

The same clinical effect, with fewer complications and higher patient comfort, can be achieved with lower doses of N-butyl cyanoacrylate in endovenous ablation therapy: A prospective, randomized study

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ABSTRACT

Objectives: This study aims to investigate the therapeutic effect of N-butyl cyanoacrylate (NBCA) administration on the treatment success and patient comfort in patients with venous insufficiency.

Patients and methods: Between March 2019 and June 2019, a total of 80 patients (29 males, 51 females; mean age 49.6±12.0 years; range, 25 to 81 years) diagnosed with great saphenous vein incompetence and underwent endovenous ablation with <1 mL or >1.5 mL NBCA were included in this prospective, randomized study. The patients were equally divided into two groups as Group 1 (n=40) receiving <1 mL NBCA and Group 2 (n=40) receiving >1.5 mL NBCA. The patients were invited for checks on the third day and first month post-procedurally and were evaluated in terms of potential complications. Post-procedural analgesic requirements, time to first analgesic requirement, number of 500 mg paracetamol doses used over three days among patients requiring analgesia, and pain experienced using the Visual Analog Scale after the procedure and on the third day were recorded.

Results: The mean lengths of vein segments subjected to NBCA application and ablation were 33 cm in Group 1 and 34 cm in Group 2 (p=0.430). Fewer adverse events were observed in Group 1 than Group 2 (phlebitis, p=0.305; ecchymosis, p=0.396; analgesic use, p=0.013; amount of analgesic used, p<0.001; time to first analgesia requirement, p<0.001).

Conclusion: Our study results suggest that the same clinical success with fewer complications (ecchymosis, phlebitis, and pain) and greater patient satisfaction can be achieved using a lower dose of NBCA in the treatment of venous insufficiency.

Keywords: Endovenous ablation, N-butyl cyanoacrylate, venous insufficiency.

Varicose vein treatment has evolved dramatically in recent years. Endovascular procedures, including radiofrequency ablation (RFA) and endovenous laser ablation (EVLA), employ thermal energy for vein wall modification and occlusion. The saphenous space must be infiltrated with tumescent anesthesia to reduce complications such as skin burns, lower extremity pain, skin pigmentation, and nerve damage and to enhance venous obliteration.^[1]

Non-thermal non-tumescent (NTNT) techniques are available options for avoiding such complications

associated with great saphenous vein (GSV) and small saphenous vein (SSV) ablation.^[2] Tumescent anesthesia is not required with these techniques, since the vein is occluded either by mechanochemical energy, or else by sealing through adhesive action. When injected via the intravascular route, the N-butyl cyanoacrylate (NBCA) quickly solidifies as a result of a polymerization reaction, leading to an inflammatory reaction in the vein wall.^[3-5] Non-thermal ablation entails a number of potential advantages in terms of patient acceptability and a lower nerve injury risk.^[6]

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Clinical studies and reviews have recently confirmed the safety, feasibility, and mid-term efficacy of NBCA.^[2,7-9] However, although uncommon, complications associated with the NBCA use such as phlebitis and ecchymosis can be still encountered. These complications mainly depend on the amount of the chemical substance applied. In the present study, we hypothesized that successful chemical ablation could be possible using a low level of NBCA and that the patient comfort could be increased by reducing the severity of inflammation in the vessel wall. We, therefore, aimed to investigate the effect of NBCA administration on early therapeutic success and patient comfort in patients with venous insufficiency.

