Biomatrix sclerofoam as a rival for endothermal ablation

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Introduction

Foam sclerotherapy, introduced in 1995 by Juan Cabrera,[1] has rapidly developed to become an alternative to surgery.[2] Today it is estimated to be the most frequently used modality to eliminate varicose veins. Cabrera-type sclerofoams are provided by mixing liquid sclerosant agents like Polidocanol (Aethoxysklerol, Asclera) or sodium tetra decyl sulfate (Fibrovein) with gases such as room air or O2/CO2, usually in a pair of syringes.[3] The application of sclerofoam by simple injection into a target vein is relatively easy, cheap and fast. Foam easily reaches remote and tortuous vascular structures. However, in comparison of primary and long-term results, foam sclerotherapy is inferior to thermo-occlusion or to surgery.[4,5] There are several reasons: common sclerofoams are very light (usually 80% gas), so they tend to float on blood. With increasing vein diameter they will not so much displace blood, but rather float on it, leaving zones of uncertain effects. Viscosity and stability are low, foams will collapse within 60–240 seconds and rapidly lose contact with the vein wall. Additionally, overdosage may lead to thrombosis and embolism.[6] Sclerosant and released transmitters like endothelin-1 appear quickly in the circulation, provoking systemic side-effects.[7]

When the first reports were published in 2008 on the deactivation of sclerosants by blood proteins,[7] we started to evaluate the interactions of heat-denatured whole blood or cell-reduced blood fractions with liquid sclerosants. We developed mixing mechanisms to prepare viscous and stable foams with an *in vitro* half-life of >60 minutes (Figure. 1), yet rapidly disintegrating without particles >20 when arriving in the bloodstream. The novel foams, e.g. containing 20% denatured autologous blood, 40% liquid and 40% gas, were called "biomatrix sclerofoam". Negotiations with the local ethics committee led to establishment in 2015 of a safety setting for a first study in great saphenous veins. To exclude the risk of foam migration via the junction, the application was combined with short proximal thermo-occlusion, comparing to cases with total thermo-occlusion treatment (Figure 1).

Patients and methods

In the study, 120 patients (78 females/42 males; mean age 32–81 years) with great saphenous vein insufficiency, diameters 6–24mm (mean: 10.3mm), and eligibility for thermo-occlusion and sclerotherapy were included. Cases were randomised into two diameter-equivalent groups, receiving different treatments: group A (n=60) first underwent junction segment closure by endovenous laser (810nm, ball tip; or

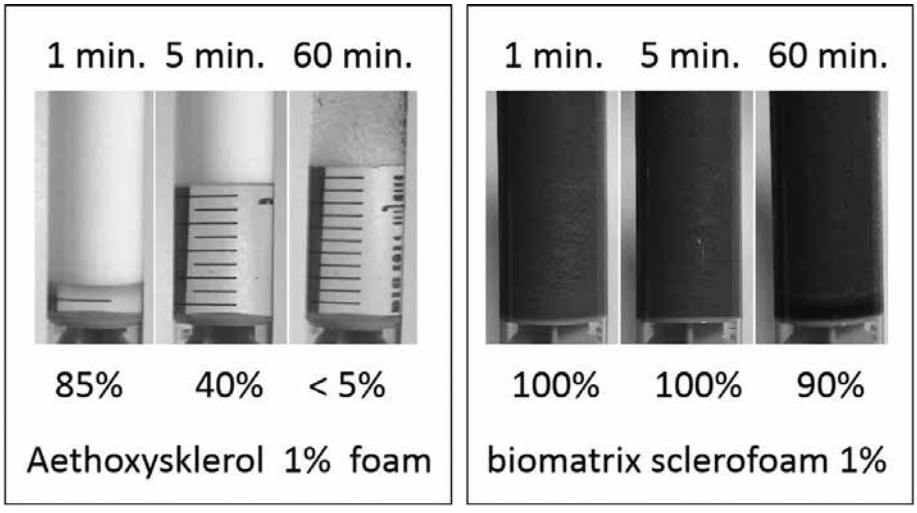

Figure 1: Stability of different foams *in vitro*.

1470nm, slim/radial fibre, PhleboCath guide catheter 2.3mm Ø) in coaxial perivenous anaesthesia with varying segment lengths of 3–20cm. In this group, biomatrix sclerofoam (1% Aethoxysklerol, foam volumes 4–10ml) was then applied via the guide catheter after proven proximal closure (flushing with 5ml of "foamed saline") during catheter withdrawal under ultrasound monitoring, treating segments of 28–35cm in length. Group B (n=60) received endovenous laser for the whole insufficient vein length (38–55cm). Post-interventional examinations with standardised ultrasound were performed after two weeks and after two, six and 12 months by independent investigators.

Results

Vein occlusion along the entire length intended to treat was obtained in all cases (120/120, visit week two) with both modalities in the first attempt. There were no adverse events; in particular, there were no thoracic or cerebral symptoms in the cases receiving sclerofoam. Group A cases required 38–77% less treatment time than those in group B, depending on the segment length. The investigators failed to discriminate modality-related intraluminal patterns of echogenicity or a borderline separating the modalities, except in a few cases (n=7) where high-energy 810nm laser left typical wall bruising. Vein diameter regression was similar (+/-12%) for laser and biomatrix sclerofoam. Both groups similarly showed mild post-interventional symptoms along the treated vein segments with no detectable difference related to the methods. In group B, veins with diameters >8 mm (n = 11) showed no post-interventional symptoms.

