Original Article

Vascular

Vascular
0(0) 1–7

DOI: 10.1177/1708538118823838
journals.sagepub.com/home/vas
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Two-year follow-up of a n-butyl-2-cyanoacrylate glue ablation for the treatment of saphenous vein insufficiency with a novel application catheter with guiding light

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Abstract

Objectives: This study aims to present the early results of a prospective study of the use of novel n-butyl-2 cyanoacrylate (VenaBlock)-based nontumescent endovenous ablation with a guiding light for the treatment of patients with varicose veins.

Methods: Five hundred and seventy-three patients with lower-limb venous insufficiency were treated within in the previous four years. The study enrolled adults aged 21–70 years with symptomatic moderate to severe varicosities (C2–C6 patients clinical, etiological, anatomical, and pathophysiological classification) and great saphenous vein reflux lasting longer than 0.5 s with great saphenous vein diameter $\geq$ 5.5 mm assessed in the standing position. Duplex ultrasound imaging and clinical follow-up were performed on the third day, first month, and sixth month. Clinical, etiological, anatomical, pathophysiological classification; venous clinical severity score; and completed Aberdeen varicose vein questionnaire were recorded.

Results: Five hundred and seventy-three patients aged 21–70 years with lower-extremity venous insufficiency treated with n-butyl-2. The mean treatment length was 30.6 ± 5.3 cm and the average n-butyl-2 delivered was 1.2 ± 0.3 ml. The mean procedure time was 10.8 ± 4.7 min. There was no deep venous thrombosis, pulmonary embolism, or paresthesia. We observed ecchymosis in eight patients (1.4%) at the entry site at the third day follow-up. Phlebitis was encountered with 10 (1.8%) patients. No skin pigmentation, hematoma, paresthesia, deep-vein thrombosis, or pulmonary embolism was observed. Procedural success was 100%, and complete occlusion was observed after treatment, at the third day follow-up and at first month. Kaplan–Meier analysis yielded with overall clinical recurrence-free rate after a mean follow-up of 23.96 months was 99.38%. All patients had significant improvement in venous clinical severity score and quality-of-life scores postoperatively ($p < 0.0001$). Venous clinical severity score scores at preintervention and 24th month were 5.8 ± 1.0 (range 4–8) and 0.6 ± 0.6 (range 0–4), respectively ($p < 0.0001$). Aberdeen varicose vein questionnaire scores at preintervention and 24th month were 19.7 ± 6.4 (range 9–30) and 4.4 ± 1.1 (range 1–9), respectively ($p < 0.0001$).

Conclusions: The procedure appears to be feasible, safe, and efficient in treating the great majority of incompetent great saphenous veins with this technique.

Keywords

n-butyl-2, cyanoacrylate ablation, nontumescent endovenous ablation, chronic venous insufficiency, varicose veins

Introduction

Chronic venous insufficiency (CVI) and related varicose veins are common vascular problems that affect a significant portion of the adult population. Besides cosmetic concerns, CVI is an important health problem that affect quality of life (QoL) and daily activities

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negatively, and even rarely life threatening. CVI incidence rate is 25–33% in adult women and 10–20% in men.[1]

Besides sex, many factors such as occupation, genetics, age, weight, and height are mentioned in the development of varicose veins. Surgery has been a traditional treatment for more than 100 years in the treatment of varicose veins. High ligation, stripping, and excision methods have been applied for many years with surgical intervention. In addition to invasiveness of these techniques, use of general anesthesia or regional anesthesia, length of hospital stay, and length of recovery led to less invasive methods. For this purpose, chemical ablation techniques, liquid or foam sclerotherapy have been developed. Despite the advantages of low cost and ease of use, major disadvantages are considered such as high recurrence rate, pigmentation, thrombophlebitis, deep-vein thrombosis, pulmonary embolism, and rarely parodox embolism.[2] With the developing technology, different endovenous ablation methods have been increasingly preferred as surgical alternatives in venous insufficiency (VI) for the last 20 years.