PATIENTS AND METHODS

This prospective, randomized study was conducted at Kahramanmaraş Sutcu Imam University, Faculty of Medicine, Department of Cardiovascular Surgery between March 2019 and June 2019. A total of 80 patients (29 males, 51 females; mean age 49.6 ± 12.0 years; range, 25 to 81 years) with GSV incompetence as assessed by Duplex ultrasound (DUS) and underwent endovenous ablation were included in the study. Patients with a GSV greater than 5.5 mm in diameter, 2 cm below the saphenofemoral junctions with the subject in a standing position, combined with reflux exceeding 0.5 sec, according to the European

Society of Vascular Surgery (ESVS) guidelines^[10] were to be eligible. Those aged less than 18 years, having deep venous system obstruction, a previous history of another invasive technique (i.e., thermal and chemical ablation, or surgery), cardiac and renal failure, those who were immobile or with secondary varicose veins, having hypercoagulability status, and local or systemic infection were excluded. A written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of the Kahramanmaraş Sutcu Imam University, Faculty of Medicine. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Block randomization was performed using the sealed envelope method at a ratio of 1:1. The patients were equally divided into two groups as Group 1 (n=40) receiving <1 mL NBCA and Group 2 (n=40) receiving >1.5 mL NBCA. The study flow chart is shown in Figure 1. Patients were blinded to treatment allocation, significantly reducing the potential for bias and allowing a direct comparison of the outcomes of the two procedures. Repeated DUS was performed by a single surgeon immediately prior to the procedure using a Mindray M7 USG device (Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, China). Patients were, then, transferred to the operating room.

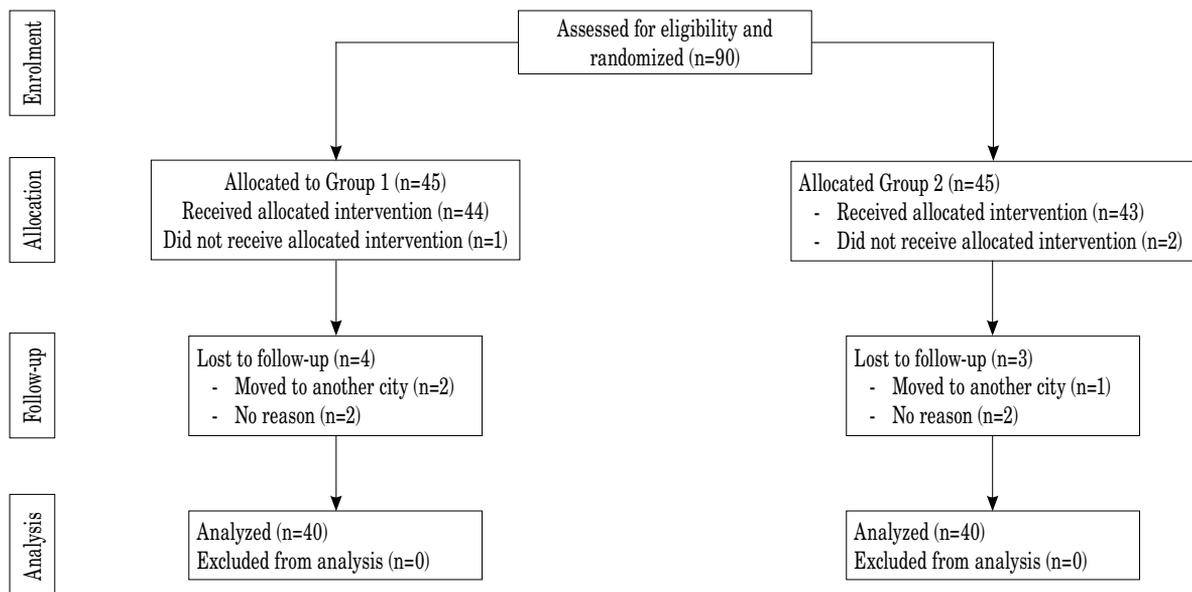


Figure 1. The CONSORT diagram of the study.

Group 1: <1 mL N-butyl cyanoacrylate; Group 2: >1.5 mL N-butyl cyanoacrylate.

The primary endpoint was the ablation rate. Secondary endpoints included the incidence of complications and patient satisfaction, as assessed by the following parameters: the absence of peri- and postoperative pain, and post-procedural complications. Data including age, sex, weight, and height were recorded preoperatively. The diameter, length and depth beneath the skin in the cannulation site of the target vein were recorded during surgery. Duration of procedure was also recorded. A Visual Analog Scale (VAS) was used to determine pain severity. The patients were asked to rate the pain experienced during the procedure on a scale from 0 to 10, where 0 indicates no pain and 10 indicates the most extreme pain.

