NTNT Methods – Efficacy and Safety Issue

NTNT-Methoden – Wirksamkeits- und Sicherheitsaspekte

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ZUSAMMENFASSUNG

In jüngster Zeit hat die Behandlung zur Beseitigung eines pathologischen V.-saphena-Reflux mit Einführung der endovenösen thermischen Ablationstechniken (EVTA), die inzwischen die Erstlinientherapie darstellen, Fortschritte gemacht. Die thermischen Techniken erfordern jedoch eine Tumeszenz-Infiltration, die Beschwerden verursachen kann. Auch geht die Anwendung der EVTA mit einem potenziellen Risiko für eine thermische Schädigung der superfiziellen Nerven einher und erfordert das Tragen von Kompressionsstrümpfen nach dem Eingriff.
Nichtthermische Techniken ohne Tumeszenz (NTNT, *non-thermal non-tumescent*) wurden als geeignete, sichere und wirksame Alternative zu EVTA mit deutlicher klinischer Besserung, hoher vollständiger Verschlussrate und hoher post-therapeutischer Patientenzufriedenheit vorgeschlagen. Die gängigsten modernen NTNT-Verfahren sind der Katheter-gestützte Verschluss mittels Cyanacrylatkleber (CA) und die mechano-chemische Ablation.
Dieser Artikel gibt einen Überblick über die aktuell vorliegenden Daten zur Wirksamkeit und Sicherheit von NTNT-Methoden.
Gemäß der Literatur besitzen NTNT-Methoden eine hohe Wirksamkeit, vergleichbar mit EVTA-Techniken, und weisen eine akzeptable Zunahme der Risiken auf. Es sind jedoch weitere Studien mit Langzeitergebnissen, auch im Hinblick auf Sicherheitsaspekte, notwendig.

ABSTRACT

The management of elimination of the pathological reflux in the saphenous vein has been developed recently by introducing the endovenous thermal techniques (EVTA), which have become the first line treatment. However, thermal techniques require tumescent infiltration, what may be the cause of discomfort. Furthermore, the use of EVTA has a potential risk of thermal damage of superficial nerves and requires to wear stocking after the procedure.
Non-thermal non-tumescent techniques (NTNT) were proposed as a valid, safe and effective alternative to EVTA with significant clinical improvement, high complete occlusion rate and high posttreatment patient satisfaction. The most common novel NTNT are catheter-directed cyanoacrylate adhesive closure (CAC) and mechanochemical ablation.
In the paper an overview of the currently available data regarding the NTNT efficacy and safety are presented.
Based on the literature, NTNT has a high efficacy, comparable with the EVTA techniques, with an acceptable risk increase. However further studies with long-term results are needed also with regard to safety aspects.

Introduction

The management of chronic venous disease and varicose veins has been developed in recent years by introducing the minimally invasive endovenous thermal techniques to eliminate the pathological reflux in the saphenous vein. Endovenous thermal ablation (EVTA) has become the first line treatment as it allows to avoid general anesthesia, enables faster recovery and return to daily activities, as well as improves patient health-related quality of life (HLQoL), compared with traditional open surgery. [1]

However, thermal techniques require tumescent infiltration for local anesthesia and to protect the surrounding tissue from thermal injury. Although the tumescent infiltration is generally well tolerated, it may be the cause of discomfort, especially in patients with the fear of injections. Furthermore, the use of EVTA has a potential risk of thermal damage of superficial nerves and it requires to wear stocking for at least 1 week after the procedure to reduce pain and improve physical function.

Non-thermal non-tumescent techniques (NTNT) were introduced as an alternative to EVTA to occlude incompetent superficial veins of lower limbs without the need for tumescent infiltration. They have a potential benefit for acceptability by patients and also for decrease risk of nerve injure. A few novel NTNT have emerged recently. The most common are catheter-directed cyanoacrylate adhesive closure (CAC) and mechanochemical ablation. In the paper an overview of the currently available data regarding the NTNT method efficacy and safety is presented.