Shortly after Bone's[3] endoluminal laser energy was first reported in 1999, Navarro et al.[4] have published their successful laser ablation results in the case of great saphenous vein (GSV) insufficiency. Weiss then performed radio frequency ablation in 2002, and thermal ablation became the golden standard for endovenous treatment of VI. Thermal ablation techniques yielded satisfactory results and lower complications rates; however, these complications include bruising along the GSV, paresthesia, arteriovenous fistula, pseudoaneurysm formation, and other potential side effects that can cause severe discomfort for the patient.[5,6] Necessity of tumescent anesthesia, multiple needle entries, relatively long recovery time, and necessity of compression stockings changed the future of treatment to new alternatives with the increasing expectations from patients.

In order to eliminate potential effects of thermal ablation and increase QoL, n-butyl-2 (NBCA) was introduced into the market as NBCA ablation. Almeida et al.,[7] Morrison et al.,[8] Bozkurt and Yilmaz,[9] and Yavuz et al.[10] reported three different NBCA ablation devices and techniques. These three techniques follow the same principle. Upon vascular injection NBCA rapidly solidifies and creates an inflammation reaction at the vein wall and external compression over the vein literally sticks endothelium oppositely. The major difference between these applications is the viscosity and the polymerization time of the glue that affect procedure time and complication rates. In this study, we used the VenaBlock Venous Closure System (Invamed, Ankara, Turkey), consisting of a proprietary formula of NBCA with dimethyl sulfoxide and a dispensing system (Figure 1). This formula of NBCA finishes initial polymerization reaction in 5 s and system has a guiding light at the tip of the catheter to visually show where to put pressure on immediately in order to catch up with the fast polymerization time. Therefore, the purpose of this study was to assess the safety and efficacy of the new VenaBlock NBCA ablation of the GSV prospectively with a significant number of patients with mid-term follow-up.

Materials and methods

Study protocol

In this independent prospective study, 573 patients with lower-limb VI were treated within in the previous four years. The study enrolled adults aged 21–70 years with symptomatic moderate to severe varicosities (C2–C6 patients Clinical, etiological, anatomical, and pathophysiological (CEAP) classification) and GSV reflux lasting longer than 0.5 s with GSV diameter $\geq$ 5.5 mm assessed in the standing position. Patients were excluded if they had a history of deep-vein thrombosis or pulmonary embolism, reflux of the femoral vein going beyond the knee, hemodynamically significant reflux of the small saphenous vein or anterior accessory GSV, symptomatic peripheral arterial disease, or GSV >20 mm. In order to better figure out effects of NBCA in VI and to achieve statistically significant results, we just focused on the patients with GSV insufficiency in this cohort despite the fact that this treatment can also be used in patients with small saphenous vein and accessory vein incompetence as well as concomitant deep vein reflux. Further eligibility criteria are shown in Table 1. Ethical approval was taken from our institution. Informed consent was taken from each patient before procedures.

Clinical and radiological assessment

After patients' eligibility was confirmed and written informed consent was obtained, the patients underwent a clinical examination by a senior surgeon and ultrasound examination by an independent radiologist. CEAP, venous clinical severity score (VCSS) assessments, and ultrasound (USG) results were recorded. In addition, patients were asked to complete a QoL survey based on the Aberdeen varicose vein questionnaire (AVVQ) on the day before the procedure and then 1, 6, 12, 18, and 24 months after the procedure. We used Turkish translated and nonvalidated version of AVVQ. The total score for the 13 questions ranged from 0 to 100 points, with 0 point indicating the best possible QoL.[11]

Figure 1. The content of VenaBlock venous closure system.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
1. Age ≥21 years and ≤70 years with symptomatic varicose veins
2. CEAP classification of C2–C6
3. GSV diameter at the SFJ while standing ≥5.5 mm and ≤20 mm
4. Reflux in the GSV ≥0.5 s, determined by CDUS
5. Ability to walk unassisted
6. Ability to come to follow-up examinations
7. Mentally healthy to approve procedure
Exclusion criteria
1. Life expectancy <1 year
2. Cancer
3. DVT history
4. Active thrombophlebitis in deep or superficial veins
5. Arterial insufficiency history or ankle-brachial index <0.9
6. Significant femoral or popliteal venous insufficiency
7. History of intervention with GSV to be treated
8. Conditions that prevent vein treatment
9. Immobilization
10. Pregnancy
11. Aneurysm of the target vein with local diameter >20 mm
12. Duplicate or accessory GSV with venous insufficiency
13. Known sensitivity to cyanoacrylate adhesives
14. Advanced tortuous GSV

