Minimally Invasive Therapy & Allied Technologies

ISSN: 1364-5706 (Print) 1365-2931 (Online) Journal homepage: http://www.tandfonline.com/loi/imit20

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To cite this article: Daniele Bissacco, Silvia Stegher, Fabio Massimo Calliari & Marco Piercarlo Viani (2018): Saphenous vein ablation with a new cyanoacrylate glue device: a systematic review on 1000 cases, Minimally Invasive Therapy & Allied Technologies, DOI: 10.1080/13645706.2018.1464029

To link to this article: https://doi.org/10.1080/13645706.2018.1464029

Published online: 19 Apr 2018.

MINIMALLY INVASIVE THERAPY & ALLIED TECHNOLOGIES, 2018
https://doi.org/10.1080/13645706.2018.1464029

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REVIEW ARTICLE

Saphenous vein ablation with a new cyanoacrylate glue device: a systematic review on 1000 cases

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ABSTRACT

Background: To review published evidence regarding an n-butyl-cyanoacrylate (NBCA) injection device for great (GSV) and small (SSV) saphenous vein incompetence in terms of occlusion rate, postoperative complications and quality of life improvement.

Material and methods: International bibliographic databases (PubMed, EMBASE, Scopus) were searched to identify possible target articles. The only inclusion criterion was the use of the Variclose® system (Biolas, Ankara, Turkey) for superficial vein insufficiency. Exclusion criteria were case reports, review, meta-analysis, article with <6-month follow-up data, abstracts and congress presentations. PRISMA guidelines were used to lead articles selection.

Results: Seven studies were included in the final data analysis. A total of 918 patients (1000 limbs) underwent an NBCA procedure for GSV (947 cases) or SSV (53 cases) incompetence. The average procedure duration was 11.7 min. The most common postoperative complications were postoperative pain (4.8%) and superficial vein thrombosis (2.1%). No deep vein thrombosis or pulmonary embolism cases were described. The occlusion rates at six, 12 and 30 months were 97.3%, 96.8% and 94.1%, respectively.

Conclusion: NBCA injection with the Variclose device seems to be a feasible, effective and safe treatment in GSV incompetence. Long-term follow-up studies and randomized controlled trials are needed to achieve high-quality evidence.

ARTICLE HISTORY
Received 29 September 2017
Accepted 9 March 2018

KEYWORDS
Venous insufficiency; varicose veins; cyanoacrylate glue; varicose; variclose

Introduction

In recent years, varicose vein treatment has radically changed. Endovascular procedures, such as radiofrequency ablation (RFA) and endovenous laser ablation (EVLA), have improved postoperative outcomes in terms of pain, length of stay, and return to work rate. These procedures yield target venous occlusion rates similar to conventional surgery [1,2].

These techniques mark an important step in lower limb superficial venous system intervention and management, decreasing the invasiveness of interventional procedures and saving non-pathological venous patrimony. However, due to the use of heat energy in RFA or EVLA procedures to modify and occlude the vein wall, it is necessary to infiltrate the saphenous space with tumescent anesthesia to minimize complications, such as skin burns, leg pain, skin pigmentation and nerve damage, and to promote vein obliteration [3].

Non-thermal non-tumescent (NTNT) methods are a viable alternative to obviate this type of complications during great saphenous vein (GSV) and small saphenous vein (SSV) ablation [4]. Indeed, these techniques do not require tumescent anesthesia because the vein is occluded either by mechano-chemical energy or by sealing due to glue action. Furthermore, no compressive stockings are required after the procedure when compared to surgery, RFA and EVLA.

Ablation with n-butyl cyanoacrylate (NBCA) has recently been proposed as a possible NTNT method in GSV and SSV ablation. Almeida and collaborators described for the first time the use of NBCA in 38 incompetent GSVs three years ago [5]. Recently, several clinical studies and reviews confirmed the safety, feasibility and mid-term efficacy of NBCA [4,6,7].

Nowadays, different devices are commercially available for NBCA use in GSV and SSV chemical ablation. Although NBCA is used in all of these, there are several differences in terms of device characteristics, release modality and intraoperative compression.

The aim of this brief data analysis is to review the current literature evidence regarding a particular type

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of NBCA device (Variclose Vein Sealing System®, Biolas Inc., Ankara, Turkey) and highlight study design, outcomes and limitations associated with GSV and SSV insufficiency treatment.

