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General Review

Cyanoacrylate Embolization: A Novelty in the Field of Varicose Veins Surgery

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In the past 2 decades, varicose veins surgery went through a great turbulence and various innovations. A number of new techniques have been introduced with a goal to increase the success rate, reduce the periprocedural complications and, overall, to improve patients' quality of life. The latest of them, named cyanoacrylate embolization (CAE) technique, threatens to shake the glory of the currently well-established endovenous methods. We have analyzed all previous studies by searching MEDLINE base using PubMed. Although the idea of using n-butyl cyanoacrylate (NBCA) glue in medical purposes was not new, the very first in vivo and animal experiments using NBCA for vein closure were conducted just at the beginning of this millennium. The results of these studies gave warranty to begin with the first interventions in humans. Early studies reported very high success rates of more than 90%, with the longest follow-up period of 36 months. There were no major adverse events reported, while the minor ones—mostly phlebotic reactions—were defined as mild to moderate. The newest head-to-head studies showed that CAE is a noninferior technique to other endovenous methods, with higher occlusion rates and fewer adverse events. Short procedure time and no need for tumescent anesthesia or compressive stockings reduce patients' discomfort to the minimum and definitely seem to be a step forward answering the modern “walk in—walk out surgery” demands. As an easily handling technique, CAE undoubtedly pierces its path to the top of varicose veins surgery but more head-to-head clinical trials with longer follow-up periods are necessary to obtain a plain picture.

INTRODUCTION

Varicose syndrome generates great health, social, and economic concern.¹ Classic surgical methods, such as vein stripping or ligations, were considered to be the most effective for a long time and, as such, they have been practiced for almost a century until nowadays.^{1,2} About 2 decades ago, introduction of endovascular vein surgery has revolutionized varicose vein surgery by minimizing the need for aggressive surgical treatment and by providing excellent results.³

The latest development in this field—cyanoacrylate embolization (CAE)—seems to have potential to increase the success rate, reduce the periprocedural complications and, overall, to improve patient's quality of life.⁴ Inspired by early results of this method, this novel and promising technique will be described in detail here.

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BACKGROUND

n-Butyl cyanoacrylate (NBCA) is a butyl ester of 2-cyano-2-propenoic acid. It is a hydrophobic, clear, colorless liquid with a sharp, irritating odor. In a monomer form, it polymerizes rapidly in the presence of ionic substances, such as blood or tissue fluids. The polymerized form has excellent tensile strength and is very effective in closing surrounding tissue. Therefore, it is the main component of medical glues.⁵

At the beginning of this millennium, Kailasnath et al. have developed a benchtop testing apparatus to quantitatively assess the polymerization-binding behavior of cyanoacrylates (CA).⁶ They had theorized that the negatively charged endothelial lining could be a significant anionic substrate for initiating and sustaining polymerization. However, in most cases, the intravascular medium (i.e. blood serum) was the one that provided most of the source of reactive anionic species. They also observed a multiphasic pattern of binding forces, consisting of three distinct phases. Furthermore, the rates of polymerization were significantly influenced by a variety of parameters, including the type of fluid within the model vessel, geometry of the model vessel, and rate of injection of acrylic into the well.⁶

A decade later, first in vivo experiment on animal model by Almeida et al. gave promising results.⁷ Superficial epigastric veins from 2 swine were used due to the vein's similarities with the human great saphenous vein (GSV).⁸ A sheath was positioned 2.0 cm caudal to the junction of the superficial epigastric and abdominal rectus veins in 2 swine, followed by ultrasound-guided injection of 0.16 mL of CA glue. After glue delivery, the catheter was pulled back 3 cm, compression was applied to the treatment site, and the process was repeated for the entire length. At 60th postprocedural day, the veins were harvested surgically and examined histologically. The findings implied to a chronic foreign body-type inflammatory response. Venous closure, segmental wall thickening, and fibrosis were observed.⁷

In the subsequent year, practically the same authors have confirmed their previous findings in a new animal model, but with 30-day follow-up.⁸ Results of this study demonstrated that intravascular injection of CA is feasible for closure of superficial veins in animal models. Such results gave warranty to begin with first interventions in humans and the very first results were published by the same group in 2012.⁹

HANDLING THE TECHNIQUE

The endovenous application of NBCA is the only nontumescent, nonthermal, nonsclerosant procedure that uses a proprietary medical adhesive delivered endovenously to close the vein. This unique approach eliminates the risk of thermal nerve injury when treating the small saphenous vein (SSV) that is sometimes associated with certain thermal-based procedures.^{10,11} The procedure is administered without the use of tumescent anesthesia, avoiding patient discomfort associated with multiple needle sticks.^{4,12}

