Non-thermal endovenous treatment: acrylate adhesion of varicose saphenous veins

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Keywords

Cyanoacrylate, acrylate adhesion, varicose saphenous veins, endovenous treatment of varices

Summary

Endovenous treatment of varicose veins, especially thermal procedures using laser and radio frequencies, has become established as an effective alternative to surgery by stripping and high ligation. Although these methods are very sparing and patient-friendly, they also entail risks and side effects. The risk of damage to peripheral and motor nerves is certainly lower than with open surgery, however it still exists as a result of heat application and tumescent anaesthesia.

Several non-thermal procedures which do not require the use of tumescent anaesthesia are coming onto the market. They carry a significantly lower risk of nerve lesions while remaining highly effective. The present work analyses the current state of knowledge on the latest to be developed, cyanoacrylate adhesion of incompetent saphenous veins.

Schlüsselwörter

Cyanoacrylat, Acrylatverklebung, Stammvarikose, endovenöse Varizentherapie

Zusammenfassung

Die endovenöse Behandlung der Varikose hat sich als effektive Alternative zur chirurgischen Behandlung mittels Stripping und hoher Ligatur etabliert - allen voran die thermischen Verfahren Laser- und Radiofrequenzablation. Wenngleich diese Methoden sehr schonend und patientenfreundlich sind, so gehen auch mit ihnen Risiken und Nebenwirkungen einher. Gegenüber der offen-chirurgischen Therapie ist das Risiko einer Schädigung peripherer und motorischer Nerven zwar reduziert, besteht aber dennoch im Rahmen der Hitzewirkung und der Tumeszenzanästhesie.

Nicht-thermische Verfahren, die ohne Tumeszenz durchzuführen sind, drängen auf den Markt. Sie besitzen ein deutlich geringeres Risiko für Nervenläsionen bei hoher Effektivität. Die Arbeit analysiert den aktuellen Kenntnisstand zur jüngsten Entwicklung, der Verklebung der inkompetenten Stammvenen mittels Cyanoacrylat.

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Nicht-thermische endovenöse Therapie: die Acrylatverklebung der Stammvarikose
Phlebologie 2017; 46: 143–147
https://doi.org/10.12687/phleb2363-3-2017
Received: February 13, 2017
Accepted: March 03, 2017

Introduction

For a hundred years, the standard treatment for varices was removal of the saphenous vein using the stripping operation developed by William Babcock (1). End of the 1990s a change in paradigm started with the development of radiofrequency ablation (RFA 1998) and endovenous laser ablation (EVLA 1999). Both procedures are based on the principal of using a catheter to apply thermal energy to the vein wall, causing shrinkage of the collagen fibres. The result is to occlude the lumen. These endovenous thermal procedures are just as efficient as open surgery, and considerably less invasive (2, 3). As a result they help to satisfy the increasing requirement for as short a convalescence as possible after outpatient treatment.

Both the guidelines of the American Venous Forum (2011) and the British NICE Guidelines (2013) recommend endovenous thermal treatment as the first choice therapy for this reason, with recommendation grade IB (4, 5).

However, both EVLA and RFA present side effects. The effects of high temperatures make the application of tumescent local anaesthesia (TLA) necessary; it serves both as an analgesic and to protect surrounding structures by cooling them.

This anaesthetic procedure involves significant pain for the patient due to the positioning of the needle through which the anaesthetic is delivered. Furthermore, heat induces inflammatory processes, which – just like advanced venous incompetence or phlebitis, or after sclerotherapy – can produce temporary, and occasionally permanent, hyperpigmentation of the skin. There is also a serious risk of damage to sensory and motor nerves (6).

Various non-thermal technologies have been developed to reduce these side effects. This review presents the data available on one of the latest developments, acrylate adhesion of saphenous veins.

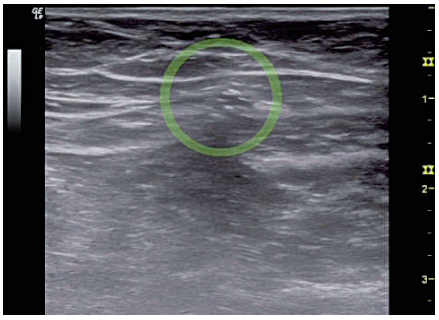

Fig. 1 The application catheter contains air-filled microchannels which create a recognizable star-shaped pattern when viewed in section in the ultrasound screen.

Adhesion of varicose saphenous veins to broaden the portfolio of endovenous methods

One of the most modern procedures for treating varicose veins is occlusion of the saphenous veins by embolisation with cyanoacrylate (CA), which was introduced in 2011 (7). The VenaSeal™ system (Medtronic, PLC Minneapolis, USA) has been approved in Germany, where it has been available since 2012. The system, originally developed by the start-up Sapheon™, received FDA approval in 2015 and has been in use in the USA since then. Another system, based on adhesion of the diseased saphenous vein with cyanoacrylate, was developed in Turkey (Biolas Variclose®, FG Group, Turkey). There are only a few users in Germany and it is no longer on the register of EU-approved devices for vein operations (2017 Buyers guide [8]).

