RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2024.17037
Ankara Üniversitesi Tıp Fakültesi Mecmuası 2024;77(3):265-271

SURGICAL MEDICAL SCIENCES / CERRAHİ TIP BİLİMLERİ

Clinical Efficacy and Safety of Using N-Butyl Cyanoacrylate in the Treatment of Perforator Vein Insufficiency

Perforatör Ven Yetmezliğinin Tedavisinde N-Butil Siyanoakrilat Kullanımının Klinik Etkinliği ve Güvenliği

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Abstract

Objectives: Venous insufficiency has traditionally been managed through various techniques, including surgical interventions and thermal ablation. A novel technique for venous insufficiency is non-thermal ablation using a vein sealing system, involving the endovenous delivery of N-butyl cyanoacrylate (NBCA) tissue adhesive to the vein. Despite advances in treatment options, the management of isolated perforator incompetence remains a challenge due to its role in the pathophysiology of chronic venous insufficiency (CVI). This single-center retrospective study aimed to evaluate the efficacy of the non-thermal, non-tumescent embolization method using NBCA for managing perforator incompetence.

Materials and Methods: We retrospectively analyzed 98 consecutive patients diagnosed with perforator vein insufficiency, treated with NBCA. The study protocol included physical examinations, Doppler ultrasonography, venous clinical severity scoring, CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classification, and quality of life assessments before and after the procedure. The primary goal was to compare clinical, functional, and duplex parameters in managing varicose vein diseases with isolated primary perforator incompetence using duplex-guided NBCA treatment. Analyses were performed using SPSS software. Categorical variables were reported as frequencies, and continuous variables as means ± standard deviations or medians with interquartile ranges. Chi-square or Fisher's exact tests were used for categorical data, and the Mann-Whitney U test for continuous variables. A p value less than 0.05 was considered statistically significant.

Results: Ninety-eight obliteration procedures were completed. The study evaluated occlusion rate, procedural pain, phlebitis, ecchymosis, and paresthesia. The occlusion rate at 6 months was 96.9%, with a significant reduction in pain and other symptoms of CVI. The incidence of complications was low. Phlebitis was observed in 3.4% of cases, ecchymosis in 2.8%, and transient paresthesia in 1.7%. There were no reports of serious adverse events, such as deep vein thrombosis or systemic allergic reactions.

Conclusion: The interruption of perforators effectively reduces the symptoms of CVI and promotes rapid ulcer healing. This non-tumescent, non-thermal embolization method can be safely applied with high success rates. The results of this study suggest that NBCA is a viable option for treating perforator incompetence.

Keywords: N-butyl cyanoacrylate, perforator vein incompetence, venous ulcer

Öz

Amaç: Venöz yetmezlik geleneksel olarak cerrahi müdahaleler ve termal ablasyon dahil olmak üzere çeşitli tekniklerle tedavi edilmektedir. Venöz yetmezlik için yeni bir teknik, N-butil siyanoakrilat (NBCA) doku yapıştırıcısının damara endovenöz olarak verilmesini içeren, bir damar kapatma sistemi kullanılarak termal olmayan ablasyondur. Tedavi seçeneklerindeki ilerlemelere rağmen, izole perforatör ven yetmezliğinin tedavisi, kronik venöz yetmezliğin patofizyolojisindeki rolü nedeniyle halen zorluk teşkil etmektedir. Bu tek merkezli retrospektif çalışma ile, perforatör ven yetmezliğinin tedavisinde NBCA kullanılarak termal olmayan, tümesan kullanılmayan embolizasyon yönteminin etkinliğinin değerlendirilmesi amaçlanmaktadır.

