include acrylates. While patch test panels for acrylates are available, these do not include *n*-BCA.
- Patch testing for acrylates should include the full panel of acrylates. A positive patch test to acrylates is an absolute contraindication to CAC due to possibility of cross-reactivity between other acrylates and *n*-BCA. However, a negative patch test to acrylate series does not exclude allergy to *n*-BCA.
- Testing for specific *n*-BCA products can be performed using appropriately low but optimal dilutions of the actual product to avoid sensitization and a false-positive ICD. To determine the appropriate dilution, the concentration of the *n*-BCA content in the commercial product needs to be known. This is currently considered proprietary information not released by the manufacturing companies making testing very difficult.
- If attempted, testing using the actual product should only be performed by experienced allergists and contact dermatologists familiar with selection of the optimal dilution of allergens, the use and significance of positive and negative controls, contraindications to prick testing and other factors that might influence the results.
- A negative allergy test does not exclude the possibility of long-term chronic inflammatory sequelae such as granuloma formation, glue extrusion and skin perforation.

Post-investigations consultation

- This consultation should include a discussion of the clinical, ultrasound findings and patch-test findings, if performed.

- Open and unbiased discussion of alternative treatment options including conservative measures to manage chronic venous insufficiency. At this stage, it would be inappropriate to strongly recommend CAC over ETA, although other treatment options such as open surgery are considered to be less favourable.^{83–88}
- Discussion of the risks and complications of each treatment option and possible remedial actions in the event of adverse outcomes.
- Discussion and documentation of patient's expectations with advice as to whether they are realistic and achievable.
- Discussion of life-style modifications during the treatment period, travel, pregnancy and other factors that might influence or interrupt the treatment.

Financial consent and cool off period

- A written estimate of cost for the anticipated course of treatments should be provided.
- The patient must be given adequate time to understand the information provided, ask questions and seek a second opinion if required.
- Treatments should ideally not be performed on the same day as the consultation, unless there are compelling reasons to do so.
- If performed for cosmetic reasons, the Medical Board of Australia stipulates there should be a cooling off period of at least seven days between an adult patient giving informed consent and a major procedure. For minors under the age of 18, there must be a cooling off period of at least three months before a major procedure, and evaluation by a general practitioner, psychologist or psychiatrist is mandatory.

Informed consent

- Informed consent should be obtained prior to every procedure.
- The discussion should include an explanation of the treatment technique provided in lay language, discussion of adverse events, alternative treatment options and the option of conservative measures such as GCS or no treatment if appropriate. Financial consent should be obtained prior to every procedure.
- It should be explained that long-term data regarding the fate of the treated veins are unavailable, and the possibility of severe and cosmetically disfiguring complications must be discussed especially for asymptomatic C1–C2 patients who may be presenting for cosmetic reasons.

Indications and contraindications

Indications

Saphenous reflux. All TGA recognized glue products in Australia are registered for the treatment of saphenous reflux.

Venous tributaries. VenaBlockTM and VeinoffTM can be directly injected and hence are registered with TGA for the treatment of tributary veins and perforators. Off label use of VenasealTM via direct injection has been reported.

Contraindications. The list of contraindications provided here needs to be revised on a regular basis to reflect clinical and scientific evidence for precautions as further knowledge is obtained. Individual practitioners should exercise care using CAC, bearing in mind that *n*-BCAs are implantable foreign bodies that trigger an immune or hypersensitivity reaction. This reaction may remain clinically silent or may become clinically detectable. Given that other ablative interventions are available beside cyanoacrylates, high-risk patients should not be offered CAC.

Hypersensitivity. History of immediate (urticarial) or delayed hypersensitivity reactions to acrylates and commercial or medical-grade CA preparations. This includes, but is not limited to, a previous reaction to household 'Super Glue' preparations, glue used for eyelash extensions or glue used in acrylic, signature nail systems and shellac nail preparations.

Previous significant adverse reactions to CAC. This includes adverse events such as extensive 'phlebitis', necrosis, suppuration, oedema and other such reactions.

Acute venous thromboembolism (VTE). This includes DVT, PE and STP.

Active or uncontrolled systemic disease. This includes systemic inflammatory disorders, un-controlled systemic autoimmune, granulomatous, hypersensitivity or mast cell disorders including vasculitis, mastocytosis, sarcoidosis, systemic lupus erythematosus (SLE), atopy and granulomatous disease or infections. In particular, we advise against the use of CAC in patients with a history of sarcoidosis where the antigen remains unknown or various antigens are implicated. We also recommend granulomatous vasculitic disorders such as Wegener's granulomatosis or Churg–Strauss disease should be considered an absolute contraindication.