Catheter directed Cyanoacrylate Adhesive Closure (CAC)

CAC involves intravascular injection of cyanoacrylate (CA) which rapidly solidifies in the polymerization reaction and produces an inflammatory reaction of the vein wall to the foreign body and finally the vein fibrosis, causing permanent vein occlusion.

Several CAC systems for treatment of superficial veins incompetence are available but currently three products are most commonly used: VenaSeal (Medtronic, Santa Rosa, Ca, USA), Variclose (BiolasInc., Ankara, Turkey) and VenaBlock (Invamed, Ankara, Turkey).

The main difference between these devices relates to the CA formulation [2].

VenaSeal uses n-butyl-2-cyanoacrylate which has the highest viscosity and the longest polymerization time. It begins to polymerize approximately 5 seconds after the contact with the blood and it takes up to three minutes to complete the polymerization. It has a soft and flexible texture after polymerization. The high viscosity prevents the CA from entering the non-target veins.

VenaBlock also uses n-butyl-2-cyanoacrylate with also high viscosity, although at least 60 times less than VenaSeal. It has a very short polymerization time and is relatively firm after polymerization.

VariClose uses n-butyl-5-cyanoacrylate with the lowest viscosity but the fastest polymerization time, what reduces the possibility of CA migration. It has a hard texture after polymerization.

These products also rely on various application techniques. With VenaSeal device, catheter tip is positioned 5 cm distally to the sapheno-femoral junction (SFJ) and CA is delivered using segmental pullback, while with VariClose and VenaBlock devices, the catheter tip is 3 cm distally to SFJ and CA is applied during the continuous pullback.

There is no evidence-based data regarding the maximum dose of CA per treatment session. Australasian College of Phlebology recommends an upper limit of 10 ml [2].

Effectiveness

Several studies have shown that CAC is effective with cumulative occlusion rates comparable to those for EVTA in the early and midterm observations. [3–10]

In the first-in-men prospective study by Almeida et al., a 36-month occlusion rate was 94.7 % in 29 out of 38 patients with great saphenous vein (GSV) incompetence and a vein diameter of 3–12 mm. [3] A subsequent multicenter European trial (eSCOPE) presented by Proebstle et al. enrolling 70 subjects with GSV incompetence and a vein diameter of 6.6–14 mm showed a 12-month occlusion rate of 92.9 %. [9] In systematic review and meta-analysis reporting CAC outcomes in 954 patients, the complete closure rate at 6 months ranged from 89.5 % to 99.1 % and the pooled anatomic success was 94.8 % (95 % CI, 92.0 %–97.6 %). The 12-month complete closure rate ranged from 78.9 % to 95.5 % and the pooled anatomic success was 89.0 % (95 % CI, 84.2–93.9 %) [10].

The WAVES study was the first to demonstrate the efficacy of CAC for GSV, small saphenous veins (SSV) and/or accessory saphenous veins (AASV) up to 20 mm in diameter. All veins were completely occluded at 1-month follow-up [7], although according to Chan at al. analysis of 108 GSV with a diameter of 2.3–11.4 mm, the mean GSV diameter > 6.6 mm appeared to be a significant predictor for recanalization ($p < 0.016$). The 12-month occlusion rate in GSV < 6.6 mm was 90 %, while in GSV > 6.6 mm, 58.6 % ($p = .002$). [5] The GSV diameter showed also a significant inversely proportional relationship with the glue extension length and veins > 7 mm had a significantly longer remnant stump length than smaller veins ($p < .001$). [11]

The feasibility of CAC in treatment of incompetent perforating veins was presented by Toonder et al. The 3-month occlusion rate was 76 %, without any serious complications. [12]

Comparison with thermal ablation

A few RCTs compared CAC with EVTA. [4, 6, 8]