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Received/Geliş Tarihi: 21.07.2024 **Accepted/Kabul Tarihi:** 10.08.2024

Gereç ve Yöntem: NBCA ile tedavi edilen, perforatör ven yetmezliği tanısı alan 98 ardışık hasta retrospektif olarak analiz edilmiştir. Çalışma protokolü, işlem öncesi ve sonrası fizik muayene, doppler ultrasonografi, venöz klinik şiddet skorlaması, CEAP (Klinik-Etiyoloji-Anatomi-Patofizyoloji) sınıflandırması ve yaşam kalitesi değerlendirmelerini içermektedir. Birincil amaç, Doppler ultrasonografi kılavuzluğunda NBCA tedavisi kullanılarak izole primer perforatör ven yetmezliği olan damar hastalıklarının tedavisinde klinik, fonksiyonel ve Doppler ultrasonografi parametreleri karşılaştırmaktır. Analizler SPSS yazılımı kullanılarak yapılmış olup, kategorik değişkenler frekanslar olarak ve sürekli değişkenler ortalama ± standart sapmalar veya çeyrekler arası aralıklara sahip medyanlar olarak rapor edilmiştir. Kategorik veriler için ki-kare veya Fisher's exact testleri, sürekli değişkenler için Mann-Whitney U testi kullanılmıştır. 0,05'ten küçük bir p değeri istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Doksan sekiz obliterasyon işlemi tamamlanmıştır. Çalışmada obliterasyon oranı, işlem esnasında ve sonrasında ağrı, flebit, ekimoz ve parestezi değerlendirilmiştir. Altıncı ayda obliterasyon oranı %96,9 olup, ağrıda ve diğer kronik venöz yetmezlik semptomlarında önemli bir azalma olmuştur. Komplikasyon görülme sıklığı düşüktür. Olguların %3,4'ünde flebit, %2,8'inde ekimoz ve %1,7'sinde geçici parestezi gözlenmiştir. Derin ven trombozu veya sistemik alerjik reaksiyonlar gibi ciddi yan etkiler bildirilmemiştir.

Sonuç: Perforatör venlerin obliterasyonu ile kesintiye uğratılması, kronik venöz yetmezlik semptomlarını etkili bir şekilde azaltmakta ve ülserin hızlı iyileşmesini desteklemektedir. Tümesan kullanılmayan, termal olmayan bu embolizasyon yöntemi, yüksek başarı oranlarıyla güvenle uygulanabilmektedir. Bu çalışmanın sonuçları, NBCA'nın perforatör ven yetmezliğinin tedavisinde uygun bir seçenek olduğunu göstermektedir.

Anahtar Kelimeler: N-butil siyanoakrilat, perforatör ven yetmezliği, venöz ülser

Introduction

Venous insufficiency has traditionally been managed through various techniques, including surgical interventions and thermal ablation. However, a novel technique for venous insufficiency is non-thermal ablation using a vein sealing system, involving the endovenous delivery of N-butyl cyanoacrylate (NBCA) tissue adhesive to the vein, causing fibrosis. Perforators are veins that connect the superficial and deep venous systems either directly to main veins or indirectly through the muscular and soleal venous plexus.

Despite advances in treatment options, the management of isolated perforator incompetence remains a challenge due to its role in the pathophysiology of chronic venous insufficiency (CVI). This study explores the effectiveness of NBCA in treating perforator incompetence, providing insights into its clinical and functional outcomes.

The primary aim of this study is to compare clinical, functional, and duplex outcomes following treatment with NBCA. Given the low prevalence of isolated perforator incompetence cases, there is a lack of comprehensive clinical studies in the literature. This study seeks to fill this gap by providing detailed observations and results from a retrospective analysis.

Materials and Methods

This retrospective study analyzed 98 varied cases of lower limb varicose vein diseases with isolated primary perforator incompetence, between February 2018 and May 2021. This retrospective study, conducted at a single center, received approval from the Human Research Ethics Committee of Ankara University Faculty of Medicine (approval no.: İ06-454-24, date: 09.07.2024) and adhered to the principles outlined in the Declaration of Helsinki. All patients provided informed consent for their participation in the study.

