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Efficiency of the endovenous cyanoacrylate for the treatment of varicose veins using the Venablock™ system: a 24-month follow-up study of 116 patients

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ABSTRACT

Objectives: Dilation of superficial veins and valvular insufficiency cause the common condition, varicose veins (VVs) on the lower extremities. The treatment modalities for VVS include endovascular thermal ablation techniques using laser, steam and radiofrequency, surgery, foam sclerotherapy, which has various adverse effects. N-butyl cyanoacrylate (NBCA) is a relatively novel polymerizating agent that is used for the treatment of VVs. The aim of this study is to evaluate and present the 24 months outcomes results of endovenous NBCA treatment in 116 patients with VV.

Methods: This is a prospective study on 116 patients (71 females, 45 males), treated in a single-center between August 2017 and March 2019. NBCA administration (Venablock®, Invamed, Turkey) was carried out with local anesthesia under ultrasound guidance. All patients were scheduled for follow-up evaluation at 2 weeks, 3, 6, 9, 12, and 24 months. Clinical assessment, VCSS, and ultrasound were performed on patients in the follow-up visits.

Results: The mean follow-up period was 16.27 ± 5.62 months. The preoperative and postoperative VCSS values were 6.93 ± 2.60 and 2.40 ± 1.12, respectively ($p < 0.0001$). The patients with a greater GSV diameter experienced an unfavorable outcome following the NBCA procedure ($p < 0.001$). The overall complication rate was 12.9%. The complete occlusion was achieved in 101 (87.0%) patients.

Conclusions: The NBCA administration is a safe treatment method for the VVs, and provides a satisfactory occlusion ratio with improved outcomes.

Keywords: cyanoacrylate, varicose veins, chronic venous insufficiency, Venablock™

Varicose veins (VVs) of the lower extremities are common chronic conditions that occur due to the dilation of superficial veins and valvular insufficiency. It has been reported that every one out of three people suffers from this condition in varying degrees, and their life quality is impaired gradually [1]. The most affected vessels are great and small saphenous veins, and the symptoms vary in a great diversity from fatigue, pain, and swelling to skin ulcers on the frontal side of the tibial surface [2]. Older age, female gender, pregnancy, family history of deep venous thrombosis and venous diseases, longer durations of standing and walking, Caucasian origin are among the risk factors for VV development [3, 4].

Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) classification is employed for the worldwide

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classification of venous diseases since 1994 subcategorizing the severity of the VVs depending on numerous variables [5].

The treatment options for VVS include thermal ablation techniques with laser, steam and radiofrequency, surgery, foam sclerotherapy, which has their own disadvantages and complications including anesthesia requirement, embolism, rec]urrence, and hematoma formation [6, 7]. Recently, an endovenous mechanochemical treatment agent, n-butyl cyanoacrylate (NBCA) has been popularized with favorable outcomes and easy-to-use methodology for the treatment of VVs. When contacted with the anions in blood, the NBCA administered into the vessel rapidly polymerizes and provides the occlusion of the VVs by an inflammatory response resulting in fibrosis [8, 9].

In this study, we aimed to evaluate and present the short-term results of endovenous NBCA treatment in 116 patients with different levels of venous insufficiency and VV severity. The patients were compared in terms of the occlusion status (partial occlusion, complete occlusion, recanalization) following the NBCA treatment procedure.

METHODS

This prospective study involved a total of 116 patients (71 female, 45 male) who were treated for VVs with NBCA administration (Venablock®, Invamed, Turkey) in a single-center between August 2017 and March 2019.

Inclusion/exclusion Criteria

All patients were evaluated according to the CEAP classification. A Doppler ultrasonography in standing position was also performed. Patients >18 years of age with a CEAP class C2-C6 VVs, GSV diameter of >5.5mm, reflux current 2 sec or longer were included. Patients with a GSV diameter of <5.5mm or >13 mm, with chronic or acute thrombophlebitis, deep venous insufficiency or thrombosis, systemic infection, hypercoagulability state, previous history of phlebectomy or sclerotherapy were excluded. Pregnant and lactating patients and patients who preferred another treatment method were also excluded.