Procedures

All procedures were carried out under aseptic conditions in the operating room, with patients in the supine position. An ultrasound-guided 21-gauge needle was used for percutaneous puncturing of the saphenous vein. Cannulation was performed at the lowest point of reflux, followed by the insertion of a 6F introducer sheath. No simultaneous phlebectomy was performed in any case.

Endovenous ablation was carried out using the VariClose® Vein Sealing System (Biolas, FG Grup, Ankara, Turkey). Briefly, a 0.035-inch, 150-cm guidewire was introduced through the introducer sheath as far as the saphenofemoral junction (SFJ). The presence of the guidewire in the SFJ was first corroborated by DUS, after which a 5F catheter was advanced to the SFJ over the guidewire. Once the position of the 5F catheter at the beginning of the SFJ was confirmed, it was retracted by 6 cm. This distance was employed, since the tip of the 4F delivery catheter protrudes from the 5F marker catheter by 3 cm. We, therefore, positioned the 4F delivery catheter 3 cm distal to the SFJ or SPJ. Confirmation of the location of the 4F delivery catheter completed the NBCA injection groundwork. Next, 2 mL of NBCA was aspirated into the 2-mL injector. In Group 1, following catheter insertion, the vein was emptied by tapping before NBCA injection. Constant compression was applied before, during, and after injection (at a speed of 0.2 mL/sec, total <1 mL NBCA). The procedure was, then, commenced. The standard procedure was performed in Group 2 (at a speed of 0.4 mL/sec; total >1.5 mL NBCA).^[8,9] The time between the saphenous vein puncture and NBCA injection was recorded as the procedural time. Pressure on the vein continued to be applied for three min following the injection.

Whether the vein was occluded after the procedure was confirmed using DUS.

Once the procedure was completed, an elastic bandage was applied to the lower extremity involved and was removed after 24 h. No restriction was placed on the patient activity, and all types of reasonable exercise were allowed from the first day of the procedure.

Follow-up

The patients were scheduled for follow-up including clinical and ultrasonographic examination on Day 3 and at one month postoperatively (at which blinding control was performed). Ultrasonography criteria for technical success were closed or absent GSV with the lack of flow. Recanalized GSV or treatment failure was defined as an open segment of the treated vein segment exceeding 5 cm in length. Post-procedural analgesia requirement, time to first analgesia requirement (in h), total number of use of 500 mg paracetamol over three days among patients requiring analgesia, and pain perceptions at the end of Day 3 using the VAS scale were recorded. The Comprehensive Classification System for Chronic Venous Disorders (CEAP) and Venous Quality of Life (VQOL) scores at the first month were recorded and compared with the baseline scores.

Primary and secondary outcomes

Anatomical success defined as the closure and absence of reflux at color DUS analysis was adopted as the primary outcome. Secondary outcomes were subdivided into intra- and postoperative outcomes. Intraoperative outcomes included data concerning NBCA applied, duration of procedure, and concomitant phlebectomies, while postoperative outcomes included clinical and subjective success in the follow-up period, minor postoperative complications (i.e., pain, bruising, hematoma, burns, pigmentation, paresthesia, and superficial vein thrombosis [SVT]) and major postoperative complications (i.e., pulmonary embolism [PE] and deep venous thrombosis [DVT]).

