VenaSeal™ Closure System

—

Is it the solution?

Thomas M. Proebstle, MD, PhD

Clinical Professor of Dermatology
Dept. of Dermatology, University of Mainz, Germany
www.privatklinik-proebstle.de Mannheim, Germany
Disclosure

I have the following potential conflicts of interest to report:

(last 12 months)

☒ Consulting: Covidien, Syneron Candela/Cooldtuch, Sapheon
☐ Employment in industry
☒ Stockholder of a healthcare company: Sapheon
☐ Owner of a healthcare company
☐ Other(s)

☐ I do not have any potential conflict of interest
Objective

Introduction of a novel technique for occlusion of Refluxing GSVs based on Cyanoacrylate Adhesive

Requiring
- no tumescent anesthesia
- no routine postinterventional compression
- Causing no postprocedural paresthesia
published Studies on Cyanoacrylate Vein Embolization

Cyanoacrylate Adhesive for the Closure of Truncal Veins: 60-Day Swine Model Results

Jose I. Almeida, MD, Robert J. Min, MD, Rod Raabe, MD, D. J. McLean, and Monte Madsen, RVT

Abstract

Background: The introduction of cyanoacrylate (CA) within a blood vessel triggers polymerization, followed by an inflammatory reaction. Methods: A sheath was positioned 2.0 cm caudal to the junction of the superficial epigastric and abdominus rectus veins in 2 swine, followed by ultrasound-guided injection of 0.16 mL of CA glue. After glue delivery, the catheter was pulled back 3 cm, compression was applied to the treatment site, and the process was repeated for the entire length. At 60 days postimplantation, the veins were harvested surgically and examined histologically. Results: The histologic changes were consistent with a chronic foreign-body-type inflammatory response. Venous closure, segmental wall thickening, and fibrosis were observed. Conclusion: Injection of CA is feasible for closure of superficial veins in animal models. Vein closure is achieved via an inflammatory process which ultimately leads to fibrosis.

Almeida JL, Vasc Endovascular Surg 2011
First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence

Jose I. Almeida, MD, Julian J. Javier, MD, Ed Mackay, MD, Claudia Bautista, MD, and Thomas M. Proebstle, MD, Miami, Naples, and St. Petersburg, Fla; La Romana, Dominican Republic; and Mainz, Germany

Objective: The primary objective of this study was to assess the feasibility of an endovenous cyanoacrylate (CA) adhesive implant, delivered with a catheter-based administration system engineered with a nonstick surface, for the treatment of incompetent great saphenous veins (GSVs). The primary safety end point was the rate of serious adverse events related to the procedure. The primary efficacy end point was vein occlusion during follow-up. Secondary end points included the rate of all adverse events and the change in Venous Clinical Severity Scores (VCSSs).

Methods: Thirty-eight incompetent GSVs in 38 symptomatic patients were treated by catheter deployment of CA under follow-up at 1, 3, and 6 months, respectively. Kaplan-Meier analysis yielded an occlusion rate of 92% at 12 months of follow-up. Side effects were generally mild and self-limited, most frequently, phlebitis in six patients (15.8%) requiring nonsteroidal anti-inflammatory drugs for an average of 5.7 days. Eight patients (21.1%) showed thread-like thrombus extensions into the common femoral vein of a mean length of 12.6 mm (range, 3.5-35 mm), which resolved spontaneously without anticoagulation. VCSS improved in all patients from a mean of 6.1 ± 2.7 at baseline to 1.5 ± 1.4 at 12 months (P < .0001). Edema improved in 34 legs (89%) at the 48-hour follow-up. At the 12-month follow-up, and without addi-
Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence

Jose I Almeida¹, Julian J Javier², Edward G Mackay³, Claudia Bautista⁴, Daniel J Cher⁵ and Thomas M Proebstle⁶