The Venous Clinical Severity Score (VCSS) was calculated for each patient before and after the procedure. For the evaluation of The VCSS, 0 corresponds to no significant venous disease and 30 is the worst available score [10].

Informed consent of all patients was obtained. The study was conducted in accordance with the Declaration of Helsinki.

Procedure

All procedures were carried out with local anesthesia under ultrasound guidance as previously described with the patient in the supine position. The administration of the Venablock® system technique has been previously described. Briefly, a 7F vascular sheath was inserted into the GSV, and a J-guide wire was inserted into the saphenofemoral junction through the sheath. The 4F micro delivery catheter was inserted and a total of 1.5-2 ml of NBCA was applied to the GSV segments with as increments of 0.2-0.3 ml. An immediate external compression was applied for 30 sec. After the procedure, a full-length elastic bandage was applied on the index leg and asked to unwrap after 24 hours. Patients were asked to walk for 15 minutes and discharged on the same day. All patients are scheduled for follow-up evaluation at 2 weeks, 3, 6, 9, 12, and 24 months. Clinical assessment, VCSS, and ultrasound were performed on patients in the follow-up visits.

Evaluation of the Patients

All patients who underwent VV treatment using NBCA were subgrouped into two main outcome groups depending on their occlusion status: Group 1: Partial occlusion and recanalization; Group 2: Complete occlusion. The occlusion status was evaluated in accordance with the Merchant *et al*. [12]. Complete occlusion (CO) was defined as the lack of flow in the treated segment of varicose GSV, whereas partial occlusion (PO) was defined as the ≤5 cm segment of flow in the treated vein. Recanalization was defined as >5 cm segment of flow in the treated vein.

Two comparative groups with different outcomes after NBCA treatment were compared in terms of weight, age, gender, diameter of the GSV, follow-up duration, the length and side of the affected vessel, a history of pake excision, CEAP class, degree of insufficiency, complications after the procedure, and VCSS before and after the procedure.

Statistical Analysis

The statistical evaluation of this study was performed using the statistical program SPSS v.11.5 (SPSS Inc, Chicago, IL). Descriptive statistics were given as mean±standard deviation for continuous variables and, as frequency and percentage for categorical variables. The student's t-test was performed if the normal distribution was provided, and Mann-Whitney U test if otherwise. When the relationship between the two qualitative variables was examined, Chi-square and Fisher's exact t-tests were used. The comparison of the variables before and after the procedure was performed using the paired samples t-test and Chi-square test. The time for occlusion was determined using a Kaplan-Meier survival curve. The statistical significance level was considered as < 0.05.

RESULTS

In our study setting, we compared the outcome characteristics of the patients who underwent NBCA treatment for the management of VVs during the follow-up. The mean follow-up was 16.27± 5.62 months. The CO was achieved in 101 (87.0%) patients. Twelve (10.3%) of the patients experienced an PO, whereas recanalization was present in three (2.7%) patients.

While patients were categorized into two subgroups depending on their occlusion status after the procedure, Group 1 consisted of 15 patients (8 females, 7 males) with an outcome of partial occlusion and recanalization after the procedure. Group 2 included 101 individuals (63 female, 38 male) with total occlusion of the affected vein. The comparison of variables between the groups was presented in Table 1.

The mean age of the patients was 52.67 ± 8.74 years with a mean weight of 74.00 ± 12.72 kg in the artial occlusion and recanalization group. The patients in the total occlusion group aged 47.85 ± 10.48 years with a mean weight of 71.59 ± 13.24 kg. The age and weight of the patients in two different outcome groups were not statistically significant ($p = 0.093$ and $p = 0.437$, respectively). The mean GSV diameter before the NBCA treatment was 8.71 ± 1.52 mm in the partial

Table 1. Comparison of the quantitative variables between the outcome groups depending on the occlusion status

