A retrospective study of a new n-butyl-2-cyanoacrylate glue treatment with application guide light (VenaBlock) for the treatment of venous insufficiency

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Abstract

Introduction: This study aims to present the early results of a retrospective study of the use of novel N-butyl-2 cyanoacrylate (VenaBlock) based non-tumescent endovenous ablation with the guide light for the treatment of patients with varicose veins.

Materials and methods: 538 patients with lower limb venous insufficiency treated with VenaBlock Venous Closure System between April 2016 – July 2016. Study enrolled adults aged between 21-70 years with symptomatic moderate to severe varicosities (C2-C4b) and GSV reflux lasting longer than 0.5 second with GSV diameter ≥ 5.5 mm and ≤ 15 mm assessed in the standing position. Duplex ultrasound imaging and clinical follow-up were performed immediately after procedure. Clinical follow-up were performed at 3rd day, 1st month and 6th month Duplex ultrasound performed by an independent radiologist at 3rd day, 1st month and 6th month.

Results: Mean treatment length was 25.69 ± 4.88 cm and the average NBCA delivered was 0.87 ± 0.15 ml. Mean procedure time was 11.75 ± 4.97 minutes. Procedural success was %100 and complete occlusion observed after treatment and at 3rd day follow-up. Ecchymosis was observed at 3rd day follow up in initial 5 patients (1.00 %) at entry site. Phlebitis was encountered with 6 (1.20 %) patients. No skin pigmentation, hematoma, paresthesia, deep vein thrombosis or pulmonary embolism was observed. Kaplan-Meier analysis yielded an occlusion rate of 99.6% at 6 months of follow-up. All patients had significant improvement in VCSS and AVVQ scores postoperatively ($p<0.0001$). VCSS scores decreased from 5.43 ± 0.87 to 1.03 ± 0.96. AVVQ scores decreased from 18.32 ± 5.24 to 4.63 ± 1.46.

Conclusions: The procedure appears to be feasible, safe and efficient that great majority of incompetent GSVs can be treated with this technique.

Keywords

NBCA ablation, cyanoacrylate ablation, nontumescent endovenous ablation, chronic venous insufficiency, varicose veins

Introduction

Varicose veins and chronic venous disorder (CVD) related problems are progressive medical conditions that affects a serious portion of community. Treatment methods for CVD had revolutionized in the past decade. Previously, surgical treatment methods such as ligation and stripping was the first choice while requiring spinal or general anesthesia and operation room.

Endovenous thermal ablation techniques (laser and radiofrequency) has been showed to be safe and effective treatment of venous insufficiency with high and long-term closure rates.[1] Although, thermal ablation techniques have satisfactory results, necessity of tumescent anesthesia, compression stockings after treatment and side effects like bruising along the GSV, paresthesia, arteriovenous fistula, pseudoaneurysm formation and other potential side effects can cause severe discomfort for the patient.[2,3] Following success of laser and radiofrequency ablation, new generation of thermal ablation introduced. Despite its thermal nature, steam ablation (SA) was presented as a new alternative to EVTA methods. In LAST Trial (Laser Ablation vs Steam Ablation), one-year occlusion rates were 96% for SA and 92% for LA.[4] Despite these satisfactory results, SA does not seem to bring advantages over current EVTA methods.[5]

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To eliminate patient discomfort and side effects of EVTA, two new nonthermal, nontumescent methods introduced in the market: mechanochemical ablation (MOCHA) and cyanoacrylate ablation (NBCA). Eekeren et al.[6] documented their one year results in 92 patients and 106 limbs and reported GSV occlusion rates as 93.2% in six months and 88.2% at one year. One-month to six-month occlusion rates of >90% were documented in other series.[7,8] When compared to RFA, it was reported that MOCA caused lesser postoperative pain and discomfort.[9]

NBCA had been using endovenously since 2000 for the treatment of AVM's and peptic varicosities.[10,11] Delivering n-butyl-2-cyanoacrylate (NBCA) endovenously for treatment of GSV reflux is a new concept which is available in market for the past three years. Almeida et al. and Bozkurt et Al. showed safety and efficiency for two different kind of NBCA and delivery system.[12,13] The purpose of this study was to assess safety and efficacy of new VenaBlock NBCA ablation of the great saphenous vein (GSV).