Patients presenting with perforator vein incompetence symptoms were examined in the outpatient clinic. A thorough history and clinical examination were conducted, assessing the venous system and recording symptoms such as dilated veins, pain, night cramps, edema, ulcers, itching, bleeding, pigmentation, eczema, activity tolerance, and quality of life (using the Short Form-36 questionnaire).

Inclusion criteria for the study were patients aged 18-70 years with CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classification class C2-C6. Exclusion criteria included patients with deep vein thrombosis, significant arterial disease, or those who had undergone previous sclerotherapy or surgical interventions for venous insufficiency.

Patients underwent duplex ultrasound to confirm the presence and location of incompetent perforator veins. NBCA was then administered under ultrasound guidance to the identified incompetent perforators. The procedure was performed under local anesthesia, and patients were monitored for immediate complications.

A duplex ultrasonographic study of the venous system was done preoperatively to assess the varicose vein diseases, the presence of saphenofemoral or saphenopopliteal incompetence, perforator vein incompetence, and the status of the deep veins.

For the superficial and perforator system, the veins are examined in standing position. Perforators were examined using transverse and oblique scanning since their long axis is seen well in those planes. The veins are visualized correctly and evaluation of the flow, compressibility, and augmentation of flow with movements are documented. The incompetent superficial and deep veins have a shorter reflux time (≤0.5 s) and those with signs of obstruction (thrombus).

For obtaining venous reflux in short perforating veins, we used the following criteria: A shorter time cut point of 0.35 s was used to define the reflux and perforators with a diameter

of >3.5 mm. We marked the site and the number of perforating veins and noted.

For patients with venous ulceration, conservative management with daily saline dressings and layered bandage application was executed until the active infection descended. The procedure was not delayed by allowing time for the complete healing of the ulcer.

After mapping the treatment area, access to the veins to be treated was visualized and a 25-30-gauge needle was placed within the vein by duplex guidance. Vein sealing system includes 3 mL of NBCA-based embolization polymer and we implemented this microdelivery system for all patients. The target veins which were most proximal were treated first. The amount of foam injected was determined by using ultrasound to visualize when the targeted vein was filled with glue. The deep venous system was carefully investigated with the ultrasound probe (Figure 1).

All cases were implemented under local anesthesia. Tumescent anesthesia was not required. Mean volume of glue delivered was 1.5 cc. An elastic bandage was then wrapped around the leg and the patients were immediately asked to walk for 20 min. The median duration time of the procedure was 15 minutes (ranges between 10 and 30 minutes).

Compression dressing with bandage was applied after the procedure, and the same was removed on day 2nd no patient underwent a secondary surgical intervention, and none of the patients developed a deep vein thrombosis or pulmonary embolism. All the patients were discharged on the same day of operation.

Patients were not given any nonsteroidal anti-inflammatory drug postoperatively, only advised to wear compression stockings for a few days.

Post-procedural assessments included duplex ultrasound to verify vein occlusion, as well as clinical evaluations to monitor for pain, phlebitis, ecchymosis, and paresthesia. Follow-up visits were scheduled at 1 week, 1 month, and 6 months post-procedure to assess the outcomes and any potential complications.

Results

Of the 98 patients, 61.2% were males and 38.8% were females, with a mean age of 47.9±12.4 years. The study found a higher prevalence of isolated perforator incompetence in males. Among the patients, 28.5% had previously used compression stockings without improvement. The primary presenting

Table 1: Patients demographics and preprocedural clinical examination

Age (years, mean)	47.9±12.4 (range 23-79)
Gender (male, n, %)	60 (61.2%)
Erythema (n, %)	15 (15.3%)
Edema (n, %)	51 (52%)
Pain (n, %)	69 (70.4%)
Telengiectasia (n, %)	49 (50%)
Pigmentation (n, %)	61 (62.2%)
Dilated veins (n, %)	61 (62.2%)
Duplex USG reflux grade (n, %)	
Grade 2	5 (5.1%)
Grade 3	62 (63.3%)
Grade 4	31 (31.6%)
CEAP classification (n, %)	
C4b	26 (26.5%)
C5	24 (24.5%)
C6	48 (49%)
Size of PV (mm) (median, min.-max.)	40 (35-52)

