

Foam sclerotherapy of segments of the saphenous vein with adjuvant hyaluronan compression

J. C. Ragg; O. R. Despa; U. Brüggemann; S. El-Chamali; K. Stoyanova

angioclinic® Venenzentren Berlin–München–Zürich, Germany and Switzerland

Keywords

Foam sclerotherapy, microfoam, compression, hyaluronan, perivenous

Summary

Background: Thermal, mechano-chemical and chemical methods of vein closure are increasingly less effective in saphenous veins with diameters above 10 mm. Furthermore, increasing vein size is associated with unpleasant inflammatory reactions, in particular in locations close to sensitive structures like the skin. External compression media are not able to prevent these unwanted sequela in a tolerable way. As a possible solution, perivenous hyaluronan compression was evaluated combined with microfoam sclerotherapy.

Methods: 34 patients (25 f, 9 m, 43–71 yr/o) with saphenous insufficiency (GSV), diameters 10.1–23.1 mm (M: 14.1 mm), distance to skin: >10 mm, received a vein lumen compression of thigh- or calf segments by perivenous injection of a NASHA gel mediated by a coaxial paravenous catheter prior to catheter-applied microfoam sclerotherapy (aethoxysklerol 1 %). Injection of both, hyaluronan and microfoam, were performed during catheter withdrawal. The aim of hyaluronan compression was a 2/3 reduction of the native vein cross section. For comparison, adjacent segments were compressed with common tumescent fluid. Segments for both modalities had similar diameter and were randomized. Due to department rules, the junc-

tion segment was closed with endovenous lasers to warrant elimination of reflux. No textile compression media were applied. Clinical controls including ultrasound were performed after 2, 8, 26 and 54 weeks.

Results: All treated vein segments showed total occlusion after 2 weeks (first visit). The lumen reduction was 54–81 % (M: 68.4 %) in segments with hyaluronan compression and 8–29 % (M: 19.2 %) in segments with tumescent fluid. Time needed for hyaluronan compression was 1.1–3.5 min (M: 2.2 min) and for tumescence 0.8–2.7 min (M: 1.8 min) per 10 cm-segment. Clinical investigations up to 8 weeks did not reveal any symptoms, visible inflammations or stainings in segments covered with hyaluronan, while tumescent-compressed segments had such findings in 20/34 cases (58.8 %). Perivenous hyaluronan did not induce any discomfort or side effects during follow-up.

Conclusions: Even large saphenous veins can be effectively and safely treated by microfoam sclerotherapy without any postinterventional symptoms when the vein lumen is reduced by perivenous injection of hyaluronan gel. However, it takes additional interventional effort to achieve this goal. Future applications could also include combinations with thermal or gluing device or support novel foams like Varithena or biomatrix sclerofoam when treating very large veins or venous aneurysms, and furthermore serve in vein shaping for the purpose of establishing laminar flow or modifying pressure relations (venoplasty).

Schlüsselwörter

Schaumverödung, Mikroschaum, Kompression, Hyaluronsäure, perivenös

Zusammenfassung

Hintergrund: Thermische, mechano-chemische und chemische Verfahren sind in Stammvenen mit zunehmenden Durchmessern (oberhalb 10 mm) nicht nur tendenziell weniger erfolgreich, sondern auch vermehrt von unangenehmen Verödungsreaktionen begleitet. Externe Kompressionsmittel oder die Kompression mit Tumeszenzflüssigkeiten lösten dieses Problem bisher nicht. Als mögliche Lösung wurde nun die Kombination von Mikroschaumverödung mit einer adjuvanten perivenösen Hyaluronsäurekompression evaluiert.

Methoden: 34 Patienten (25 w, 9 m, 43–71 J) mit Stammveneninsuffizienz der VSM, Durchmesser 10,1–23,1 mm (MW: 14,1 mm), Abstand zum Hautniveau >10 mm, erhielten vor einer Katheter-Mikroschaumverödung (Aethoxysklerol 1 %) eine Lumenkompression durch ein thermo-behandeltes NASHA-Gel über einen ultraschall-kontrollierten paravenösen Mikrokatheter. Zum Vergleich dienten Segmente, die mittels herkömmlicher Tumeszenz im Durchmesser verringert wurden. Das Krossensegment war aufgrund einer klinikinternen Richtlinie von der Randomisierung ausgenommen und wurde laserokkludiert. Auf textile Kompressionsmittel wurde verzichtet. Klinische und sonographische Kontrollen erfolgten nach 2, 8, 26 und 54 Wochen.