Materials and methods

Study protocol

In this independent retrospective study, 538 patients with lower limb venous insufficiency treated between April 2016 – July 2016. Study enrolled adults aged between 21-70 years with symptomatic moderate to severe varicosities (C2-C4b patients CEAP: Clinical, Etiological, Anatomical, Pathophysiological Classification) and GSV reflux lasting longer than 0.5 second with GSV diameter ≥ 5.5 mm assessed in the standing position. Patients were excluded if they had history of deep vein thrombosis or pulmonary embolism, reflux of femoral vein going beyond the knee, hemodynamically significant reflux of the small saphenous vein or anterior accessory GSV, symptomatic peripheral arterial disease or GSV > 15 mm. Additional eligibility criteria are shown in Table I. No additional procedures performed (mini phlebectomy or sclerotherapy).

Assessment

After patients' eligibility was confirmed and written informed consent obtained, patients underwent clinical examination by a senior surgeon and ultrasound examination by an independent radiologist. CEAP, Venous Clinical Severity Score (VCSS) assessments and ultrasound results were recorded. Additionally, patients completed Quality of Life (QoL) survey based on Aberdeen Varicose Vein Questionnaire (AVVQ). 13 questions range from 0 to 3 points (in total 0 – 36 points) surveyed with 0 point indicating the best QoL.[14]

All procedures went under local anesthesia with standard sterile technique. After the procedure patients rated procedural pain on a scale of 1-10 (10 extreme pain, 0 no pain). Additionally, patients asked for evaluate if they have a burning sense in their legs during the procedure.

VenaBlock Procedure

VenaBlock Venous Closure System (Invamed, Ankara, Turkey) consists of n-butyl-2-cyanoacrylate with DMSO (NBCA) and a dispensing system. Dispensing system includes 6F, PTFE, braided microcatheter which is marked on every 2 cm with a guide light adapter, 3 ml syringe, 2x21 G seldinger needles, 6F Introducer sheath and a dilator, 45 cm 0.035" J-Tip guidewire and a dispensing gun. Catheter tip glows with a guide light when the adapter switched on and helps to determine position of catheter and also guides for pressure points during the procedure. Amount of supplied NBCA is in 1 ml separate packages and minimum 2 ml and comes with a different package. In other words, amount of NBCA can be determined by physician and supplied as many as needed according to the length of the target vein.

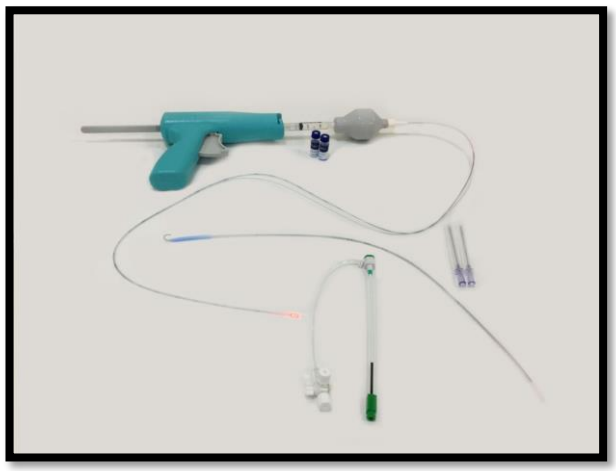

Figure 1. The content of VenaBlock Venous Closure System

The GSV accessed percutaneously with a micro puncture kit. NBCA transferred into the 3-ml syringe by 2 ml without leaving any air inside. Syringe attached to the dispensing gun from distal end with a spin lock mechanism. VenaBlock catheter has a guide light adapter at distal that is connected to syringe's proximal end with a spin lock mechanism. After catheter, syringe and dispensing gun connected, catheter primed with 2 pushes on trigger for 1 second by filling catheter lumen with NBCA except the final 3 cm at the proximal tip. Catheter has an atraumatic round tip and can be easily advanced through introducer sheath without a guidewire and without a long introducer catheter since it is PTFE and hydrophilic. Adapter has a light switch on it. After turning light switch on VenaBlock catheter advanced through GSV and placed 3 cm away from the