Variables	Outcome Following NBCA Treatment				*p* value
	Partial occlusion & recanalization (n = 15)		Complete occlusion (n = 101)		
	Mean ± SD	Median (Min - Max)	Mean ± SD	Median (Min-Max)	
Weight (kg)	74.00 ± 12.72	73.00 (54.00-91.00)	71.59 ± 13.24	70.00 (51.00-105.00)	0.437
Age (years)	52.67 ± 8.74	53.00 (39.00-68.00)	47.85 ± 10.48	49.00 (26.00-71.00)	0.093
Diameter of the GSV (mm)	8.71 ± 1.52	8.00 (6.80-12.00)	7.26 ± 0.95	7.10 (5.50-11.00)	**< 0.001**
Follow-up duration (months)	14.73 ± 5.51	13.00 (8.00-23.00)	16.50 ± 5.63	17.00 (8.00-26.00)	0.221
Length of the affected segment on the vessel (cm)	39.13 ± 4.75	40.00 (29.00-49.00)	40.64 ± 4.90	40.00 (28.00-53.00)	0.341
Preop VCSS	6.93 ± 2.60	7.00 (3.00-14.00)	6.85 ± 2.82	6.00 (3.00-18.00)	0.623
Postop VCSS	2.40 ± 1.12	2.00 (0.00-5.00)	2.18 ± 1.04	2.00 (0.00-5.00)	0.453

NBCA = N-butyl cyanoacrylate, GSV = great saphenous vein, VCSS = The Venous Clinical Severity Score

Table 2. Comparison of the categorical variables between the outcome groups depending on the occlusion status.

Variables		Outcome Following NBCA Treatment				*p* value
		Partial occlusion & recanalization (n = 15)		Complete occlusion (n = 101)		
		N	%	N	%	
Gender	**Male**	7	46.7	38	37.6	0.502
	Female	8	53.3	63	62.4	
Side	**L**	10	66.7	59	58.4	0.544
	R	5	33.3	42	41.6	
Pake Excision	**No**	2	13.3	20	19.8	0.733
	Yes	13	86.7	81	80.2	
CEAP	**C2**	4	26.7	28	27.7	0.857
	C3	8	53.3	56	55.4	
	C4	3	20.0	11	10.9	
	C5	0	0.0	3	3.0	
	C6	0	0.0	3	3.0	
Complications	**None**	13	86.6	87	86.2	1.000
	Ecchymosis	1	6.7	7	6.9	
	Phlebitis	1	6.7	6	5.9	
	Hematoma	0	0.0	1	1.0	
Degree of the Insufficiency	**2 sec**	0	0.0	6	5.9	0.098
	3 sec	10	66.7	83	82.2	
	4 sec	5	33.3	12	11.9	

CEAP = Clinical-Etiologic-Anatomic-Pathophysiologic classification, NBCA = N-butyl cyanoacrylate

occlusion and recanalization group and 7.26 ± 0.95 mm in the complete occlusion group ($p < 0.001$). The mean length of the affected segment on the vessel was 39.13±4.75 for the partial occlusion and recanalization group and 40.64 ± 4.90 for the complete occlusion group ($p = 0.341$).

The preoperative and postoperative VCSS values were 6.93 ± 2.60 and 2.40 ± 1.12 for the partial occlusion and recanalization group, whereas, 6.85 ± 2.82 and 2.18 ± 1.04, respectively for the complete occlusion group ($p = 0.623$ and $p = 0.453$, respectively). The number of patients with different CEAP classes was not significantly different between the outcome groups ($p = 0.857$).

The gender, the side of the affected extremity, history of a pake excision and the degree of insufficiency did not differ between the groups ($p = 0.502$, $p = 0.544$, $p = 0.733$ and $p = 0.098$, respectively) (Table 2).

The complication rates were also compared between the groups. The overall complication rate was 12.9%. The most common complication was ecchymosis in eight (6.9%) patients, followed by phlebitis in seven (6.0%) and hematoma in one (0.9%) patient. While we evaluated patients overall, the mean VCSS was 6.86 ± 2.78 before the procedure, whereas it was 2.20 ± 1.05 following the NBCA application ($p < 0.0001$). The number of patients distributed in different CEAP score groups was significantly different before the procedure and at the end of the follow-up period ($p < 0.01$) (Table 3).

