Treatment of Venous ulcers utilizing n-Butyl Cyanoacrylate (Super Glue)

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AZH WAVE CENTERS
Milwaukee WI
Venous disease

Etiology

• Are the result of **Venous valvular insufficiency**

• Which cause **Venous hypertension**

• These typically occur along the **medial or lateral distal (lower) leg**

• In addition, the **increase in the hydrostatic pressure** within the vein walls, allowing proteins and blood cells to leach resulting in **edema** and the eventual **breakdown** of the tissues due to **lack of oxygen and nutrients**

• There is also the **Fibrin Cuff Theory**, of fibrin around the capillaries develops preventing oxygen and nutrients from flowing to the surrounding muscle and tissue and in turn **leads to necrosis and ulceration**
Demographics

- At least 70% of all lower extremity ulcers are venous.
- Over 1 million patients in the U.S. are affected by venous leg ulcers.
- More than half of venous ulcers treated are recurrent ulcerations.
- Over $14.9 billion are spent in the U.S on managing venous leg ulcers.
- A venous leg ulcer patient costs payers $6,000 – $7,000 more each year than a matched non-venous leg ulcer patient.
Risk Factors

- Causes = Blood Pool + Other Causes

- Diabetes mellitus
- Varicose veins
- Congestive heart failure
- Peripheral vascular disease
- Deep vein thrombosis
- Pregnancy
- Obesity
Demographics / Age

- Not just a disease of the elderly
- Over 40% report their first ulcer by age 50
- 13% of patients with Chronic Venous Insufficiency had their first ulcer by age 30
Recurrence is Common

• Of the ulcers that heal, as many as 72% may recur at one year

• Improving clinical outcomes is important

• Costs of treatment are considerable

• Cost of Days lost of work

• Quality of life issues

HISTORICAL REVIEW OF TECHNOLOGIES

Surgical Stripping & Ligation

Thermal Ablation
- Endovenous Laser Ablation (EVLA)
- Radiofrequency Ablation (RFA)

Mechanical Sclerotherapy (Clarivein™ catheter)

Ambulatory Phlebectomy

Sclerotherapy

Endovenous Steam Ablation (EVSA)
## CURRENT TREATMENT DISADVANTAGES

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Thermal Therapies¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Manually removes the vein segment from the leg</td>
<td>• Hyperpigmentation</td>
</tr>
<tr>
<td>• General anesthesia required</td>
<td>• Endothermal heat-induced thrombus (EHIT)</td>
</tr>
<tr>
<td>• Long incision scar</td>
<td>• Phlebitis</td>
</tr>
<tr>
<td>• Extended post procedure discomfort and wound care</td>
<td>• Nerve injury</td>
</tr>
<tr>
<td>• 2-3 weeks recovery</td>
<td>• Compression stockings</td>
</tr>
<tr>
<td>• Compression stockings</td>
<td></td>
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</tbody>
</table>

Non Thermal Non Tumescent Treatment

OPPORTUNITIES FOR IMPROVEMENT

Elimination of

- Tumescent anesthesia
- Post-procedure compression stockings
- Thermal Nerve injury
If we can glue high-flow cerebral AVMs, why can’t we glue low-flow varicose veins?”

— Dr. R. Raabe, 2008

Large amount of adhesive/thrombus is left in the AVM as seen on MRI.

Courtesy of Dr. R. Raabe
# Adhesives in Medicine

<table>
<thead>
<tr>
<th>Adhesive</th>
<th>Date</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanoacrylate adhesives</td>
<td>1950s</td>
<td>Wound adhesives</td>
</tr>
<tr>
<td>Histoacryl Blue™* topical skin adhesive</td>
<td>1980s</td>
<td>Skin incisions</td>
</tr>
<tr>
<td>Dermabond™* topical skin adhesive</td>
<td>1998</td>
<td>Skin incisions/lacerations</td>
</tr>
<tr>
<td>Ethicon OMNEX™* surgical sealant</td>
<td>1998</td>
<td>Surgical adhesives</td>
</tr>
<tr>
<td>Trufill™* n-BCA liquid embolic system</td>
<td>2000</td>
<td>Liquid embolic system, AVM embolization</td>
</tr>
<tr>
<td>Indermil™* tissue adhesive</td>
<td>2002</td>
<td>Skin incisions/lacerations</td>
</tr>
</tbody>
</table>

1. Not a complete listing
CYANOACRYLATE ADHESIVE APPLICATIONS *

**Intravascular Use: Occlusion**¹

Vascular closing agent for:
- Cerebral arteriovenous malformations (AVM)
- Pelvic congestion syndrome and varicoceles
- Gastric varices