Material and methods

International bibliographic databases of life sciences and biomedical information (PubMed, EMBASE, Scopus) were used to identify possible target articles. The search was performed following the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8]. A first search was performed in January, 2017 and updated in December, 2017.

Search strategy

Keywords were selected using medical subject headings (MeSH) for MEDLINE and The Cochrane Library, and the EMTREE terms for EMBASE. English language was applied as restriction, while no time restrictions were applied. The keywords used included 'varicose vein', 'vein incompetence', 'small saphenous vein', 'great saphenous vein', 'venous reflux', 'n-butyl-cyanoacrylate', 'Variclose', 'saphenous vein', 'cyanoacrilate' and 'vein glue' in the title, abstract, and MeSH or EMTREE terms. The Boolean operators 'OR' and 'AND' were used to connect terms to each other. The references of all the included studies, for each PRISMA level, were investigated to identify additional relevant reports.

Inclusion and exclusion criteria

All articles including patients treated with an NBCA device for saphenous insufficiency (either GSV, SSV and/or perforator veins) were included in the first article cluster. The only inclusion criterion was the use of the Variclose® system (Biolas Inc., Ankara, Turkey) for superficial vein insufficiency. Exclusion criteria were case reports, review, meta-analysis, article with <6-month follow-up data, abstracts and congress presentations. Studies describing cohorts that did not solely use NBCA treatments could only be included if the data for patients with NBCA could be specifically extracted from the study results. If more than one study reported the same patient cohort, only the most recent and complete manuscript was included in this review.

Primary and secondary outcomes

The primary outcome was anatomical success, defined as closure and absence of reflux on color Doppler ultrasound scan (CDUS) analysis. Secondary outcomes were divided into intra-operative and post-operative outcomes. Intra-operative outcomes included information about NBCA used, procedure time, concomitant phlebectomies, use of compression bandage or stockings; post-operative outcomes included clinical and subjective success during multiple follow-up period, minor (pain, bruising, hematoma, burns, pigmentation, paresthesia and superficial vein thrombosis [SVT]) and major postoperative complications (pulmonary embolism [PE] and deep venous thrombosis [DVT]).

Data extraction

Based on the title, abstract, and MeSH or EMTREE terms, two reviewers (DB and FMC) independently selected potentially relevant papers. Data from all included studies were then independently extracted. In case of discrepancies in article or data extraction, a third researcher (SS) was consulted in order to find an agreement. References of all identified relevant studies were used to perform a recursive search of the literature. Metalib® (Università degli Studi di Milano, Milan, Italy), SBBL (Lombard Biomedical Librarian System) and personal journal subscription were used to obtain full text articles in case of eligible titles and abstracts. The peer-review journals Annals of Vascular Surgery, European Journal of Endovascular and Vascular Surgery, Journal of Vascular Surgery, Angiology, International Angiology and Phlebology were investigated in order to find articles published 'online first'.

Statistical analysis

Data analysis was performed using JMP 11.2.0 (SAS Institute Inc., Cary, NC). Continuous variables were presented as mean ± standard deviation; nominal or categorical variables were presented as range. Results were presented as weighted average, based on the number of patients involved in each single analysis.

Results

Research flowchart according to PRISMA guidelines is reported (Figure 1). The search process yielded 538 potential results. Among these, 501 articles were excluded due to inconsistent title or abstract. The