Abstract
Objectives: To evaluate the safety and effectiveness of endovenous cyanoacrylate-based embolization of incompetent great saphenous veins.
Methods: Incompetent great saphenous veins in 38 patients were embolized by cyanoacrylate bolus injections under ultrasound guidance without the use of perivenous tumescent anesthesia or graduated compression stockings. Follow-up was performed over a period of 24 months.
Result: Of 38 enrolled patients, 36 were available at 12 months and 24 were available at 24 months follow-up. Complete occlusion of the treated great saphenous vein was confirmed by duplex ultrasound in all patients except for one complete and two partial recanalizations observed at, 1, 3 and 6 months of follow-up, respectively. Kaplan-Meier analysis yielded an occlusion rate of 92.0% (95% CI 0.836–1.0) at 24 months follow-up. Venous Clinical Severity Score improved in all patients from a mean of 6.1 ± 2.7 at baseline to 1.3 ± 1.1, 1.5 ± 1.4 and 2.7 ± 2.5 at 6, 12 and 24 months, respectively (p < .0001). Edema improved in 89% of legs (n = 34) at 48 hours follow-up. At baseline, only 13% were free from pain. At 6, 12 and 24 months, 84%, 78% and 64% were free from leg pain, respectively.
Conclusions: The first human use of endovenous cyanoacrylate for closure of insufficient great saphenous veins proved to be feasible, safe and effective. Clinical efficacy was maintained over a period of 24 months.
From the American Venous Forum

The European multicenter cohort study on
cyanoacrylate embolization of refluxing great
saphenous veins

Objective: Cyanoacrylate (CA) embolization of refluxing great saphenous veins (GSVs) has been previously described. The outcomes from a multicenter study are still lacking.

Methods: A prospective multicenter study was conducted in seven centers in four European countries to abolish GSV reflux by endovenous CA embolization. Neither tumescent anesthesia nor postinterventional compression stockings were used. Varicose tributaries remained untreated until at least 3 months after the index treatment. Clinical examination, quality of life assessment, and duplex ultrasound evaluation were performed at 2 days and after 1, 3, 6, and 12 months.

Results: In 70 patients, of whom 68 (97.1%) were available for 12-month follow-up, 70 GSVs were treated. Two-day follow-up showed one proximal and one distal partial recanalization. Three additional proximal recanalizations were observed at 3-month (n = 2) and 6-month (n = 1) follow-up. Cumulative 12-month survival free from recanalization was 92.9% (95% confidence interval, 87.0%-99.1%). Mean (standard deviation) Venous Clinical Severity Score improved from 4.3 ± 2.3 at baseline to 1.1 ± 1.3 at 12 months. Aberdeen Varicose Vein Questionnaire score showed an improvement from 16.3 at baseline to 6.7 at 12 months (P < .0001). Side effects were generally mild; a phlebitic reaction occurred in eight cases (11.4%) with a median duration of 6.5 days (range, 2-12 days). Pain without a phlebitic reaction was observed in five patients (8.6%) for a median duration of 1 day (range, 0-12 days). No serious adverse event occurred. Paresthesia was not observed.

Conclusions: Endovenous CA embolization of refluxing GSVs is safe and effective without the use of tumescent anesthesia or compression stockings. (J Vasc Surg: Venous and Lym Dis 2014;1:1-6.)
The 24 months update of the European Multicenter Study on Cyanoacrylate Embolization of Refluxing Great Saphenous Veins

Principal Investigators:

Thomas M. Proebstle and Alun Davies
Methods

- 0.09 ml of cyanoacrylate each injection
- first injection 5 cm from SFJ
- second injection 1 cm below first injection
  then every 3 cm
- polymerization time:
  initial injection: 3 minutes
  afterwards 30 s polymerization time
Results
typical clinical picture
1 day after study
treatment of right GSV
study characteristics

- Enrollment from Dec 2011 to Jul 2012
- 7 sites involved – total N=70 patients
  - Thomas Proebstle, Germany  n = 20
  - Jens Alm, Germany  n = 15
  - Sameh Dimitri, UK  n = 11
  - Lars Rasmussen, Denmark  n = 10
  - Mark Whiteley, UK  n = 7
  - James Lawson, Netherlands  n = 4
  - Alun Davis, UK  n = 3
### Adjunctive Procedures Performed (Phlebectomy and Sclerotherapy)