The disposable system (VariClose[®] Vein Sealing System [VVSS]; Biolas, Ankara, Turkey) includes NBCA glue and the delivery system.⁴ At the very beginning of the procedure, a small amount of local anesthetic is to be injected below the knee in the projection of GSV and sheath introduction spot. The GSV is to be accessed with the introducer set with the assistance of color-doppler ultrasonography (CDUS). A guidewire is passed through the introducer sheath to the sapheno-femoral junction (SFJ). Once the guidewire was confirmed to be in the SFJ by CDUS, a new, long introducer sheath is to be advanced to the SFJ over the guidewire. After confirmation of the position of the long introducer sheath at the beginning of the SFJ, the long introducer sheath has to be pulled back from the SFJ by 5–6 cm. Thus, the delivery catheter remains positioned at 5 cm distal to the SFJ. Once the position of the delivery catheter is confirmed, the NBCA injection setup is completed.⁴

A delivery system gun and syringe have to be connected to each other and the NBCA aspirated into the syringe. The syringe has to be connected to the gun adaptor and the end of the delivery catheter by a spin lock mechanism. After completing the setup and positioning of the delivery system, the procedure can begin. First, pressure over the SFJ has to be applied with CDUS, with a confirmation of SFJ closure. Before injecting the NBCA inside the vein lumen, the delivery catheter is to be primed with a single 1-sec trigger push. After priming, the glue is injected into the vein with continuous pressure applied over the treated vein segment simultaneously with the pulling back of the delivery catheter. Every 5 seconds or 10 cm, the trigger had to be pressed, until the target vein segment was fully sealed. The CDUS probe is mandatory during the whole procedure. Once the entire vein segment was injected with NBCA with the continued application of pressure during the procedure, a final pressure was applied for 30 sec over the entire target

vein segment.⁴ Although the procedure course is well determined, different manufacturers suggest slight differences in some of the steps. Therefore, we recommend user's instructions to be followed, regarding the using kit.⁴ (Table I)

Right after the treatment, the patients are mobilized without any prescription of compression stockings. Avoiding the multiple needle sticks, with minimal or no bruising after the procedure, the patients' discomfort is reduced to the minimum. Facilitating the rapid return to normal daily activities, the glue treatment definitely answers the modern "walk in—walk out surgery" demands.^{3,4,12}

FROM EVIDENCE TO RECOMMENDATIONS—THE PROMISING ONE

Results of the first human use of CA glue for treatment of GSV incompetence have been published by Almeida et al. (using VenaSeal™ closure system, Medtronic, Minneapolis, USA) in 2012.⁹ The primary efficacy endpoint of the study was vein occlusion during follow-up, while the primary safety endpoint was the rate of serious procedure-related adverse events.

In 38 symptomatic patients, 38 incompetent GSVs were treated with CA glue and were evaluated by CDUS immediately after the procedure, at 48 hours, and 1, 3, 6, and 12 months. At the 48-hour follow-up, GSV occlusion was observed in all patients. During the follow-up at 1, 3, and 6 months, one complete and two partial recanalizations were observed respectively. A year after the procedure, an occlusion rate of 92% percent was noted.⁹

Side effects were described as generally mild and self-limited. Eight patients (21.1%) showed thread-like thrombus reaching into the common femoral vein, which resolved spontaneously without anticoagulation. Phlebitis occurred in 6 patients (15.8%). Edema improved in 89% of patients, just 2 days after the procedure. At the 12-month follow-up, 50% of the patients had no visible varicosities, while an additional 8 patients (25%) showed mild varicosities.⁹

At 2-year follow-up, 24 patients were available for examination, maintaining the very high occlusion rate of 92%. A 64% of the patients were free from leg pain compared with only 13% at the baseline.¹³

The results of 36-month follow-up have been published just recently, reporting the 94.7% occlusion rate in 29 available subjects for CDUS examination. Pain, edema, and varicosities improved in 75.9%, 62.1%, and 41.4% of patients, respectively.