saphenofemoral junction (SFJ). Position of the catheter confirmed with an USG. VenaBlock catheter has an advanced visibility under USG since it has a dense formation and coil braiding **(Figure 3).** Catheter is specifically consisting of PTFE in order not to give any reaction with NBCA and stick to the vein wall. After catheter position confirmed, operating table set to the supine position to minimize blood flow in GSV.

The dispensing gun set up for continuous delivery which is 0.06 ml per second. 5 second push on the gun trigger delivers 0.3 ml of NBCA continuously. This 0.3 ml applied on every 10 cm. Pull back rate of the catheter is 2 cm/sec. Every 5 second push on the gun trigger dispenses 0.3 ml NBCA with a pullback rate of 2 cm/secs applied on every 10 cm until the vein segment fully applied with NBCA. At the end 0.03 ml of NBCA will be applied on every cm.

Table 1. Inclusion and Exclusion Criterias

Inclusion Criteria

1. Age ≥21 years and ≤70 years with symptomatic varicoe veins
2. CEAP Classification of C2 - C4b
3. GSV diameter at the SFJ while standing ≥ 5.5 mm and ≤15 mm
4. Reflux in the GSV ≥ 0.5 second determined by CDUS
5. Ability to walk unassisted
6. Ability to come to follow-up examinations
7. Mentally healty 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. Coniditions that prevent vein treatment
9. Immobilization
10. Pregnancy
11. Aneurysm of the target vein with local diameter >15 mm
12. Duplicate or accessory GSV with venous insufficiency
13. Known sensitivity to cyanoacrylate adhesives
14. Advanced tortuous GSV

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

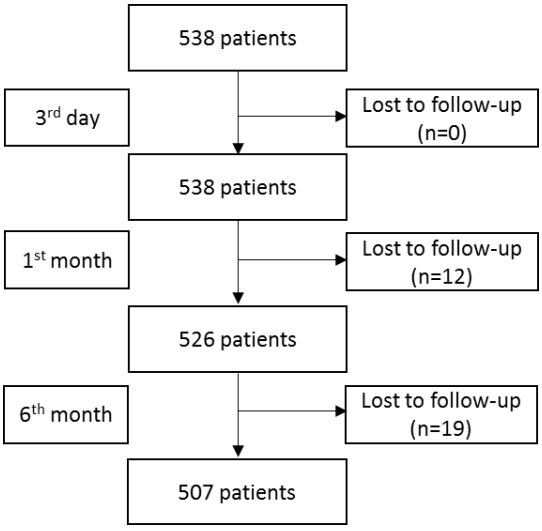

Figure 2. Flow Chart

VenaBlock's NBCA gives a rapid polymerization reaction that can close target vein in 5 seconds. That's why continuous delivery is really important in order to catch up with rapid polymerization time. Another important point is applying pressure over the vein following injection of NBCA. With this treatment, our aim is the stick opposed endothelia of the vein together without causing thrombus formation like in the thermal ablation. Since the polymerization time is rapid and injection of the glue is continuously, pressure should be applied immediately after injection of the NBCA. Before first injection, pressure applied on SFJ with an USG probe while probe is in longitudinal position and closure of SFJ confirmed in order not to create bolus of NBCA in deep vein. While pressuring SFJ, NBCA injection started and guide light at the end of the proximal tip followed with a continuous pressure with an USG probe until the targeted vein segment is fully closed.

