Cyanoacrylate Closure For Treatment Of Venous Leg Ulcers

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Abstract: An open label, prospective single centre, single arm clinical trial enrolling patients with active venous ulcers with a planned enrollment of 20 patients was conducted to evaluate the effectiveness and safety of cyanoacrylate closure combined with standard of care compression therapy for the treatment of venous leg ulcers in the setting of an incompetent saphenous vein. Inclusion criteria were active venous ulceration, saphenous vein reflux confirmed by duplex ultrasound (US) and ankle brachial index ≥0.9. Primary outcomes included change in ulcer size, ulcer healing and adverse events at three months. At three months, 50.0% of ulcers were healed (14/28), and 56.2% of subjects were ulcer-free (10/19). At 12 months, 79.2.% of ulcers were healed (19/24), and 68.8% of subjects were ulcer-free (11/16) The average percent reduction in ulcer size at three months and 12 months was 88.1% and 95.6%, respectively. Cyanoacrylate closure of an incompetent saphenous vein was shown to be safe and effective for treating patients with chronic venous leg ulcers.

Key words: *venous leg ulcer, saphenous vein, cyanoacrylate, endovenous closure*

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Venous leg ulcers (VLUs) are a common wound with significant morbidity and cost, and suboptimal therapeutic options. VLUs result from chronic venous insufficiency, including venous reflux and post-thrombotic syndrome. About 1% of the adult population has a history of a healed or unhealed ulcer.[1,2] In France and Belgium in 1995, venous disease represented 2-2.6% of total national health-care spending. Similar figures were reported by other studies in Europe and in the US.[3] In the US, an estimated 600,000 people are affected per year,[4] and a study of patients at the Cleveland Clinic Foundation revealed a total medical cost per patient of $9685 USD, with 48% for home care, 25% for hospitalizations, and 21% for home dressing changes.[5]

Risk factors are advanced age, prior leg injury, obesity, deep venous thrombosis and phlebitis, legs in dependent position for long periods, and female gender. Individuals with VLUs in Canada often have multiple comorbidities (30% have three or more), and most have significant pain, and limitations to function and mobility.

VLU can take from months to years to heal, and 54-78% recur.[6-8] Current therapies include wound care (cleansing, debridement of damaged tissue, dressings and topical agents), compression therapy (bandages or stockings to limit blood pooling and fluid leak), and medications (agents to improve blood flow, e.g., pentoxifylline, aspirin, etc). These treatments can increase the rate of healing, and reduce recurrence, however these therapies can be burdensome, painful, and ineffective. Despite these therapies, ~50% of wounds become chronic.[9,10] Chronic VLUs can be painful, malodorous and infected, and they often significantly limit an individual's function and mobility.

An emerging therapy for symptomatic venous reflux is the closure of the culprit vein by endovenous closure with a cyanoacrylate adhesive implant. Recent studies show cyanoacrylate closure (CAC) to be a safe and effective treatment for varicosities resulting from symptomatic incompetent great saphenous veins.[11-13]

In these prospective, multi-centre studies, CAC was compared to conventional endothermal radiofrequency ablation (RFA) and post-interventional compression for treatment of varicose veins. A study of 70 patients at seven European sites demonstrated closure rates of 92.9% at 12 months, and an Average Venous Clinical Severity Score improvement from 4.3 +/- 0.3 at baseline to 1.1 +/- 1.3 at 12 months.[13] CAC was safe, with phlebitis occurring in five cases (8.6%), and no serious adverse events observed. In a subsequent study of 222 patients randomized to receive either RFA or CAC, three month closure rates were 99% for CAC and 96% for RFA.[11] CAC was found to be non-inferior to RFA, with less post-procedural ecchymosis in the CAC group, but otherwise similar safety profiles.

CAC is now increasingly used to treat VLUs. Despite promising anecdotal evidence, studies demonstrating safety and effectiveness of CAC for treating VLUs are lacking. This study evaluates the safety and effectiveness of CAC for VLUs.

