

# Review of Non-Thermal Non-Tumescent Endovenous Ablation using Cyanoacrylate

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## Abstract

Non-thermal non-tumescent (NTNT) technique of venous ablation using cyanoacrylate is an upcoming treatment modality for refluxing varicose veins. Good anatomical success rate has been reported with this technique with significant improvements in the patient and physician measured quality of life parameters. Apart from minor complications such as phlebitis and thrombus like extension reported in initial studies no major complication such as deep vein thrombosis and pulmonary thromboembolism has been reported. Significant advantage of this technique over thermal ablation techniques is the avoidance of thermal heat (that leads to pain and paresthesia's) and need for tumescent anesthesia that prolongs the procedure. Further, as it leads to immediate occlusion of treated veins compression stockings are not required routinely.

## Keywords

Cyanoacrylate; Varicose veins; Non-thermal non-tumescent

## Introduction

Varicose vein is a common disease entity with around 23% of people in United States [1] and 27-69% of European population [2] affected by it. Treatment of varicose veins has seen revolutionary changes in the past two decades from traditional open surgery to endovenous therapies. Open ligation and stripping of varicose veins made way for Endovenous therapies including Endovenous laser ablation (EVLA) [3,4], Radiofrequency ablation (RFA) [5] and Ultrasound guided foam sclerotherapy (UGFS) [6,7] that didn't require general anesthesia and could be performed as an office procedure under local anesthesia. It caused less pain and discomfort, associated with improved quality of life with similar short and midterm results [8,9]. However, application of thermal ablation with EVLA or RFA required tumescent anesthesia which has its own complications and makes the procedure lengthy. Non thermal and non tumescent (NTNT) ablation techniques were thus introduced. ClariVein used to perform mechanochemical ablation (MOCA) of saphenous veins was the first device introduced which has shown good results in the initial studies [10,11]. Another recently introduced NTNT device is VenaSeal<sup>TM</sup> using cyanoacrylate for ablation of refluxing veins. After the initial safety studies in animal [12,13] and then further studies in man, short term follow up data regarding the efficacy, feasibility and safety of this technique is available. The aim of this article is to review the available literature on CA ablation technique as well as critically analyze the results.

## Cyanoacrylate

Cyanoacrylate (CA) is widely used for embolization of arterio-venous malformations, intra-cerebral arterial aneurysms and gastrointestinal hemorrhages [14,15]. CA has high viscosity to assure exact positioning of an appropriate dose of glue and to prevent unwanted wash-out into the deep venous system. The adhesive polymerizes rapidly after coming in contact with blood and the vein wall thus allowing procedure to be conducted swiftly. It induces an inflammatory reaction within the wall of the vein, eventually leading to long term fibrotic occlusion of the vein.

Commercially two devices are available for CA endovenous ablation i.e., VenaSeal<sup>TM</sup> (Medtronic) and VariClose<sup>TM</sup> (Biolas). Both of these devices use CA glue and have identical delivery system and mechanism of action, but differ in viscosity of CA used and method of delivery.

**VenaSeal<sup>TM</sup>:** This device was developed by Sapheon Inc (Santa Rosa, CA, USA) in 2011. It received CE mark certification in 2011 and FDA approval in 2015 for "the permanent closure of lower extremity superficial truncal veins, such as the great saphenous vein (GSV), through endovascular embolization with coaptation". Sapheon was later taken over by Covidien. Presently, manufacturing, marketing and surveillance are done by Medtronic.

The VenaSeal device consists of a pistol type dispenser handle, a 5 cc vial with the cyanoacrylate adhesive, two Luerlock syringes, dispenser tips, blunt needles for aspirating the glue, a 7F introducer/dilator sheath, 5F delivery catheter and a 180 cm J-guide wire 0.035 inches.

