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ENDOVENOUS TECHNIQUES

US-guided perivenous hyaluronan injection or saline tumescence?

By Johann Chris Ragg, MD

The success of today's endovenous treatments is tremendous, as all methods provide reliable success in vein closure at very low complication rates. However, it should not be ignored that there still remain unsolved problems.

The major drawback is symptomatic inflammatory reaction occurring due to the metabolic resorption process following endothelium destruction and the intended intraluminal clotting. Some patients will have to take oral analgesics to cope with pain, some have to undergo mini-thrombectomy to get rid of indurations and prominent residuals[15], and some at least feel a certain discomfort which makes them refrain from work, sports or social life.

Frequency and severity of symptoms are increasing with the vein diameter and with proximity to the skin. Ugly brownish discolorations may follow inflammation as hemoglobin and its degradation products will diffuse through the altered vessel wall into the skin, taking many months to resolve[4].

The first way to escape these side effects is to minimize the vein lumen and thus the amount of intraluminal clot. A second way could be to seal the vein with a biocompatible substance, or to increase the distance to the skin for a couple of weeks. Tumescent anesthesia is used with most thermal modalities to prevent pain and nerval injuries, and to approach the vessel walls close to the probe. Amounts of 300-800 ml are used for a GSV and minor discomfort due to the large injected volume is frequent. However, saline-based fluids will vanish within hours to days as they are rapidly absorbed by the body, and the compression effect is lost. Effective external compression is highly uncomfortable, requiring pressures of 40-80 mmHg[3, 8, 10], and its benefit is rapidly lost when discontinued, e.g. over night.

Ultrasound images of tumescent anesthesia give a nice impression how effective perivenous compression can be, as it makes even large veins shrink for the moment and brings them in touch with the interventional tool, contributing to harmonic energy distribution. Modalities not using tumescence compression, like microfoam sclerotherapy when used for saphenous treatment, show side effects similar to thermal device. Obviously, short-time perivenous compression with saline will not prevent symptomatic inflammation.

The question is if potentially viscous fluids consisting of larger molecules and offering a longer persistence within the saphenous fascial structures could solve the problem.

PATIENTS AND METHODS

In this first feasibility study, 44 patients (28 f, 16 m, 42-71 yrs.) were included to receive perivenous hyaluronan solution instead of tumescent anesthesia. Inclusion criteria were: Insufficiency of the GSV, diameter 7-25 mm, intrafascial course, distance to skin > 10 mm, indication and informed consent for endovenous laser treatment (1470 nm, n = 22) or catheter microfoam (Aethoxysklerol 2%, n = 22).

The cases were randomized for two modalities of adjunctive lumen reduction: One group (A, n = 12) received a viscous hyaluronan solution (NASHA-Gel, derived from Macrolane, Galderma, by investigator-initiated heat degradation), injectable via G18 lumen with < 10 N. Another group (B, n = 12) received tumescent fluid (modified Klein´ solution with laser, n = 6 or saline if with microfoam, n = 6). A third group (C) received hyaluronan and tumescent fluid or saline in separate segments of the same vein (20 patients, 32 segments; laser n = 16; microfoam n = 16; fig. 3). The selected veins varied from 7.4 to 23.1 mm in diameter (mean: 12.8 mm), 7.7-23.1mm (mean: 13.1 mm) in segments randomized for hyaluronan and 7.4-22.7 mm (mean: 11.9 mm) in segments randomized for saline tumescence.

The application of hyaluronan was performed using very a flexible cannula (200 mm in length, fig. 1), consisting of a relocatable metal cannula with a triple-cut sharp tip to penetrate skin and fasciae, and a plastic outer catheter with blunt tip. The approach was coaxial along the ventral side of the GSV within the saphenous fascia. Hyaluronan deployment was done during slow withdrawal of the device.

All actions were strictly performed under ultrasound monitoring. For microfoam sclerotherapy, it was attempted to place a continuous quantity of hyaluronan ventrally of the target vein to reduce its cross-section by about 75% (fig. 2), while for endovenous laser obliteration in addition to the hyaluronan a small amount of diluted local anaesthetic (< 1 ml/cm) was placed around the target vein (fig. 3) by coaxial approach with a 18 G cannula of 120 mm length. Bandages or stockings were not applied. There was clinical and sonographic follow-up after 2, 8, 26 and 52 weeks.

RESULTS

All interventions, including those with laser and minimal local anesthesia, could be performed without patient discomfort. All target veins showed complete closure at 2-week follow-up. At 52 months follow-up there were recanalizations in 4/44 foam-related segments (9.1%), all without previous hyaluronan application. Hyaluronan injection was technically successful in 41/44 cases (93.2%), while three cases with laser did not show the aimed distribution patterns for segments of 5-12 cm in length. Hyaluronan volumes varied from 22-34.5 ml (mean: 28.5 ml) per segment, equivalent to 0.7-2.3 ml/cm (mean: 1.7 ml/cm.