CDUS: color Doppler ultrasonography; CEAP: clinical, etiology, anatomy, and pathophysiology classification; DVT: deep-vein thrombosis; GSV: great saphenous vein

VenaBlock procedure

All procedures were performed under local anesthesia with standard sterile technique. The GSV was accessed percutaneously with a 7 French sheath. The catheter was advanced through an introducer sheath without a guidewire and without a long introducer catheter. After turning on a light switch on the VenaBlock catheter, it was advanced through the GSV and placed 3 cm away from the saphenofemoral junction (SFJ). After the catheter position was confirmed, the operating table was set to the supine position to minimize blood flow in the GSV. Every 5 s push on the gun trigger delivered 0.3 ml NBCA with a pullback rate of 2 cm/s applied on every 10 cm until the vein segment was fully supplied with NBCA. At the end, 0.03 ml of NBCA would be applied on every centimeter. This procedure was repeated for every 10 cm of GSV. In vein segments over 10 mm, double amount (0.06 ml) of NBCA was applied in every centimeter by slowing down catheter pullback speed to 1 cm/s. At the end, the catheter and the sheath were removed and manual compression was applied on the puncture site. Occlusion of the GSV was confirmed with ultrasonographic evaluation during the procedure (Figure 2). If there was any un-occluded segment, the procedure was repeated through separate access by needle with direct NBCA injection. We did not perform phlebectomy or sclerotherapy in the same session. We waited for three months and then performed phlebectomy or sclerotherapy as needed. No compression stockings were used after the procedure.

Follow-up

Follow-up visits were performed at the 3rd day, 1st, 6th, 12th, 18th, and 24th month. At each visit, an independent ultrasound study and a clinical examination were performed. Treatment success was defined as complete occlusion of the treated GSV. Any patency or recanalization, reflux, or open segment >5 cm in length was considered a failure.[7–10]

Statistical analysis

Complete closure of the GSV was calculated using Kaplan–Meier methods. Changes from baseline in VCSS and AVVQ were compared between control periods by repeated measures analysis of variance and paired *t*-test. Values are expressed as mean ± standard deviation or number and percentage (*n*, %). All

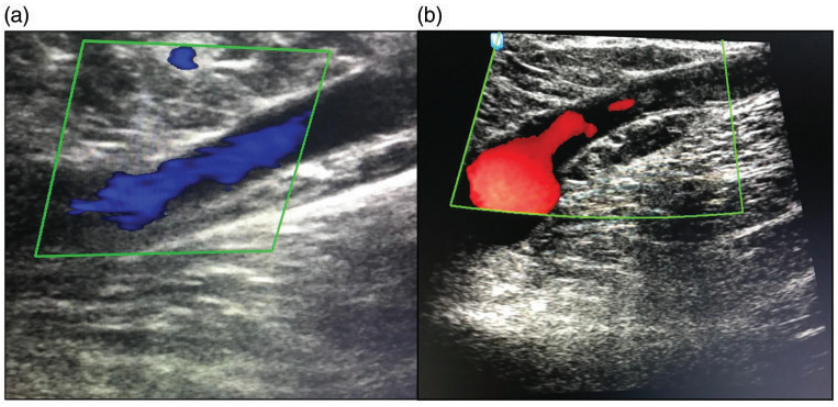

Figure 2. Ultrasonographic evaluation: (a) preprocedural examination and (b) postprocedural examination.

statistical comparisons were made using the SPSS version 24 statistical package.