<table>
<thead>
<tr>
<th>Procedure Performed</th>
<th>Number of Subjects</th>
<th>Number of Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-72 hours</td>
<td>0/70 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Day 30</td>
<td>0/70 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Month 3</td>
<td>2/70 (2.9%)</td>
<td>2</td>
</tr>
<tr>
<td>Month 6</td>
<td>23/70 (32.9%)</td>
<td>28</td>
</tr>
<tr>
<td>Month 12</td>
<td>13/68 (19.1%)</td>
<td>16</td>
</tr>
<tr>
<td>Month 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** Includes procedures on either limb.  
**Data Source:** eSCOPE Table 20.1 (April 24, 2014)

Protocol did not allow adjunctive procedures until after Month 3 visit.
patient characteristics

- follow-up: median 6 months [range 3 - 12]
- age: median 48y [range 22 - 72]
- BMI: median 26.0 [range 18.9 – 39.0]

- Max GSV diameter: median 8.0 mm [range 2.5 – 14]
patient characteristics

CEAP baseline

- C2  n = 29
- C3  n = 33
- C4  n =  8
Results

Median GSV length treated
38 cm [range 7-72]

Median CA volume delivered
1.3 ml [range 0.4 - 2.2]

corresponding
to a median number of
injections of
N = 14 [range 4 - 24]
Results

All 70 patients technical successful (100%)

Recanalizations (all partial)

48h \( n = 2 \) proximal (25 cm) + distal (20 cm)

3 months \( n = 2 \) 2 proximal (12 + 25cm)

6 months \( n = 1 \) proximal (20 cm)

until 12 months follow-up stable, connected to tributaries, no impact on clinical symptoms
53/70 Subjects returned for their 24 Month Visits with ultrasound exams.

Closure rate = 89.1%. (incomplete data set, 11 subjects with no ultrasound exam to date, but have had other data collected)
64/70 Subjects returned for their 24 Month Visits with VCSS Exams
## Adverse Events

<table>
<thead>
<tr>
<th>Pat #</th>
<th>Adverse event</th>
<th>Procedure date:</th>
<th>Onset date: interval after treatment</th>
<th>specific treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP012</td>
<td>Phlebitis</td>
<td>01.17.12</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>CP013</td>
<td>periphlebitis reaction around access site</td>
<td>01.17.12</td>
<td>02.20.12</td>
<td>*NSAID</td>
</tr>
<tr>
<td>AA002</td>
<td>phlebitis</td>
<td>03.27.12</td>
<td>05.22.12</td>
<td>none</td>
</tr>
<tr>
<td>AA004</td>
<td>possible glue/thrombus in femoral vein</td>
<td>05.1.12</td>
<td>05.13.12</td>
<td>Anticoagulation treatment</td>
</tr>
<tr>
<td>AA008</td>
<td>Phlebitis thigh</td>
<td>04.23.12</td>
<td>5.21.12</td>
<td>*NSAID</td>
</tr>
<tr>
<td>AA009</td>
<td>phlebitis</td>
<td>05.14.12</td>
<td>05.25.12</td>
<td>none</td>
</tr>
<tr>
<td>CO001</td>
<td>Thrombophlebitis area treated VSM</td>
<td>07.17.12</td>
<td>week 2</td>
<td>compression</td>
</tr>
<tr>
<td>CO002</td>
<td>Thrombophlebitis reaction treated VSM</td>
<td>07.17.12</td>
<td>week 2</td>
<td>*NSAID</td>
</tr>
<tr>
<td>CO004</td>
<td>Thrombophlebitis area treated</td>
<td>07.18.12</td>
<td>week 2</td>
<td>*NSAID</td>
</tr>
</tbody>
</table>
### Adverse Events by Coding Dictionary

<table>
<thead>
<tr>
<th>Coded Term</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>70</td>
</tr>
<tr>
<td>Access site infection</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other (not target limb/procedure associated)</td>
<td>7 (10.0%)</td>
</tr>
<tr>
<td>Paresthesia in the treatment zone</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Phlebitis in both treatment and non-treatment zones</td>
<td>9 (12.9%)</td>
</tr>
</tbody>
</table>
VeClose Randomized Control Trial

