Review

Varicose vein therapy and nerve lesions

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Summary: Treating varicose veins using endovenous thermal techniques – especially laser and radio frequency ablation – has emerged as an effective alternative to open surgery with stripping and high ligation. Even though these methods are very gentle and patient-friendly, they are nevertheless accompanied by risks and side effects. Compared to open surgical therapy, the risk of damage to peripheral and motor nerves is reduced; however, it still exists as a result of heat exposure and tumescent anaesthesia. Non-thermal methods that can be applied without tumescent anaesthesia have been introduced to the market. They pose a considerably lower risk of nerve lesions while proving to be much more effective. This paper investigates data on postoperative nerve damage and paraesthesia using internet research (PubMed). It analyses the current state of knowledge regarding non-thermal treatment methods and takes into account the latest developments in the use of cyanoacrylate to close insufficient saphenous veins.

Keywords: Thermal ablation, RFA, EVLA, radiofrequency ablation, laser ablation, paraesthesia, tumescent local anaesthesia, TLA, nerve lesion, ultrasound-guided foam-sclerotherapy, UGFS, mechanochemical ablation, MOCA, adhesive closure, cyanoacrylate allergy

Introduction

Numerous endovenous methods for treating varicose veins have been established since Babcock first described the procedure of stripping more than 100 years ago [1]. Thermal methods, like endovenous laser ablation (EVLA) and radio frequency ablation (RFA), which have been performed for more than 15 years, are considered to be standard. Both methods use a catheter (or a laser fiber) to apply thermal energy to the vein wall. This results in shrinkage of the lumen. Both methods have been thoroughly investigated. In 2014, Van Eekeren et al. listed 85 studies on EVLA in 15,055 limbs, and 47 studies on RFA in 8,372 limbs [2]. In a randomised multi-centre study Rasmussen et al. were able to verify a closure rate for the great saphenous vein (GSV) of 93.2% after EVLA and of 93.0% after RFA after 3 years, which was comparable to results after high ligation and stripping with a closure rate of 93.5% [3]. In a current paper Boersma et al. also confirmed such non-inferiority with respect to the treatment of the small saphenous vein (SSV) [4].

Hence, both the guidelines of the American Venous Forum (2011) and the UK's NICE guidelines (2013) recommend endovenous thermal treatment as a first-line therapy and give it a grade-1B recommendation [5, 6].

However, EVLA and RFA also can have side effects. The closure of the diseased saphenous veins is based on exposure to high temperatures. This requires the use of tumescent local anaesthesia (TLA), which serves to achieve analgesia as well as to cool down surrounding structures. The anaesthetic procedure represents relevant pain impairment for the patient caused by the insertion of the tumescence needle. Heat also induces inflammatory processes which cause a transient, and, in rare cases, permanent hyperpigmentation of the skin similar to that which occurs with advanced venous insufficiency (or a phlebitis), or even following sclerotherapy [7, 8]. One important aspect is the risk of damaging sensory and motor nerves.

This review highlights neurological side effects of established thermal methods and presents recent data on the latest non-thermal treatment procedures.