Ergebnisse: Alle behandelten Venen zeigten nach zwei Wochen einen vollständigen Verschluss. Die Reduktion des Venenquerschnitts betrug in Segmenten mit Hyaluronsäurekompression 54–81 % (MW: 68,4 %) und 8–29 % (MW: 19,2 %) in Segmenten mit Tumeszenz. Der Zeitbedarf für die Hyaluronsäurekompression betrug 1,1–3,5 min (MW: 2,2 min) und für die Tumeszenz 0,8–2,7 min (MW: 1,8 min) pro

Correspondence to:

Dr. med. Johann Christof Ragg
angioclinic® Venenzentrum Berlin
Bayreuther Str. 36, 10789 Berlin, Germany
Tel. +49-171/3717424
E-mail: dr.ragg@angioclinic.de

Schaumverödung von Stammvenensegmenten mit adjuvanter Hyaluronsäurekompression

Phlebologie 2017;46:-
<https://doi.org/10.12687/phleb2362-2-2017>
Received: March 3, 2017
Accepted: March 6, 2017

10-cm-Segment. Die klinischen Nachuntersuchungen nach 8 Wochen zeigten keinerlei symptomatischen Reaktionen oder Verfärbungen in den hyaluronsäurekomprimierten Segmenten, während Segmente mit herkömmlicher Tumescenz in 20/34 Fällen (58,8%) sichtbare Entzündungen oder fühlbare Residuen aufwiesen. Die Hyaluronsäuredepots verursachten weder lokale Missgefühle noch unerwünschte Reaktionen.

Folgerungen: Auch große Stammvenen können mit Mikroschaum effektiv, sicher und ohne Folgesymptome behandelt werden, wenn der Venenquerschnitt adjuvant mittels Hyaluronsäure reduziert wird. Für diese neue Qualität ist allerdings ein vermehrter interventioneller Aufwand zu leisten.

Introduction

Microfoam sclerotherapy of saphenous veins is now used world wide (26). In most comparative studies, thermal procedures present slightly better results in both initial and long-term outcomes (21, 35, 37), however microfoam sclerotherapy can be more cost-effective and is also – especially as tumescent anaesthesia is not required – simpler and quicker to carry out (3, 6, 18, 26, 36, 38). Both microfoam sclerotherapy and thermal procedures present one significant disadvantage in the treatment of saphenous veins: a frequent, locally symptomatic regression phase (ablation reaction).

Both thermal and sclerotherapy procedures need a certain volume of blood to induce a thrombotic-inflammatory reaction for permanent occlusion. However, as a result of activated cell infiltration, larger volumes lead to troublesome inflammation, with pain caused by movement, pressure or even contact, reddening, and diffusion of blood degradation colourants, which may last for months. The intensity of the pain is directly related with the volume of degraded blood to be eliminated and the proximity of the vein to sensitive structures (especially the skin). The problem cannot be solved with conventional compression media, as tolerable pressures – at least in the thigh – are too low to compress the saphenous vein significantly (15, 24).

After reports that the saline injected for perivenous tumescent anaesthesia produced some useful effects through vein compression during thermal ablation (20, 22, 27), the next step was to investigate the significance of the minimisation of the lumen caused by perivenous fluid injection in the context of foam sclerotherapy in saphenous veins (12). Advantages that might be expected were:

- minimised lumen could be treated with much smaller quantities of foam,
- less mixing with blood might lead to better effects, and
- the vein lumen would be contracted over a longer period resulting in limitation of inflammatory reaction, making the post-intervention course more comfortable.

As was to be expected from the rapid liquid resorption of physiological salt solutions, investigation showed no important advantage from adjuvant fluid compression on outcomes and symptoms (12); there is little doubt about this result (7, 8).

If, however, perivenous liquid compression works in principle, but unfortunately not for a long enough period, perhaps a liquid with more protracted resorption would provide a solution. As we were investigating vein moulding by perivenous hyaluronan injections in 2013–2014, we came up with the idea of trying this out in conjunction with foam sclerotherapy. Hyaluronan was chosen because of its tissue compatibility, which has been investigated for years (5, 10, 13).