**Other Common Applications**
- Ophthalmic surgery
- Cosmetic procedures
- Dental
- Skin adhesion
- Orthopaedic

*Not all applications are approved in the USA.*
SAFETY OF CYANOACRYLATE ADHESIVES

Widely used medical tissue adhesive.\(^1\)

Antimicrobial effect against gram-positive organisms.\(^2\)

Used safely on millions of patients with no reported carcinogenicity in humans (1986 study).\(^2\)

1 Lawson et al. Sapheon: the solution? Phlebology 2013, 28 Suppl 1:2-9, p3
2 Quinn J., Tissue Adhesives in Clinical Medicine, 2nd ed.(2005) p 34-35
IDEAL ADHESIVE FOR CHRONIC VENOUS INSUFFICIENCY

1. Needs to be viscous in order to prevent migration of adhesive outside the treatment area by maintaining good contact with intimal surface.

2. Needs to polymerize quickly in order to prevent embolization outside the treatment area.

3. Needs to be soft and elastic to reduce the ability to feel the implanted adhesive.

4. Must be a strong bond in order to prevent recanalization.
- When cyanoacrylate (CA) comes in contact with blood or plasma, it begins to polymerize.
  - The body encapsulates the polymer as a foreign body.
  - CA triggers inflammatory reaction in the vessel wall resulting in fibrosis and occlusion.
    - The polymerization damages the vessel intima, triggering the injury response cascade and fibrosis.
The reason why the Tip of the catheter is held 5cm from the SFJ

**Summary:** Adhesive migration extends 1-2 cm from the compression point. Compression with an ultrasound probe provides a broad area of compression (~2 cm in width). Therefore, the extent of the adhesive migration is within the area of the compression. No adhesive migration is detected in the vein or in the lungs.

WAVES TRIAL 12 MONTH DATA RESULTS

98% CLOSURE RATE of GSV, SSV & ASV at 1 year¹

20 mm VEIN DIAMETER

Treated successfully in a single session

NEED FOR ADJUNCTIVE PROCEDURES

PHLEBECTOMY

<table>
<thead>
<tr>
<th>Predicted</th>
<th>Actual 3 mos.</th>
<th>Actual 5-12 mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 (74%)</td>
<td>7 (14%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

¹ Predicted vs. actual adjunctive procedures statistically significant.
MOST COMMON SIDE EFFECT-PHLEBITIS

PHLEBITIS POST PROCEDURE CARE AS REPORTED IN PUBLISHED LITERATURE

**WAVES Trial**
Most common AE was phlebitis defined as pain, tenderness, and/or erythema in the treated segments or side branches. Treated with acetaminophen or non-steroidal anti-inflammatory agents.¹

**VeClose Trial**
Post treatment phlebitis was somewhat more common in the CAE group. Most cases in both groups were mild, transient, and successfully treated with over-the-counter nonsteroidal anti-inflammatory medication (ibuprofen).²

**Feasibility Study**
Post treatment inflammation was treated with NSAIDs +/- compression stockings.³

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It is the discretion of the physician to determine the course of treatment.
THE KIT

VENASEAL™ CLOSURE SYSTEM

(1) 5 cc vial of VenaSeal™ adhesive
(1) dispenser gun
(1) 7 Fr, introducer (blue)
(1) 5 Fr, delivery catheter (white)
(1) 5 Fr, dilator (gray)
(2) 3 cc syringes
(2) 14 gauge dispensing tips
(1) 0.035 inch, 180 cm J-wire guidewire
• Triaxial system
1. The Sheath
2. The outer catheter
3. The inner catheter (the longest of them)
4. Keep the inner catheter tip 5cm from the SFJ
Successful use of VenaSeal system for the treatment of large great saphenous vein of 2.84-cm diameter

Insoo Park
CONCLUSIONS:
The efficacy and safety analysis shows that cyanoacrylate ablation is a safe, simple method which can be recommended as an effective endovenous ablation technique.
Comparison of Cyanoacrylate (VenaSeal) and Radiofrequency Ablation for Treatment of Varicose Veins in a Canadian Population

Gary K. Yang, Marina Parapini, Joel Gagnon, Jerry Chen
Division of Vascular Surgery, University of British Columbia, Vancouver, BC

Methods
Between January 2014 and December 2016, there were 335 patients with 476 venous segments who were treated with either CA (n = 148) or RFA (n = 328) for varicose veins at the Vancouver General Hospital vascular clinic. Charts were reviewed to assess demographics of the patients, location and severity of disease, treatment details, and outcome at short-term and midterm follow-ups. Outcome parameters included treatment success and presence of short-term and midterm complications.