Methods

This is an open-label uncontrolled clinical trial. Eligible patients had a venous leg ulcer, venous insufficiency, and an ABI of ≥0.9. Patients with coagulation disorders, occlusive deep venous thrombosis (DVT), diabetic foot ulcers, hypersensitivity to cyanoacrylates or the VenaSeal® adhesive, or an inability to tolerate compression were excluded. (See Table 1 for full list of inclusion and exclusion criteria). Institutional research ethics approval for this study was obtained from Sunnybrook Health Sciences Centre (REB #2974).

Informed consent was documented for all subjects. Subjects underwent a pre-procedure physical exam and clinical assessment of the ulcer, including a Revised Venous Clinical Severity Score (rVCSS), as well as a Doppler ultrasound of the superficial and deep venous systems of the legs to assess for venous reflux, obstruction, and the presence of deep-vein thrombosis if an adequate Doppler was not available in the last six months. A final determination of eligibility was made following review of information collected during the pre-procedure visit. Demographics, medical history, bloodwork (if not available in the previous 30 days) and baseline quality of life questionnaires (EQ-5D) were collected for all eligible subjects prior to CAC intervention.

Table 1: Eligibility Criteria

Inclusion Criteria	1. Age ≥18 years old at time of screening
	2. Venous leg ulcer
	3. Venous insufficiency (>0.5 seconds; confirmed by Doppler within last 6 months)
	4. ABI of ≥0.9
	5. Capable of understanding the study and providing informed consent
Exclusion Criteria	1. Previous hypersensitivity reactions to the VenaSeal® adhesive or cyanoacrylates
	2. Acute superficial thrombophlebitis
	3. Bilateral treatment
	4. Thrombophlebitis migrans
	5. Occlusive deep venous thrombosis (a recannalized DVT is not an exclusion)
	6. Deep venous incompetence or occlusion in external iliac or common iliac vein in the affected limb or the IVC (as assessed based on spontaneity, phasicity, augmentation, pulsatility, and compressibility on ultrasound)
	7. Post-thrombotic syndrome
	8. Acute sepsis
	9. Coagulation disorders
	10. Radiation or chemotherapy within three months of study
	11. Pregnant or lactating females
	12. Uncontrolled diabetes (HbA1c >10%)
	13. Diabetic foot ulcers
	14. Current use of systemic anticoagulation that cannot be held prior to the procedure, and resumed post-procedure
	15. Previous treatment of target vein
	16. Tortuous veins
	17. Current participation in another interventional study, or participation within 30 days prior to screening
	18. Inability to tolerate compression, or to receive endovenous treatment

Intervention: Compression therapy and wound care dressings were removed prior to the start of the procedure. Ultrasound was used to map the target vein and to guide the procedure. CAC was performed according to the directions provided in the VenaSeal® device *Instructions for Use*, and following surgical protocols of sterile technique. Briefly, the treated leg was cleaned with chlorhexidine solution, the leg was draped with sterile drapes, and the skin overlying the target vein below the knee was anesthetized with lidocaine solution. Under ultrasound guidance, a needle was used to access the target great saphenous vein in a retrograde fashion towards the groin and a guidewire was fed into the vein to position the catheter proximal to the saphenofemoral junction. After an initial injection of cyanoacrylate glue was dispensed, pressure was applied to the vein for three minutes. Adhesive injections were then serially administered in 3cm increments, with pressure held on each segment. Once the complete length of the target vein had been injected, the catheter was removed and pressure was applied to the entry site for five minutes. In some patients, the procedure was repeated in an antegrade fashion in the great saphenous vein up to the foot. The procedure was similarly repeated in the small saphenous vein when indicated. Refluxing perforators connected to the saphenous vein requiring treatment were also treated. After the procedure, the local area was cleaned, and a compression socks was placed on the leg. Complete vein blockage was confirmed post-procedure by ultrasound. The procedures were done on an outpatient basis and study subjects returned home following the procedure.