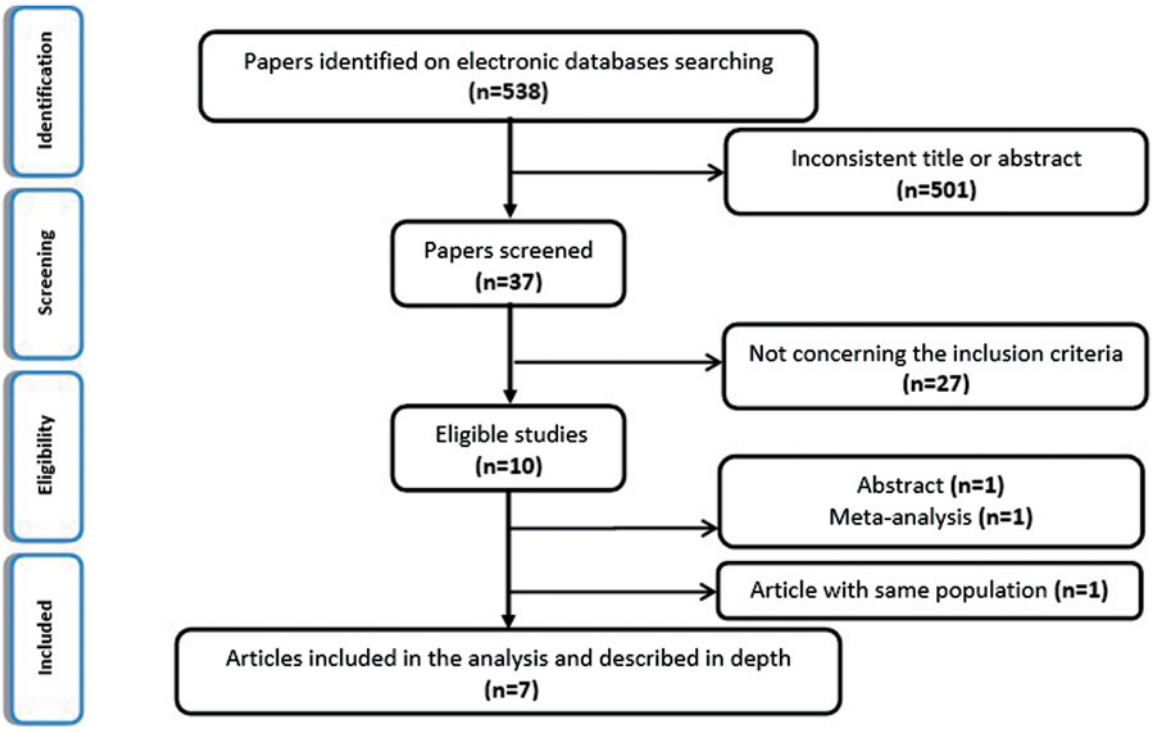

Figure 1. Search process flow chart according to PRISMA guidelines.

remaining articles were analyzed and formed the first reviewed article cluster. Among these, 27 articles were excluded because they did not match with the inclusion criteria; one article was excluded because it was a meta-analysis on all NTNT procedures; one article was excluded because it was an abstract presented during an international congress with a very short follow-up time; two articles used the same study population to investigate early and mid-term results so they were treated as one, according to the inclusion criteria [9,10]. Two articles seemed to use the same population because of the similar patient recruitment period and the same participant center and author [11–13]. Because there was no author statement about these similarities, they were considered as two separate studies. After article selection, seven studies were included in the data analysis (Table 1) [10–16]. The selected papers were published by Turkish groups. In all cases, at least one author was associated with a cardiovascular surgery department. Only two studies [11,12] were prospective, and only two studies compared NBCA ablation with another endovenous ablation technique (EVLA) [11–13]. The average enrollment period was 13.4 months (range 7–18). All studies were published in peer-reviewed and indexed scientific journals during the last two years. Furthermore, all articles were published in vascular medicine and/or surgery journals.

Population and operative data

A total of 1000 NBCA procedures in 918 patients were documented in the selected studies (Table 1). The average patient age was 43.2 years, and females represented half of the cases. In the majority of patients, the GSV was treated (947 limbs, 94.7%); however, the SSV was subjected to NBCA ablation procedures in 53 patients (5.3%). No patient was treated for both GSV and SSV incompetence in the same surgical session. The average GSV diameter was 7.2 mm, and the average SSV diameter was 6.6 mm. In one study, the diameters of the GSV and SSV were mixed [10]. Anatomical and pathophysiological classifications of chronic venous disorders (CEAP) were used in all studies to assess disease severity. One study used NBCA in patients with an active venous ulcer (CEAP grade C6) [14]. The average length of the treated vein segment was 29.5 cm. Only one article described separately the average length of GSV and SSV treated [14]. In five studies 0.03 cc of NBCA per centimeter of treated vein was injected during catheter pullback [10,11,13,15,16] except in one case in which the injection rate was 0.05 cc per centimeter [12]. One study declared only the total amount of NBCA used to treat the entire vein segment for GSV (0.91 ± 0.12 cc) and for SSV (0.58 ± 0.11 cc) procedure [14]. The average time required to perform the procedure was 11.7 min. The surgical time in different articles ranged between 5.4 (15) and 25 (16) min. The

Table 1. Selected studies and perioperative data.