Results
The average age of patients was 57 ± 1 years, with the majority being female (78%) and with an average body mass index of 24.8 ± 0.5. Clinical, Etiology, Anatomy, and Pathophysiology classes were 2 (49%), 3 (26%), 4a (22%), and >4b (3%). Of the 148 segments treated with CA, the vein types were as follows: 112 great saphenous veins (GSVs), 24 small saphenous veins, 2 accessory GSVs, and 8 perforator veins. The average amount of CA delivered for GSV treatment was 1.8 ± 0.1 mL, with a treatment length of 43 ± 1 cm. Subgroup comparison was done for GSV segments. Treatment success was 100% in CA and 99% in RFA. Superficial phlebitis was the most common complication noted at midterm follow-up in 5% of CA and 16% of RFA treatments. There was one patient in each group who had asymptomatic proximal thrombus extension treated with anticoagulation for 2 weeks. Three superficial glue protrusions requiring minor incision and drainage were noted in the CA group. Five patients in the RFA group had persistent numbness and two had nonhealing wounds at the access site.

Conclusions
CA is a minimally invasive endovenous technique for treating varicose veins without the need of tumescent analgesia. In our experience, CA offers success rates equivalent to RFA with lower midterm complication rates.

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POTENTIAL ADVERSE EFFECTS

ASSESSMENT PERFORMED TO DETERMINE ADVERSE REACTIONS THAT ARE UNIQUE TO CYANOACRYLATES

- Allergic reactions to cyanoacrylates, such as hives, asthma, hay fever and anaphylactic shock
- Arteriovenous fistula
- Bleeding from the site of access
- Deep vein thrombosis (DVT)
- Edema in the treated leg
- Embolization, including pulmonary embolism (PE)
- Hematoma
- Hyperpigmentation
- Infection at the access site
- Non-specific mild inflammation of the cutaneous and subcutaneous tissue
- Pain
- Paresthesia
- Phlebitis
- Superficial thrombophlebitis
- Urticaria or ulceration may occur at the site of injection
- Vascular rupture and perforation
- Visible scarring

As noted within the IFU the use of the VenaSeal™ closure system is contraindicated when the following conditions exist:

- Previous hypersensitivity reactions to the VenaSeal™ adhesive or cyanoacrylates
- Acute superficial thrombophlebitis
- Thrombophlebitis migrans
- Acute sepsis exists

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COUP D’OEIL

The VenaSeal™ Abnormal Red Skin Reaction: Looks Like but is not Phlebitis!

Tjun Y. Tang *a, Alok Tiwari b

aDepartment of Vascular Surgery, Singapore General Hospital, Singapore
bDepartment of Vascular Surgery, Queen Elizabeth Hospital, Birmingham, UK

The VenaSeal™ closure system is a new technique using cyanoacrylate glue (CAG) to treat superficial varicosities resulting in a recently described treatment-related complication. This abnormal cutaneous erythema (panel A) is an adverse event thought to be a delayed hypersensitivity reaction to CAG. This occurs as an abnormal skin finding such as erythema, itching, pain, oedema, and tenderness over the treated vein area. Although it looks like phlebitis, it is generally more widespread, occurring 7-14 days post procedure with predilection in the great saphenous vein location and in females. The course is self-limiting and treatment with anti-inflammatory drugs is only given if painful (panel B).

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ADVANTAGES

- NON TUMESCENT
- NON THERMAL
- POTENTIAL SINGLE TREATMENT
- NO PROLONGED COMPRESSION
- RAPID RECOVERY
- DECREASED RISK OF NERVE INJURY
- SIMILAR EFFICACY AS OTHER ABLATIVE PROCEDURES
DISADVANTAGES

• PRODUCT EXPENSE

• NOT COVERED BY ALL INSURANCE PROVIDERS

• CONSIDERED A LONG TERM IMPLANT

• LIMITED LONG TERM DATA
PERSONAL EXPERIENCE

- Over 352 cases over the last 8 months.
- 2 hypersensitive reactions-self limited.
- 1 case of STP
- Zero recanalizations.
- Over 99.1% efficacy on follow up US
IN SUMMARY

• Venous glue therapy is a safe and an efficacious method of treatment for venous ulcers.

• It is minimally invasive.

• It requires no tumescent.

• It does not require prolonged compression.

• It diminishes the risks of paresthesias and neuropathies compared to ablative procedures.

• And it is as efficacious as other proven technologies.
Treatment of Venous ulcers utilizing n-Butyl Cyanoacrylate (Super Glue)

Awais Siddique MD
Endovascular Radiologist
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Milwaukee WI