USG: Ultrasonographic, CEAP: Clinical-Etiology-Anatomy-Pathophysiology, min.-max.: Minimum-maximum

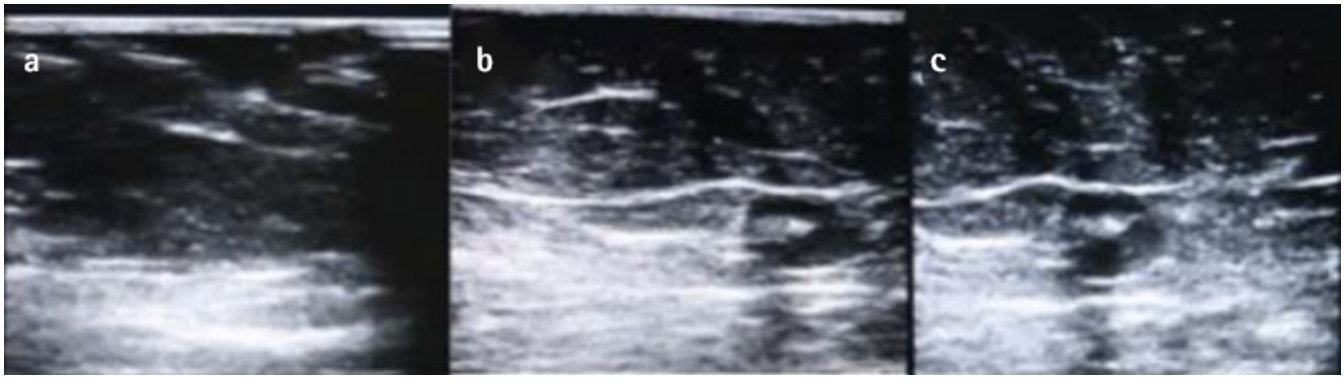

Figure 1: a) Ultrasonographic images of perforator veins. b) After mapping the treatment area, access to the veins to be treated was visualized and a 25-30-gauge needle was placed within the vein by duplex guidance. c) Vein sealing system includes 3 mL of NBCA-based embolization polymer and visualized within the vein via Doppler ultrasonography

NBCA: N-butyl cyanoacrylate

symptom was pain (70.4%) (Table 1).

The primary outcome measure was the occlusion rate of treated veins, assessed at one week, one month, and six months. Secondary outcome measures included procedural pain, assessed using a visual analogue scale (VAS), and the incidence of complications such as phlebitis, ecchymosis, and paresthesia.

Vein closure rates after the procedure were classified as total and partial, and according to the follow-up days. On the first day, total closure rate was 80.61%, first week was 90.82% and 6 months was 97.96% in accordance with our expectations. Only minor complications were reported, including mild phlebitis (8.16%), ecchymosis (12.2%), and transient paresthesia (5.1%). No major adverse events or significant side effects were observed.