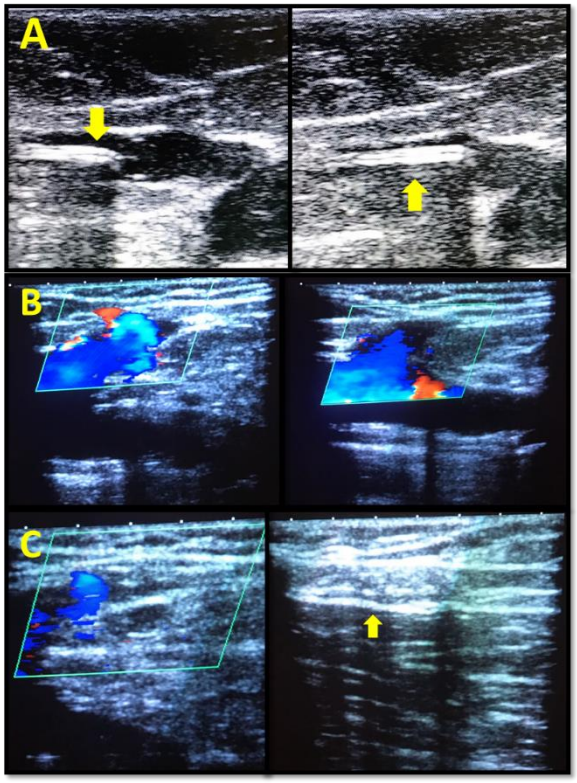

Figure 3. Ultrasound images of incompetent great saphenous vein (GSV) **(A)** VenaBlock Catheter at SFJ **(B)** After treatment with NBCA **(C)** Color Doppler of SFJ after treatment

Postprocedural Management

Follow-up

Follow-up visits performed at 3rd day, 1st month and 6th month. At each visit, independent ultrasound study and clinical examination performed. Treatment success was defined as complete occlusion of treated GSV. Any patency or recanalization, reflux or open segment > 5 cm in length considered as failure.[15,16]

Statistical Analysis

Complete closure of 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 statistical comparisons were made by using SPSS version 22 statistical package.

Results

A total of 538 patients aged between 21-70 years old with low extremity venous insufficiency enrolled in the study. 31 patients lost to follow up (12 patients at first month, 19 patients at sixth month) and their data excluded from the study that is resulted with 507 patients' data analyzed in total. Patients (360 women [67%]) were a mean age of 45,56 ± 10,04 (range 21-70 years). By the CEAP classification, 176 patients (33%) were C_2, 339 (63%) were C_3 and 23 (4%) were C_4. The average preprocedural VCSS was 5.43 ± 0.87 (range 4-8). Mean preprocedural diameter of GSV at the SFJ in the standing position was 6.70 ± 1.65 mm (range 5.50 – 14.60) with a mean reflux of 1.90 ± 0.81 seconds (range 1 – 5).

Mean treatment length was 25.69 ± 4.88 cm (range 10 – 43) and the average NBCA delivered was 0.87 ± 0.15 ml (range 0.4 – 1.39) which is fully dependent on treated vein length. Mean procedure time was 11.75 ± 4.97 minutes (range 5 – 33). The GSV accessed in 52% of the patients above the knee and 48% above the knee level.

Procedural success was %100 and complete occlusion observed after treatment and at 3rd day follow-up. Ecchymosis was observed at 3rd day follow up in initial 5 patients (1.00 %) at entry site. We connected this ecchymosis to applying NBCA to the entry point. Therefore, NBCA injection stopped before 2 cm from the entry point by the help of the guidelight for the rest of the patients. No ecchymosis observed after this procedural change. Phlebitis was encountered with 6 (1.20 %) patients. No skin pigmentation, hematoma, paresthesia, deep vein thrombosis or pulmonary embolism was observed.

Closure Data

Duplex ultrasound performed by an independent radiologist at 3rd day, 1st month and 6th month. All veins found occluded at 3rd day. Partial recanalization observed with 2 (%0.4) patients at the SFJ over 5 cm at 1st month. 6th month follow up resulted with the same

results as 1st month with 99.6% complete occlusion rate.