Statistical analysis

Power analysis was performed to calculate the sample size. We planned to enrol 80 patients, 40 in each group, based on an α : 0.05 Type 1 error and β : 0.20 Type 2 error level with 0.80 test power based on the parameters used in our reference studies.^[17]

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean

Table 1. Baseline demographic and clinical characteristics of the patients

	1 mL or less			More than 1 mL			p
	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			49.4±12.7			49.9±11.4	0.846
Weight (kg)			79.2±14.9			84.8±13.5	0.084
Height (cm)			166.8±8.4			164.9±9.8	0.361
Body mass index (kg/m ²)			28.8±5.3			31.1±5.4	0.060
Gender							0.356
Male	17			13			
Female	23			27			
Diabetes mellitus	8	20		7	17.5		1.000
Hypertension	9	23		11	27		0.775
Hyperlipidemia	1	2.5		1	2.5		0.651
Chronic obstructive pulmonary disease	0	0		1	2.5		1.000
Smoking	7	17.5		10	25		0.412

SD: Standard deviation; Independent samples t-test; Chi-square test; Fisher's exact test; α : 0.05.

± standard deviation (SD), median (interquartile range [IQR] 25th-75th) or number and frequency. Normality of data distribution was examined using the Shapiro-Wilk test. Group comparisons of normally distributed variables were carried out using the independent samples t-test. Group

comparisons of non-normally distributed variables were performed using the Mann-Whitney U test. The chi-square and Fisher's exact tests were used to analyze significant differences between categorical variables. A *p* value of <0.05 was considered statistically significant.

Table 2. Pre- and postoperative data

	1 mL and lower					1 mL +					p
	n	%	Mean±SD	Median	Q1-Q3	n	%	Mean±SD	Median	Q1-Q3	
Amount of drug (mL)				1.0	1.0-1.0				2.0	1.8-2.0	0.001*
Preoperative vessel diameter (mm)				6.75	6.30-7.45				7.50	6.70-8.30	0.098
Saphenous vein length (cm)				33	31-35				34	32-35	0.430
Duration of procedure (min)				5.0	4.0-6.0				6.0	5.5-8.0	0.001*
Visual Analog Scale				0.0	0.0-1.5				1.0	0.0-2.0	0.034*
Day 3 Visual Analog Scale				1.00	0.00-1.00				2.50	2.00-4.00	0.001*
Use of analgesia	17	42.5				28	70				0.013*
Postoperative time to start of analgesia use (hour)				18	6-24				4	3-6	<0.001*
Number of analgesics (tablet)				2	2-4				6	4-8	<0.001*
Phlebitis	1	2.5				3	7.5				0.305
Ecchymosis	2	5				4	10				0.396
CEAP†				3	2-3				3	2-3	1.000
CEAP 1 st month†				2	2-3				2	2-3	0.742
				p<0.001*,‡					p<0.001*,‡		
VQOL†				20	16.5-22				20	15.5-22	0.811
VQOL 1.month†				16.4±3.6					16.7±4.1		
				p<0.001*,‡					p<0.001*,‡		

CEAP: Comprehensive Classification System for Chronic Venous Disorders; Chi-square test; Mann-Whitney U test; Fisher's exact test; † Mann-Whitney U test; Independent samples t-test; ‡ Wilcoxon test; α : 0.05; * Differences between groups statistically significant.

RESULTS

Ablation was successfully performed in 80 patients with GSV incompetence. Occlusion was observed in all patients in both groups at the post-procedural control USG, and no partial occlusion was detected in any case. Bilateral procedures were not performed in the same session in any case. All patients were symptomatic. The mean age was 49.3 ± 12.6 years in Group 1 and 49.8 ± 11.4 in Group 2. The mean pre-procedural GSV diameters were 6.7 (range, 6.3 to 7.4) mm in Group 1 and 7.5 (range, 6.7 to 8.3) mm in Group 2, indicating no statistically significant difference. Baseline demographic and clinical characteristics of the patients are shown in Table 1.

