Review article

Sapheon: the solution?

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Abstract

Less invasive endovenous techniques have been shown to be as effective as open surgery in the treatment of varicose veins. Furthermore, they cause less postoperative bruising and pain and enable early return to normal activities and work. Tumescent anaesthesia is safe and obviates complications of general or spinal anaesthesia. Drawbacks are a steep learning curve and painful administration during treatment. Tumescentless techniques like Clarivein™ or VenaSeal™ Sapheon Closure System are recently under investigation. Short-term results of VenaSeal™ are comparable with thermal ablation. The procedure is safe without serious adverse events. Perioperative pain and patient discomfort with this tumescentless approach is minimal but postoperative recovery is temporarily hindered by thrombophlebitis in 14–15 % of patients. One-year results in a small feasibility study has demonstrated durable closure at this endpoint. No longer-term results are available. A randomized control trial between VenaSeal™ and Covidien ClosureFast™ is in a preparatory phase.

Keywords: endovenous technique; endovascular treatment; varicose veins; cyanoacrylate; Tumescentless

Introduction

For decades open surgery has been the gold standard of treating patients with venous disease in the lower limb attributable to saphenous vein truncal incompetence. Endovenous thermal ablation under tumescent anaesthesia and foam sclerotherapy were established as more patient-friendly alternatives with equal or better results. The safety and success of these interventions has been widely published. Occlusion rates of over 90% at the short- and midterm are consistently reported in clinical trials, with low complication rates.[1,2] Nevertheless, the primary closure rate of foam sclerotherapy is lower compared with the thermal techniques and open surgery.[3] In some countries, like the USA or The Netherlands, thermal ablation (RFA or Laser) has replaced high ligation and stripping. Health Care Insurance companies in the Netherlands only contract with vein clinics and hospitals if 90% of truncal insufficiency is treated by thermal ablation. Sclerotherapy (foam) is not reimbursed as a single treatment due to lack of evidence of efficacy. To obviate the need of tumescent anaesthesia, tumescent-less procedures have recently been developed.

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Accepted November 2012

Tumescent anaesthesia

Tumescent local anaesthesia is the preferred method for performing varicose vein surgery, especially during thermal ablation and Muller phlebectomy.[4,5] Concomitant sedation is not necessary in most patients.[6] In a patient preference study in Great Britain comparing local versus general anaesthesia for varicose vein surgery, only 6% refused local anaesthesia. Thirty one percent did not mind and a majority, 63%, chose local anaesthesia.[7] However, it is evident that the greatest

challenge to the success of thermal ablation is still administration of tumescent anaesthesia. The learning curve for surgeons is steeper for administration of tumescent anaesthesia than for the ablative procedure.[8] The greatest procedural discomfort for patients is tumescent anaesthesia injections. In a randomized controlled trial (RCT) studying stripping versus endovenous laser ablation (EVLA) in our centre,[9] visual analogue scale (VAS) maximum pain scores on a 10-point scale had a mean of 4.69 (SD 2.48) during tumescent infiltration and a mean of 2.21 (D 2.40) during ablation. Roos *et al.*[10] found an overall mean maximum pain score of 4 during the ClosureFast™ (Covidien plc, Dublin, Ireland) procedure.

Tumescentless ablative procedures

The current patient-centred approach is leading to new and safer inventions that improve the experience of patients during and after treatment.[11] To obviate the need of tumescent anaesthesia, recently, tumescent-less procedures have been developed. From two tumescentless ablative techniques scientific evidence is published in peer reviewed journals.

These procedures include: Clarivein™ (Vascular Insights LLC, Madison, CT, USA) mechanochemical endovenous ablation (MOCA) and VenaSeal™ (Sapheon Inc., Morrisville, NC, USA) Sapheon closure system (cyanoacrylate adhesive). The Clarivein (MOCA) catheter induces occlusion by endovenous mechanical damage to the endothelial cells with a rotating dispersion wire combined with infusion of a liquid sclerosans. Van Eekeren *et al.*[12] reported a safety study in 25 patients and 30 limbs with great saphenous vein (GSV) incompetence. During the procedure, the median maximal pain score was 4 (IQR 3–6) on a 10-point scale. Six weeks total occlusion rate was 87%. Four (16%) patients with superficial phlebitis had prolonged pain for more than one week. No serious adverse events like deep venous thrombosis, nerve injury, skin necrosis or infection occurred. Elias and Raines[8] studied and treated 30 incompetent GSVs in 29 patients. The average follow-up was 260 days with a range of 140–510 days.