In RCT by Çalık et al. including 400 patients with GSV incompetence, CAC was compared with endovenous laser ablation (EVLA) and at 12-month follow-up the occlusion rate was 96.6 % and 94.1 %, respectively. [4] The VeClose multicenter RCT, involving 10 centers in USA and 222 patients with GSV reflux in veins up to 12 mm in diameter has shown that CAC was noninferior to radiofrequency ablation (RFA), because the 36-month occlusion rate for CAC was 94.4 % and for RFA, 91.9 %. [8]

Another RCT compared CAC with EVLA and RFA in 525 patients and found 24-month occlusion rates of 94.7 %, 90.9 % and 91.5 % after CAC, RFA and EVLA, respectively. [6]

A systematic review and meta-analysis by Hassanin et al. has also shown that there was no significant difference in outcomes, when CAC was compared with EVLA and RFA (RR, 1.02; 95 % CI, 0.94–1.11). [13]

Clinical and quality of life assessment

All studies on CAC, reporting the Venous Clinical Severity Score (VCSS) found a significant or clinically relevant reduction in these scores after treatment, compared with the baseline value [3, 9,

10], with no statistical difference between EVTA techniques and CAC in comparative studies, [4, 8, 13] with an exception of RCT by Eroglu et al., where VCSS scores were significantly lower in the CAC group than in EVTA groups at 6-month and 2-year follow- up ($p < 0.001$). [6]

The HLQoL, measured by Aberdeen Varicose Vein Questionnaire (AVVQ), EQ-D5 quality of life survey and Chronic Venous Insufficiency Quality of Life Questionnaire (CVIQ), improved significantly after CAC in all studies. No statistical difference between EVTA techniques and CAC was found in any comparative studies. [4, 6, 8–10, 13] Both clinical and HLQoL assessment reminded improved at all follow-up intervals in all studies reporting these patient-reported outcomes.

According to Morrison et al., 84.7 % of patients from CAC group were very satisfied with the treatment, compared to 78.4 % patients after RFA ($p > .05$), and according to Gibson, 98 % were satisfied with CAC procedure. [7, 8]

Procedural duration

The average procedural duration of CAC, analyzed by Proebstle et al. was 18.6 minutes [9] and in the direct comparative study, it was significantly shorter than the duration of EVLA procedures (13 ± 3.4 vs 31.7 ± 8.8 min, $p < 0.001$). [4]

Pain and recovery

Çalık et al. noticed that procedural pain was significantly less in the CAC group compared to EVLA ($p < 0.001$). [4] Morrison et al. found no difference in pain when compared to RFA (2.2 vs 2.4, on a 10-point scale; P = 0 0.11). [8] Eroglu demonstrated that CAC was significantly less painful than EVLA and RFA ($p < 0.001$), but found no difference between groups in term of pain in the post-operative period. [6]

The recovery time and time to return to daily activities were significantly shorter after CAC group than after EVTA. [4, 6]

The great advantage of CAC is that there is no need for compression therapy after the procedure. [2–14]

Adverse events

Adverse events were reported in all studies of CAC, although their type and rate varied. [3–10]

The most common reported adverse event was a local inflammatory reaction of the skin and subcutaneous area overlying the treated vein, reported at a rate of 11.4 % in the study by Almeida et al. and 20 % in a study by Morrison et al. [3, 8] Usually it's not specified if it is a truth phlebitis or an immune skin reaction resembling phlebitis, related to a local hypersensitivity reaction to the CA implantation. In most studies it is grouped together and includes hypersensitivity, granulomatous- type phlebitis and typical phlebitis.

There have been no clinical reports of anaphylactic reactions and only a few reports concerning allergic reactions have been published. [2] According to systematic review a rate of hypersensitivity reaction to the CA is 7 %. [10] Gibson et al. reported the appearance of hypersensitivity in 6 % of patients. [14] The reaction was mild in 4.2 % of patients, moderate in 1.3 % and severe in 0.3 %. In most cases the hypersensitivity reaction is transient, benign and self-limiting, although it sometimes requires treatment, which includes the combination of nonsteroidal anti-inflammatory drugs and oral antihistamines and in severe cases, systemic immunosupperssant such as oral or intravenous steroids.