The VenaSeal™ system set contains all the equipment necessary for treatment. Apart from a suitable ultrasound machine, no other additional equipment is needed. As with thermal methods and conventional vein surgery, the success of adhesion treatment depends on the quality of the pre- and perioperative diagnosis. The use of a 12 MHz (minimum) linear probe is recommended. The cyanoacrylate used in the system has been modified so that its high viscosity allows exact application. It also requires contact with blood to trigger polymerisation, preventing the catheter from sticking.

The occlusion procedure occurs in two steps:

Once the guide wire and the sheathare prepared, as well as the treatment catheter and the delivery gun, the saphenous vein is occluded in the region of the saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ). The treatment catheter is introduced under ultrasound control along the 180 cm long guide wire to the SFJ or SPJ. To avoid the adhesive being carried into the deep vein system, the treated vein is closed completely proximal of the catheter tip by external compression with the probe before the first application of exactly 0.09 ml of adhesive. A second dose is applied at a distance of 1 cm. Finally the treated region must be compressed for 3 minutes until polymerisation is complete. For safety reasons the supplier prescribes a minimum distance of 5 cm between the catheter tip and the deep vein system. The visibility of the catheter tip in the ultrasound screen is optimised by air-filled microchannels (▶ Fig. 1).

In the second step, the course of the saphenous vein is occluded by withdrawing the catheter 3 cm at a time and delivering further doses of cyanoacrylate with the delivery gun at each interval. The area must be compressed for 30 s after each delivery of adhesive. To treat a 45 cm vein segment for example, 1.53 ml of adhesion is applied (▶ Fig. 2).

Apart from a slight emission of energy due to the exothermal polymerisation reaction, no heat is applied, meaning that tumescent anaesthesia is not required. The procedure therefore causes little or no pain.

Vein puncture is the only trauma, so the risk of nerve damage is very small. For this reason, the method is particularly suitable for treating the small saphenous vein (SSV), in which thermal treatment is limited by the proximity of the crossing sural nerve.

The varicose vein is permanently occluded immediately after polymerisation of the cyanoacrylate. The patient can therefore return to any activity immediately after treatment. If only the saphenous vein is treated, use of a compression stocking is not essential.

The method is very easy to learn for operators who already have experience in other endovenous treatments. In their study, Kolluri et al. found similar success and safety results among first-time users and operators who used the technique routinely (9).

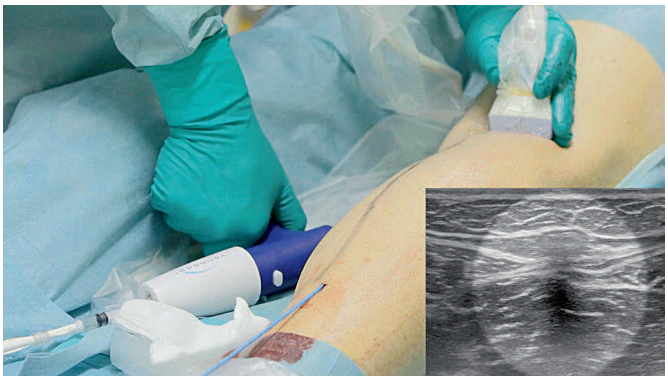

Fig. 2 As the catheter is withdrawn, 0.09 ml doses of N-butyl- cyanoacrylate are applied at 3 cm intervals under ultrasound control. The application of the glue can be seen in the ultrasound screen.

Cyanoacrylate – Super adhesive with a long history of medical application

In principle, polymerised acrylate is an implant, like a stent, suture or clip, which becomes encapsulated and endothelialised. Very slow metabolic degradation of the materials occurs, as ultrasound observations over a period of 12 months show (▶ Fig. 3) (9). It is not yet clear how long complete resorption will take. Individual cases of temporary inflammatory reactions and even eosinophilic vasculitis have been published, in which inflammatory processes have played a part in vessel obliteration (10, 11).

Various chemical derivatives of cyanoacrylate (CA) have been used in medicine

for decades. In the 1960s, methyl-2-cyanoacrylate started to be used for repairing nerve lesions (12). Isobutyl-2-cyanoacrylate (IBCA) was used in surgery at first for closing wounds; then in 1996 N-octyl-cyanoacrylate was introduced and is still widely used (13). N-butyl-2-cyanoacrylate (NBCA) was introduced in 1989 for intravascular use, e.g. for treating acute gastrointestinal bleeding, embolisation of vessel malformations and treatment of malignant tumours (14). It is also used in varicose vein treatment.