Author	Country	Study design	Study period (months)	Patients	Veins treated	Comparator	Age	% Female	% GSV	% SSV	GSV diameter (mm)	SSV diameter (mm)	CEAP	Treated segment length (cm)	NBCA used (cc/cm)	Procedure time (min)	Percentage of concomitant phlebectomyear/ foam	Post-procedure compression
Bozkurt [11]	Turkey	Prospective	December '2013–September '2014 (10)	154	154	156 EVLA	42.5 ± 13.1	51.3	100	0	7.2 ± 1.8	–	2–4b	29.8 ± 5.4	0.03	15 ± 2.5	24	No
Eroglu [10]	Turkey	Retrospective	May '2014–November '2015 (18)	180	180	–	47.7 ± 11.7	52.2	93.9	6.1	7.7 ± 2.1		2–5	26.2	0.03	15.2	–	Yes
Tekin [12]	Turkey	Prospective	January '2014–July '2014 (7)	62	62	–	44.5	38	100	0	7.5 ± 1.5	–	2–4	28[a]	0.05	17	–	Yes, for 1 day
Koramaz [13]	Turkey	Retrospective	May '2013–May '2014 (12)	150	150	189 EVLA	45.09 ± 12	50.7	100	0	6.9 ± 1.8	–	2–5	32.0 ± 6.8	0.03	7	–	Yes, for 2 weeks
Tok [14]	Turkey	Retrospective	March '2014–July '2015 (16)	141	189	–	42.5 ± 14	53	82.5	17.5	7.6 ± 2.1	7.0 ± 1.8	1–6	30.2 ± 4.1 and 19.5 ± 3.8	0.91 ± 0.12 and 0.58 ± 0.11[b]	14.3 ± 7.5	0	–
Çalik [15]	Turkey	Retrospective	April '2014–September '2015 (17)	181	215	–	37.6 ± 13.2	51.6	95.8	4.2	6.5 ± 1.4	5.2 ± 1.3	2–5	31.6 ± 6.1	0.03	5.4 ± 2.5	1,4	Yes, for 1 day
Bademci [16]	Turkey	Retrospective	September '2015–September '2016 (12)	50	50	–	46.4 ± 3.9	60	100	0	7 (5.5–9)	–	2–4	29.5[a]	0.03	25	0	No
Total/Average	–	–	13.4	918	1000	345	43.2	49.7	94.7 (947)	5.3 (53)	7.2[c]	6.6[d]	–	29.5	–	11.7	–	–

EVLA: endovenous laser ablation; GSV: great saphenous vein; SSV: small saphenous vein; CEAP: clinical, etiology, anatomy and pathophysiology classification; NBCA: n-butyl cyanoacrylate.
[a]Median.
[b]mL for the entire length of the treated vein.
[c]In 767 veins.
[d]In 42 veins.

articles did not state whether the time reported was related only to NBCA injection or whether it included the entire procedure (operative field preparation, percutaneous access, catheter and introducer removal after NBCA injection). Concomitant phlebectomies were performed only in one study in 24% of cases [11]. Foam sclerotherapy was associated to the NBCA procedure in 1.4% of cases in one study [15].

In two retrospective non-randomized trials, NBCA was compared with EVLA in 154 verus 156 (11), and 150 versus 189 (13) cases. Both studies used the Evlas Circular Fiber EVLA (Biolas, Ankara, Turkey) kit consisted of 600 mm of radially extending fiber that functioned at a wavelength of 1470 nm. No preoperative and demographic differences between the NBCA and EVLA cohorts was detected. Both studies described a shorter procedural time in NBCA group compared to EVLA group, 15 ± 2.5 min versus 33.2 ± 5.7 min; $p < .001$ (11), and 7 (range, 4–11) versus 18 (range, 14–25); $p < .001$ (13), respectively.

After discharge a compression bandage or stocking were indicated and maintained for different periods (from 1 to 14 days after the procedure), although in two articles no postoperative compression was indicated [11,16], and in another one it was not declared [14]. The use of postoperative low molecular weight heparin (LMWH) is avoided or not declared in all studies.