However, it was difficult to design a study because of our Centre's previous history: microfoam sclerotherapy of saphenous veins has never been accepted as an independent treatment in the Centre because the modified laser technique which we have used since 2001 produces extraordinarily precise, long-lasting and thus clearly superior outcomes (22, 28). We therefore decided to carry out a small pilot study in saphenous veins, comparing two groups in which the saphenofemoral junction segment (SFJ) was treated with laser, but the thigh and leg were treated with microfoam, with randomised use of tumescent solution or hyaluronan.

Patients and Methods

The study examined 34 patients (25 f, 9 m, aged 43–71). Inclusion criteria were: Incompetence of the great saphenous vein (GSV) with minimum diameter 10 mm, minimum distance between the vein and the skin 10 mm, HACH Class 2–3, CEAP: C2, in which endovenous treatment with laser and microfoam sclerotherapy was indicated and patient agreement was obtained. The SFJ was first occluded with laser (940–1470 nm) under tumescent anaesthesia (modified Klein's solution) to a point 7 cm distal of the femoral vein. The remaining refluxive segment, as long as its minimum diameter was greater than 10 mm (L: 28–65 cm, mean: 46 cm), was divided into two halves: one was surrounded with tumescent solution and the other with a hyaluronan gel. Refluxive segments in the lower leg of less than 10 mm diameter were also treated, but not included in the study. Application of hyaluronan to the proximal or distal segment was randomised. The diameters of the selected vein segments varied from 10.1–23.1 mm (mean: 14.3 mm) in the segments where hyaluronan was applied and 12.3–22.7 mm (mean: 13.9 mm) in segments with tumescent solution. Microfoam sclerotherapy (aethoxysklerol 1%) was carried out using a PTFE catheter. The sclerosant was injected as the catheter was withdrawn after emptying the vein to a large extent by leg elevation, aspiration or draining massage.

The hyaluronan product selected was a sterile NASHA gel (Macrolane™, Galderma), which was subjected to heat degradation to reduce the half-life (by shortening chain length). The hyaluronan was applied using a specially developed, very flexible cannula (length 200 mm, ► Fig. 1): It had a triple-cut tip for easy penetration of skin and fascia, and a synthetic external catheter (PTFE) with a conical tip. It was introduced, under ultrasound guidance, coaxially along the ventral side of the GSV preferably in the interfascial compartment, with pre-injection of 2–5 ml 1:5 of a diluted local anaesthetic (Scandicain 2%). The hyaluronan was injected during catheter withdrawal under ultrasound guidance.

The aim was to introduce a continuous volume of hyaluronan ventral of the treated



Fig. 1 Flexible injection cannula for perivenous injection of hyaluronan (prototype)

vein in order to reduce its diameter by around 2/3 (technical success, ► Fig. 2). The tumescent solution was introduced through a 120 mm 18G-cannula.

Compression bandages or stockings were not applied initially, except for compression of the puncture point for two hours. Superficial varices were treated separately (after >8 weeks) with foam sclerotherapy and standard compression. The patients came for clinical and ultrasound check-up, including measurement of the diameter of the saphenous vein (video), after 2, 8, 26 and 52 weeks.

Results

All interventions were completed without pain; in particular, the paravenous catheter