Table 2: Procedural and postprocedural features		
Procedure duration (minutes) (median, min.-max.)	15 (10-30)	
Pain during procedure (n, %)	19 (19.4%)	
Echymosis (n, %)	12 (12.2%)	
Parestesia (n, %)	5 (5.1%)	
Phlebitis (n, %)	8 (8.16%)	
Vein closure rates (%)	**Total**	**Partial**
1st day	80.61%	19.39%
1st week	90.82%	9.18%
6th month	97.96%	2.04%
Symptom relief (%)		
Good improvement	73.5%	
Moderate improvement	22.4%	
Mild improvement	4.1%	
Unchanged	0%	
Worsening	0%	
Ulcer healing (n, %)		
Granulation tissue formation	33 (33.7%)	
Decrease in size	53 (54.1%)	
Decrease in itching sensation	10 (10.2%)	
Non-healing	2 (2%)	
Ulcer recurrence (n, %)	4 (4.1%)	
Recurrent perforator incompetence (n, %)	4 (4.1%)	
Recanalization (n, %)	1 (1%)	
Technical success (n, %)	97 (99%)	
Venoactive drugs (%)	46.9%	
Compression bandage (%)	61.2%	
Postoperative pain (VAS 1-10) (median, min.-max.)	2 (1-3)	
Return to normal days (days) (median, min.-max.)	2 (1-5)	

Min.-max.: Minimum-maximum, VAS: Visual analogue scale

Patients (19.4%) reported minimal pain during the procedure, with a mean VAS score of 2.1±0.7. No severe pain episodes were recorded (Table 2).

Patients were instructed to return for follow-up in intervals of one week and 6 months respectively. Their symptomatic and clinical improvement was documented at the end of the one week and six months (+3 good improvement/asymptomatic, +2 moderate improvement, +1 mild improvement, 0 unchanged, -1 worsening). Symptomatic improvement was as the following; good improvement rate was 73.5%, moderate improvement was 22.4%, mild improvement 4.1%, and there was no patients described worsening or unchanged symptoms.

The duration of return to normal day activities and the perioperative complications following the procedures were also noted. At follow-ups, the patients were assessed clinically for presence of varicosities, resolution of skin changes, and healing of ulcers. The symptomatic improvement of active ulcer (granulation tissue, decrease in size of ulcer, decrease itching sensation in ulcer) began around the first week, and signs of satisfactory healing of ulcer took an average of 8 weeks. The initial size of the ulcer did not correlate neither with the rate of ulcer healing nor with the time taken for the healing of the ulcer. Healing rates was noted as; decrease in the size of ulcer was mostly seen with percentage of 54.1, granulation tissue formation was 33.7%, decrease in itching sensation was 10.2%, and 2% was in same status (Figure 2).

Return to normal day activities and quality of life assessment was also applied on follow up by Short Form-36 before the procedure, on first day, week and 3 months. Post procedural quality of life scores were significantly increased ($p<0.001$) (Figure 3).

Vein closure rates after the procedure were classified as total and partial, and according to the follow up days. On the first day, total closure rate was 80.6%, first week was 90.8% and 6

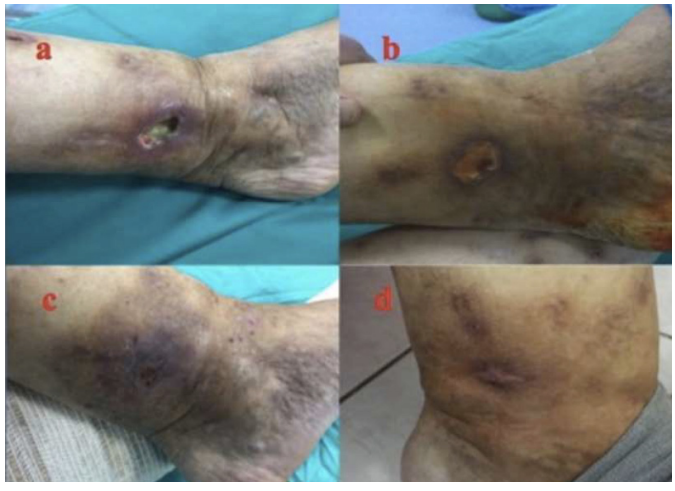

Figure 2: Significantly healing ulcer on follow-up (Figure a to d respectively)