**VariClose<sup>TM</sup>:** Biolas manufactures the VariClose<sup>TM</sup> vein sealing system (VVSS) that consists of 4F delivery system with 6F introducer sheath and a J shaped 150 cm 0.035 inches guide wire. Technique of administration differs from that of VenaSeal<sup>TM</sup> and it also uses low viscosity CA glue with purported advantages of faster polymerization and sealing of the veins thus culminating into shorter duration of the procedure. Presently, only a handful number of studies have evaluated this device but results from the available studies appear to be promising [16-18].

## Indications

Venous embolization using CA is indicated in patients with primary symptomatic (C<sub>2s</sub>-C<sub>4</sub>) varicose veins diagnosed clinically or by Duplex USG suggestive of incompetent GSV. It may also be indicated in patients with asymptomatic varicosities for cosmetic improvement. Reported studies have been conducted in GSV up to maximum diameter of 12 mm and vein diameter might influence the outcome [19,20].

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## Contraindications

Reported series have included wide range of exclusion criteria [12,21-23]. Absolute contraindications include hypersensitivity to CA, previous history of deep vein thrombosis and superficial thrombophlebitis of GSV. Pregnancy, patients with hypercoagulable disorders, patients on anticoagulants and recurrent varicose veins have been excluded from most of the studies. Lane et al. [20] reported early technical success and symptom resolution in a patient on anticoagulant therapy, but 6 month follow up showed failure of treatment. Tortuous GSV that can limit catheter placement or require more than one primary access site is considered relative contraindication.

## Mechanism of Action

Three phases of polymerisation of CA have been described in a previous study in swine model [24].

- (1) First phase that lasts for around 10 seconds consists of initial rapid polymerization with increasing tensile forces.
- (2) Second phase which displayed a constant tensile force (lasting up to 1 minute).
- (3) Final phase characterized by a rapid, exponential rise of tensile strength.

## Preoperative Preparation

Standard preoperative measures are taken as described before any endovenous ablation therapy. Patient's history to previous exposure to CA should be pursued to determine history of sensitivity to CA. Sensitization to CA glue after dermal wound repair, after occupational contact have been previously reported in the literature [25]. However, role of preoperative testing without history of CA intolerance is ill-defined. Patient's targeted vein is carefully assessed using USG, for areas of extensive tortuosity. Tumescence anesthesia used regularly in the endovenous thermal ablation is not required.

## Technique

Almeida et al. [12] described the technique in the earliest human study of CA since then further refinements have been made.

### Priming of delivery catheter

Syringes are first loaded with CA and then attached to the delivery catheter. The delivery catheter is primed with CA up to a mark 3 cm from the last; this avoids premature contact of CA with blood.

Under ultrasound guidance 5F/7F introducer sheath/dilator is inserted and positioned 2 cm distal to the SPJ or SFJ. The primed catheter is introduced in to the introducer and under USG guidance catheter tip is placed 5 cm distal to the SFJ/SPJ to avoid thrombus extension into the deep venous system. After this first dose of CA is dispersed into the vein by pressing and holding the dispenser gun trigger for 3 seconds. Then the device is pulled out for 3 cm. and vein walls are compressed manually for 3 minutes. Following this, a dose of CA is administered every 3 cm followed by 30 seconds of manual compression till the entire length of the vein segment is treated.

Technique of administration using VariClose™ differs from VenaSeal™. In VariClose™, delivery catheter is kept about 3 cm distal to SFJ and continuous pull back technique is used in which catheter is pulled back continuously at the rate of 2cm/second delivering 0.03ml of CA at each cm of vein.

Finally, the device is quickly removed, thereby avoiding spillage of CA into the subcutaneous tract. Post procedure, stockings or compression bandages are not applied. Postoperatively, patients are discharged same day and can resume routine activities.

## Animal studies

Two studies in swine model have been published by the Almeida et al. [13,26], in these studies CA was injected into the bilateral superficial epigastric veins. At 30 and 60 days post treatment, the treated veins remain occluded. Histological findings at 30 days revealed that the vein lumen was enlarged and filled with coalescing, arborizing clear spaces with entrapped lytic erythrocytes, demarcated by a narrow band of eosinophilic granular material. At 60 days post treatment, venous occlusion with segmental wall thickening and fibrosis were observed suggestive of foreign body type chronic inflammation.