Acute or un-controlled localized or systemic infections. This includes cellulitis in the affected leg, widespread folliculitis and organ-specific infections.

Warnings and precautions

Pregnancy. Treatment in the first trimester is a contraindication. Treatment in the third trimester should only be delivered for medical indications where there is no other treatment option available.

Breastfeeding within 48 h of the procedure. There is no data on the excretion of the *n*-BCA or the product additives in breast milk. Venous interventions in the first three months postpartum should be avoided due to the increased risk of VTE. Then, venous interventions should only be performed for significant medical reasons while the patient is breastfeeding. In such situations, a pump and store strategy would provide the mother's milk to be used via bottle feeding. For 48 h following intervention, breast milk should be pumped and disposed of.

Low body fat percentage. Patients with reduced subcutaneous fat or thin legs can frequently feel the firm cord of the treated vein which usually resolves in less than three months. Accordingly, caution should be exercised in patients with low body fat percentage (<10%) or thin legs may constitute a relative contraindication to CAC.

Systemic autoimmune disorders. Care should be taken in treating such patients with *n*-BCA and consideration to pre- and post-treatment steroid administration should be given. Until further data on the safety of *n*-BCA in patients with autoimmune disease are available, ETA should be offered as the first option and CAC should be offered when there are no other safe treatment options available.

Thrombophilia and hypercoagulable state. In patients predisposed to VTE, prophylactic anticoagulation for seven days postoperatively should be offered. This includes documented known significant thrombophilias, immobility including long-haul travel of more than 5 h continuous travel, not including travel on ships or trains, within a two-week period. Treatment in patients with active malignancy or those on tamoxifen should be performed with care and prophylactic treatment with low-molecular weight heparin or direct oral anticoagulant should be provided for seven postoperative days. There are validated methods such as the Caprini score that should be adopted for risk stratification.⁸⁹

Techniques: General considerations

The following summary of techniques are those recommended by the manufacturers. It does not provide sufficient information to perform the procedures, and this must be gained by hands-on supervised training.

Variation of techniques can be considered based on the practitioner's experience.

Technique overview. CAs are liquid polymers that polymerize on exposure to free radical and anions. Care should be taken not to draw up the product in a catheter or syringe flushed with saline, water or containing blood. When used for vascular embolization, *n*-BCA is delivered via selective catheterization where the catheter is flushed with 5% dextrose prior to delivery of the combination of *n*-BCA and lipiodol. However, when used for peripheral venous interventions, *n*-BCA is delivered via non-stick special purpose made catheters to avoid catheter retention and adhesion to vessel wall. The technique is promoted as a 'non-thermal non-tumescent' procedure not requiring postoperative compression. Practitioners should exercise caution, common sense and good medical practice when customizing the treatment to individual patients' needs, anatomy and pathology.

Dose. There is no scientific data regarding the maximum dose of *n*-BCA per treatment session. There is no upper or lower limit for CA in IR and the volume of *n*-BCA is determined on a case-by-case basis and depends on the size of the target vein or vascular lesion. However, the volume of CA to be administered using the commercial systems is determined by the delivery device and if more than one delivery device is used in the same sitting. The Venaseal™ product packaging provides 5 mL of *n*-BCA allowing for treating 90 cm of vein length if the vein diameter is less than 6 mm (see below) and hence to treat two legs would require 10 mL. The consensus group has agreed on an arbitrary upper limit of 10 mL of adhesive per CAC treatment session, although this can be modified depending on the clinical indication. The safe life-time upper limit of *n*-BCA is not known. Practitioners should not 'save' leftover CA from single use kits for use in other patients. This cost saving practice can result in cross-contamination and jeopardize sterility and adhesive quality of the product.

Peri-venous TA. TA has been routinely used in conjunction with ETA to provide anaesthesia, target vein compression and heat dissipation reduction. Polymerization of *n*-BCA is exothermic at temperatures of 40–45°C in the peri-venous space. Given that CAC does not generate significantly high temperatures and is not a painful procedure, TA has not been routinely used in conjunction with CAC. Peri-venous TA 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. Reported incidence of phlebitis post-CAC is up to 20%, whereas by comparison the incidence of phlebitis in EVLA is up to 7.9%⁶⁷ and for RFA is up to 14%.² The high rates of phlebitis reported in the literature post-CAC could represent misclassification of HTP and not attributed to the lack of post-treatment compression. Direct comparative studies of CAC with and without GCS are required to evaluate the role of compression. GCS 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.