Results

A total of 573 patients aged 21–70 years with lower-extremity VI were enrolled in the study. One hundred and seventeen patients were lost to follow-up that resulted in 450 patients' data followed up for 24 months in total (Table 2). Patients (436 women (76%)) were a mean age of 44.7 ± 11.8 (range 21–70 years). By the CEAP classification, 156 patients (27%) were C_2, 310 (54%) were C_3, 46 (8%) were C_4, 37 (6%) were C_5, and 24 (4%) were C_6. The average preprocedural VCSS was 5.8 ± 1.0 (range 4–8). The mean preprocedural diameter of GSV at the SFJ in the standing position was 11.7 ± 3.4 mm (range 5.50–16) with a mean reflux of 2.3 ± 0.9 s (range 1–5) (Table 3).

The mean treatment length was 30.6 ± 5.3 cm (range 10–45), and the average NBCA delivered was 1.2 ± 0.3 ml (range 0.4–2), which is fully dependent on treated vein length and diameter. The mean procedure time was 10.8 ± 4.7 min (range 4–35). The GSV was accessed in 55% of the patients above the knee and 45% above the knee level. No significant morbidity or mortality was related to the procedure. There was no deep venous thrombosis, pulmonary embolism, or paresthesia. We did not observe the common femoral vein thrombosis or polymerized glue extending to the common femoral vein. We observed ecchymosis in eight patients (1.4%) at the entry site at the third day follow-up. Phlebitis was encountered with 10 (1.8%) patients. No skin pigmentation, hematoma, paresthesia, deep-vein thrombosis, or pulmonary embolism was observed (Table 4).

Procedural success was 100%, and complete occlusion was observed after treatment, at the third day follow-up and at first month. Partial recanalization was observed in one (0.2%) patient at 6th month, in two patients (0.4%) at 12th and 18th month, and in one patient (0.2%) at 24th month at the SFJ over 5 cm (Table 5).

Table 2. Follow-up.

Follow-up time	Patients controlled (n)	Lost to follow-up (n)	Recanalization (n)	
			Partial	Full
3rd day	573	0	0	0
1st Month	570	3	0	0
6th Month	535	34	1	0
12th Month	508	25	2	0
18th Month	483	23	2	0
24th Month	450	32	1	0

Table 3. Demographics.

	$n = 538$ Mean ± Std (*n*)	*n* (%)
Age (years)	44.7 ± 11.8	
Female gender		436 (76)
Diameter at SFJ (mm)	11.7 ± 3.4	
Reflux at SFJ (s)	2.3 ± 0.9	
CEAP category		
C2		156 (27)
C3		310 (54)
C4		46 (8)
C5		37 (6)
C6		24 (4)
VCSS	5.8 ± 1.0	
AVVQ	19.7 ± 6.4	

AVVQ: Aberdeen varicose vein questionnaire; CEAP: clinical, etiology, anatomy, and pathophysiology classification; SFJ: saphenofemoral junction; VCSS: venous clinical severity score

Table 4. Procedure results.

	Mean ± Std (*n*)	*n* (%)
Length of treated segment (cm)	30.6 ± 5.3	
Procedure duration (min)	10.8 ± 4.7	
Pain during procedure	2.8 ± 1.2	
Ecchymosis		8 (1.4)
Skin pigmentation		0 (0)
Phlebitis		10 (1.8)
Paresthesia		0 (0)
DVT		0 (0)
PE		0 (0)

DVT: deep-vein thrombosis; PE: pulmonary embolism.

All patients had significant improvement in VCSS and QoL scores postoperatively.

VCSS scores at preintervention and 24th month were 5.8 ± 1.0 (range 4–8) and 0.6 ± 0.6 (range 0–4), respectively ($p < 0.0001$). AVVQ scores at preintervention and 24th month were 19.7 ± 6.4 (range 9–30) and 4.4 ± 1.1 (range 1–9), respectively ($p < 0.0001$) (Table 6).

For the life table (Kaplan–Meier) analysis, all patients were included. The overall clinical recurrence-free rate after a mean follow-up of 23.96 months was 99.38% (Figure 3). The standard error of the survival curve point estimate was below .05. Overall mean survival time (95% CI) was (23.92–23.99).