Postoperative outcomes – complications

The postoperative complication rate after NBCA ablation was very low (Table 2). Postoperative pain (POP) was investigated in three studies and documented in 4.8% of cases. POP was defined according to the visual analog scale (VAS) [11] or as requiring analgesics/local cooling or limitation of daily life activities [13]. One study did not propose a POP definition [15]. Post-procedural paresthesia, skin burns, DVT, and PE were not described after the procedure in all studies. Superficial vein thrombosis (SVT)/thrombophlebitis was documented in 2.1% of the cases (14/666) and treated conservatively with medical therapy. No complication regarding SVT was described. No thrombus in close proximity to or extending into the saphenofemoral junction (SFJ) as a type of endovenous heat-induced thrombosis (EHIT) was demonstrated. It is difficult to interpret what kind of examination system (CDUS, computed tomography, magnetic resonance, etc.) was used to identify the absence/presence of SVT, DVT or PE after the operation. Compared to EVLA, the NBCA procedure showed less postoperative complications. In particular, Bozkurt and

Table 2. Postoperative complications.

Author	Pain	Bruising	Hematoma	Burns	Pigmentation	Paresthesia	SVT	DVT	PE
Bozkurt [11]	3.1 ± 1.6[a]	–		–	1.3	0	–	–	–
Eroglu [10]	–	0	0	–	–	–	–	0	0
Tekin [12]	–	–	1.6	–	–	–	3.2	0	0
Koramaz [13]	4.7[b]	0	–	0	0	0	2.1	0	–
Tok [14]	–	2.0	0	–	–	0	3.0	0	0
Çalik [15]	6.1	–	–	–	–	0	0.5	0	0
Bademci [16]	–	2.0			2.0	0	4.0	0	0
Total	4.8[c]	0.8[d]	0.2[e]	0[f]	0.8[g]	0[h]	2.1[i]	0[j]	0[k]

[a]According to the VAS scale.
[b]Requiring analgesics in the first week.
[c]In 519 cases.
[d]In 569 cases.
[e]In 431 cases.
[f]In 150 cases.
[g]In 354 cases.
[h]In 758 cases.
[i]In 666 cases.
[j]In 846 cases.
[k]In 696 cases.

Table 3. Varicose veins severity grading scales.

Author	VCSS pre	VCSS post	AVVQ pre	AVVQ post	CEAP pre	CEAP post	CIVIQ pre	CIVIQ post
Bozkurt [11]	5.7 ± 2.3	2.4 ± 0.9[b]	18.1 ± 5.0	7.5 ± 2.1[b]	–	–	–	–
Eroglu [10]	10.2	3.9[c], 4.2[d], 2.9[e], 2.7[f]	–	–	–	–	–	–
Tekin [12]	–	–	–	–	3	0.8	–	–
Koramaz [13]	7.5 ± 1.0	2.8 ± 1.0	–	–	–	–	–	–
Tok [14]	8.3 ± 2.2	3.3 ± 1.8	–	–	–	–	–	–
Çalik [15]	–	–	–	–	–	–	42.9 ± 18.6	17.4 ± 3.8[d]
Bademci [16]	7	3[b], 2[d], 1[e]	18	7[b], 5[d], 4[e]				
Total	7.9[a]	–	–	–	–	–	–	–

VCSS: Venous Clinical Severity Score; AVVQ: Aberdeen Varicose Vein Questionnaire; CEAP: clinical, etiology, anatomy and pathophysiology classification; CIVIQ: Chronic Venous Insufficiency Questionnaire.
[a]In 723 patients.
[b]At 30 days.
[c]At 3 months.
[d]At 6 months.
[e]At 12 months.
[f]At 30 months.

collaborators [11] showed less postoperative ecchymosis (14.3% versus 46.8%; $p < .001$) and paresthesia (0 versus 4.5%; $p < .015$), while Koramaz et al. [13] described less pigmentation (0 versus 5.9%; $p < .02$) and phlebitis (2.1% versus 7.9%; $p < .015$) in the NBCA cohort.