Documentation. Make a written record of the following:

- The date and time of the procedure
- The treated leg(s)
- The treated vein(s)
- The length and diameter of veins treated
- The type and the brand name of the *n*-BCA used
- Retain the product label and stick it on the operation report to document the batch number which will be required in the case of an adverse reaction
- Dosage of *n*-BCA used
- Details of any other concurrent or adjunctive procedures performed
- Whether or not compression was applied
- Any immediate adverse reactions
- Post-treatment management.

Catheter-directed treatment of saphenous reflux

Catheter directed *n*-BCA (VenaSealTM and VenaBlockTM) can be used to treat saphenous reflux as an alternative to ETA or surgical stripping. 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. We consider that it is a requirement to use full sterile surgical technique of gowning and gloves for all operating members including assisting sonographers and scrub nurses. Ultrasound equipment used must include a high-frequency linear array probe with colour flow and Doppler capabilities, and the probe must be in a sterile sheath.

VenaSealTM procedure. The procedure involves an introducer sheath, a dispensing catheter and a 3 mL syringe to be attached to a dispenser gun. The total amount of adhesive to be delivered in one treatment session needs to be calculated as a function of the vein length and diameter. A total of 5 mL of glue is provided in one

package, 1.4 mL of which is wasted in the dead space of the catheter. The remaining 3.6 mL can be used to treat up to 90 cm of vein length if the vein diameter is less than 6 mm. When treating two legs, 10 mL of glue will be required, 8.6 mL of which can be used considering 1.4 mL is wasted in the catheter dead space. This allows for treating larger lengths of target veins and veins of larger diameter (discussed below where 0.1 mL of *n*-BCA is injected at 2 cm intervals).

- Select the access point based on the clinical indications and the treatment plan.
- Inject local anaesthetic to access the target saphenous vein. The local anaesthetic should be lignocaine only, as adrenaline would vasoconstrict the target vessel.
- Access the vein using a Seldinger technique.
- Insert the introducer sheath and advance to 5 cm distal to the saphenous junction and flush with normal saline.
- Prime the syringe with *n*-BCA then connect to the dispenser gun and the dispensing catheter.
- Prime the catheter with *n*-BCA to 3 cm short of the tip.
- Insert the dispensing catheter into the introducer sheath and pull back the sheath so that the tip of the dispensing catheter is 5 cm distal to the junction.
- Guide and follow the procedure on ultrasound and use the ultrasound probe to compress the saphenous junction.
- Inject a 0.1 mL aliquot of adhesive into the vein by pulling the trigger of the dispenser gun and hold for 3 s, then pull back 1 cm and deliver another 0.1 mL of adhesive for 3 s.
- Pull the catheter and sheath back by 3 cm, maintain proximal compression with the ultrasound probe and light digital compression for three full minutes before the next trigger pull.
- Maintain proximal compression with the probe and deliver 0.1 mL aliquots of adhesive at 3 cm intervals down the vein waiting each time for 30 s after each subsequent trigger pull.
- Confirm vein closure with ultrasound, then withdraw the delivery systems. For veins larger than 6 mm diameter, consider 0.1 mL aliquots at 2 cm intervals.
- Stop 5 cm proximal to the access site, withdraw the dispenser catheter into the introducer sheath and remove the system, then apply pressure until haemostasis occurs.

VenaBlockTM procedure. The system uses a 6F PTFE catheter with an atraumatic tip with a laser guiding light that shines through the skin to allow precise

placement of the tip in relation to the saphenous junction. It also has high echogenicity for ultrasound guidance.