Discussion

VI is a chronic and progressive disease of the lower limb that adversely affects the QoL.[12] VI affects 25 million people every year in the US.[13] Although thermal ablation techniques have become golden standard in the literature for the past 20 years in the treatment of VI, rapidly changing technology and medical literature with increasing patient expectations are accelerating the search for more comfortable therapies. Even though thermal ablation techniques have proven themselves, they have a significant disadvantage, such as tumescent anesthesia. Because of multiple needle entries, TA is not easily tolerated by patients, and the learning curve is not short for accurate application. In addition, tumescent anesthesia is associated with paresthesia, ecchymosis, and hematoma risks.[7] Thus, in the last five years, the use of NBCA in the treatment of VI has become popular, but when the background is examined it is seen that there is a research and development period of about 10 years. NBCA can be performed with local anesthesia and the risks of side effects are eliminated such as burn, ecchymosis, and paresthesia because of the absence of thermal energy and tumescent anesthesia.

Table 5. Closure rates.

	n (%)
3rd Day	573
Total	573 (100)
Partial	0 (0)
Recanalization	0 (0)
1st Month	570
Total	570 (100)
Partial	0 (0)
Recanalization	0 (0)
6th Month	536
Total	535 (99.8)
Partial	1 (0.2)
Recanalization	0 (0)
12th Month	511
Total	508 (99.4)
Partial	3 (0.6)
Recanalization	0 (0)
18th Month	488
Total	483 (99)
Partial	5 (1)
Recanalization	0 (0)
24th Month	456
Total	450 (98.7)
Partial	6 (1.3)
Recanalization	0 (0)

Table 6. Clinical assessment.

	Mean ± Std (*n*)
VCSS	
Pre-Op	5.8 ± 1.0 (573)
1st Month	3.1 ± 0.9 (570)
6th Month	1.6 ± 0.8 (535)
12th Month	0.9 ± 0.7 (508)
18th Month	0.6 ± 0.7 (483)
24th Month	0.6 ± 0.6 (450)
AVVQ	
Pre-Op	19.7 ± 6.4 (573)
1st Month	8.3 ± 3.3 (570)
6th Month	5.1 ± 1.9 (535)
12th Month	5.0 ± 1.7 (508)
18th Month	4.7 ± 1.3 (483)
24th Month	4.4 ± 1.1 (450)

AVVQ: Aberdeen varicose vein questionnaire; VCSS: venous clinical severity score.

Although cyanoacrylates have pretty long history in medical use, venous use of NBCA is pretty new. In 2006, Wang et al. published the histopathological changes in the vessel wall after cyanoacrylate injection in rabbits. Results showed that after rapid polymerization of the NBCA, acute inflammatory effects were observed in two weeks, then chronic granulomatous

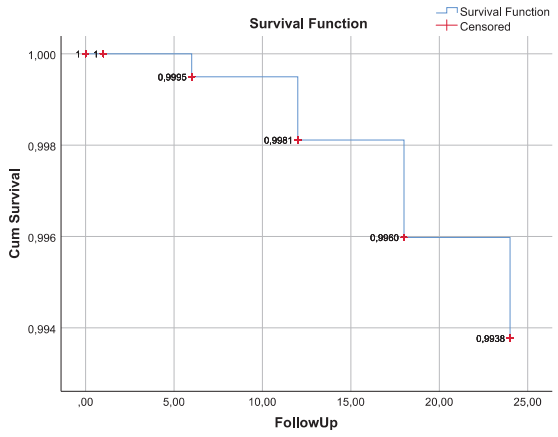

Figure 3. Kaplan–Meier analysis of time to GSV recanalization after endovenous NBCA.

foreign-body reaction at two months and, finally, fibrosis. Another important point in this study was mainly inflammation without proliferation of elastic fibers in the veins.[14] Almeida et al. showed similar results in a 60-day swine model. After NBCA was injected in the vein, acute inflammation, formation of foreign-body giant cells, and granulomas and fibrosis were seen histologically.[15]