Table I. Handling the technique step by step

- Introduction of a small amount of local anesthetic in the projection of sheath introduction spot	277
- Placing the introducer sheath 6 cm to SFJ (confirmed by CDUS)	278
- Placing the delivery catheter 5 cm to SFJ (confirmed by CDUS)	279
- Loading delivery gun with NBCA glue	280
- Priming the delivery catheter	281
- Applying the glue into the vein, with pulling back the delivery catheter and applying constant pressure on the sealing segment (confirmed by CDUS)	282
- Removing the sheaths	283

^aVariClose Vein Sealing System [VVSS]; Biolas, Ankara, Turkey. Q5

The overall adverse events were reported as mild to moderate and self-limited.¹⁴ (Table II)

Subsequent studies with greater number of enrolled subjects showed similar results. In 70 patients, of whom 68 (97.1%) were available for 12-month follow-up, Proebstle et al. have treated 70 GSVs (using VenaSeal closure system, Medtronic, Minneapolis, USA).¹⁵ Two-day follow-up showed one proximal and one distal partial recanalization. Three additional proximal recanalizations were observed at 3-month ($n = 2$) and 6-month ($n = 1$) follow-ups. At 1 year, the success rate was 92.9%. Side effects were generally mild; a phlebitic reaction occurred in 8 cases (11.4%) with a median duration of 6.5 days (range, 2–12 days). Pain without a phlebitic reaction was observed in 5 patients (8.6%) for a median duration of 1 day (range, 0–12 days). No serious adverse event occurred. Moreover, paresthesia was not observed.

Tekin et al. have treated GSV insufficiency in 62 patients (using VVSS; Biolas, Ankara, Turkey).¹⁶ The difference between their and previous studies was that they have advised patients to wear elastic bandages for 1 day. At 1 week and 1-month control, CDUS showed total occlusion for 100% and 93.5%, respectively, while subtotal occlusion was seen in 4 patients (6.5%) at third month. At the end of 6 months, total occlusion in 90.3% and subtotal occlusion in 3.2% of patients were observed. For 4 (6.5%) patients, no occlusion was observed, and the vein diameter was >11 mm. Although they had slightly lower GSV occlusion rate compared with previous studies, the phlebitis rate was not as high as reported. The authors emphasized that it may be caused due to shorter time of follow-up in the hospital.

In the largest retrospective study, enrolling 180 patients (86 males, 94 females), Yasim et al. (using VVSS; Biolas, Ankara, Turkey) have treated 169

Table II. Noncomparative studies' characteristics and findings

Authors	Year	N	Follow-up	Closure rate	Adverse events
Almeida et al. ^{9,a}	2012	38	1 year	92%	Thread-like thrombus reaching in femoral vein in 21.1% of patients Phlebitic reaction in 15.8%
Almeida et al. ^{13,a}	2015	24	2 year	92%	Mild to moderate
Proebstle et al. ^{15,a}	2015	68	1 year	92.9%	Mild phlebitic reaction in 11.4% Pain in 8.6% of patients
Tekin et al. ^{16,b}	2016	62	6 months	90.3%	Few phlebitic reactions
Yasim et al. ^{17,b}	2016	180	5.5 months	100%	No complications observed
Almeida et al. ^{14,a}	2017	29	3 year	94.7%	Mild to moderate
Eroglu et al. ^{18,b}	2017	180	30 months	94.1%	No complications observed
WAVES study ^{19,a}	2017	50	1 month	100%	Phlebitic reaction in 20% of cases
WAVES study ^{20,a}	2017	50	1 year	100%	The data are not yet published

^aVenaSeal closure system, Medtronic, Minneapolis, USA.

^bVariClose Vein Sealing System [VVSS]; Biolas, Ankara, Turkey.

GSVs and 11 SSVs.¹⁷ CDUS examination immediately after the procedure and at 5.5-month follow-up showed closure of the treated vein in 100% of cases, with no complications observed. The midterm results, published earlier this year, showed ablation rates of 98.3% at the sixth month, 96.6% at 1 year, and 94.1% at 30 months. The authors have emphasized the need of long-term results.¹⁸ (Table II)

It should be pointed out that all abovementioned studies have been limited to moderate-sized GSVs and some have mandated postoperative compression bandage.^{9,13–18} In addition, all of them had retrospective design. In contrary, a prospective WAVES study (using VenaSeal closure system, Medtronic, Minneapolis, USA) has been designed to investigate the quality-of-life, safety and effectiveness outcome for treatment of GSV, SSV, and/or accessory saphenous veins up to 20 mm in diameter.¹⁹