The primary closure rate was 96.7%. There were no adverse events. In a comparative recovery study with VNUS ClosureFast™, the procedural pain (VAS RF: 2.7 [1.5], MOCA: 2.2 [1.6] $P = 0.16$) was not significantly different between the groups. Adding tumescent anaesthesia to a standard treatment does not seem to contribute to a clinically relevant increase in procedural pain.[13] Pain during the Clarivein procedure can occur as the rotating wire stucks in a side branch or fibrotic valve. Often the wire has to be pulled loose causing thigh ecchymosis and pain.

Sapheon™ Inc. (Santa Rosa, CA, USA) has developed a proprietary cyanoacrylate adhesive (SCA) with a hydrophobic delivery catheter for permanent closure of incompetent superficial truncal leg veins in an attempt to eliminate the need for the tumescent anaesthesia and postoperative compression used in thermal and surgical ablation procedures. The procedure and preliminary results are described below.

Cyanoacrylate

Cyanoacrylates are used widely as a tissue adhesive, a vascular closure agent and as an intracranial embolic agent for arteriovenous malformations, pelvic congestion syndrome or varicoceles.[14] The cyanoacrylate monomers are clear, colourless, low-viscosity liquids that spread rapidly and polymerize quickly upon contact with negatively charged anions in water or blood. The contact of cyanoacrylate (CA) with blood or plasma creates an adhesive bond. Upon contact with an anion, a stable highly reactive carbanion is formed by bonding of the anions to the B carbon of the monomer. With this, the A carbon becomes negatively charged and contributes further negative anions to adjacent B carbons, thus initiating polymerization.[15] The polymerization of the substance causes moderate intimal damage and induces an immune response. To prevent embolization and migration during treatment of superficial veins CA should have a higher viscosity. The CA used in the Sapheon™ delivery system (SCA) is a proprietary mixture of *n*-butyl cyanoacrylate with small amounts of biocompatible additives to slow down polymerization, increase viscosity and produce a flexible adhesive when fully cured.

Toxicology

The SCA is an *n*-butyl cyanoacrylate, like many adhesive and embolic agents used in Europe and the USA. US Food and Drug Administration reviewed and approved *n*-butyl cyanoacrylate toxicology data demonstrates that the material does not induce a mutagenic, pyrogenic, grossly hemolytic, sensitizing, irritating or cytotoxic effect. The median lethal dose LD_{50} for butyl and isobutyl cyanoacrylate was determined in rats as 230

Figure 1 The CA glue is extracted from its glass vial and loaded into a syringe and attached to the 5F delivery catheter

and 196 mg/kg, respectively, and these values are considered to be more than safe for clinical employment. Furthermore, various tests carried out *in vitro* and *in vivo* have failed to detect any carcinogenic properties of these tissue adhesives, and extensive clinical experience over more than 30 years with no report of the development of a malignancy allowed to consider them almost definitely not carcinogenic.[16]

The current procedure

Access to the GSV is performed with Seldinger technique using a standard micro puncture kit under ultrasound localization. The Sapheon™ introducer sheath and dilator is advanced to the saphenofemoral junction (SFJ) over a 0.035 wire. The CA glue is extracted from its glass vial and loaded into a syringe and attached to the 5F delivery catheter (Figure 1). The combined syringe and catheter are connected to a dispenser gun. The catheter is then primed by advancing the glue with the dispenser gun to within 3 cm of the catheter tip. To prevent thrombus extension through the SFJ the hydrophobic delivery catheter is placed approximately 5 cm below the SFJ. The SFJ is manually compressed with the ultrasound transducer and the proprietary adhesive is delivered using the Sapheon™ Delivery System in two injections in a 1-cm interval. Compression of the SFJ and the delivery site is held for three minutes. The adhesive is delivered at 3-cm intervals through the remainder of the target vein using 30 seconds of compression for each subsequent delivery of adhesive. The last injection site is 2–4 cm from the entrance site to prevent migration of glue outside the vein. Usually no compression stocking or compression dressing is prescribed.