QoL Assessment

All patients had significant improvement in VCSS and AVVQ scores postoperatively (p<0.0001). VCSS scores decreased from 5.43 ± 0.87 (range 4-8) to 1.03 ± 0.96 (range 0-4). AVVQ scores decreased from 18.32 ± 5.24 (range 9-30) to 4.63 ± 1.46 (range 1-9). Both VCSS and AVVQ scores found statistically significantly different ($p < 0.0001$) using repeated measures of ANOVA between preoperational and 6th month scores.

Discussion

Results from this study confirm that NBCA is safe and highly effective for the treatment of venous insufficiency. No serious adverse events or toxicologic effects were registered during the 6-month follow-up. To date, no toxicologic, carcinogenic or mutagenic effect has been reported for NBCA.[10,11,17]

Table 2. Demographics

	n=538	
	Mean±Std (n)	**n (%)**
Age (years)	44.56 ± 10.04	
Female gender		360 (67)
Diameter at SFJ (mm)	6.70 ± 1.65	
Reflux at SFJ (sec)	1.90 ± 0.81	
CEAP category		
C2		176 (33)
C3		339 (63)
C4		23 (4)
VCSS	5.43 ± 0.87	
AVVQ	18.32 ± 5.24	

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

Table 3. Procedure Results

	Mean±Std (n)	**n (%)**
Length of treated segment (cm)	25.69 ± 4.88	
Procedure duration (min)	11.75 ± 4.97	
Pain during procedure	2.19 ± 0.94	
Burning sensation		378 (70)
Ecchymosis		5 (0.9)
Skin pigmentation		0 (0)
Phlebitis		6 (1.1)
Paresthesia		0 (0)
DVT		0 (0)
PE		0 (0)

DVT: deep vein thrombosis; PE: pulmonary embolism

Wang et Al. showed histopathological changes in the vessel wall after cyanoacrylate injection with a study on adult rabbits. Results showed that after rapid polymerization of the NBCA, acute inflammatory effects observed in 2 weeks, then chronic granulomatous foreign body reaction at 2 months and finally fibrosis. Another important point in this study was mainly inflammation without proliferation of elastic fibers in the veins.[18] Almeida et al. also showed similar results in 60-day swine model. After NBCA injected in vein acute inflammation, formation of foreign body giant cells and granulomas and fibrosis was histologically seen respectively.[19] Chaloupka et Al. identified 3 phases of polymerization in an explanted swine common carotid artery model: (1) initial rapid polymerization with increasing tensile forces lasting approximately 10 seconds; (2) a second phase which displayed a constant tensile force and spanned up to 1 minute in length; and (3) a final phase characterized by a rapid, exponential rise of tensile force that completed polymerization. The polymerization times varied based on the formulation and type of CA and the amount of intravascular blood or saline.[20]

Following validation of NBCA in animal models, Almeida at Al. published two-year follow-up of first human use of NBCA for treatment of saphenous vein incompetence.[12] NBCA viscosity was dense like honey and application technique was pulsed that injects 0.08 ml per 3 cm with each dispenser gun trigger. First

pressure at SFJ was 3 minutes and 30 seconds for the rest of each bolus. 38 patients follow-up completed and they found the occlusion rate of 92.0 % at 24 However, first 8 patients (21 %) had postablation thrombus extension into the SFJ.[21] Therefore, modification in their technique with the first NBCA injection located 5 cm distal from the SFJ was necessary and seemed to solve the problem.

Table 4. Closure Rates

	n (%)
Third Day	
Total	538 (100)
Partial	0 (0)
Recanalization	0 (0)
First Month	
Total	525 (99.6)
Partial	2 (0.4)
Recanalization	0 (0)
Sixth Month	
Total	505 (99.6)
Partial	2 (0.4)
Recanalization	0 (0)