Kaplan-Meier curve presents the analysis results of the treatmenr with a statistical uncertainty of 95% confidence interval (CI) in dot plots (Fig. 1). The ratio

Table 3. Comparison of the variables before and after the NBCA treatment.

	Before the NBCA treatment (n = 116) Mean ± SD	After the NBCA treatment (n = 116) Mean ± SD	*p* value
VCSS	6.86 ± 2.78	2.20 ± 1.05	**< 0.0001**
CEAP (n)			
C1	0	101	
C2	32	5	**< 0.01**
C3	64	8	
C4	14	2	
C5	3	0	
C6	3	0	

VCSS = The Venous Clinical Severity Score, CEAP = Clinical-Etiologic-Anatomic-Pathophysiologic classification, NBCA = N-butyl cyanoacrylate

of cases with CO was 100% on the first nine months of the study period. At the end of the first year, 93.4% of the cases still had CO. At the end of the second year follow-up duration, 75.5% of the cases were with CO.

DISCUSSION

Vascular surgeons are in search of a method with high efficiency, which requires the absence or minimal amount of anesthesia and allows the patient to return to routine daily activities within a shorter amount of time. Recently, minimally invasive techniques have replaced the surgical procedures for the treatment of lower extremity VVS. Although techniques using radiofrequency or laser beam are used frequently, they still manifest complications and adverse reactions in a range from pain and swelling to the development of hematoma and ecchymosis [13, 14].

NBCA is a relatively novel agent in the management of VVs with high efficacy, minimum pain control and complication ratio, and a higher amount of patient satisfaction. As the use of NBCA increases in vascular practice worldwide, the number of newly developed NBCA-based products increase in the markets. Since the method does not use a thermally-induced closure, the risk of thermal injury and unfavorable cosmetic outcomes such as increased skin pigmentation are also out of concern. On the other hand, thermal ablation techniques were shown to be

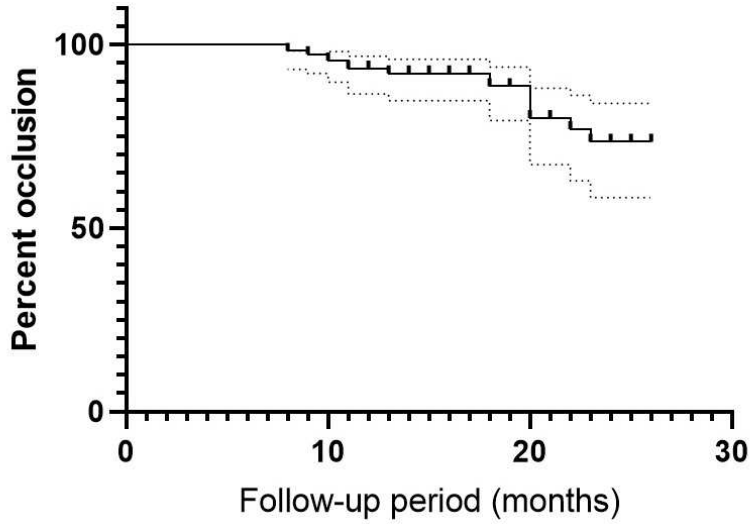

Fig. 1. The Kaplan-Meier curve analysis of occlusion rate of incompetent saphenous veins after NBCA treatment. The results were given within 95% CI. NBCA = N-butyl cyanoacrylate, CI = Confidence interval.

more traumatic and require tumescence analgesia, and require correct setting of the power and energy in terms of Watt and Joule.

This study followed up a total of 116 patients who underwent embolization with NBCA for the treatment of lower extremity VVs. In the study setting, we attempted to compare the demographics and post-procedural data between the patients with total, partial, and no evidence of occlusion.