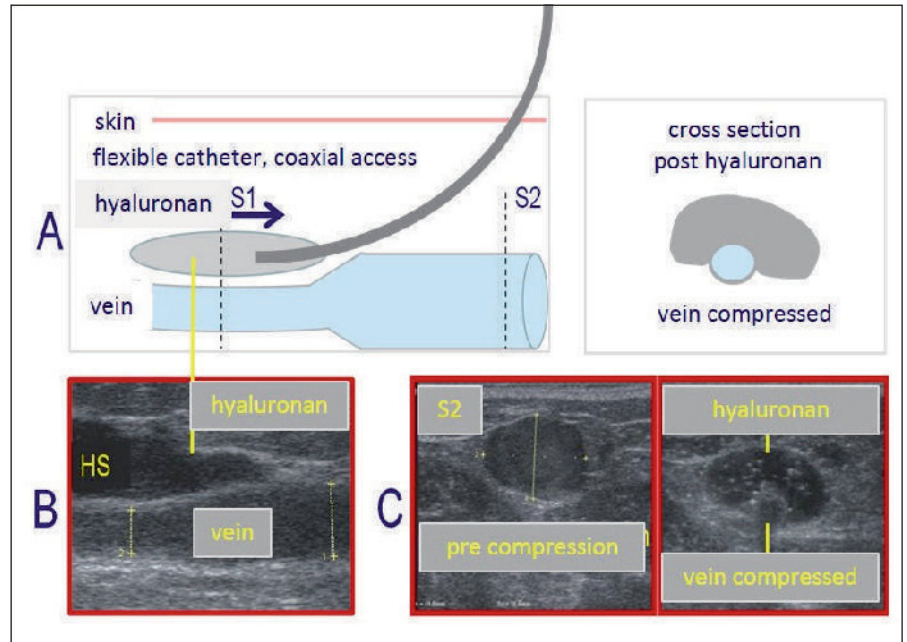


Fig. 2 Diagram of hyaluronan injection, longitudinal and cross sections (A). Corresponding ultrasound images (B and C). C1 shows the vein before compression, C2 with helmet-shaped intrafascial compression

was introduced and the hyaluronan was injected without the patients suffering distress either at the time or subsequently. The time required for compression with hyaluronan was 1.1–3.5 min (mean: 2.2 min) and with tumescent solution 0.8–2.7 min (mean: 1.8 min) per 10 cm segment.

The intrafascial positioning of the hyaluronan injection was technically successful in all cases (27/27), while extrafascial positioning did not achieve the desired distribution pattern in 3/7 cases (42.8%) resulting in a diameter reduction of only <60%. The amount of hyaluronan applied varied overall from 19–44.5 ml (mean: 35.5 ml) per segment, representing 0.7–3.8 ml/cm (mean: 1.8 ml/cm). In intrafascial cases (27/34) 12–28 ml were required (mean: 22.8 ml) per segment, representing 0.7–2.6 ml/cm (mean: 1.2 ml/cm).

All the treated veins presented complete occlusion at the first check-up after two weeks. The reduction in vein diameter after 14 days was 54–81% (mean: 68.4%; treatment target: 75%) in segments with hyaluronan compression and 8–29% (mean: 19.2%) in segments with tumescent solution. After 8 weeks the reduction measured was 62–86% (mean: 72.4%) in

segments with hyaluronan and 21–58% (mean: 38.2%) after tumescent solution.

Visible haematomas at the two-week check-up and according to patient interviews were present in segments with hyaluronan compression in 3/34 patients (8.8%), and in segments with tumescent solution in 26/34 patients (76.4%). Clinical check-up and patient interviews after two and eight weeks produced no indications of symptomatic inflammatory reaction or discoloration in the segments with hyaluronan compression, while in segments with conventional tumescent solution patients reported inflammation in 20/34 cases (58.8%). In 19 of these 34 cases (55.9%) brownish discoloration appeared along the course of the vein (► Fig. 3). In 8/34 patients (23.5%) mini-thrombaspiration had to be carried out due to symptomatic induration; all these cases occurred in zones without hyaluronan compression (► Tab. 1).

Throughout the whole observation period, the use of hyaluronan did not give rise to any discomfort or local irritation. About 15–35% of the product volume was still visible in ultrasound as a residue after 8 weeks; in some cases it was difficult to dis-

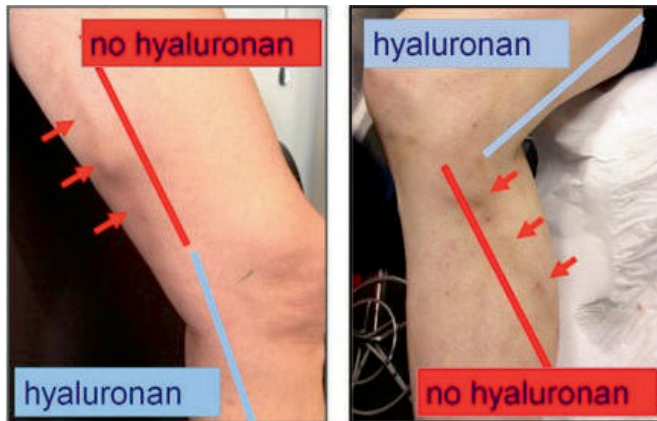


Fig. 3

Two examples of cases with the use of hyaluronan and tumescent solution in neighbouring segments of the same leg. In zones without hyaluronan compression, discoloration appears and a prominent residuum (left), as well as traces of thrombospiration (right).

tinguish (► Fig. 4), and it was not palpable in any case.