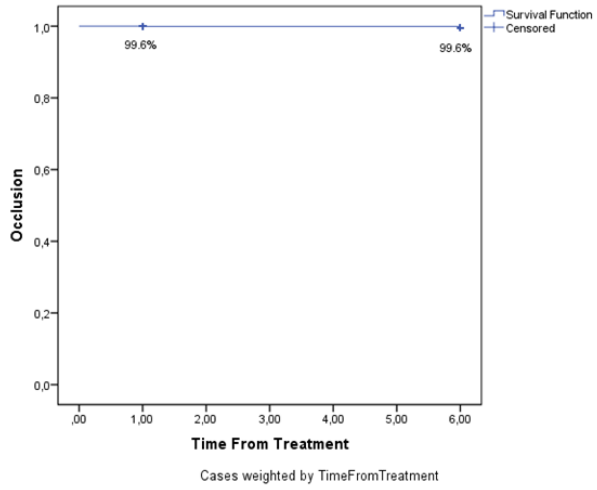

Figure 4. Kaplan-Meier analysis of time to GSV recanalization after endovenous NBCA.

In European Multicenter study on pulsed NBCA embolization of incompetent GSVs[22], 70 patients treated and one year follow-up completed in 60 (86 %) patients. Occlusion rate was 94.3 % at 6th month with a improvement of VCSS from 4.3 ± 0.3 baseline to 1.13 ± 1.27. Phlebitis occurred in six cases (8.7 %). Morrison et Al. compared radiofrequency ablation (RFA) with pulsed NBCA embolization (CAE) in randomized VeClose trial. 222 patients with symptomatic GSV incompetence were randomly assigned to receive either CAE (n=108) or RFA (n=114). Three-month closure rates were 99 % for CAE and 96 % for RFA. Phlebitis rates were 20 % for CAE and 14 % for RFA. Authors reported that CAE was found to be noninferior to RFA for the treatment of GSV insufficiency at month 3 and is associated with less postprocedure ecchymosis.[23]

month follow-up. Baseline VCSS improved from a mean of 6.1 ± 2.7 to 2.7 ± 2.5 (p < 0.0001). No significant side effects or complications observed.

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. In this study, authors especially mentioned that the NBCA viscosity was lower, polymerized in 5 seconds and application procedure was continuous. Each trigger of dispensing gun was delivering 0.03 ml of NBCA per each cm with a following continous compression over targeted vein. 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. Authors reported differences statistically significant for procedure time, pain during procedure and ecchymosis on NBCA's favor.[13]

Table 5. Clinical Assesment

		Mean±Std (n)
VCSS		
	Pre-Op	5.43 ± 0.87 (538)
	First Month	2.43 ± 0.75 (527)
	Sixth Month	1.03 ± 0.96 (507)
AVVQ		
	Pre-Op	18.32 ± 5.24 (538)
	First Month	7.12 ± 2.38 (527)
	Sixth Month	4.63 ± 1.46 (507)

VCSS: venous clinical severity score; AVVQ: Aberdeen varicose veins questionnaire

Results on use of NBCA alone have been published very recently in three consecutive studies from Turkey in considerable number of patients. Yasim et Al.[24] documented their experience with NBCA in 180 patients. The mean follow-up time was 5.5 months and recanalization rate was 0 %. The authors used compression stockings postoperatively without any scientific rationale, but due to surgical habits, and claimed that this high success rate was possibly due to this. Similarly, Tok et Al.[25] published their results with 141 patients and 189 GSVs. The mean follow-up time was 6.7 months and occlusion rate was 98.4%. Calik et Al.[26] documented their results on 181 patients and 215 legs (206 GSV and 9 LSV) with the sixth month occlusion rate of 97.2%. VCSS improved from baseline of 4.9 ± 1.2 to 1.4 ± 0.8 (p<.0001).