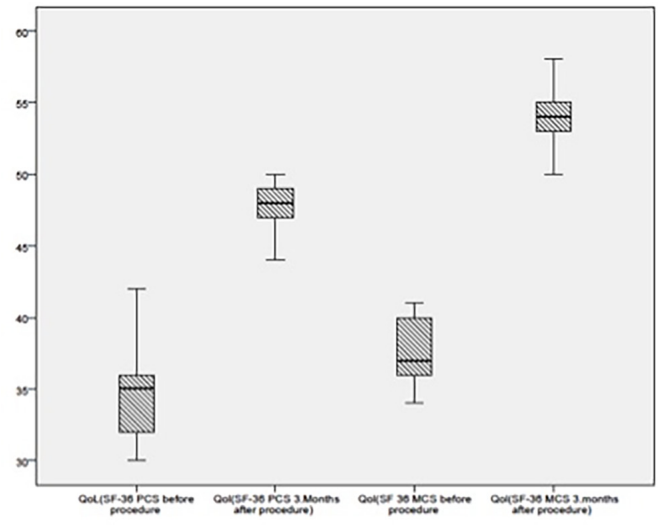

Figure 3: Quality of life (short form 36) ($p<0.001$) return to normal day activities and quality of life assessment was also applied on follow up by short form 36 before the procedure, on first day, week and 3 months. Post procedural quality of life scores were significantly increased

months was 97.6% in accordance with our expectations.

The elasticity of the stockings was checked during the follow-up period, and the patients were instructed on the proper application of the stockings as well. Ulcer recurrence was seen 4.1% of the patients, and recurrent perforator incompetence was accompanied. Technical success rate was 99%. And on 6 months follow-up, recanalization was 1%.

Statistical Analysis

Categorical variables were reported as frequencies, and continuous variables as means ± standard deviations or medians with interquartile range. Chi-square or Fisher's exact tests were used for categorical data, and the Mann-Whitney U test for continuous variables. A p value less than 0.05 was considered statistically significant. Analyses were performed using SPSS software.

Discussion

Isolated perforator vein incompetence has been under-studied as an independent factor in varicosities, though it significantly impacts CVI severity. Compression therapy is often the first treatment choice for CVI and venous ulcers with perforator incompetence. However, compression therapy alone did not yield satisfactory results for most patients with isolated perforator incompetence (1,2).

The clinical outcomes of NBCA embolization demonstrate a highly effective alternative to traditional thermal ablation methods for treating perforator vein insufficiency. Endovenous thermal ablation (EVTA), including radiofrequency ablation and endovenous laser ablation, has been the gold standard for many years due to its high occlusion rates and favorable long-term results. However, EVTA procedures are associated with certain drawbacks, such as the need for tumescent anesthesia, potential thermal injury to surrounding tissues, and post-procedural pain and bruising. The use of NBCA for the management of perforator incompetence offers several advantages, including the elimination of tumescent anesthesia and thermal risks associated with endothermal ablation. The high occlusion rate and minimal complications observed in this study support the efficacy and safety of this non-thermal embolization method (3-5).

NBCA embolization, as a non-thermal, non-tumescent technique, addresses many of these issues. By eliminating the need for thermal energy, NBCA reduces the risk of thermal damage to nerves and other adjacent structures, which can be a significant concern in EVTA. Furthermore, the absence of tumescent anesthesia streamlines the procedure, reducing both the duration and complexity of the treatment. The high vein occlusion rates observed in this study (95.9% at one week, 94.3% at one month, and 92.8% at six months) are comparable to those reported for EVTA, underscoring the effectiveness of NBCA embolization.

The results of this study indicate that NBCA embolization is a highly effective and safe method for treating perforator vein insufficiency. The high occlusion rates and low incidence of complications compare favorably with traditional thermal ablation techniques. The non-thermal nature of the procedure eliminates the risk of thermal injury to surrounding tissues, which is a significant advantage (6).