The mean lengths of vein segments subjected to the NBCA application and ablation were

33 (range, 31 to 35) cm in Group 1 and 34 (range, 32 to 35) cm in Group 2 ($p=0.430$). The mean procedural times were 5.0 (range, 4.0 to 6.0) min in Group 1 and 6.0 (range, 5.5 to 8.0) min in Group 2. A summary of the procedural characteristics is presented in Table 2. Fewer adverse events were found after <1 mL NBCA administration compared to >1.5 mL NBCA administration, although it did not reach statistical significance (phlebitis, $p=0.305$, and ecchymosis, $p=0.396$). However, statistically significant differences were observed between the two groups in terms of analgesia requirements, time to first analgesia requirement, and amounts of analgesic used, CEAP at one month, and VQOL at one month ($p=0.013$, $p<0.001$, $p<0.001$, $p<0.001$, and $p<0.001$, respectively) (Figures 2 and 3, Table 2).

DISCUSSION

This study was designed based on the hypothesis that if the amount of NBCA administered inside the vessel was reduced, the severity of the inflammation which might develop would also decrease, in turn, resulting in improved patient comfort. Our study results showed that the same clinical success, with fewer complications (such as phlebitis, thrombophlebitis, ecchymosis, and pain) and greater patient comfort, can be achieved using a lower dose of NBCA in the treatment of venous insufficiency.

Endothermal treatment of the GSV has become the therapy of choice in superficial venous reflux. Endothermal ablation entails various advantages over open surgery, such as obviating the need for general anesthesia, a reduced operative time, and lower levels of postoperative pain and morbidity.^[11] However, one disadvantage of thermal endovenous ablation of truncal incompetence in cases of varicose veins is that tumescence anesthesia is required, a potential source of procedural discomfort, hematoma, and ecchymosis. Tumescence anesthesia is also a particularly difficult technique to master and extends the procedural time.^[12]

The current NTNT methods are practical means of avoiding such complications during GSV and SSV ablation.^[2] One study reported a granulomatous foreign body reaction in the vein lumen 30 days following catheter-directed endovenous insertion of N-butyl polymer into the superficial epigastric veins in a porcine model.^[13] Fibroblast invasion into the contents of the vein lumen and total occlusion were also observed 60 days post-procedurally in the same model.^[14]

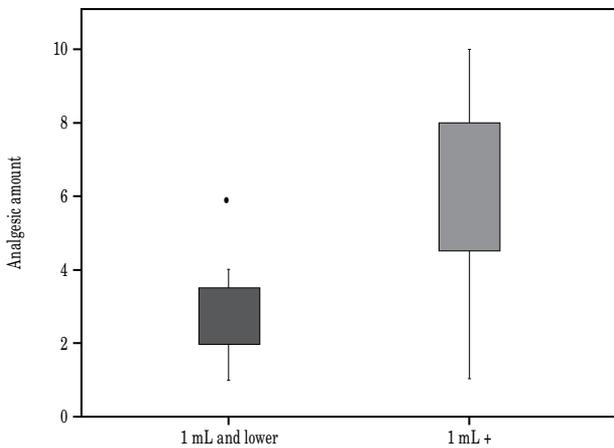


Figure 2. Amount of analgesia used.

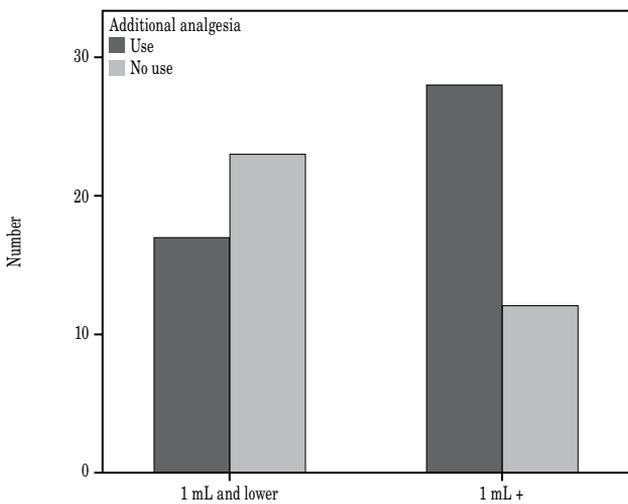


Figure 3. Rate of analgesia use.