Methods

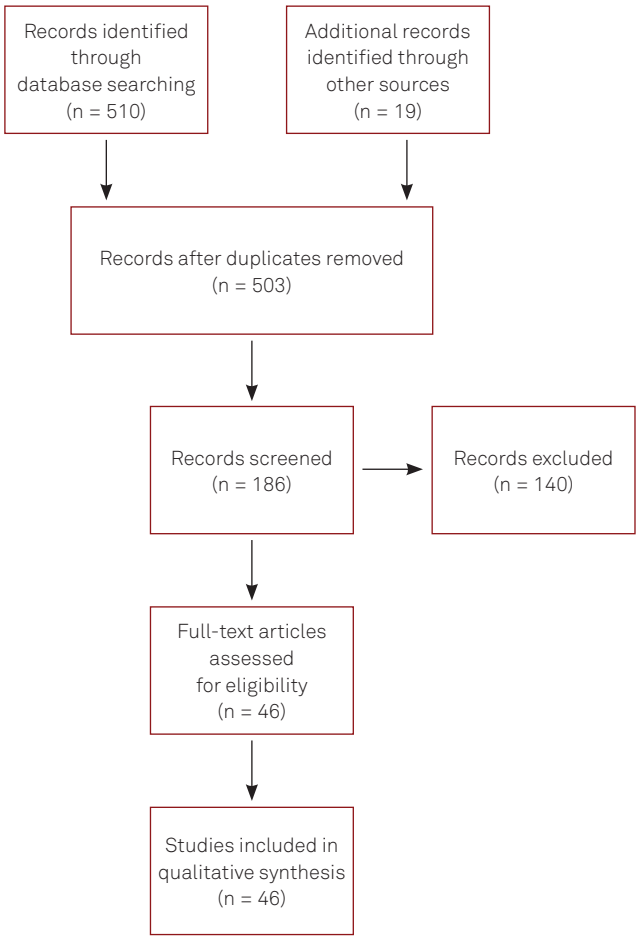
Internet research (PubMed, search date July 31, 2016) served as a method for extracting data. The key words that were used and the search algorithm as per the PRISMA guidelines are listed in Table I and Figure 1, respectively. Since only 86 entries appeared for vein stripping + paresthesia (30), RFA + paresthesia (32) and EVLA + paresthesia (24), the search was extended to include the key words tumescent anesthesia and SSV. Entering the key words with respect to to non-thermal ablation resulted in a total of 510 entries. An additional 19 publications on the toxicity and allergenic potential of cyanoacrylate were also available (University Library Halle, Germany). Of the 186

screened entries, 46 papers could be used in which the correlation between the thermal methods for treating varicose veins and nerve damage was investigated or which provided data on non-thermal methods. 140 papers contained no useful information on the topic in question.

Table 1. Keywords used to obtain data in PubMed.

Keywords	Number of publications
Vein stripping + paresthesia	30
Radiofrequency ablation + paresthesia	32
EVLA + paresthesia	24
Tumescent anesthesia + paresthesia	16
SSV + paresthesia	17
Mechanochemical ablation	29
Adhesive closure + veins	25
Cyanoacrylate + incompetent veins	8
Cyanoacrylate toxicity	239
Cyanoacrylate + allergy	90
Total	510

Figure 1. Flow chart to demonstrate review progression and article inclusion/exclusion.



The risk of nerve damage as part of endovenous thermal treatment of varicose veins

Paraesthesia occurs in up to one third of all treatment cases after open surgical treatment of varicose veins. This persists in a relevant number of cases six to even 12 months after treatment [9–11]. In 2014, Pan et al. published a meta-analysis of 13 studies on a total of 2,245 treated limbs. In their analysis they were able to identify that, at 6.73%, EVLA posed only half as much of a risk of nerve lesions and consecutive paraesthesia as stripping/high ligation at 11.27%, as confirmed by previous comparative studies [12].

Dermody et al. described paraesthesia in 7.4% of patients after stripping/high ligature, in 5.5% of patients after RFA, and in 3.8% of patients after EVLA [13].

The results also prove that thermal treatment of varicose veins is also accompanied by a risk of nerve lesions.

Affections of the saphenous nerve when treating the GSV have been described by various investigators. Gifford et al. described paraesthesia after treating the whole GSV with EVLA/RFA in 4%, Liu et al. after laser treatment (bare fibre) even in 27% of cases [14, 15].

Treating the SSV goes hand in hand with the risk of damaging the sensory sural nerve, which crosses the vein in the calf region. An irritation of the nerve leads to paraesthesia near the lateral ankle. Boersma et al. evaluated 28 studies on laser treatment on 2,950 SSV and nine articles on RFA (three studies only looking at the SSV). Postoperative paresthesia was found in 4.8% (EVLA) and 9.7% (RFA) of the cases [4]. Park et al. described numbness and a sensory disturbance after RFA in an astonishing 26% of the patients treated [16].

A very rare form of complication described in the literature are lesions of the sensory and the motor tibial nerve, which is located in the back of the knee in close proximity to the saphenopopliteal junction. If this is damaged by heat or through the insertion of a needle, sensory disturbance, as well as talipes calcaneus, can be expected [17–19].

The data produced in the individual studies fluctuated widely as a result of the use of different laser and RFA devices and due the different definitions of nerve lesion. However, it can be deduced that, even though thermal methods are highly efficient and very gentle, they are not completely free of the relevant risk of causing nerve lesions.