## Safety studies

Almeida et al. [12,21] conducted the first study in men with the objective to evaluate the feasibility of endovenous CA for the treatment of incompetent GSV. In this study 38 men with incompetent GSV were treated with CA and were followed by serial DUS at 48 hours, for 1 month, 3 months, 6 months, 1 year and 2 years by the same investigator. They reported their results in two articles in which all 38 patients were available for follow-up at 48, 1 and 3 months. 2 patients were lost to follow up at 6 and 12 months, and 24 patients were seen at 24 months.

Of the 38 patients treated, only 3 patients had recanalization at follow up to 24 months and all the veins were occluded at 48 hours. Significant improvement in Venous Clinical Severity Score (VCSS) was seen in all patients from a mean of 6.1 at baseline to 1.3, 1.5 and 2.7 at 6, 12 and 24 months, respectively. Minor Side effects such as phlebitis in six patients (15.8%) and thread-like thrombus extensions into the common femoral vein (CFV) was seen in eight patients (21.1%).

## Clinical studies

Since the initial safety study in men, multiple studies have been reported in the literature documenting safety and efficacy of CA as a treatment modality. In the only Randomized control trial (RCT) conducted by Morrison et al. [23,27] in the United States, enrolled 222 subjects with symptomatic incompetent GSV, and of these 108 were randomly assigned to receive CA whereas rest 114 received Radio frequency ablation (RFA). Study subjects were assessed at day 3 and months 1, 3, 6, and 12 using DUS for vein closure. At 1 and 12 month follow up 100% and 97.2% of CA patients demonstrated complete occlusion which was comparable to the results of RFA 87% and 97% at 1 month and 12 month follow up respectively. Recanalization rate was similar in both the groups. This study led authors to conclude that CA had faster time to complete occlusion and lower vein recanalization rates after CAC. Quality of life scores improved equally with both therapies.

Proebstle et al. [28,29] reported on a prospective multicenter study, conducted at specialized vein clinics in 4 European countries: Netherlands, Denmark, Germany and the United Kingdom from December 2011 to July 2012. Study enrolled 70 patients with incompetent GSV, of whom 68 (97.1%) were available for 12-month follow-up two patients showed recanalization at 48 hours. Three additional recanalization's were seen at 3-month (n=2) and 6-month (n=1) follow-up leading to an anatomical success rate of 93% at 1 year.

WAVES study [30] in a prospective manner, evaluated CA therapy in a cohort of patients with symptomatic venous reflux disease in short saphenous veins (SSV), accessory saphenous veins (ASV) in addition to GSV up to a vein diameter of 20 mm. This study had brief follow up of 1 week and 1 month during which vein occlusion was achieved in all the patients.

Toonder et al. [31] reported on the feasibility of CA ablation in incompetent perforator veins (IPV) in the CAPE study. In this study, 33 IPV 27 legs of 23 patients were treated with CA. On the follow-up DUS, vein closure was achieved in 25 (76%) whereas 8 (24%) of the

treated IPV had persistent reflux at 3 months. Minor complications were experienced during the study like wound infections at the access point and thrombophlebitis in one patient.

### Clinical Studies Using VariClose™

Bozkurt et al. [16] conducted a prospective comparison of CA with Endovenous laser ablation (EVLA). In this study, 310 patients were treated with either CA ablation or EVLA. At One, three, and 12 months closure rates were 96.7, 96.6, and 95.8% for CA ablation groups which was significantly better than EVLA at first month ( 96.7% vs. 87.1%, p<0.001). Results were comparable between two groups at 6 and 12 months of follow up. Both groups had significant improvement in VCSS and Aberdeen Varicose Vein Questionnaire (AVVQ) postoperatively but there was no significant difference in between the two groups in VCCS and AVVQ scores between the groups at first, sixth, and 12 months follow up.