Initial diameter reduction obtained by hyaluronan was 54-81%, mean: 68.3%, in particular 54-78% (mean: 65.5%) for microfoam and 68-81% (mean: 71.3%) for laser interventions.

Clinical follow up at 2 and 8 weeks showed a complete absence of symptomatic phlebitic reactions and no discolorations in hyaluronan-treated segments (fig. 4), while segments not supplied with hyaluronan had visible or symptomatic inflammations in 30/44 cases (68.2%). 10/44 segments (22.7%) underwent mini-thrombaspirations because of symptomatic indurations in locations not compressed by hyaluronan (tab. 1). Visible hematoma were present in 2/22 patients (8.7%) after hyaluronan versus 18/22 (81.8%) after tumescence. When applying hyaluronan with microfoam (44 segments), no hematoma were visible.

At 8 weeks follow up, the vein diameters in hyaluronan-treated segments were 41-58% (mean: 46.1%) smaller than in segments receiving tumescence, according to ultrasound estimations in 5 cm intervals. Segments undergoing thrombaspiration were excluded in

this calculation. At 1-year follow up, no residuals of hyaluronan were observed. There were no adverse events due to hyaluronan, in particular no allergies or local irritations.

DISCUSSION

Compression has been a main topic in phlebology for decades. There has been early recognition of the value of compression during sclerotherapy and for a long time post-treatment,[2] but there was no comfortable way to provide it so far, except recently for superficial varicosities[13].

Concerning saphenous treatments, manufacturers and users of thermal and chemical device tend to keep quiet about postinterventional inflammation problems. However, the development of new modalities such as vein gluing show that at least a few investigators have noticed the need for improvements[1, 7]. Physicians and patient´s alertness to the disease[6, 11] but even more to rapid esthetic outcomes is rising, and also high expectations concerning frequently advertised "pain free treatments."

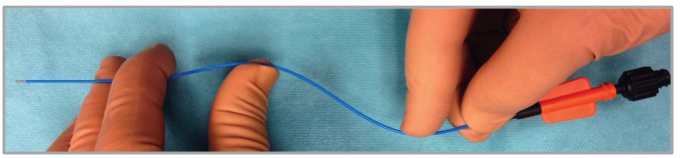

Fig. 1: Flexible cannula for perivenous injection of hyaluronan (prototype)

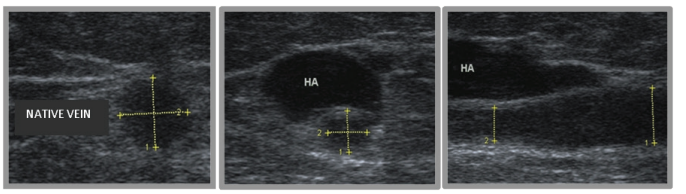

Fig. 2: Ultrasound images, a) native vein in standing patient, b) vein compressed by hyaluronan (HA) prior to foam sclerotherapy, c) longitudinal view showing edge of HA compressed segment.

> **"The procedure is effective and safe in great saphenous veins even if diameters are very large. The procedure provides invisible vein compression with no need for bandages or compression stockings, and thus offers an alternative to vein gluing."**

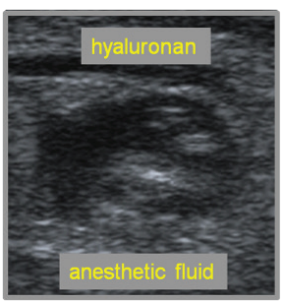

Fig. 3: Ultrasound pattern of perivenous hyaluronan with ventral focus, with a small amount of local anaesthetic added around the vein prior to endovenous laser.

Indeed, vein gluing has been the first endovenous technique not causing relevant hematoma and not requiring bandages when limited to saphenous veins without varicosities, congestion or edema[7]. However, vein gluing is still using more or less aggressive cyanoacrylate glues and many well-established physicians, in particular from surgical background, still object to this kind of substance. Furthermore, marketing of glue is high-priced with above $1,500 per unit. The use is restricted to moderately sized veins of up to 12 mm in diameter, excluding exactly those large veins which would benefit the most from novel non-symptomatic endovenous closure techniques.

Hyaluronan has been proven in large numbers of cases to reside within the human body with very few adverse reactions[5, 12]. This new application, in aspects of tissue compatibility, will even be safer than former use, e.g., for breast enhancement, as it occurs within well-defined fascial borders.