VenaSeal Sapheon Closure System vs Radiofrequency Ablation
For Incompetent Great Saphenous Veins

PI: Nick Morrison, Phoenix, AZ, USA

CAUTION: This device has not been approved for sale by the FDA. It is pending a clinical investigation and FDA review.
Study Design

- Pivotal, randomized 1:1 study
- Up to 12 Clinical Sites
- 220 patients (110 per arm) 1:1 randomization
- Up to 244 subjects (including up to 24 roll-in subjects)
- FU period for each patient: total of 36 months
- 9 visits/patient
  - Baseline, Procedure, Day 3, 30 days, 3 month, 6 Month, 12 Month, 24 Month, 36 Month
- Subjects are randomized on the day of the procedure.
- **Adjunctive therapies not allowed until after 3 Month visit**
  - Phlebectomy, foam sclerotherapy

CAUTION: This device has not been approved for sale by the FDA. It is pending a clinical investigation and FDA review.
6 Month Data VeClose

VeClose Randomized Clinical Trial
# Closure Data

3 Month CoreLab (VasCore) Data (Endpoint)

<table>
<thead>
<tr>
<th>3 Month Visit (CoreLab data)*</th>
<th>Number with Non-closure (&gt;5cm)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA (n=108)</td>
<td>5</td>
<td>95.4%</td>
</tr>
<tr>
<td>VenaSeal (n=104)</td>
<td>1</td>
<td>98.9%</td>
</tr>
</tbody>
</table>

p > .0001

*There was complete agreement between sites and the CoreLab. Both were blinded to the results from each other.

## 6 Month Investigator Data

<table>
<thead>
<tr>
<th>6 Month Visit</th>
<th>Number with Non-closure (&gt;5cm)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA (n=105)</td>
<td>6</td>
<td>94.3%</td>
</tr>
<tr>
<td>VenaSeal (n=101)</td>
<td>1</td>
<td>98.9%</td>
</tr>
</tbody>
</table>

p > .0001
### VCSS Mean SD) by Visit and Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>1 Mo</th>
<th>3 Mo</th>
<th>6 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA</td>
<td>5.6 (2.6)*</td>
<td>2.6 (2.0)</td>
<td>2.0 (2.0)</td>
<td>1.6 (1.9)</td>
</tr>
<tr>
<td>VenaSeal</td>
<td>5.5 (2.6)*</td>
<td>2.3 (1.7)</td>
<td>1.9 (1.6)</td>
<td>1.5 (1.8)</td>
</tr>
</tbody>
</table>

*mean (SD)
AVVQ Mean (SD) by Visit and Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>1 Mo</th>
<th>3 Mo</th>
<th>6 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA</td>
<td>19.4 (9.9)</td>
<td>12.6 (8.3)</td>
<td>10.7 (8.6)</td>
<td>9.1 (6.9)</td>
</tr>
<tr>
<td>VenaSeal</td>
<td>18.9 (9.0)</td>
<td>11.9 (7.5)</td>
<td>11.6 (7.5)</td>
<td>10.2 (7.2)</td>
</tr>
</tbody>
</table>

Follow-up, Months
EQ-5D by Visit and Treatment

Follow-up, Months
Adverse Events Within 6 Months

- Subjects with events related to device and/or procedure

<table>
<thead>
<tr>
<th>Treatment</th>
<th># Total Subjects</th>
<th># Subjects with Events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>VenaSeal</td>
<td>108</td>
<td>34</td>
<td>31%</td>
</tr>
<tr>
<td>RFA</td>
<td>114</td>
<td>29</td>
<td>25%</td>
</tr>
</tbody>
</table>

NO SAEs in the study were categorized as related to device and/or procedure.
endovenous embolization with cyanoacrylate glue is ready for routine use

the concept of

• no anesthesia
• no compression stockings and
• and no risk of paresthesia

is attractive to many patients
VenaSeal™ Closure System
– Is it the solution?

Thomas M. Proebstle, MD, PhD

Clinical Professor of Dermatology
Dept. of Dermatology, University of Mainz, Germany
www.privatklinik-proebstle.de Mannheim, Germany