We defined the CO as the absence of patency or recanalization in any treated segment of >5 cm in length as described earlier by Merchant *et al*. [12]. The CO was achieved in 87% of our patients within the 24 months of the follow-up period, whereas 10.3% patients had PO and 2.7% did not show evidence of occlusion. There are similar studies with varying follow-up times reporting a total occlusion between 92-96% with NBCA treatment. However, their sample size is relatively small compared to our sample size (23 and 77 vs. 116 patients). The follow-up period of these studies was 6-12 months, and we suggest that a longer follow-up period would result in a higher ratio of recurrence cases [15, 16]. Supporting this, several reports present a decline in the rate of patients with CO during the time, as the ratio of 100% reversed to 78.5% after one year [17]. We suggest that the type of the NBCA product, the characteristics of the patient, and the experience of the treating physician might have an important effect on the outcomes. Besides, Tang suggested that the distance of the catheter tip from the saphenofemoral junction (SFJ) is of concern for the prevention of adverse effects including incomplete occlusion and recurrence [16].

In our study group, the patients with a greater GSV diameter experienced an unfavorable outcome following the NBCA procedure. This might be a consequence of a decline in the efficiency of the procedure in patients with a greater GSV diameter. We suggest that, the incidence of a CO is decreased in this patient group.

In our study, we have also evaluated the clinical improvement in patients' conditions using the VCSS System. Although the VCSS did not differ between the favorable and unfavorable outcome groups, taken together, the scores significantly improved in the patient population following the procedure as an indicator of the procedur's efficiency. These data suggest that there might be additional factors contributing to the outcomes, and these factors should be evaluated before choosing the most appropriate option for an individual patient in the treatment of VVs.

Despite various adverse effects reported following the treatment with NBCA, the complications we experienced in our patients were ecchymosis in eight patients, phlebitis in seven patients, and hematoma in one patient. Our data is comparable to those of endovascular thermal ablation techniques and surgery, with a low ratio of complications which completely resolved in a short amount of time without decreasing the life quality of the patients. We also did not experience serious reactions including DVT and embolism, which are previously described with the use of thermal ablation methods. Possibly, some predictive markers such as homocysteine, lupus anticoagulant, high sensitive-CRP, D-dimer, fibrin-derived products should be used before the procedure, in order to define and exclude the patients with an increased risk of thrombotic events [18]. Furthermore, Tang *et al*. [19] reported an acellular foreign body reaction in the adventitia tissue suggesting that possible extravasation of the NBCA should be taken into consideration. In their series of VV patients, Acıpayam *et al*. [20] demostrated that a lower than 1 mL dose of NBCA was related to a fewer complication ratio and greater patient satisfaction at the end of the first month following the procedure. Thus, studies established with various dosing regimen of NBCA are required to consider the appropriate dosing for each individual in order to lower the complication rate and obtain a greater procedure efficiency.

Limitations

Our study has several limitations to discuss. First of all, we did not compare the CEAP classes during the follow-up period. Also, we used VCSS in the evaluation of postprocedural outcomes, other scoring techniques such as the Aberdeen Varicose Vein Questionnaire might yield an additional perspective.

CONCLUSION

In conclusion, the NBCA system provided a satisfactory occlusion ratio with improved outcomes and comparable results with the previous data in the literature. Of the patient group, only GSV diameter dif-

fered, whereas other study variables gender, weight, the side of the affected extremity, length of the GSV, VCSS before and after the procedure, implementation of a pake excision, CEAP classification, and the degree of insufficiency were shown to not affect the outcome following the NBCA administration. Thus, the NBCA administration is a safe approach in the treatment of VVs, and key safety measures should be considered as suggested by the guidelines.

Authors' Contribution

Study Conception: ACD; Study Design: ACD; Supervision: FK; Funding: ACD; Materials: ACD; Data Collection and/or Processing: ACD; Statistical Analysis and/or Data Interpretation: Eİ; Literature Review: Eİ, FK; Manuscript Preparation: Eİ and Critical Review: Eİ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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