Postoperative outcomes – grading scales

The evaluation of quality of life (QoL) and of the clinical varicose disease severity before and after the NBCA procedure was very heterogeneous (Table 3). The most commonly used clinical grading scale was the Venous Clinical Severity Score (VCSS) in five articles [10,11,13,14,16]. Average VCSS differences from baseline to postoperative values were confirmed. Unfortunately, it was difficult to calculate the average VCSS decline, as it was not described in most cases when this metric scale was evaluated after the procedure (1, 7 or 30 days). Two studies reported a VCSS decline at 30-days of 3.3 (11) and 4 (16) points. No VCSS increase was detected also at 6- and 12-month follow-up time in two studies [10,16], with a decline of 6 and 5 points, and 7.3 and 6 points, respectively, from preoperative evaluation. One study described VCSS decline among a 30-month follow-up period (3.9 at 3 months, 4.2 at 6 months, 2.9 at 12 months and 2.7 at 30 months) [10].

Regarding the QoL analysis, two studies used the Aberdeen Varicose Vein Questionnaire (AVVQ), reporting a decline of 10.6 (11) and 11 (16) points, 30 days after the treatment. The Chronic Venous Insufficiency Questionnaire (CIVIQ) was used in one study with a decrease of 25.5 points at 30-day follow-up time [15]. CEAP classification was also used to compare preoperative and postoperative venous clinical severity grading, with a 2.2 points reduction 30 days after the procedure [12].

Comparing NBCA versus EVLT, one study described no significant difference in terms of VCSS and AVVQ decline after the procedure after 1-month, 6-month and 1-year follow-up period [11]. Similar

Table 4. Postoperative occlusion rate.

Author	1 week	1 month	3 months	6 months	12 months	30 months	Average follow-up time (months)
Bozkurt [11]	100	96.7	–	96.6	95.8	–	–
Eroglu [10]	100	100	–	98.3	96.6	94.1	30
Tekin [12]	100	100	93.5	90.3	–	–	–
Koramaz [13]	99.3	–	–	98.6	98.6	–	–
Tok [14]	–	–	–	98.4[a]	–	–	6.7 ± 4.1
Çalik [15]	100	100	99.1	98.3	–	–	7.5
Bademci [16]	–	100	–	96.0	94.0	–	12
Total	99.9[b]	99.1[c]	97.8[d]	97.3[e]	96.8[f]	94.1[g]	14.0[h]

[a]At average follow-up time.
[b]In 761 cases.
[c]In 661 cases.
[d]In 277 cases.
[e]In 1000 cases.
[f]In 534 cases.
[g]In 180 cases.
[h]In 634 cases.

results were detected only for post-treatment VCSS in another BCA versus EVLT comparative study [13].

Postoperative outcomes – recanalization rate

We exclusively considered the complete recanalization rate in the analysis to avoid confusion regarding partial recanalization definitions among articles (Table 4). The average follow-up time, declared in four studies [10,14–16] was 14.0 months. The 1-week postoperative obliteration rate was 99.9% based on 761 NBCA injections performed in five studies [10–13,15]. All studies reported 6-month recanalization rates, and the average result was 97.3%. One-year data were presented in four studies (534 cases), with an average occlusion rate of 96.8% [10,11,13,16].

One study reported 30 months occlusion rate (94.1%) [10]. No significant differences in total occlusion rate were observed between NBCA and EVLT group at 12-month follow-up period (in Bozkurt study [11] 95.8% and 92.2%, respectively; $p = .318$; In Koramaz study [13] 98.6% and 97.3%, respectively; $p = .65$.)

Discussion

Alkyl cyanoacrylate compounds were synthesized in the 1940s for military use. These substances possess a strong cohesive force, and their use was particularly enhanced in industrial fields. In addition, in medical fields, NBCA had a huge impact and was used in numerous surgical applications [17–20]. Its characteristics include high strength, strong adhesion, rapid polymerization and hemostatic and bacteriostatic properties. Currently, three types of NBCA are commercially available, designed specifically for superficial vein incompetence: Variclose® (Biolas Inc., Ankara, Turkey), VenaBlock® (Invamed, Ankara, Turkey) and VenaSeal® (Medtronic, Santa Rosa, CA, USA) [21]. Although NBCA is used in all for the same purpose, these three devices and the technique of NBCA release differ considerably (Table 5). Therefore, it is very difficult to consider all patients as being operated with the same device and technique, and thus make a summary analysis. Moreover, very little information is found for the Venablock system, due to no published studies: the only information on this interesting NBCA device is derived from the web [22].