Future hyaluronan products will be manufactured by closer-to-nature cross-linkage mechanisms instead of BDDE and become even more agreeable. Within this feasibility study not even local discomfort was observed.

Initial and long-lasting compression by perivenous hyaluronan, according to the data of this study, is definitely feasible by perivenous hyaluronan injection. For the first time, long lasting compression can be provided invisibly and even without patient´s perception, fulfilling FEGAN's suggestions[2].

Hyaluronan seems to seal puncture sites, so hematoma are very rare compared to tumescent fluid. Maybe there is a further sealing effect preventing even reduced amounts of colored hemoglobin products to approach the skin surface. The exact degree of vein compression required to prevent inflammatory symptoms is not known yet, but the applied

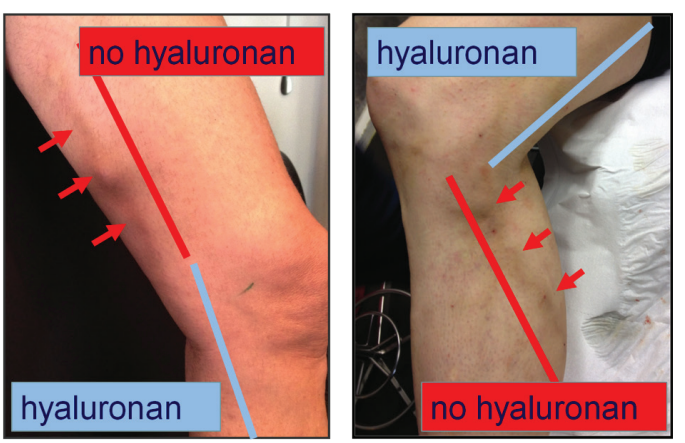

Fig. 4: Two cases receiving hyaluronan and tumescent fluid in separate segments of the same laser-treated leg. There are discolorations and a large residual (a) and traces of thrombaspiration (b) in segments without hyaluronan cover.

quantities were a good estimation as they were effective and not even perceived by the patients.

Thus, vein shaping by perivenous hyaluronan provides exactly what patients ask for: Painless nonsurgical saphenous treatment without any need for external compression[3, 8, 10], without any inflammatory

sequelae and with nice esthetic results (fig. 4). As hyaluronan products today are usually designed for maximum durability within the human body, it now requires new effort to manufacture a viscous fluid or gel for this new application with just 6-8 weeks half-life, and to provide it reasonably priced.

The study outcome, in spite of the small number of cases, may indicate a new significance of microfoam sclerotherapy[9, 14]: Its effects, hyaluronan compression-provided, may become equal to thermal occlusion as foam effects are more reliable in smaller diameters. The application of hyaluronan is much easier and much more comfortable with microfoam treatments as no anesthetic component is needed. Hyaluronan compression even might increase the long term success of occlusive methods. All this has to be subject of further investigations.

The procedure of hyaluronan covering of target veins is a little bit challenging for newcomers in the interventional field as is different from "putting a needle in and starting the saline pump." Incidental intraluminal injection has to be prevented, which is widely achieved by coaxial approach. For maximum safety, continuous ultrasound guidance when advancing the cannula tip is crucial. Preferably, the tip should be monitored in cross-sectional planes in the first phase of approach, and in longitudinal planes when closer (< 2 mm) to the vein. There is no other way to achieve it than by bimanual action of the physician. The procedure is no option for users who prefer vein gluing just because it does not require tumescent anesthesia.

While there is much bias when comparing different vein sizes in small collectives (groups A, B) it seems to be a better study concept to compare methods in different segments of the same patient (group C), preferably in veins with the same vein diameter and the same distance to the skin. A clinical multicenter study is scheduled for 2016 with a coming novel hyaluronan product.

CONCLUSIONS

Initial and permanent vein lumen reduction of saphenous veins can be obtained by using injectable hyaluronan solution instead of tumescent fluids on saline basis. The procedure is effective and safe in great saphenous veins even if diameters are very large. The procedure provides invisible vein compression with no need for bandages or compression stockings, and thus offers an alternative to vein gluing. Immediate ambulation and presentable aesthetic results confirm this modality to be worthwhile further investigating. **VTN**

Johann Chris Ragg, MD, *is the founder and head of angioclinic Vein Centers in Berlin, Munich and Zurich. His medical background is angiology, interventional radiology and, starting in 2000, interventional phlebology. With more than 100.000 catheter-based interventions and 25 years of clinical work, he is one of the world's most experienced vascular specialists. Listening to the desires of his patients, he developed a number of innovative treatment modalities, such as vein restoring percutaneous valvuloplasty and the "magic invisible bandage." His clinical units were the first in Europe to offer 100 percent endovenous solutions for any venous case. Recent projects are accessible on venartis.org.*

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