In a prospective study by Yasim et al. [18], 180 patients with incompetent GSV were treated with CA. In the initial reported study at a mean follow up of 5.5 months no recanalization was noted. In the subsequent report by the same group on long term data available in 168 patients' occlusion rates of 100%, 98%, 96.6% and 94% were observed at the months 3, 6, 12 and 30. Significant improvement in VCSS was also observed at follow up [32].

Turkish investigators [33] in a single centre prospective observational study in 62 patients with incompetent GSV reproduced similar results. In this study, at one week and months 1, 3 and 6 follow up DUS showed vein closure in 100%, 93.5% and 90.3% of the patients.

Koramaz et al. [17] in their retrospective study using this device achieved a total occlusion rate of 98.6% at 12 months which was comparable to EVLA. Similarly significant improvement was seen in both the groups i.e. CA ablation and EVLA with fewer adverse events in the CA ablation group.

### Discussion

The Intention behind introduction of NTNT mode of therapy was not only to achieve good anatomical success rates but also to reduce pain associated with the procedure, improving quality of life and reducing the risk of complications. With NTNT thermal energy is avoided which eschews associated common complications such as pain and parasthesias due to nerve injuries. UGFS was the initial NTNT ablation technique introduced but has fallen out of favor after multiple

meta-analysis found it to be inferior to surgery for varicose veins [6,7]. Studies reported thus far have multiple limitations. Most of the studies have reported on short term follow up data and more over high dropout rates raises the concern of selection bias. Chan et al. study reported 60% drop out rate thus jeopardizing the whole study. Concerns have also been raised regarding the potential conflict of interests of the first authors in the initial reported studies using Vena Seal device. Also all the studies reported on VariClose device have been conducted in the Turkey where the treatment is reimbursed by government.

### Anatomical success rate

The anatomical success rate of CA therapy is 97 to 100% at 1 month and between 92 to 100% at 1 year. In the study but Chan et al. in whom 60% of patients were lost to follow up at one year observed the lowest success rate at 1 year of 75% (Table I). Significant improvements in VCSS and ABVQ scores have been reported in the studies. The improvement in clinical symptom scores have been comparable to improvement seen with RFA [23,27] or EVLA [16,17]. Anatomical success rate might be influenced the diameter of the treated vein and most of the studies have been reported on veins with diameter between 3-12 mm. Chan et al. observed poor success rates with an arbitrary GSV diameter greater than 6.6 cm. Although the effect of CA ablation on large diameter veins has been explored by the WAVES study but this study had limited follow up of 1 month. Thus, further studies including large vein diameters and long term follow up is required (Table II).

### Duration of the procedure

In the VeClose study [23], mean produre duration was longer for CA ablation as compared to RFA (24 min vs. 19 min, p<0.01). This difference has been attributed to the learning curve associated with the new procedure and the fact that surgeons were well versed with RFA.

In the two non-randomized studies using VariClose device procedure duration using this device was significantly shorter (mean 7-15 min) as compared to EVLA [16,17]. Low density CA and continuous pull back technique used for the procedure has been accounted for same (Table III).

### Complications

Major complications such as deep vein thrombosis (DVT) and Pulmonary thromboembolism (PTE) have not yet seen with CA ablation technique except for a study by Kolluri et al. [34] that reported serious adverse events but did not specify it further. Minor complications,

Table I: Anatomical success rates in reported studies.

Parameter	Almeida [12,21]	Morrison [23,27]	Proebstle [28,29]	Gibson [30]	Yasim [18,32]	Bozkurt [16]	Chan [19]
Year of Publication	2013/2015	2015/2017	2015	2016	2016/2017	2016	2017
Study design	P	RCT	P	P	P	P	P
Anatomical success							
<1 month	97% (38)	100% (105)	97% (NA)	100% (70)	100% (180)	96.7 (153)	92% (102)
3 months	95% (38)	97% (104)	94% (NA)	NA	100% (180)	96.6 (145)	NA
6 months	92% (36)	NA	93% (NA)	NA	98% (159)	NA	89% (63)
12 months	92% (36)	97% (95)	93% (68)	NA	96.6% (159)	95.8 (142)	75% (37)
24 months	92% (24)	NA	NA	NA	NA	NA	NA
30 months	NA	NA	NA	NA	94% (159)	NA	NA

Table II: Type of veins and duration of procedure.