Non-thermal, non-tumescent methods

Various alternatives to endovenous thermal treatment have been established which are not based on exposure to heat. Because these methods do not require such exposure to heat, tumescent anaesthesia becomes unnecessary and there is a significantly lower risk of damaging peripheral nerves.

The non-thermal treatment of insufficient saphenous veins is based on two methods: pharmacological sclerotherapy using polidocanol or sodium tetradecyl sulfate (STS), and adhesion using cyanoacrylate.

Sclerotherapy and mechanochemical ablation

The use of ultrasound-guided sclerotherapy to treat saphenous varicose veins has been around for approximately 20 years [20]. Treatment results improved considerably with the introduction of foam sclerotherapy in 2003 [21, 22]. During the procedure, 1 part sclerosing agent (polidocanol, STS) is mixed with 4 parts air or CO_2/O_2 to produce a fine-bubble microfoam. The foam is injected into the saphenous vein under ultrasound guidance. Because of its low invasiveness and good primary technical success, ultrasound-guided foam sclerotherapy is recommended by the American Venous Forum as an alternative to thermal methods and has received a grade-1B recommendation. Its disadvantage to open surgery, as well as to EVLA and RFA, is that it has a considerably higher rate of recurrence. Gillet et al. found a 90.3 % closure rate in 1,025 treated extremities after one month. However, during follow-up investigations of their patients (n = 203), Chapman-Smith and Browne found that there was a closure rate of only 26 % after five years [23, 24]. Rasmussen et al. confirmed this lack of long-term success of treatment results [3].

Nevertheless, this gentle and very cost-effective treatment can be considered very effective for selected patients, also because it can be performed repeatedly with considerably better results.

A further development of ultrasound-guided sclerotherapy is mechanochemical ablation (MOCA™, ClariVein™, Vascular Insights, LLC Massachusetts, USA), which has been performed since 2010. In addition to the application of the liquid sclerosing agent, this form of treatment destroys the endothelium using a wire that rotates at 3,500 rpm at the end of a catheter [25]. Studies show a closure rate of between 88 and 94 % after 12 months [26, 27].

Mechanochemical ablation appears to be a highly effective way to close insufficient saphenous veins with low invasiveness. Currently no long-term results on larger groups of patients have been published in the literature even though the system has been approved for more than 6 years.

Thermal lesions are ruled out with this method and ultrasound-guided foam sclerotherapy, as is mechanical damage to neighboring nerves as a result of tumescent anesthesia. Impairment due to pain can also be classed as much lower than in the case of thermal methods [28].

As a limitation the sclerosing agents polidocanol and STS have a dosage limit of 2 mg/kg body weight. Since a concentration of 2 % is used, treatment of more than one saphenous vein is usually not possible per treatment session. Furthermore, results with larger vein diameters appear to be less satisfactory. The success rate seems to be higher for the treatment of the SSV than for the GSV. Currently no reliable data exist on this question.

Acrylate adhesion of the saphenous veins: gimmick or useful additional treatment?

Introduced in 2011, the latest technique involves closure of the saphenous veins through embolization with cyanoacrylate (Venaseal™ Medtronic, PLC Minneapolis, USA, and Biolas Variclose® FG Group, Turkey). Cyanoacrylate has been used in medicine for decades in different chemical derivatives. In the 1960s methyl 2-cyanoacrylate was introduced for the repair of nerve lesions [29]. Isobutyl 2-cyanoacrylate (IBCA) was then used to close wounds during surgery until N-octyl-cyanoacrylate, which is still in wide use today, was introduced in 1996 [30].

Since 1989 N-butyl 2-cyanoacrylate (NBCA) has been used intravascularly, for example to treat acute gastrointestinal bleeding, embolization of vascular deformities, and malignant tumors [31]. This active ingredient is also used to treat varicose veins.

The substance has proven to have good tissue tolerance in thousands of patients over a long period of time. Histotoxic inflammatory reactions are infrequent when today's longer-chain derivatives, like NBCA and N-octyl-cyanoacrylate, are used in vitro and in animal testing. This is in contrast to the short-chain compounds (methyl- and ethyl-cyanoacrylate) previously used [32–34]. Clinical investigations reinforce these observations [35].