In particular, the Variclose device consists of 3 ml of NBCA and the delivery system. A 6 F short-introducer is positioned after achieving percutaneous access to the target vein. A 0.035-inch/150-cm J-tip guidewire is inserted through the introducer and passes by the SFJ under CDUS surveillance. Then, a 5 F long-sheath is advanced toward the SFJ over the guidewire and stopped 3 cm distal to the SFJ. A 4 F delivery catheter is introduced and advanced to the tip of the 5 F sheath. The sheath is pulled back 3 cm in order to position the delivery catheter 3 cm behind from the SFJ; thus, the catheter is free of sheath coverage for its distal 3 cm. Afterwards, the Variclose injection system is prepared by connecting the delivery system with the adaptor and aspirating 2 ml of NBCA into the injector. Before NBCA injection, a CDUS pressure is obtained next to the SFJ to occlude it. NBCA injection is performed by pulling back the delivery catheter and the sheath simultaneously at 2 cm/sec and constantly applying a pressure along the vein during system retraction. Meanwhile, pressure at the SFJ must be maintained during the entire procedure. Finally, a pressure along the entire target vein is applied.

Almeida and collaborators performed venous NBCA injection in an animal model, reporting histologic acute inflammation and foreign body giant cell and granuloma formation followed by fibrosis and

Table 5. NBCA devices differences.

↓Characteristic/Device →	Variclose	Venaseal	Venablock
Company	Biolas	Medtronic	Invamed
Country	Turkey	US	Turkey
FDA approved	no	yes	*nd*
CE marked	yes	yes	yes
Glue	syrupy	viscous	*nd*
Polymerization	3–4 s	20 s	*nd*
NBCA per kit	1.5 cc x2	5 cc	*nd*
Short introducer	6F	no	*nd*
Long Introducer	5F (80 cm)	7F (80 cm)	*nd*
Delivery catheter	4F (83 cm)	5F (91 cm)	6F (90 cm)
Laser-guided catheter	no	no	yes
Distance back from SFJ	3 cm	5 cm	3 cm
Glue release during pull-back	continuous	segmental	continuous
Intraoperative compression	follows the NBCA release	3 min at SFJ, then 30 s per segment	follows the NBCA release

SFJ: saphenofemoral junction; *nd*: not declared.

wall disruption from NBCA action on the lumen of the veins [23]. NBCA was first used for GSV insufficiency in 38 patients in 2013 [5]. The mean treated vein length was 33.8 cm. The complication rate was 21%, including phlebitis (15.8%), cellulitis (4%), hyperpigmentation in a vein located close to the skin (4%) and thrombus extensions across the SFJ (21.1%), which completely had resolved at the 12-month follow-up. The VCSS score improved from 6.1 at baseline to 1.5 at 12 months ($p < .0001$). Compression stockings after the NBCA procedure were avoided. The 12-month freedom from complete recanalization rate was 97.4%. A 2-year follow-up study performed in 21 patients reported a 92.1% occlusion rate without any major complications [24]. A good occlusion rate was also confirmed at the 3-year follow-up (94.7%) [6].

A multicenter prospective European trial was performed in 70 patients using the VenaSeal device [25]. The mean GSV diameter at the SFJ was 7.8 mm. Post-procedural complications included phlebitic reaction (11.4%), pain (8.6%) for a median duration of one day and glue extension beyond the SFJ (1.4%). The 12-month survival free from recanalization rate was 93%. VCSS improved from a mean of 4.3 at baseline to 1.1 at 12 months. The AVVQ score was also used to assess QoL. The score improved significantly from a baseline value of 16.3 to 6.7 at 12 months ($p < .0001$). No compression stockings were used after the NBCA procedure.