Almeida et al. published the results of the first NBCA use on human and saphenous vein insufficiency in their study. The NBCA used in this study has a higher viscosity and the application time was around 30 min. In a study conducted on 38 patients, complete occlusion rates after the procedure were reported as 100%, 30 days of occlusion rate of 97%, and postoperative occlusion rate of 92%. The rate of thrombophlebitis was 16%.[7] Morrison et al. compared radiofrequency ablation (RFA) with pulsed NBCA embolization (CAE) in a randomized VeClose trial. Three-month closure rates were 99% for CAE and 96% for RFA. Phlebitis rates were 20% for CAE and 14% for RFA. The authors reported that CAE was not found to be inferior to RFA for the treatment of GSV insufficiency at month 3 and was associated with less postprocedure ecchymosis.[8]

There is a fairly extensive literature in the low viscosity NBCA used in our study. The findings of the first study, Bozkurt and Yilmaz showed similar occlusion rates and lower phlebitis and procedure time. Bozkurt and Yilmaz compared NBCA (CAA, $n = 154$) and endovenous laser ablation (EVLA, $n = 156$) treatment in patients with GSV insufficiency in their prospective study. With the new NBCA and technique, 12-month follow-up closure rates were 95.8% for CAA and 92.2% for EVLA. VCSS scores improved from the baseline of 5.7 ± 2.3 to 0.6 ± 0.7 for CAA and from 5.7 ± 1.2 to 0.7 ± 0.5 for EVLA. Phlebitis rates were 4.5% for CAA and 7.7% for EVLA. The authors reported statistically significant differences for procedure time, pain during procedure, and ecchymosis in NBCA's favor.[9] There are also supportive studies published by Yasim et al.,[16] Tok et al.,[17] and Çalık et al.[18]

Yavuz et al.[10] published their results with VenaBlock with a substantial number of patients. Five hundred and thirty-eight patients with GSV incompetency enrolled in this study. The mean procedure time was 12 min. Procedural success was 100%, and complete occlusion was 99.4% at 12-month follow-up. VCSS scores decreased from 5.43 ± 0.87 to 0.6 ± 0.75. AVVQ scores decreased from 18.32 ± 5.24 to 4.61 ± 1.42. The authors reported that the procedure appears to be feasible, safe, and efficient and that the great majority of incompetent GSVs can be treated with this technique.[10]

Our results are also supporting the literature with 99.38% survival rate, 1.8% phlebitis, and 1.4% ecchymosis rate.

VenaBlock's NBCA gives a rapid polymerization reaction that can close the target vein in 5 s. We believe continuous delivery is important to catch up with the rapid polymerization time. Another important point is applying pressure over the vein following injection of NBCA. With this treatment, our aim is to stick the opposed endothelia of the vein together without causing thrombus formation as in thermal ablation. Because the polymerization time is rapid and injection of the glue is continuous, pressure should be applied immediately after injection of the NBCA. In this manner application guide light is a nice touch in order to decrease learning curve. Another important point is to deliver double dosage when the diameter of the vein is above 10 mm. In our initial experience, we found out that poor administration of glue in the wide diameters was not working well. When the distal end of the GSV that opens to junction did not close, we administered more amount of glue by direct injection with a syringe and it worked well. Then we came up with the administration of double dosage at the wide diameter veins. It can also be observed from the literature review that this study is also the first study that includes patient group with a vein diameter of up to 20 mm.

Although we report a single center experience in a substantial number of patients with GSV incompetence, this study has several limitations. Probably, one of the most important limitations of this study is that we just focused on the technique and closure rate of incompetent GSV and we did not analyze disappearance of varicosities and recurrence of varicose veins. Nature of the study is not comparing this treatment to currently well-known treatments and maybe it is not giving enough information to compare what

everybody already knows. Also, we did not analyze the overall cost of treatment including treatment cost and the cost related to return to work. This is a simple ambulatory procedure requiring local anesthesia which may be associated with early return to work or daily life.

Conclusions

After the 24-month follow-up of the study cohort, we conclude that the procedure appears to be feasible, safe, and efficient for the treatment of incompetent GSVs. With the current studies about NBCA treatment of GSV, our study provides efficacy similar to current NBCA and endovenous ablation methods. Absence of tumescent anesthesia, short procedure time, and absence of the need for a compression stocking after treatment seemed appealing to patients. Initial mid-term findings are good; however, comparative randomized trials with long-term follow-up are needed to confirm these findings.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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