A granulomatous-type phlebitis reaction may develop in the mid -term and long term follow up after the CAC. It commonly remains asymptomatic, but may progress to suppuration, necrosis and ulceration. [2] Despite the large number of cases performed worldwide, only a few late granulomatous reactions have been reported, some of them with considerable morbidity. [15]

Immediate and delayed hypersensitivity reaction with granulomas formation have been reported to be the most significant concerns of clinicians. Further registration and adequate follow-up after CAC are required. In case of patients with systemic autoimmune disorders, Australasian College of Phlebology recommend EVTA instead of CAC, which should be offered only if no other safe treatment options are available, and with pre and post treatment steroid administration. [2]

Phlebitic reaction has been reported by Proebstle et al. in 11.4 % with a median duration of 6.5 days. [9] In the Waves study phlebitis in the treatment area or in tributaries occurred in 20 % of patients but completely resolved in all but one, in a month. [7]

Other complications included deep venous thrombosis (0 %–3.5 %) [10] and CA protrusion into the SFJ, found by Proebstle et al. in 1.4 % and by Chan et al. in 1.8 % of patients, that resolved within a week after subcutaneous low-molecular-weight heparin injections. [5, 9] Earlier studies reported higher rates of CA extension, up to even 21 % at the 48-hour follow-up. [3] It was likely due to the catheter being positioned 3 cm from SFJ. With current technique modifications involving an increase of the distance to 5 cm, the incidences of CA protrusion are less common. Pulmonary embolism following CAC has not been published.

Hyperpigmentation had a reported incidence of 1.6 %–3.5 %, and appeared more often after the treatment of veins coursing close to the skin surface. Other adverse events included access site infection or cellulitis (1.4 %-3 %), hematoma (1.4 %–1.6 %), nerve injury or paresthesia (0 %-2 %). [2, 9, 10] Proebstle noticed that 8.6 % of patients had pain over treated vein without phlebitis. [9]

Compared to EVTA, induration, ecchymosis and paresthesia were found statistically significant less in the CAC group ($p < 0.001$), but there was no significant difference in appearance of deep venous thrombosis (DVT) and hyperpigmentation. [4]

Morrison et al. and Hassanin et al. found that only ecchymosis at day 3 was significantly more often after CAC than after EVTA ($p < 0.01$) with no difference identified with regard to rates of paresthesia, phlebitis and skin pigmentation between groups. Adverse events were generally mild and well tolerated. [6, 8, 13]

Mechanochemical Ablation

Mechanochemical ablation is another NTNT technique commonly used in daily practice. It uses a dual mechanism of action that combines mechanical injury to the venous endothelium with simultaneous chemical endovenous ablation by delivery and disper-

sion of injected sclerosing agent. Because no heat is generated during the therapy, there is no need of tumescent anesthesia application.

At least two devices have been recently introduced for the treatment of superficial venous incompetence: Clarivein (Vascular Insights, Quincy, Mass, USA) and Flebogrif (Balton, Poland).

Mechanochemical Ablation with Clarivein (MOCA) mechanically damages the venous endothelium by the tip of the catheter's rotating wire, while simultaneous catheter- guided infusion of the sclerosant agent. Usually the sclerosants, such as the sodium-tetradecyl-sulphate (STS) or polidocanol (POL), are used in a liquid form, what limits the total dose that can be applied during the procedure. Since the introduction of MOCA several procedural changes have been introduced. The latest recommendation from the manufacturer includes a minimum of 3 seconds of rotating time under the SFJ to create vasospasm and the retreatment is advised if the proximal 10 cm is not occluded after the first run. The different concentrations and the forms of the sclerosant have also been tested in terms of the effectiveness. In RCT by Lam et al. liquid POL (2 % and 3 %) has been compared with 1 % POL microfoam and according to the results, the foam was significantly less effective than 2 % or 3 % liquid POL (p <.001) for treatment of GSV incompetence. [16]

Effectiveness

The effectiveness of MOCA for ablating saphenous trunks have been shown in several studies. [10, 17–20]