Type of vein	Almeida [12,21]	Morrison [23,27]	Proebstle [28,29]	Gibson [30]	Yasim [18,32]	Bozkurt [16]	Chan [19]
GSV	38	108	70	48	169	154	108
SSV	0	0	0	8	11	0	0
ASV	0	0	0	14	0	0	0
Total	38	108	70	70	180	154	108
Duration of the procedure (min)	21 (14-32)	24 (11-44)	18.6 (8-74)	23 (11-43)	15.2 (10-25)	15 ± 2.5	64 (28-116)

Table III: Complications.

Complication	Almeida [12,21]	Morrison [23,27]	Proebstle [28,29]	Gibson [30]	Yasim [18,32]	Tekin [33]	Bozkurt [16]	Chan [19]
Phlebitis	16%	20%	11%	20%	0	3.2%	7%	4%
SVT	3%	4%	NR	NR	NR	NR	NR	4%
SSI	3%	1%	1%	2%	NR	NR	NR	1%
DVT/PE	NR	0/0	0/NR	0/0	0/0	0/0	NR	0/NR
Allergic reaction	NR	NR	NR	2%	NR	NR	NR	NR

such as phlebitic reactions have been reported frequently in 3-20% of cases. Majority of phlebitis reported have been mild and successfully managed with nonsteroidal anti-inflammatory medication (NSAIDS). Continuous delivery method may be associated with reduced rates of thrombophlebitis, due to absence of empty veins (not filled with glue) and lack of residual blood inside the vein [16]. Type I hypersensitivity reaction following CA ablation has also been reported that responded to antihistaminics and steroids. Whether, these reactions are caused by CA or by some other unknown substance such as preservatives remains largely unknown. Full blown anaphylactic shock has not been reported with CA use in venous ablation. As stated earlier routine use of sensitivity testing is not well defined but certainly in a patient with of previous history of reaction to CA Dermatology consultation and patch test is advisable. CA extension into the deep venous system has been reported which was managed with anticoagulant therapy [12,19,30]. In the initial study by Almeida et al. described the safe distance to be about 4 cm distal to SFJ but further studies extended limit to 5 cm in order to avoid this complication. Yet this complication was observed in these studies. In the studies using VariClose CA ablation technique, delivery catheter was placed 3 cm distal to SFJ and despite using watery consistency (low viscosity) CA no cases of CA extension into the deep system have been reported. Thus further research into this matter is required to determine safe distance from SFJ to further limit these complications without compromising the efficacy. Surgical site infection is uncommon (<5%).

### Advantages

Endovenous ablation by avoiding the use of tumescent anesthesia avoids associated complications such as accidental venous puncture by anesthetic needle that could result in ecchymosis [12]. TA has been the most time consuming part of thermal ablation techniques thus accounting for shorter duration of procedures [16]. Secondly, by avoiding the use of thermal energy risk of injury to surrounding structures such as nerves is reduced. Thus, accounting for the reduced rates of post-procedural pain and paresthesias. Lastly, CA ablation results in immediate occlusion of treated veins thus avoiding the need for compression stockings after the procedure that can be uncomfortable in hot and humid conditions.

### Future prospects

NTNT endovenous ablation using CA appear to be safe and effective form of therapy yet long term data regarding the safety and efficacy of the CA as endovenous ablation technique are yet to come up. Further randomized studies comparing CA ablation with thermal ablation techniques are needed. Also, direct comparison between the two available CA endovenous devices i.e. Variclose and VenaSeal need to come up before recommending one over another.

### Conclusion

NTNT endovenous ablation using CA appears to be propitious with initial studies reporting high anatomical success rates and good improvements in clinical venous symptom scores. Initial studies have also reported similar lower pain rates as compared to thermal ablation techniques without using TA and yet avoiding associated complications of the thermal energy.

### Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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