Since its introduction NBCA has proved to present good tissue tolerance in thousands of patients. Histotoxic inflammatory reactions were found in a very small numbers with the use of the long-chain derivative usually used today (N-butyl-cyanoacrylate, octyl-2-cyanoacrylate) *in vitro* and in animal trials, in contrast to the short-chain compounds used previously (methyl- and ethyl-cyanoacrylate) (15–18). Clinical trials support these observations (19). The resorption time also correlates directly with chain length.

In pigs, the polymerised CA was never detected outside the adventitia, from which it may be concluded that the inflammatory reaction is not strong enough to damage the surrounding tissue and nerves (7). To date no case of nerve damage as a result of acrylate adhesion of varices has been described.

Contact allergic reactions have been described repeatedly in different groups of professional workers who regularly handle acrylate glues (cosmeticians, nail-designers, dental technicians). A similar connection with medical use has been documented in various case reports of application for wound closure (20–22). This may be because it is a Type IV allergic reaction. Sensitisation is caused by the acrylate monomer (not the inert polymer), which binds to the keratin in the skin. The reaction of the dendritic cells, which only occur in the cutis, may finally lead to a contact allergy with pruritus and efflorescence (23).

There are no case descriptions in the literature to date in the context of the intravascular use of cyanoacrylate derivatives to treat gastrointestinal bleeding and intracranial aneurysms, for which they have been used for decades. This may be explained by the fact that the acrylate monomer is introduced into the vessel directly through a catheter, so that when correctly applied it does not come into contact with the immunity-inducing cells of the skin.

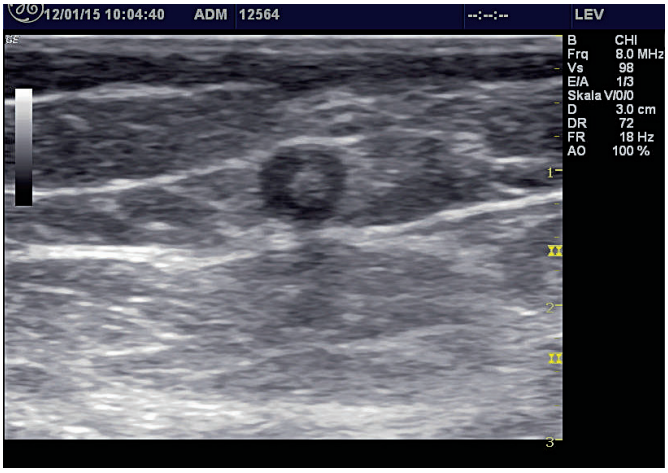

Fig. 3
Typical finding on follow-up: the acrylate polymer presents an echo-rich central area with an ultrasound shadow, surrounded by an echo-poor ring (thrombus).

In the context of varicose vein treatment, occasional urticarial efflorescences have been observed which responded to anti-histamines and steroids and were of limited duration. So far there is only one case described in the literature, by Kathleen

Conclusions

Acrylate adhesion of varicose saphenous veins is minimally invasive and produces comparable results to those achieved with thermal methods. The procedure is safe and easy to learn and has few side effects. The risk of nerve damage in particular is lower than with thermal methods as tumescent anaesthesia is not required.

A local reaction frequently observed in the early postoperative phase should be discussed in conversation with the patient during preparation for the operation.

One technical limitation results from the supplier's recommendation to maintain a safety distance of 5 cm from the saphenofemoral and saphenopopliteal junctions. This runs counter to the principle, generally recognised in Germany, of leaving as short a stump of saphenous vein as possible. On the other hand there is a shortage of reliable data to support higher long-term freedom from recurrence with either a short or completely absent stump.

To date there are no large randomised, controlled studies of acrylate adhesion. In contrast, thermal methods, which are also regarded as very sparing, have been the subject of excellent scientific investigation. They have been proved in hundreds of thousands of treatments all over the world, and in the coming years they will continue to gain significance, especially in Germany. Until more, and more reliable, data from large patient groups are available, and more extensive cover is available from the institutions which bear the costs, the acrylate adhesion procedure for varicose saphenous veins will continue to be a useful addition to the established endovenous thermal methods in Germany.

It could gain a special niche in treatment of the small saphenous vein. Moreover the method offers an endovenous treatment option for patients in whom TLA is contra-indicated because they are allergic to local anaesthetic, as well as patients with cardiac arrhythmia whose treatment would react with amino-amide local anaesthetics.

In the author's opinion, acrylate adhesion of varicose saphenous veins is a useful addition to the established methods. In addition to the niche use mentioned above, it is also attractive to many patients because of its sparing approach. A final advantage is that it does not require any additional investment in technical facilities.