Animal studies

Several, multiple animal studies were performed to demonstrate that the Delivery System operates as intended, and that the Delivery System cannot be accidentally glued to the vessel wall. Simultaneously, these studies demonstrate that the Sapheon™ Cyanoacrylate (SCA) can coapt the vessels in a permanent manner, that the SCA does not migrate and that it does not cause an unexpected immunological response.

The rabbit study (one 30-day follow-up animal; two 90-day follow-up) shows that the SCA implant triggers a mild biological response to foreign objects during the monitoring time of three months. In this case, the adhesive generated nearly the same immunological response as implanted suture materials.

The goat study (two each at 30, 90 and 180 days) shows that the SCA implant procedure is efficacious. Chronic implant studies were carried out to as long as six months and the results show that the vein remains closed. Histopathology was consistent with the injection of foreign material and the inflammation associated with the long-term presence of foreign material and did not extend into surrounding tissues. The similar immune and inflammatory response for the groups indicates that the response can be considered complete after 30 days.

To test the feasibility of closure in longer veins by CA, superficial epigastric veins from swine models were used because of their similarity to the human GSV. Thirty days postimplantation the swine results were described by Min *et al*.[17] There were no signs of recanalization or migration. In the lumen coalescing, arborizing clear spaces with entrapped lytic erythrocytes were found. Around the spaces a well-demarcated, thin band of granular eosinophilic material was visible. The tunica intima was replaced by spindle cells and a disruption the tunica media was observed. In the intima, numerous aggregates of histiocytes with fewer multinucleated giant cells, lymphocytes, plasma cells and eosinophils were seen as well. The signs of inflammation extended into the tunica media and tunica adventitia.

Almeida *et al.*[18] described the 60-Day Swine Model Results. The changes observed in the treated veins are consistent with chronic foreign body-type inflammatory response with fibrotic segments. The inflammatory reaction was contained within the vessel lumen and did not affect perivascular tissues.

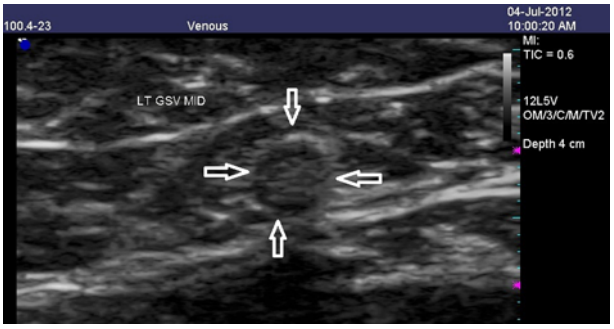

Figure 2 Successful mid-thigh GSV closure. Ultrasound image after one year. GSV, great saphenous vein

First-in-Man feasibility study

First-in-Man Studies were performed in the Dominican Republic by Almeida *et al.*[19] The protocol for this procedure was approved and performed in accordance with the Dominican National Council on Bioethics in Health (CONABIOS).

Thirty-eight patients (29 female) with a median age of 51 years (range 26–77) and an average Venous Clinical Severity Score (VCSS) score of 6.0 ± 2.7 (range 2–17) received study treatment. Average maximum SFJ diameter was 8.0 ± 2.2 cm (range 4.1–12.0) before treatment. The mean length of ablated GSV segments was 33 cm (range 15–52) and the average treatment duration was 20.3 minutes (range 11–33). The mean volume of CA delivered was a total of 1.3 mL (range 0.63–2.25). Postablation thrombus extension through the SFJ was seen in eight of 38 (21%) patients in the study. These resolved without progression. Immediately postprocedure, and at 24–72 hours, 100% (38 of 38) were closed. No DVTs were detected. VCSS scores improved to a mean of 1.9 ± 2.1 (range 0–11; $P < 0.001$ compared with baseline) at 30 days in 37 patients. Thirty-one of 37 patients reported no pain during the 30 days after treatment; the remaining six with signs of thrombophlebitis were successfully treated with non-steroidal anti-inflammatory drugs (NSAIDs). No significant side-effects or complications were observed. At 30 days follow-up, 97% (35 of 36) of treated GSV segments were completely closed and one limb had a 1-cm segment of incomplete ablation. At one year follow-up, there were one total and two partial recanalizations in 36 patients .The one-year occlusion rate was 92.1% using life table analysis. Ultrasound images (Figures 1 and 2) after one year shows a still visible occluded vein. The cyanoacrylate mixture disappeared in most cases.