The mechanism by which NBCA embolization achieves vein occlusion involves a chemical reaction that induces an inflammatory response, leading to fibrosis and permanent closure of the vein. Upon injection, NBCA rapidly polymerizes and adheres to the endothelial lining of the vein, causing an immediate cessation of blood flow. This is followed by an inflammatory process that culminates in fibrosis and eventual obliteration of the vein lumen. This process is highly efficient and does not rely on the application of thermal energy, thereby avoiding the complications associated with thermal ablation (7,8).

The safety profile of NBCA embolization observed in this study is favorable, with minimal complications reported. The most common adverse events in the recent studies were mild and transient, including phlebitis (3.4%), ecchymosis (2.8%), and transient paresthesia (1.7%). These rates are lower than those typically associated with EVTA, where complications such as post-procedural pain, bruising, and thermal injuries are more prevalent. Notably, there were no instances of serious adverse events such as deep vein thrombosis or systemic allergic

reactions, highlighting the safety of NBCA as a treatment modality (9).

Patient comfort is a critical consideration in the management of CVI. The mean VAS score of 2.1±0.7 observed in this study indicates minimal procedural discomfort, which is a significant advantage over thermal methods. The absence of tumescent anesthesia and the minimally invasive nature of NBCA embolization contribute to this low pain score. Additionally, the rapid recovery and immediate return to normal activities post-procedure are likely to enhance patient satisfaction and compliance with treatment (10).

The findings of this study have important clinical implications for the treatment of perforator vein insufficiency. NBCA embolization emerges as a viable and effective alternative to traditional thermal ablation techniques, offering high efficacy with a superior safety profile. This is particularly relevant for patients who are contraindicated for thermal ablation or those who seek a less invasive treatment option. The results also pave the way for further research. While the short-term outcomes are promising, longer-term studies are necessary to evaluate the durability of vein occlusion and the long-term safety of NBCA embolization. Comparative studies with larger patient cohorts and randomized controlled trials will be instrumental in establishing NBCA embolization as a standard treatment for perforator vein insufficiency (11,12).

Additionally, exploring the cost-effectiveness of NBCA embolization compared to EVTA could provide valuable insights for healthcare providers and policymakers. Given the lower procedural complexity and potential reduction in post-procedural care associated with NBCA, this technique may offer economic advantages that warrant consideration (13,14).

Perforator interruption effectively reduces CVI symptoms and promotes rapid ulcer healing. Endovenous ablation with cyanoacrylate-based glue is feasible and safe, with high success rates and minimal significant side effects. Further developments in this technique may offer an attractive solution to venous reflux disease, provided it is cost-effective.

Conclusion

In conclusion, NBCA embolization is a highly effective and safe treatment for perforator vein insufficiency. Its non-thermal, non-tumescent nature provides significant advantages over traditional thermal ablation methods, including reduced procedural pain, minimal complications, and rapid recovery.

The results of this study suggest that NBCA is a viable option for treating perforator incompetence, particularly in patients who do not respond to conventional compression therapy. Future research should focus on long-term outcomes and comparative studies with other treatment modalities to further establish its role in clinical practice and to explore the long-term benefits and cost-effectiveness of this promising technique.

Ethics

Ethics Committee Approval: This retrospective study, conducted at a single center, received approval from the the Human Research Ethics Committee of Ankara University Faculty of Medicine (approval no.: İ06-454-24, date: 09.07.2024).

Informed Consent: All patients provided informed consent for their participation in the study.

Authorship Contributions

Surgical and Medical Practices: E.Ö., Z.E., Concept: N.D., E.Ö., M.Ş., Design: N.D., E.Ö., M.Ş., Data Collection and/or Processing: N.D., A.K., N.P., Analysis and/or Interpretation: N.D., E.Ö., Z.E., M.Ş., Literature Search: N.D., A.K., N.P., Writing: N.D., E.Ö.

Conflict of Interest: There is no potential conflict of interest to declare.

Financial Disclosure: This study received no financial support.

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