- Select the access point based on the clinical indications and the treatment plan.
- Inject local anaesthetic to access the target saphenous vein. The local anaesthetic should be lignocaine only, as adrenaline would vasoconstrict the target vessel.
- Gain access using an 18G angio-needle.
- Insert the short introducer (11 cm) into the target vessel and flush with saline then remove the guidewire.
- Draw up VenaBlock™ into the provided syringe to a volume of 2 mL.
- Attach the syringe to the dispensing gun, check the catheter laser tip by turning the switch on.
- Attach the catheter to the syringe which is already connected to the dispensing gun then prime the catheter to 3 cm short of the tip.
- Insert the catheter via the introducer into the target vessel and follow the tip of the catheter as it approaches the saphenous junction on ultrasound.
- Place the tip of the catheter at approximately 2.5 cm distal to the saphenous junction.
- Apply pressure over the saphenous junction cephalad to the catheter with the help of an assistant and maintain for 10 s after the first injection.
- Use continuous infusion of *n*-BCA from the 3 mL syringe with a slow steady rate of catheter withdrawal to produce a continuous column of glue. Aim for delivery of 0.06 mL/s with a pull-back rate of 2 cm/s. This equates to 0.3 mL of polymer delivered to a 10 cm length of vein.
- Maintain proximal pressure following the laser beam as the catheter is withdrawn.
- Confirm venous closure by ultrasound, remove the catheter and apply compression to the catheter entry site until haemostasis is achieved.

Technique: Percutaneous treatment of tributaries

VenaBlock™ and Veinoff™. Direct percutaneous administration can be used to treat tributary veins. Venous tributaries can be dealt with at the same time as treatment of saphenous trunks or at a later date. Only VenaBlock™ and Veinoff™ are registered by TGA for direct percutaneous injection. VenaBlock™ has been used to treat saphenous veins less than 3 mm diameter, tributaries located at least 5 mm deep to the skin, neovascularization and perforators. Similarly, Veinoff™ should only be used to treat superficial tributaries at least 5 mm deep to the skin. Care should be taken with the injection of these substances

superficially and monitoring is required to report glue extrusion as observed in gastric cases.

Veinoff™ can be mixed with 5% dextrose in a ratio of 2:1 (dextrose:Veinoff™), but the syringe needs to be shaken to ensure that the mixture is homogenous. The volume injected at each site is determined by the vein diameter. This technique has been used in other countries, and to our knowledge it has not been refined or used in Australia or New Zealand. Withdraw the adhesive into a 1 mL syringe and inject with a 22–25 gauge needle. The adhesive must be injected as expeditiously as possible to avoid hardening within the syringe.

- Inject approximately 0.1–0.2 mL of adhesive into the target vein at 2–3 cm intervals.
- Apply firm compression after each injection for 60 s to prevent palpable lumps forming in the vein.
- It is highly recommended not to draw blood back into the hub of the needle as this will result in casting of the CAC in the syringe and needle, making it virtually impossible to inject the medical adhesive
- If injection is performed close to the deep system, ideally it is advisable to deliver adhesive at least 2 cm away from the deep veins where possible.
- Confirm venous closure by ultrasound after each injection.

Venaseal™. Although designed and approved for use as a catheter-directed procedure only, clinicians have used Venaseal™ by direct percutaneous injection.⁹⁰ In view of the increased viscosity of this product compared with other glues, direct percutaneous injection of Venaseal™ is best achieved with a 22–25 gauge needle and a 1–3 mL luer lock syringe.

When used via direct percutaneous injection, small aliquots of 0.1–0.2 mL per injection site are recommended and precise dosing is facilitated via the use of a 1 mL syringe. Be wary that these aliquots may cause palpable lumps if injected in sub-dermal veins close to skin surface. It is difficult to compress the small occlusive blocks of *n*-BCA after polymerization in the target veins. One way of countering this is to inject a little harder and faster through a 21 gauge needle and compress the vein as the injection is performed.

Postoperative management

Postoperative course. The postoperative course is usually benign. Most patients experience 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. Apart from CAC-induced phlebitis and DTP, inflammation may occur in target veins close to the cutaneous surface where mast cell degranulation and the inflammatory

process may trigger a cutaneous inflammatory response. It may also be due to phlebitis in untreated tributaries communicating with the CAC treated veins. Treatment usually requires applying compression and oral NSAIDs.

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

An inflammatory reaction over the treated vein may occur comparable to that frequently seen after ETA. Many patients find comfort from support stockings for a few days after treatment. Therefore, elastic compression stockings can be worn at the patients' discretion and based on medical advice to prevent phlebitis especially when large adjoining tributaries are present. In addition, Morrison et al. recommend routine use of NSAIDs to commence a day before the procedure and continued for five days.²

Continuous air or vehicle travel of more than 5 h duration is not advised within two weeks before or after the procedure. If such travel is necessary, then consider the need for prophylactic anticoagulation to commence immediately prior to travel and continue for two days after arrival at the destination.⁹¹

Postoperative ultrasound examinations. We currently recommend that the treated legs be examined with an ultrasound scan within seven days of treatment to exclude VTE.