E-scope study

A prospective observational multicentre study was performed in seven European vein centres in Germany, Denmark, UK and the Netherlands between December 2011 and July 2012. Sapheon sponsored the study. The protocol for this procedure was approved and performed in accordance with local ethics committees. Study treatment consisted of endovenous closure of the incompetent GSV with Sapheon™ Closure Adhesive (SCA), delivered with a proprietary hydrophobic delivery catheter system. Tumescent anaesthesia, perioperative sedation and routine use of compression stockings were omitted. Varicose tributaries were not treated during the first three months after the procedure. Duplex ultrasound and clinical follow-up was scheduled immediately, at two days, and at one, three and six months after the procedure. During the first months post-treatment, patients recorded pain and side-effects in a validated diary.

Results: Sixty-nine GSVs of 69 patients were followed for a median interval of three months (range 1–6). Average CA volume was 1.3 ± 0.4 mL (range 0.4–2.2). At two-day follow-up all 69 patients (100%) showed complete occlusion of the GSV. No full recanalization occurred during follow-up. Partial recanalization's were observed at three months ($n = 4$) Total occlusion rate was 94.2%. During follow-up, no serious adverse advents (SAEs) were observed. Side-effects were phlebitis in six cases (8.7%), five (7.2%) of which received NSAIDs for an average period of seven days. One patient (0.7%) had a thrombus extension into the common femoral vein with a length of 0.5 mm. This resolved without progression. VCSS improved from a mean of 4.4 ± 2.3 at baseline to 1.8 ± 1.6 at one month.[30,31]

Four-month VenaSeal™ Closure therapy in Saphenion in Berlin and Rostock

Since 30 July 2012, the new VenaSeal™ Closure procedure is in use at Saphenion Clinics in Germany. Preliminary results are described by Dr Ulf Zierau (personal communication).

Until 30 November 2012, VenaSeal™ procedures were performed in 65 saphenous veins. In 43 cases the GSV and in 22 cases the SSV was treated. In 19 patients both GSVs were treated simultaneously in one session. With a follow-up period of three months the occlusion rate was 99%. In 15% (10/65) of cases a postoperative erysipeloid-phlebitic skin reaction was observed after about

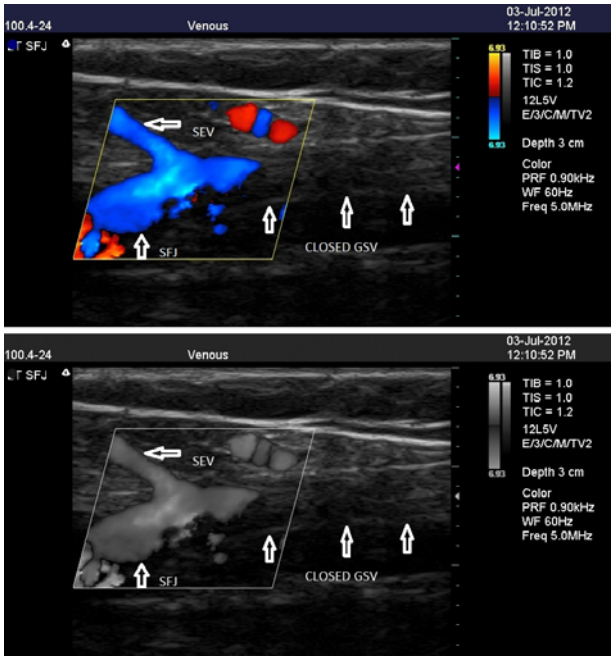

Figure 3 Closure of the GSV at the SFJ. Ultrasound image after one year. GSV, great saphenous vein; SFJ, saphenofemoral junction; SEV, superior epigastric vein

8–12 days. The skin and tissue reactions resolved quickly after conservative compression therapy. No SAEs occurred or signs of paraesthesia or hypesthesia. There were no permanent skin reactions. The patient's experience was extremely good. There was no discomfort, no serious pain or visual abnormalities. Particularly, the absence of sensory loss was a positive experience for the surgeon (Figure 3).