A systematic review and meta-analysis by Vos et al. including seven studies, reported outcomes in 691 patients found that complete closure rate ranged from 87.1 % to 98.1 % at 6 months and 87.7 % to 95.2 %. at 12 months. The pooled anatomic success was 94.7 % (95 % CI, 93.3 %-98 %) and 94.1 % (95 % CI, 91.5–96.8 %, at 6- and 12-months, respectively. Anatomic success at 2-year follow-up ranged from 89.5 % to 95.0 %. To date, only one study has reported the 3-year follow-up results and the occlusion rate was 86.5 %. [10]

Comparison with EVTA

In the LAMA trial including 150 patients with GSV, SSV or AASV incompetence, MOCA was compared with EVLA and the complete occlusion of the treated vein was found in 77 % of patients in MOCA group at 1-year follow-up, what was significantly lower than in EVLA group (p = .020), in which the complete occlusion was noticed in 91 % of patients. [19]

The comparison of MOCA with RFA was presented in the multicenter MARADONNA trial, which included 209 patients with GSV incompetence. The 1- and 2-year anatomic success rate after MOCA was 83.5 % and 80 %, respectively, what was significantly lower than after RFA (p = .025 and 0.066), where the complete occlusion was found in 94.2 % and 88.3 % of patients, respectively. The anatomic failure was mainly caused by partial recanalization. Analyzing the clinical success, no significant differences were found between groups. [20] Another RCT similarly revealed significantly worse results after MOCA, with the complete occlusion rate at 1 year of 82 %, compared to 100 % after EVLA and RFA (p = .009). In this study a strong association between recanalization and the preoperative GSV diameter was found. A mean GSV diameter of 8.6 mm was significantly more often associated with proximal recanalization at one year, compared to a mean GSV diameter of 6.5 mm (p = 0007). [18]

In systematic review and meta-analysis of comparative studies comparing NTNT techniques with EVTA, including 178 patients treated with MOCA, 281 with RFA and 385 with EVLA, no difference in success between groups during immediate, 6-month, 12-month and > 12-month follow-up periods was observed (RR0.96; 95 % CI, 0.89–1.03). [13] Considering complete and proximal occlusions (> 5 cm proximally occluded vein, with > 5 cm open distally), another multicenter RCT also didn't find the significant difference between MOCA and RFA at 6- month follow up (MOCA vs RFA: 87 % vs 93 %, p = .483). [17]

Clinical and quality of life assessment

All MOCA studies reporting VCSS noticed a significant or clinically relevant reduction in these scores after treatment, compared to baseline. There was no significant difference in the improvement of VCSS between MOCA and EVTA patients in the mid-term and long-term results [10, 17, 19], although MARADONNA trial has showed significantly lower VCSS at after MOCA than after RFA at 30-day follow-up (p = 0.001). [20]

The HLQoL measured by AVVQ, SF-36 improved significantly after MOCA procedure. No statistical differences were observed between MOCA and EVTA groups. [10, 13, 17–20]

Pain and recovery

Maximum and median pain during the procedure was significantly lower in the MOCA group then in RFA group with both VAS (15 vs 34; p = .003 and 10 vs 19.5; p = .003) and Number Scale (3 vs 4 p = .002 and 2 vs 3 p = .004). [17] Pain scores during the first 14 days were significantly lower after MOCA than after RFA (p = .01). [20] In systematic review by Hassanin et al. postprocedural pain compared by a visual analogue scale was also lower in those undergoing MOCA than RFA, with a mean difference of –9.83 (95 % CI, –19.4 to –0.25). A significantly lower median pain scores were found in the MOCA group compared with RFA and EVLA, respectively (1 vs 5 vs 6; p < .01). [13]

One RCT, the LAMA trial by Mohamed et al. did not confirm such results, because they found no difference in pain score during MOCA and EVLA (15 vs 22; p = .210). The intergroup comparison showed a nonsignificant trend of lower pain scores in the MOCA group most days, except for day 3 where there was a significant difference between groups. [19]