During one-year follow-up, the laser-treated junction segments showed reperfusion in 2/60 cases in group A (3.33%) and in 1/60 in group B (1.6%). The thigh-to-knee segments showed partial reperfusion in 5/60 cases after biomatrix sclerofoam (8.33%, sources: junction n=2, side branches n=3) and in 6/60 cases after endovenous laser (10%, sources: junction n=1, perforator veins n=3, side branches n=2).

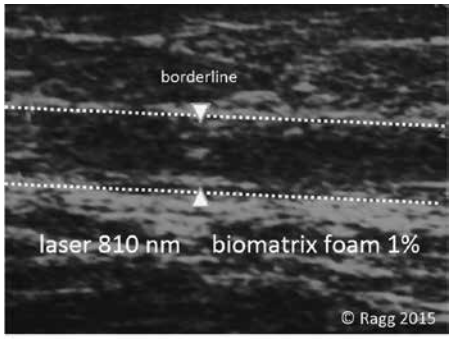

Figure 2: Similar appearance of vein occlusions by 810nm laser and biomatrix sclerofoam.

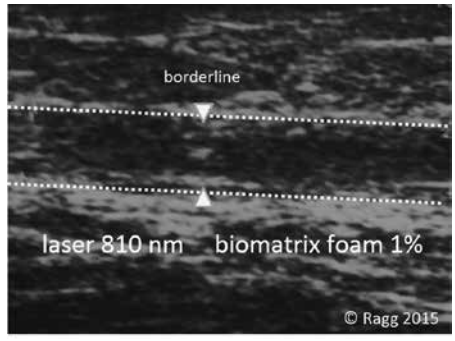

Figure 3: Inferiority of standard foam to 810nm laser: Less diameter reduction, lower echogenicity indicating soft thrombus (study 2006).

Discussion

The effect of stabilising foams by heated proteins is well known in the food and beverage industry, e.g. milk proteins for cappuccino. To use a blood protein matrix to provide a dense, viscous and stable sclerofoam may be a step further towards improving sclerotherapy. Foam placement, in particular when using catheters instead of cannulas, seems to be more precise with the novel composition, as blood replacement is more effective, and unintended foam washout is reduced. The biomatrix foam furthermore seems to be more effective than common foam, as contact time with the vein wall is increased. This is very different from recent attempts to provide an optimised sclerofoam in a constant quality from a pressurised dispenser (Varithena, BTG), as the concept still leans on the Cabrera principles with light and instable foams. It is no surprise that proof of progress is still missing.[9]

The first clinical application of a biomatrix sclerofoam presented in this report was surprisingly successful, as the effect on the target vein, according to closure rates, diameter reduction and echogenicity patterns was similar to laser-induced occlusion (Figure 2). This outcome was very different from earlier experience when our working group compared common Aethoxysklerol sclerofoam to endovenous laser in 2006 in a setting equivalent to this study, showing less lumen reduction and much higher rates of failure or relapse in foam-treated segments (32% after one year), so the strategy was abandoned (Figure 3). To replace thermo-occlusion by a foam-based modality is not just motivated by the redundancy of tumescent anaesthesia but also by the option to selectively include perforator veins and relevant side branches.

The junction is a difficult target for sclerofoam treatment as it is not possible to stop a foam column, expanding with the vein spasm, precisely at a certain spot without separate means. In most cases, the terminal valve is missing or destroyed, with the consequence of local turbulence and washout. Furthermore, epigastric vein inflow will flush the junction, limiting foam effects. Single or double balloon catheters have been proposed to stop foam propagation, and permanent or temporary occluding device (plugs) may become an alternative. Our group is currently developing a temporary occluding device integrated within a guidewire. Another project is vein lumen reduction by perivenous injection of hyaluronan[10] which could potentially provide a totally symptom-free regression phase even in

very large saphenous diameters (>15mm diameter), competing with vein gluing. Focal hyaluronan injection, being more precise and durable than tumescent fluids, could also be used to achieve a low-cost blockage of the junction.

Future applications of the novel biomatrix foam could include saphenous veins of all diameters, but also short targets like vein stumps or perforator insufficiencies, large recurrent varicosities, abdominal varices, varicoceles and maybe even low-flow vascular malformations, and skipping expensive coils.

Conclusion

According to these first results, biomatrix sclerofoam seems to be a safe and effective modality to provide vein closure. The primary and one year results are similar to endovenous laser, apart from the excluded junction segment. Future studies will include biomatrix sclerofoam application in the saphenous junction (stand-alone), with temporary or permanent blocking devices and hyaluronan vein compression, and comparison to common foam sclerosants.

Summary

- To improve foam sclerotherapy for larger veins, the development of more viscous and stable sclerofoams is required
- Biomatrix sclerofoam, integrating autologous heat-denatured blood proteins, is a new way to provide foams with the desired properties
- Apart from the junction segments, the tested biomatrix sclerofoam performs at a quality level similar to thermo-occlusion, but without need for anaesthesia
- The novel foams could become an alternative as a stand-alone modality in veins up to 8mm diameter, and combined with thermo-occlusion, blocking device or hyaluronan compression for veins of any diameter
- Approval studies will be carried out as soon as manufacturers have succeeded to provide a reasonably priced single use foaming device

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