In the check-up after 52 weeks partial recanalisation was found in 7/34 foam-treated vein segments (20.5%), of which 5/7 were in segments with tumescent solution as adjuvant and 2/7 in segments with hyaluronan. By this stage no hyaluronan residue could be seen in ultrasound.

Discussion

Now that endovenous occlusion no longer presents a serious problem, interest is focusing on avoiding complications and above all on making the treatment more comfortable for the patient. The ideal method should produce precise (<1 cm), pain-free occlusion, without general anaesthesia and without critical chemicals. It should allow selective concurrent treatment of perforating veins and tributaries without additional punctures, and afford the patient a completely symptom-free regression phase without any limitations on his normal activities, ideally without a compression stocking – and as long-lasting an outcome as possible. The patient's atten-

tion is directed towards comfort and the ability to work, and to a lesser degree to the aesthetic aspect.

The post-foam sclerotherapy care of superficial and shallow varices, even of a considerable size, offers very satisfactory and comfortable solutions for avoiding post-interventional symptoms, residues or discoloration (foam compression bandage, individual eccentric compression with a silicon pad) (30–32); however in most GSV (and SSV) configurations external compression media are unfortunately not effective (15, 24).

When thermal procedures were first introduced, it was assumed in the absence of detailed investigation that the treated veins would shrink at once, and that the volume of the vein would be kept small by the tumescent solution. This is not the case, since tumescent solution is resorbed within a few days allowing the vein to recover a large volume, and then gradually reform over a period of months until a strand of connecting tissue is formed. It is irrelevant whether the tumescent solution contains adrenalin or other additives (7, 8), because in any

case it is resorbed far too quickly to prevent symptomatic reactions to sclerotherapy.

There are only two physical alternatives for immediate, long-lasting minimisation of the lumen: firstly by using the now well-known glue treatments in order to occlude the lumen „from within“ (2, 4, 23, 29); a second generation glueing technique will shortly become available consisting of spot glueing in combination with foam sclerotherapy through the same coaxial catheter (33). The second option is the technique investigated here of attempting to minimise the lumen with slow-degrading perivenous media.

When the two options are weighed up, the use of hyaluronan gel as an adjuvant offers at least a theoretical advantage in that the bio-chemistry of the product has long since been investigated and tested (1, 5), while there are still questions surrounding the toxicity and degradation process of the cyanoacrylate used in glueing. Furthermore, use of intravenous cyanoacrylate presents symptomatic courses in more than 20% of cases (23). The fact that hyaluronan can be used in very large lumina is another advantage. One disadvantage is the high demand on the operator, who must learn the unfamiliar technique of paravenous injection. The ever-present risk of accidentally injecting the hyaluronan intravasally (11) can be avoided with proper ultrasound guidance. If safety concerns are raised, the hyaluronan could be injected promptly after the microfoam sclerotherapy. If there were an error in injection it would then enter a vein isolated from the circulatory system by vasospasm and in the process of thrombosis.

When injecting the adjuvant hyaluronan, we did not attempt to obtain a complete circumferential distribution; helmet-shaped compression was easier to achieve and very effective (► Fig. 2). The presented technique allows Fegan's historic recommendation for continuous compression over a period of weeks (14) to be achieved for the first time in a new quality: Invisible, unperceived by the patients and not requiring any further care (unlike textile compression media), and with no limitations affecting work, sport and hygiene.