Fifty subjects were treated because of symptomatic vein incompetence. Postprocedure evaluations were performed at week 1 and again at 1 month. Procedural pain was described as mild. All treated veins (48 GSV, 14 accessory saphenous veins, and 8 SSVs) had complete closure by CDUS at 7 days and 1 month. Mean time to return to work was 0.2 ± 1.1 days, while return to normal life and exercise activities was obtained at 2.4 ± 4.1 postprocedural day. Once again, phlebitis was the most common adverse event, reported in 20% of subjects. Regarding the patient attitude to the very procedure, interestingly 98% of subjects were “completely” or “somewhat” satisfied, and 2% “unsatisfied” with the procedure at 1 month, despite the protocol disallowance of concomitant side branch treatment.¹⁹ In addition, although not

yet published, the preliminary data of 1-year follow-up imply to the closure rate of 100%.²⁰ (Table II)

Toonder et al. (using VenaSeal closure system, Medtronic, Minneapolis, USA) have addressed the question of cyanoacrylate adhesive perforator embolization of incompetent perforating veins of the leg.²¹ The results showed a 76% occlusion rate of incompetent perforating veins without serious complications leading to the conclusion that further investigation in a larger patient population is warranted.

Simultaneously with the benefits of the novel technique, several authors have reported relatively high percentages of phlebitic reactions as the most common adverse event.^{9,15,16,19} As Proebstle et al. reported, 11.4% of patients had a postprocedure phlebitic reaction along the treated vein or its tributaries, defined as reddening of the overlying skin and pain on palpation. The median onset of symptoms was observed on the sixth postprocedural day, while the median duration was 6.5 days. Only 2 patients received nonsteroidal antiinflammatory drugs.¹⁵ In addition, the authors of WAVES trial reported phlebitis occurrence in the treatment area or side branches in 20% of subjects. In all but one patient (2%), the symptoms completely resolved within 1 month.¹⁹

The reason of high phlebitis rates remains unknown. It may be hypothesized that it could be device-related or that the very mechanism of action of the adhesive might induce the inflammatory response.¹¹ Another fact that should be concerned is the difference in glue viscosity between 2 manufacturers.

The VenaSeal closure system uses a rapidly polymerizing, high viscosity CA glue, aiming to prevent

potential embolization into the deep venous system.²² On the other hand, VVSS uses CA glue with limited modifications to the chemical structure, resulting in lower viscosity and a faster polymerization time, compared to VenaSeal glue.²² This could lead to easier embolization of the less viscous adhesive in a deep vein and the sticking of the catheter inside the vein, due to faster polymerization. Although manufacturer claims that this will improve the adhesive effects of the very glue, such a statement should be taken with precaution; however, no comparative studies between the 2 types of CA have been published so far.²²

Q4

FROM EVIDENCE TO RECOMMENDATIONS—A STEP FURTHER

In the newest head-to-head clinical trials, the still young CA embolization technique was confronted with 2 “giants” of vein surgery, namely endovascular laser ablation (EVLA) and radiofrequency ablation (RFA) (Table III).

VeClose (using VenaSeal closure system, Medtronic, Minneapolis, USA) was designed as a randomized trial, aiming to compare results of GSV incompetence treatment with CAE and RFA.¹¹ The study’s primary endpoint was closure of the target vein at month 3 as assessed by CDUS, while the secondary endpoints included patient-reported pain during vein treatment and extent of ecchymosis at day 3. Two hundred twenty-two subjects with symptomatic GSV incompetence were randomly assigned to receive either CAE ($n = 108$) or RFA ($n = 114$). Maximum diameter of treated GSV was 5.9 mm in CEA group and 6.2 mm in RFA group.

At the 3-month follow-up, closure rates were 99% for CAE and 96% for RFA. Primary endpoint analyses showed that CAE is a noninferior technique, compared with RFA. In addition, some analyses supported the trend toward superiority. Pain experienced during the procedure was mild and similar between treatment groups (2.2 and 2.4 for CAE and RFA, respectively, on a 10-point scale), while the less ecchymosis in the treated region was seen in CAE group, compared with RFA group. Phlebitis occurred in 20% of patients in CAE and 14% of patients in RFA group, and it was mostly located in the treated zone. Other adverse events, such as access site infection or paresthesia in treatment zone, occurred at a similar rate between groups and were generally mild and well tolerated.¹¹

At the 1-year follow-up, the complete occlusion rate was almost identical in both groups (97.2% in

CAE, 97% in RFA). Symptoms and quality of life improved in both groups equally. Most of the reported adverse events were mild and not procedure related.²³ At the 2-year follow-up, the closure rate was 95.3% and 94.0% for CAE and RFA, respectively. No serious adverse events were reported.²⁴

In a recent prospective comparison of CAE (using VVSS; Biolas, Ankara, Turkey) and EVLA, a total of 310 adult subjects were treated.²⁵ The primary endpoint was complete occlusion of the GSV. Secondary endpoints were procedure time, procedural pain, ecchymosis at day 3, adverse events, changes from baseline in Venous Clinical Severity Score (VCSS), and Aberdeen Varicose Vein Questionnaire (AVVQ).