Polymerization time depends on the tissue type, the fluid characteristics, and the amount of product administered. Administered under appropriate conditions, NBCA polymerization commences within one to two sec and is completed in approximately five sec. Significant decreases in the procedural time, postoperative thrombophlebitis, and pain were observed in the present study due to the faster polymerization rate and lower viscosity of the NBCA polymer ($p=0.001$, $p=0.002$, and $p=0.001$, retrospectively). The mean procedural times in previous studies were 21, 18.6, 24, and 13.3 min, respectively.^[15-18] However, the duration of procedure requires more specific definition. The reported procedural time in a study was 5.4 ± 2.5 min,^[19] indicating that some patients received NBCA treatment within <3 min. Our procedure resulted in a mean procedural time of five and six min for <1 mL and >1.5 mL administration, respectively, with a high total occlusion rate. Our relatively short procedural time may be due to the learning process having long since been completed, and to the widespread application of the technique in our routine practice.

The NBCA was first employed to treat GSV insufficiency in 2013 in a series of 38 patients.^[20] The mean treated vein length was 33.8 cm. A complication rate of 21% was reported including phlebitis (15.8%), cellulitis (4%), hyperpigmentation in a vein located close to the skin (4%), and thrombus extensions across the SFJ (21.1%), although these all resolved completely during 12-month follow-up.

A multi-center, prospective European trial involving 70 patients was conducted using the VenaSeal™ device.^[16] The mean GSV diameter in the SFJ was 7.8 mm. Post-procedural complications included phlebotic reaction (11.4%), pain (8.6%) for a median one-day time frame, and adhesive extension beyond the SFJ (1.4%). The rate of thrombophlebitis development in the present study was lower in Group 1 than in Group 2 (1:31, $p=0.305$). This is due to the absence of any cavity not filled with NBCA and of any residual blood in the vessel in the continuous technique. We attribute this to the lower viscosity of NBCA, the use of a smaller amount of NBCA, and the continuous compression employed in this study.

In their study, Almeida et al.^[20] reported mild pain and inflammation in as few as 13.2% of patients, that this was easily controlled by means of oral nonsteroidal anti-inflammatory drugs, and that all cases were self-limited. However, in the present study, analgesia

requirement rates were higher, although none of our patients required oral non-steroidal anti-inflammatory drugs. Our patients used only paracetamol. Forty-two percent of the patients in Group 1 and 70% of those in Group 2 required analgesia. Pain, time to analgesia requirement (h), and amount of analgesia (tablet) used were significantly lower in the group receiving <1 mL NBCA ($p=0.013$, $p<0.001$, and $p<0.001$, respectively). A significant improvement was also observed in the CEAP and VQQ scores measured at the first month in both groups, compared to the baseline scores ($p<0.001$ for both). Furthermore, the lower development of thrombophlebitis and pain in this technique can be attributed to the absence of any empty spaces not containing glue and of any residual blood inside the vessel, and to the use of a lower amount of NBCA. In addition, continuous compression, rapid closure, and a very short procedural time have been shown to be capable of preventing DVT. Due to the rapid polymerization of NBCA, the SFJ section of the GSV was rapidly closed, and administration of optimal pressure over the SFJ lowered the risk of flow into the deep vein.

The small sample size and relatively short follow-up are the main limitations of the present study.

In conclusion, our study findings suggest that this novel NBCA technique is both safe and effective. We attribute our success rate in the <1 mL group in particular to the polymerization rate, viscosity, and continuous compression which distinguishes our procedural technique from other methods. The technique allows rapid application with no open segments in the vein. We, therefore, believe that the same clinical success, with fewer complications (such as phlebitis, thrombophlebitis, ecchymosis, and pain) and greater patient comfort, can be achieved using a lower dose of NBCA in the treatment of venous insufficiency and the vast majority of incompetent GSV cases can be treated in this manner.

Declaration of conflicting interests

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