The exact volume required for vein compression while avoiding inflammatory

Treatment	Pain*	Discolouration**	Thrombectomy***
Tumescent solution	20/34 (58.8%)	19/34 (55.9%)	8/34 (23.5%)
Hyaluronan gel	0	0	0

*: localised pains at rest or with contact, requiring administration of analgesics or behaviour modification up to week 8; **: time: 8 weeks; ***: technique: mini-thrombaspiration under local anaesthesia

Tab. 1

Comparison of saphenous vein segments with adjuvant compression by tumescent solution or hyaluronan gel

symptoms is unknown, however the target used here of a 2/3 reduction in diameter proved to be a good estimate which turned out to be effective but unperceptible by the patient. Restriction of the study to the great saphenous vein helped us to identify the important parameters for hyaluronan compression quickly (amount, suitable vein depth). However, the technique could equally be used on segments of the anterior accessory saphenous vein and the small saphenous vein, so long as the minimum depth of 10 mm below the skin is respected. More superficial veins respond to eccentric compression. Hyaluronan compression could be used in these cases, but might lead to unwanted temporary swelling. In optimum application, most of the hyaluronan occupies the volume previously taken up by the dilated vein, and is therefore not perceptible (► Fig. 2 and ► Fig. 4).

The question whether hyaluronan compression has any impact on the long-term outcome or in reducing complications after microfoam sclerotherapy (9, 16, 17) cannot be answered from the present data. To do so we would have had to treat veins of the same diameter from the SFJ downwards using one method in each leg. If conventional microfoam – including Varithena® (19, 39) – should be shown in future studies to be inferior to other techniques despite the use of hyaluronan as an adjuvant, a new viscous sclerosant (Biomatrix sclerosant foam) enhanced with autologous proteins (34) could be considered.

The potential of hyaluronan as an adjuvant for vein compression is not limited to microfoam sclerotherapy – it could also be used to support thermal procedures, ClariVein® or glueing techniques in large-diameter veins or aneurysmal alterations for symptom-free post-treatment phases.

In addition to occlusion methods, it might also be applied for the shaping of vein lumina in vein-restoring treatments (percutaneous venoplasty), either temporary to establish laminar flow e.g. during valve- and anatomy-related reconstructions of SFJ or SPJ, or long-term as a part of modifications of pressure and flow, an option yet scarcely explored.

There are a number of hurdles on the road to a commercial product: at present, the producers of hyaluronan preparations

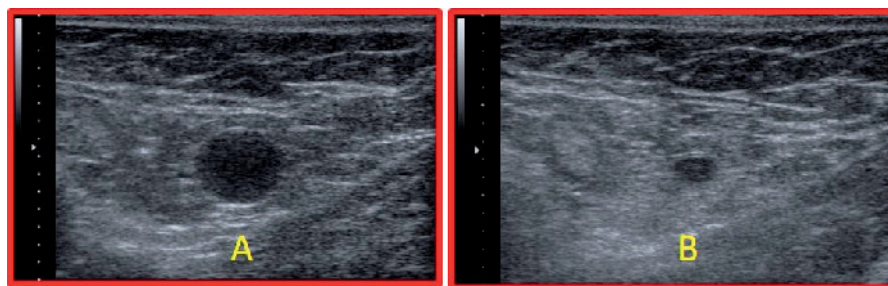


Fig. 4 GSV segments in standing patient. (A) before compression, diameter 8.2 x 8.7 mm, and (B) after eight weeks, 2.6 x 3.6 mm. Diffuse hyaluronan residue, only distinguishable with difficulty in this case.

are directing their research towards maximum persistence in the tissue, whereas for an interventional adjuvant a volume half-life of 4–6 weeks is required, meaning a lower degree of cross-linkage. One technical development in favour of this technique is the current substitution of butanediol diglycidyl ether (BDDE) as the standard interlacing medium, which must be washed out at significant cost during the production process, by a more natural agent. It will be replaced by a more natural agent. An authorised product with a half-life and viscosity suitable for perivenous use will not be available before 2018.

Conflict of interests

The authors declare no conflict of interests. They have no financial participation in the commercial products mentioned.

Conclusions

The pilot study shows that an initial and permanent reduction in saphenous vein diameter can be obtained by injecting hyaluronan instead of tumescent solution as an adjuvant. The procedure is safe and effective even with very large vein diameters >20 mm. The total absence of post-interventional symptoms is a positive surprise. The method offers many possibilities for invisible, comfortable, temporary vein compression.

As hyaluronan effectively reduces the vein diameter, primary and long-term success rates might be improved. However, there is inadequate proof due to the small number of cases and study design.

Ethical guidelines

The study complies with national guidelines and the current Helsinki declaration.

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