An RCT by Vähäaho also found no difference in VAS pain score during the procedure in MOCA, EVLA and RFA group (p = .118), however the procedures were performed under the sedatives and patients treated with MOCA received significantly less propofol than patients who received EVTA (p < .001). The amount of painkillers taken did not differ between the groups. [18]

Median time to work and to normal activity also did not differ significantly between MOCA and EVTA patients. [17–19]

Adverse events

The most common adverse events after MOCA are induration (12 %–18 %), superficial venous thrombosis (2 %–13 %), hemato-

ma (1 %–11 %), DVT (0 %-1 %) and hyperpigmentation (5 %). No nerve injuries, skin injuries and infections have been reported. [10]

Comparing the incidence of adverse events, most studies reported no significant differences between MOCA and EVTA, both in major (DVT) and minor (phlebitis, ecchymosis, paresthesia and skin pigmentation) adverse events [13, 17], although in MARADONNA trial the incidence of ankle edema was significantly lower after MOCA than after RFA, with similar incidence at baseline ($p = 0.002$). [20] An RCT by Vähäaho et al. found no sensory disturbances after MOCA, compared to 8 % of patients after EVTA with such adverse event ($p = .090$). [18]

Flebogrif

Flebogrif is another mechanochemical ablation device used for ablation of the incompetent saphenous vein. It mechanically scarifies the vein wall by a specially designed endovenous catheter, at the end of which sharp hooks are deployed, which damage the endothelium. During the continuous withdrawing the catheter, the chemical ablation is performed by simultaneously injecting a foam sclerosant. Up to now the available evidence is very limited. A first study has shown promising results with the complete occlusion rate of 92 % after 2 years. [21]

Other non-thermal and non-tumescent Techniques

The V-Block Occlusion System

Another new NTNT method of treatment the incompetent saphenous vein is the V-Block occlusion system, which uses self-expandable vein occluder inserted below the SFJ to eliminate the possibility of forwarding passage of clot and sclerosant to the deep veins and dual procedure syringe system. During the foam sclerotherapy, the blood is simultaneously evacuated from vein. The analysis of 51 patients has shown the complete occlusion rate of 98 % at 7 day and 77.8 % at 3 years, without device-related complications. [22]

Coil Embolization and Foam Sclerotherapy

The combination of coil embolization and foam sclerotherapy of GSV has also been alternative described in the literature as a novel and effective NTNT treatment for varicose veins with good short-term results. [23]

There is currently no high-quality evidence to support the use of physical embolic agents, such as coils, to treat axial venous reflux, therefore the International Union of Phlebology, the Australasian College of Phlebology, the Australia and New Zealand Society for Vascular Surgery, the American Venous Forum, the American Vein and Lymphatic Society, and the Interventional Radiology Society of Australia recommend against the use of such approaches for the treatment of saphenous incompetence outside of the clinical trial settings (Grade 2C against). [24]

Further research is needed to confirm the validity of these new methods.

Summary

NTNT represent the next generation of endovenous therapy. The currently available evidence demonstrated high clinical and anatomical success rates for novel techniques, comparable to those previously reported for thermal ablation.

The main advantage over established treatment modalities for saphenous vein incompetence is no need for tumescent anesthesia, what leads to reduce the procedure time and increase comfort of patients during and after the procedure with less hematoma and ecchymosis formation. Furthermore, no thermal energy is used with a related risk of nerve injury, therefore these NTNT may be a valuable alternative, in particular if ablation of the more distal part of the below-knee GSV or the SSV is considered. Additionally, the use of CAC obviates to wear the postprocedural compression stockings what is an important advantage for the compliance of the patients.

The safety of these NTNT is also well documented, although precautions should be taken in case of CAC due to the possibility of late hypersensitivity reaction and granuloma formation.

The novel non-tumescent non-thermal are a valuable alternative to well- established thermal techniques, however further studies with long-term results are needed, also with regard to safety aspects.

Conflict of Interest

The authors declare that they have no conflict of interest.

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