Procedure time was shorter (15 ± 2.5 min vs. 33.2 ± 5.7 min), and periprocedural pain was less (3.1 ± 1.6 vs. 6.5 ± 2.3) in CAE group compared with the EVLA group. Ecchymosis at the third day was also significantly less in CAE group. Paresthesia developed in 7 patients in EVLA group and none in CAE group ($P = 0.015$). One-, 3-, and 12-month closure rates were 96.7, 96.6, and 95.8% for CEA and 87.1, 91.7, and 92.2% for EVLA groups. Although there is a trend of better closure rates in CAE patients, this difference did not reach to the statistical difference at sixth and 12th month. Both groups had significant improvement in VCSS and AVVQ postoperatively, but there was no significant difference in VCSS and AVVQ scores between the groups at first, sixth, and 12th months. Only a slightly better well-being trend was noted in cyanoacrylate ablation group in terms of AVVQ scores.²⁵

In the latest study, conducted by Koramaz et al. (using VVSS; Biolas, Ankara, Turkey), the data of 339 patients treated with either NBCA embolization or EVLA were retrospectively collected.⁴ The average preprocedural GSV diameters were 6.88 mm (range, 5.5–15 mm) in the CAE group and 7.15 mm (range, 5.5–14 mm) in the EVLA group. All patients were symptomatic. The average procedure times were 7 minutes (range, 4–11 minutes) in the CAE group and 18 minutes (range, 14–25 minutes) in the EVLA group.

At the 12-months follow-up, total occlusion rates were 98.6% and 97.3% in the CAE and EVLA groups, respectively. Pigmentation and phlebitis were less frequent after CAE treatment compared with EVLA treatment. The most important adverse events were pain and phlebitis in the CAE group, which occurred at rates of 4.67% and 2%, respectively. In EVLA group, deep vein thrombosis (DVT) occurred in 1.59% of the patients and was treated with low molecular weight heparin. The authors hypothesized that minimal procedural time

Table III. The results of comparative studies

Authors	Morrison et al. ^{11,22,23,a}	Bozkurt et al. ^{24,b}	Koramaz et al. ^{4,b}
Year	2015	2016	2017
Study design	Prospective, randomized controlled	Prospective, comparative	Retrospective, comparative
N	222	310	339
Follow-up	2 years	1 year	1 year
Closure rate	CAE 95.3%	RFA 94%	CAE 98.6%
		EVLA 92.2%	EVLA 97.3%
Adverse events	Phlebitis	Few mild events	Pain Phlebitis DVT

^aVenaSeal closure system, Medtronic, Minneapolis, USA.

^bVariClose[®] Vein Sealing System [VVSS]; Biolas, Ankara, Turkey.

Table IV. Advantages and disadvantages of cyanoacrylate embolization technique**Advantages**

- Easy handling, minimally invasive technique
- No need for anesthesia and multiple needle sticks
- No paresthesia and thermal injury, with minimal or no bruising
- No need for elastic stockings
- Short procedure time
- Rapid return to daily activities
- High success rates
- Very few mild-to-moderate adverse events

Disadvantages

- High postprocedural phlebitis rates
- Lack of long-term studies with great number of patients
- Lack of experience in treatment of perforating or tributary varicose veins
- Equipment costs

and rapid closure of GSV play a pivotal role in preventing DVT and pulmonary embolism.⁴

Although there are not many, the so far published studies and head-to-head trials gave us insight into some of the characteristics of NBCA embolization treatment, warming up the professional community for further investigation.^{3–25} (Table IV)

CONCLUSIONS AND PERSPECTIVES

The NBCA endovenous ablation is a novel and promising technique for treatment of varicose syndrome. The results of present studies imply that CA ablation treatment is feasible, with high GSV occlusion rates and very few mild-to-moderate adverse events. Short procedure time and no need for tumescent anesthesia or compressive stockings reduce patients' discomfort, and the CAE technique

definitely seems to be a step forward in venous surgery.

Studies with greater number of patients and with longer follow-up are necessary to obtain a plain picture.

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