Personal experience

Fourteen VenaSeal™ procedures were performed in 12 patients at Skin and Vein Centre Oosterwal, Alkmaar and University Hospital of Maastricht. Four procedures were included in the E-scope study and are described elsewhere. All eight GSVs remained occluded with a follow-up from three to six months. All GSVs were closed to the SFJ with no or minimal stump length. In one patient treated with double AASV insufficiency, one side was only partially occluded three days after the procedure and recanalized totally two months after the procedure. No patients showed thrombus extension in the common femoral vein. There were no serious adverse events. Side-effects were self-limited thrombophlebitis of the GSV, accompanied with pain after four procedures starting between two and seven days postoperative. Only one of these patients needed pain medication. One patient with

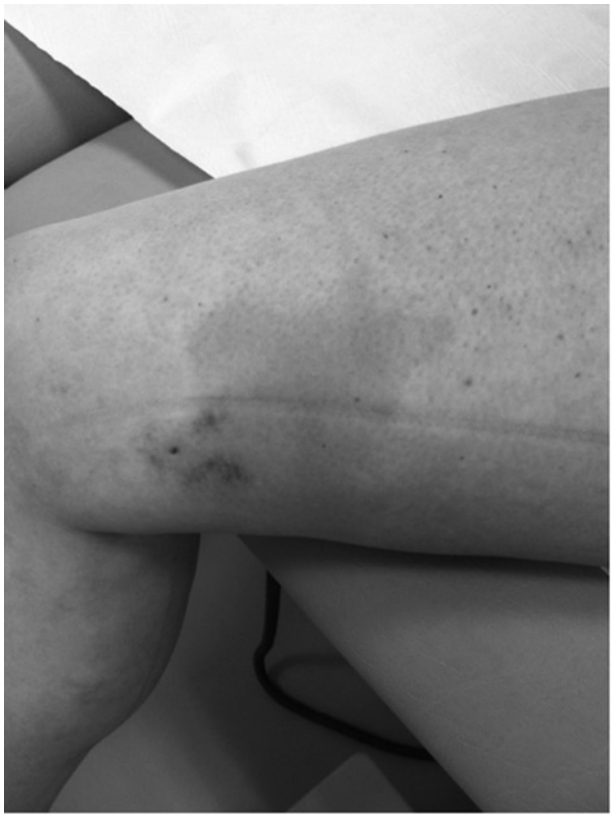

Figure 4 Hypersensitivity reaction at the entrance side of treated vein probably caused by subcutaneous delivery of the adhesive

simultaneous ablation of both incompetent anterior accessory saphenous veins developed a hypersensitivity reaction at the entrance side probably caused by subcutaneous delivery of the adhesive (Figure 4).

Discussion

Recent innovations and refinements in thermal ablation have improved the postoperative recovery.[10,20] Mean VAS pain scores in the first two weeks after ablation range between 0 and 2. Patients return to work in less than three days.[21] Occlusion rates with EVLA or ClosureFast are >98% at 6 months and 92% at three years.[2,21] The incidence of SAEs is rare.

How should the new tumescentless techniques be assessed and compared with the current standard of endovenous procedures? Abolition of tumescent anaesthesia has different potential advantages. It should save time, but normally an experienced physician does not need more than two minutes using an infiltration pump. The total procedure time takes about 15 minutes treating an average GSV without phlebectomies. Secondly, tumescentless procedures theoretically would avoid complications as bruising or nerve damage caused by

Table 1 VenaSeal closure rates and complications/side-effects

Studies	Almeida	E-scope	Lawson	Zierau	Total	%
GSV or SSV Procedures	38	69	8	65	180	
Occluded 3 months	35/36	65/69	8/8	64/65		96.6
Occluded 12 months	33/36					91.7
Paraesthesia	0	0	0	0	0	
DVT	0	0	0	0	0	
Other SAEs	0	0	0	0	0	
Thrombophlebitis	6	6	4	10	26	14.4

inadvertently puncturing the vein, or accompanying nerve.