Following published results of NBCA from Turkey, Turkish Society of Cardiovascular Surgery, National Society of Vascular and Endovascular Surgery and Society of Phlebology strongly suggested use of NBCA embolization treatment for venous insufficiency in their "National Treatment Guideline 2016".[27]

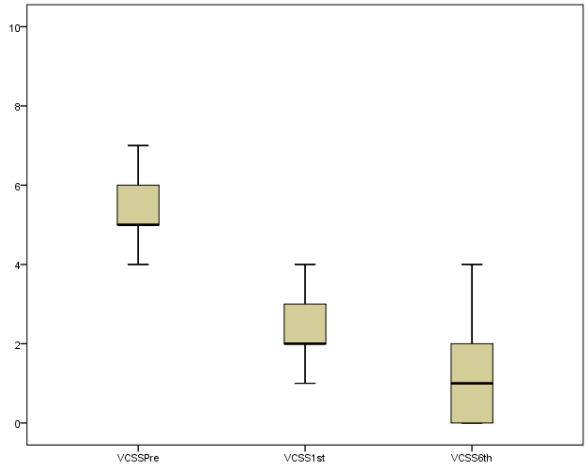

Figure 5. Venous Clinical Severity Score (VCSS) at baseline and follow-up.

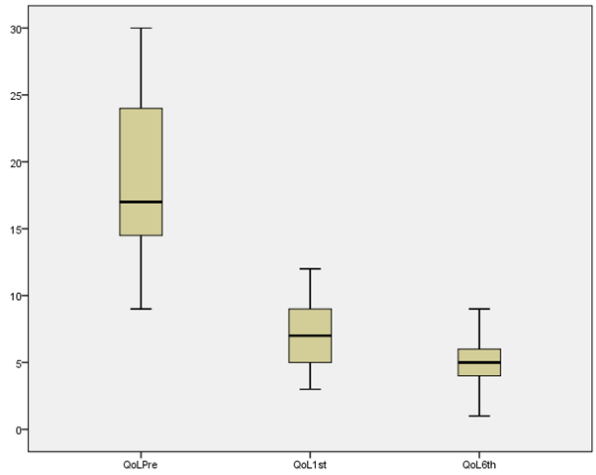

Figure 6. Quality of Life Scores (QoL) at baseline and follow-up.

Most important criteria in NBCA treatment of GSV are viscosity and procedure technique (pulsed or continuous). Current treatments show significant differences in procedure time and phlebitis. Both procedures have similar success rates with parallel benefits. In our study continuous technique was the procedural technique with a new brand system and resulted with similar results with current studies of Bozkurt, Yasim, Tok and Calik. We believe, phlebitis occurring after NBCA procedure relates to excess amount of glue in a certain vein segment entering reaction with blood and creating thrombus like formation. We call this phenomenon "phlebitis like". Bozkurt, Yasim and Calik also observed this phlebitis like formations that dissolves in a week. Right amount of pressure, at the right time and place, is necessary to stick endothelia walls together oppositely without leaving thrombus formation inside. We believe that's why Bozkurt observed less phlebitis rate with continuous NBCA delivery compared with Almeida's and Morrison's reports. In our study, we observed less phlebitis than reported articles. We believe guidelight at the tip of the catheter assisted with the pressure location and pressure time immediately after glue injection. Yet with continuous technique and low viscosity NBCA, phlebitis rate can be lowered after a learning curve without the aid of the guidelight.

Inflammatory reaction at the vein wall creates 45-50 C^{O} heat as it stated in the IFU of the product. 70.4 % of the patients felt minor heat increase in treatment zone. Additional studies can be done over if heat effect have any contribution for occlusion or closure mechanism. Pain evaluation of the patients were 2.19 ± 0.94 which seems very low compared to published EVTA results.

One additional note on the NBCA is benefit for coumadin patients. Since procedure can be done in outpatient conditions, local anesthesia is enough for the procedure. So, it is not necessary to change coumadin dose or schedule of the patient. Closure of the treated vein is so quick that it reduces the risk of bleeding or hematoma at the entry point.

Conclusions

After 6-month follow-up of the study cohort, we conclude that the procedure appears to be feasible, safe and efficient that great majority of incompetent GSVs can be treated with this technique. 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 compression stocking after treatment seemed appealing to patients. Initial findings are good, however, long term results and comparative randomized trials are needed to confirm these findings.

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Conflict of Interests / Funding

None

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