Early and long-term follow-up to assess ultrasonic success should be arranged at 6–12 weeks and annually afterwards. At each examination, the treated vein should be assessed for residual patency at any site, the appearance and diameter of the occluded vein, the upper level of occlusion in relation to the saphenous junction, residual varices and tributaries, and DVT or deep vein occlusion from the injected glue. Ultrasound examination should then be followed by a clinical review to assess resolution of symptoms, control of varices, any complications and patient satisfaction.

Postoperative ultrasound surveillance shows an echogenic material with a strong shadow artefact in the vein, corresponding with the injected glue with a similar appearance with serial scans going out to three years. Morrison et al.² have reported some of the treated veins to have completely disappeared after five years.

Follow-up clinical examination

- A complete medical history and physical examination should be performed.

- CEAP classification should be recorded.
- Follow-up photographs of lower limbs and other relevant photographs should be obtained.

Reporting of complications

Any complications arising from the use of all CA products should be reported to the ARTG. The registered title for these products is 'Venous Adhesive Occlusion System' and the ARTG entry number needs to be used in the search engine (Tables 3 and 4). In addition, the ACP has provided a method of reporting of the safety data following endovenous procedures and including CAC, available from its website.

Advertising and business considerations

While it may be tempting to advertise this new and seemingly attractive treatment option, be aware that Section 133 of the Australian National Law prohibits advertising that:

- is false, misleading or deceptive or is likely to be so,
- offers a gift or discount or other inducement to attract a user of the health service without stating the terms and conditions of the offer,
- provides a service without stating the terms and conditions of the offer,
- uses testimonials or purported testimonials,
- creates an unreasonable expectation of beneficial treatment and/or encourages the incrimination or unnecessary use of health services.

In New Zealand, Section 58 of the Medicines Act 1981 states that:

- advertising direct to the consumer must not mislead the public and
- practitioners must not front, speak or appear in advertisements for medical clinics.

These guidelines cover all types of advertising including social media, blogs and websites. Practitioners should adhere to the published advertising guidelines and ensure the public is not misled in believing CAC is a 'miracle' treatment with no adverse reactions.

Summary

Scientific literature dealing with CAC is sparse and only limited long-term studies on the biologic effects and the tissue response to *n*-BCA when used to occlude superficial veins is available. Current studies lack accurate description of complications and long-term data on complications is not available. Future studies need to clearly differentiate between the reported

complications of CAC and in particular should differentiate between ICD, ACD, HTP, STP and GTP.

Technically, CAC provides a simple alternative to surgical stripping and ETA of the saphenous veins. This treatment should not be offered to patients with a documented allergy to CA products, acrylates, and in particular commercial preparations of 'Super-glue', eyelash extension glues and acrylic nails. Other contraindications include concurrent acute uncontrolled inflammatory, granulomatous or autoimmune disorders. Care should be exercised in using these products in patients with a history of inflammatory granulomatous or autoimmune disorders. It is also recommended that phlebologists using *n*-BCA keep a record of adverse outcomes and communicate these regularly to colleagues until a formal reporting register is established.

It is strongly recommended that medical and allied health professionals using CA avoid direct skin contact with the product to prevent sensitization.

Finally, this is best practice advice, based on relatively sparse current information, to provide some early structure and safety for the use of this new technology. Future advice and recommendations will supersede this document when further information becomes available.

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Appendix I

1. The manufacture and approval timeline of the product around the world.
2. The official registration document summary as well for each of the approvals, e.g. the TGA/FDA/CE product summary.
3. Toxicology information on the product.
4. Information on all the studies done on the product – observational or randomized trials (human/animal/in vitro).
5. Information on the histopathology of the healing process of the injected vein. Is there a granuloma formation with a foreign body reaction? Please also provide the histology slides if available.
6. Composition, viscosity, polymerization, pliability, tensile strength and adhesion strength of the glue.
7. Biodegradability of the glue.
8. Why is the glue blue?
9. Does it use a PTFE catheter? If not, what catheter does it use?
10. Information on Dr Raabe, Saphen doctor who invented the glue.
11. Relationship between temperature and viscosity of the glue and the mechanism behind it.
12. Is there any cross-reactivity with the adhesive used in dressings?