The first prospective, multicenter, randomized clinical trial comparing NBCA with RFA was conducted in the United States and published in 2015 [26]. A total of 222 patients were enrolled and treated (108 NBCA, 114 RFA) for GSV incompetence. The VCSS, AVVQ and EQ-5D time trade-off (EQ-5D TTO) utility index were used to assess pathology degree and QoL before and after treatment. Approximately 90% of the cases had C2-C3-stage disease, and the mean GSV diameters were 5.0 and 6.45 mm in the mid- and proximal GSV segments, respectively. In the NBCA group, the mean treated segment length was 32.8 cm. The procedure duration was significantly longer for RFA treatment than the NBCA group (19 min versus 24 min, $p < .01$). Phlebitis was the most commonly observed post-procedural complication (20% in the NBCA group versus 14% in the RFA group, $p = .36$). Paresthesia in the treatment zone, stocking irritation and access site infection were observed in 3%, 2% and 1% of the NBCA patients, respectively, with no significant differences compared to the RFA group. No subject developed DVT or PE. Three months after the procedure, the total occlusion rate was comparable between NBCA ablation and RFA (99% and 96% respectively, $p < .01$). The VCSS, AVVQ and EQ-5D TTO demonstrated improvements in both groups without significant differences. Recently, 1-year outcomes confirmed that the recanalization-free survival rates for NBCA and RFA were 97% versus 90.7%, respectively ($p = .08$ for superiority, $p < .0001$ for non-inferiority) [27].

This systematic review describes 1,000 cases that underwent NBCA injection with the Variclose system. Nine hundred and forty-seven patients underwent treatment for GSV incompetence, whereas 53 patients underwent NBCA for SSV incompetence. Intraoperative and postoperative outcomes are promising considering that published data derive from retrospective studies. Postoperative complication and recanalization rates remain low in selected studies, particularly in studies in which a high number of patients are enrolled. Unfortunately, only two studies compared NBCA ablation with EVLA, although both concluded that NBCA seems to be a viable alternative method with a reduced procedure time that does not involve the use of tumescent anesthesia or require the postoperative use of compression stockings. In addition, vein occlusion and complication rates were not

inferior to those noted with EVLA [11,13]. Indeed, NBCA ablation demonstrated lower rates of phlebitis, ecchymosis, paresthesia, skin pigmentation and DVT compared with EVLA [13].

There are several limitations in the selected articles, including lack of randomized controlled trials (RCTs) with the Variclose system; lack of data analysis for C6 patients (in whom the use of a minimally invasive treatment could be the correct choice); and lack of randomized studies comparing NBCA with EVLT, RFA, surgery or other NTNT techniques. Also studies comparing NBCA with EVLA provide only retrospective datasets, with no details concerning randomization or other methodological expedients used to minimize bias. The lack of RCTs and the follow-up limited to an average of about one year makes this systematic review inconsistent in terms of study quality, although it offers a preliminary view on NBCA use in venous incompetence using Variclose system. Moreover, due to poor published data, it is not yet possible to propose meta-analytical analysis. This review first provides a useful although original 1,000 patients sample. A clinical and instrumental follow-up of at least three years would be highly desirable in order to judge long-term efficacy and safety. In addition, no data regarding the long-term effect of glue implantation were provided. In fact, NBCA is not adsorbed and long-term effects are not yet evaluated.

Furthermore, extensive data about SSV treatment are necessary to improve outcomes and achieve robust evidence.

Procedural duration needs to be better defined. In one study procedure time is 5.4 ± 2.5 min [15], so there are patients that receive NBCA treatment in <3 min. Despite the use of NBCA without concomitant phlebectomies results very simple and fast, authors should declare if reported time is referred to only NBCA pull-back injection or if it is referred to the entire procedure (percutaneous access, vein cannulation and NBCA injection). In our limited experience, if phlebectomies are not carried out, procedure time is very short but it is always longer than 7–8 min.

The use and duration of post-operative compression stockings are very heterogeneous among studies. Although the NTNT procedure does not theoretically require their use, a consensus or guidelines regarding this issue are not yet defined.

The use of postoperative LMWH seems to be avoided. Further studies are needed to investigate whether the lack or the presence of prophylactic or anticoagulant heparin dose regimen after NBCA injection could improve outcomes and decrease post-operative complications.

Conclusion

The results of this review confirmed that NBCA injection with the Variclose device seems to be a feasible, effective and safe treatment in patients with GSV incompetence. Postoperative complication and low recanalization rates during follow-up are promising compared with EVLA, although published data were derived from only two non-randomized trials with few cases. Unfortunately, published data on comparisons between NBCA and other surgical or endovascular ablation techniques (RFA or other NTNT systems) are lacking. Regarding SSV incompetence treated with NBCA, more robust results are needed. Long-term follow-up studies and randomized controlled trials are needed to achieve high-quality evidence.

Declaration of interest

No potential conflict of interest was reported by the authors.

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