In principle, polymerised acrylate is an implant which, like a stent, suture material or staples, is encapsulated and endothelialised. A very slow metabolic decomposition of the material occurs, which sonographic observations over a period of 12 months substantiate [36]. However, it is currently unclear how long it takes for it to be completely absorbed. Individual cases of transient inflammatory secondary reactions and eosinophilic vasculitis have been published, whereby it can be assumed that inflammatory processes also play a role in the obliteration of the veins [37, 38].

In animal trials using pigs, the adhesive was never detected outside the adventitia. This suggests that the inflammatory reaction is not strong enough to damage surrounding tissue and nerves [39]. No case of nerve damage as a result of the acrylate adhesion of varicose veins has been identified.

Contact-related allergic reactions have been repeatedly reported in various professional groups when handling acrylate adhesives (beauticians, nail designers, dental technicians). A link to medical use has been documented in various case studies when used to close wounds [40, 41]. This is predicated on the basis that this is a type-IV allergic reaction. Sensitisation occurs through the acrylate monomer that binds to keratin in the skin. Mediation of dendritic cells, which are only present in the cutis, can trigger a contact allergy with pruritus and efflorescence [42]. There has been no evidence in the literature of this when cyanoacrylate derivatives are applied intravascularly, something which has been performed for decades, e. g., to treat gastric bleeding and intracranial aneurysms.

In the context of varicose vein treatment, Gibson and Ferris reported a case of allergic reaction with body hives within the first week after intervention, which improved after treatment with antihistamines and steroids (43). A feasibility study on adhesive closure with cyanoacrylate for the Venaseal™ system resulted in a closure rate of 92 % [44]. Proebstle et al. confirm these results in the European

multi-centre study (n = 70, 24 months eSCOPE). Transient irritation with sensitivity to touch and localised redness were documented in 12.9 % of the patients studied [45]. None of the studies identified any paraesthesia or hyperpigmentation. The author is unable to substantiate the total lack of hyperpigmentation. This can be observed in rare cases after treatment of very superficial vein segments that run extrafascially.

In the randomised study for device approval (VeClose) that included 242 patients, Morrisson et al. were able to establish a closure rate of 98.9 %, which was higher than in the RFA comparison group (94.3 %). In terms of clinical improvement, both study arms demonstrated comparable results. The Venous Clinical Severity Score (VCSS) at the time of closure was 5.6 (±2.6) for RFA and 5.5 (±2.6) for acrylate adhesion. After six months the scores were 1.6 (±1.9) for RFA and 1.5 (±1.8) for acrylate adhesion [46].

In their current publication, Calik et al. describe a closure rate of 97.2 % after six months (215 treated saphenous veins). They observed one case of thrombophlebitis [47].

Cases of thrombophlebitis have been observed for all saphenous vein treatment methods. This applies to stripping/HL and to thermal and non-thermal endoluminal methods and its origin can be found in the remaining tributaries. A slightly painful localised reddening after acrylate adhesion is not to be assigned to thrombophlebitis in the narrow sense but rather to the histotoxic reaction described above.

Zierau published the currently largest case series in 2014. In the non-randomised study of 795 treated veins (561 GSV, 234 SSV), a closure rate of 97.75 % was identified at the follow-up six months after treatment (response 71.07 %). A short-term transient inflammatory redness of the skin was identified at around five to eight days in 11.7 % of the cases. The author presumes that this is connected to the higher amounts of adhesive, and because it is simultaneously administered with polidocanol. Paraesthesia was also not observed in this investigation [48].

Conclusions

The cost-effective methods of ultrasound-guided foam sclerotherapy and mechanochemical ablation prove to be effective in the investigations, but a meticulous preoperative patient selection is necessary.

Acrylate adhesion to close insufficient saphenous veins is effective with minimum invasiveness, which is comparable with thermal methods.

The advantage of the non-thermal methods over open surgery, EVLA, and RFA appears to be the much lower risk of peripheral neurological complications.

There is currently a lack of large randomised studies on mechanochemical ablation and acrylate adhesion. In contrast the likewise very gentle thermal methods have been superbly investigated scientifically and have proven themselves in hundreds of thousands of procedures. Until there are reliable data on larger patient cohorts, non-thermal methods for treating varicose veins, subject to individual findings, should be considered to be a useful addition to the established methods.

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