Lidocaine is toxic in high doses, but it is possible to dilute lidocaine to a very low dose without diminishing the analgesic effect from tumescent. Two legs can easily be anaesthetized without reaching the toxic dose. Although the MOCA technique does not need tumescent anaesthesia, the limiting factor is the use of sclerosant. The maximum allowed dose of polidicanol restricts the treatment to only one leg per visit.

The Sapheon™ Closure System (SCS) Kit contains 5 mL Sapheon™ Closure Adhesive (SCA) in a separate vial. For one leg, 1.5 mL is needed so it is possible to treat a bilateral GSV insufficiency safely.

Many surgeons routinely perform stab phlebectomy of branch varicose veins in conjunction with endovenous ablation. They believe that complete removal of all varicose veins at the initial operation is the preferred treatment method for eradication of the reservoir with better cosmetic results.[2,21] With this philosophy in mind it is not very sensible to perform a tumescentless ablation and use local anaesthesia during the same procedure for performing the phlebectomies. Several authors are challenging these conventional treatment strategies. They advocate subsequent sclerotherapy after regression of varicosities postablation[22,23].

Thermal ablation has specific complications, which could be obviated by using Sapheon™ Closure Adhesive. Superficial burns at the entrance site are rare but fully preventable.[24] Nerve damage after open surgery and endovenous ablation is one of the most common causes of litigation.[25] The risks of paraesthesia after thermal ablation is 4–20%.[26] Especially, the sural nerve is prone to thermal damage after SSV ablation. In recent studies, a well-administrated tumescent anaesthesia obviates the transfer of thermal energy to non-target tissues by creating a heat sink, so the incidence of paraesthesia is much lower (1–3%).[27,28]

Administration of cyanoacrylate induces an exothermic reaction with a temperature rise as low as 50°C and as high as 70°C. Heat dissipating agents added to cyanoacrylate adhesive reduces the amount of heat generated upon polymerization of the monomer. Moreover, while the tissue reaction to methyl and ethyl derivatives causes acute inflammation with coagulative necrosis, this is almost totally absent with hexyl and decyl derivatives, and with all the alkyl cyanoacrylates of $n > 4$. Only, a slight chronic inflammation with multinucleated foreign body giant cells has been seen.[16] No nerve damage was observed after 180 VenaSeal™ procedures as of this writing.

Postoperative thrombophlebitis after endovenous ablation is the presence of inflammation at the site of the treated GSV trunk or tributaries associated with localized inflammatory changes such as hyperaemia, oedema and tenderness.[26] Although self-limiting, the postoperative recovery is sometimes delayed because of inflammatory pain. In a recent Cochrane meta-analysis, incidences of 7–8% after thermal ablation were reported.[29] After MOCA procedures, phlebitis of tributaries is described in 0–14% of cases.[12,13] In the First-in-Man SCA study, 15.8% (6/38) of patients developed thrombophlebitis accompanied with pain. In the E-scope study the incidence was lower: 7.2% (5/69). In our personal series outside the E-scope trial, four of eight patients showed signs of thrombophlebitis in the full length of the treated truncal vein diagnosed in the first week follow-up. Only one of them needed pain medication. Cumulative incidence is described in Table 1.

More important, successful GSV or SSV closure at short term with the VenaSeal™ procedure was high and varied between 94% and 100% in different studies (Table 1), which is in the same range as the results of thermal ablation.

Conclusion

The tumescentless VenaSeal™ Sapheon Closure System procedure is a promising technique for treating saphenous insufficiency. The procedure is

simple and safe after completing a comprehensive training course. No SAEs were observed. Advantages are minimal discomfort during the procedure and absence of bruising and nerve damage. Postoperative recovery is temporarily hindered by thrombophlebitis in about 14–15% of patients. Short-term closure results are comparable with thermal ablation. Long-term results have to be awaited. An RCT comparing Venefit™ (Covidien ClosureFast) versus VenaSeal™ is in a preparatory phase.

Acknowledgements

The authors like to Dr Ulf Zierau for his approval to describe the preliminary results from the 65 VenaSeal™ procedures performed in the Saphenion Clinics in Berlin and Rostock.

Conflicts of interest
Nothing to declare.

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