Tab. 1 Studies published since 2013 of the effectiveness of acrylate adhesion with the *VenaSeal*™ and *Biolas VariClose*® treatment systems. Many data review studies show clearly that the technique provides just as good occlusion rates as thermal procedures. Only one randomised prospective study is mentioned (Morrison et al., VeClose study). Temporary, self-limiting, painful skin irritation is described in almost all the studies and called „phlebitis".

	Study type	N	Follow-up Month	Occlusion rate (%)	Phlebitis (%)
Almeida et al.* 2013 (31)	Feasibility	38	12	92.0	16
Almeida et al.* 2015 (32)	Feasibility	38	36	94.7	–
Morrison et al.* 2015 (27)	RCT (vs. RFA)	108/114	3 24	99.0/96.0 94.3/94.0	20/14
Langfellner* 2015 (33)	Retrospective	130 86	1 3	96.5 95.4	8.8
Tekin et al.** 2016 (34)	Single centre	62	6	90.3	k.A.
Proebstle et al.* 2015 (26)	Prospective	70	12	92.9	11.4
Zierau* 2015 (29)	Multicentre	795	6	97.8	11.7
Çalık et al.** 2016 (28)	Prospective	215	6	97.2	0.5 Pain 6.1 %
Gibson et al.* 2016 (24)	WAVES	70	1	100	20
Zierau* 2016 (30)	Retrospective (vs. RFITT)	1139/256	46	97.5/95.3	12.0/8.5
Bozkurt et al.** 2016 (35)	Retrospective (vs. EVLA)	141/142	6 12	96.6/91.7 95.8/92.2	4.5/7.7
Yasim et al.** 2016 (36)	(vs. EVLA)	180	5.5	100	Not reported

*: Venaseal™, Medtronic, USA; **: Biolas VariClose® FG Group, Turkey

Gibson in the context of the WAVES study (24). As the symptoms in this case are not those of a typical Type IV allergy, the author considers that alternative mechanisms for this intolerance reaction should also be discussed. In any case, a history of allergies must never be forgotten when explaining the operation to the patient, since a pre-existent allergy to acrylate or suspect events in the patient's prior history would be an absolute contra-indication for the procedure.

Effectiveness and side-effects

Acrylate adhesion is generally not covered by statutory health insurance in Germany. On the basis of insufficient data, some private health insurance companies also refuse to accept treatment costs. However, although the procedure has only been in use for 5 years, and was only approved in the USA in 2015, there is a large fund of record data.

The feasibility study of CA adhesion for the VenaSeal™ system presented a closure rate of 92 % (25). Proebstle et al. confirmed this in the European Multicenter Study. It was remarkable here that treatment of tributary veins was not included as a consequence. At the start of the study, 1.4 % of the treated legs were free of visible varices; three months after closure of the saphenous vein the figure was 41.4 % (26).

In the only randomised trial to date (VeClose, FDA approval study) Morrison et al. compared acrylate adhesion with radio frequency ablation (ClosureFast™). In the two-year follow-up, the patient group treated with VenaSeal™ presented an occlusion rate with a higher trend (94.3 %) than the RFA comparison group (94.0 %). In terms of clinical improvements, both arms of the study presented comparable outcomes. The Venous Clinical Severity Scores (VCSS) at the start of the study were: RFA 5.6 (±2.6), acrylate adhesion 5.5 (±2.6); after 6 months: RFA 1.6 (±1.9), acrylate adhesion 1.5 (±1.8) with lasting effect (27).

In a current publication on the use of CA with the Biolas VariClose® system, Çalik et al. report an occlusion rate of 97.2 % after 6 months (215 saphenous veins treated). They describe thrombophlebitis in one patient. A temporary, self-limiting, local sensitivity to pain was observed in 6.1 % (28).

A few cases of thrombophlebitis are known to occur with all procedures for treating saphenous veins. This is as true of stripping/HL as it is of thermal and non-thermal endoluminal procedures and originates in remaining tributaries. Strictly speaking, the slightly painful local reddening sometimes observed after acrylate adhesion is not thrombophlebitis but the histotoxic reaction described above. This temporary sensitivity may be observed in up to one patient in five in the postoperative phase, and is also described in all the studies available to date. The studies betray a terminological uncertainty in the interpretation of this side effect. It is described as „phlebitis", „painful reddening" or even „thrombophlebitis".

No paresthesia is observed in the studies and no hyperpigmentation is described. In our own observations the complete absence of hyperpigmentation cannot be confirmed. It can be observed especially after treatment of very superficial and extrafascial vein segments. A review of all the

studies and records published to date can be found at ▶ Tab. 1.

Conflict of interests

The author carries out consultancy work at the company Medtronic.

Ethical guidelines

The study was prepared in compliance with national guidelines and the current Helsinki declaration.

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