Post-procedure: Subjects were encouraged to walk around regularly following the procedure, and to take ibuprofen for any mild discomfort in the first 48 hours. Subjects were instructed to continue wearing the compression therapy, and to continue with wound care therapy as directed by the wound care physician (AK) until the wound healed completely, after which patient were transitioned to customized knee-high elastic compression stockings.

Subjects continued to receive wound care and compression therapy two to three times per week by a wound care nurse and assessment by a wound care physician (AK) every two to three weeks until the wound was deemed to be healed. Patients were be instructed to contact study staff with any concerns.

Subjects returned 3-10 days post-procedure for a clinical assessment and Doppler ultrasound to assess vein ablation. Subjects returned at one, two, three, six, and 12 months post-procedure for a clinical assessment, Doppler ultrasound and to complete quality of life questionnaires.

Data Analysis: The effectiveness of the procedure was determined by calculating the percent of ulcers healed at three and 12 months, and the percent change in ulcer size at three and 12 months. The closure rate of the target veins was calculated as the proportion of patients with absent flow in the treated saphenous vein segment on post-operative ultrasound.

Complete closure was defined as vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5cm on Doppler ultrasound.

Quality of Life (QoL) and Functional Outcomes were determined by assessing the change in patient-reported function and QoL (EQ5D; rVCSS). Safety was measured as the adverse event rate at three months.

Adverse events related to the study procedure or device were collected up to 12 months post-procedure. Categorical variables were calculated as frequency and percentage changes. Continuous variables were calculated as mean +/- standard deviations (if normal distribution), or as median with interquartile ranges (if not normally distributed).

Results

Baseline Characteristics: Twenty one patients consented to participate. One subject was excluded following the pre-procedure visit. Twenty subjects were enrolled (11 male, 9 female). (See Table 2 for baseline characteristics). Subjects ranged in age from 33 to 89 years with a BMI range of 7.5 to 42.7. Most subjects (15, 75%) were ambulatory without assistance. Four subjects (20%) were ambulatory with assistance, and one subject (5%) required a wheelchair for mobility. More than half of the subjects engaged in regular exercise, either walking (9, 45%) or vigorous exercise (2, 10%). Twelve subjects had one ulcer (60%), six subjects had two ulcers (30%) and two subjects had three ulcers (10%), for a total of 30 study ulcers with an average size of 695.9 mm2 +/- 1382.6 (See Table 3.) Median ulcer duration was 641.5 days (158, 1571). Clinical outcome and QoL data for 19 and 16 subjects was collected at the three month and 12 month time-points, respectively. At the final time-point, two subjects were lost to follow-up and two were deceased.

Table 2: Baseline Characteristics

		n (%)
Sex	Male	9 (45.0)
	Female	11 (55.0)
Age	Average Age	66.3 +/- 16.77
Ethnicity	White or Caucasian	12 (60.0)
	Black	1 (5.0)
	Asian	4 (20.0)
	West Indian	2 (10.0)
	Middle Eastern	1 (5.0)
Smoking	Current	2 (10.0)
	Former <1 yr	2 (10.0)
	Former >1 yr	5 (25.0)
	Never	11 (55.0)
Comorbidities	Prior MI	1 (5.0)
	Diabetes	4 (20.0)
	Hyperlipidemia	2 (10.0)
	Asthma	2 (10.0)
	BMI	24.63 +/- 8.47
Ambulation	Ambulatory without assistance	15 (75.5)
	Ambulatory with assistance	4 (20.0)
	Uses wheelchair	1 (5.0)
ADL	Vigorous exercise	2 (10.0)
	Walking for exercise	9 (45.0)
	Walking around house only	5 (25.0)
	Limited walking from room to room	3 (15.0)
	Patient unable to walk	1 (5.0)

Table 3: Ulcer and Index Leg Characteristics

		n (%)
Index Leg	Right	9 (45.0)
	Left	11 (55.0)
Number Of Ulcers At Baseline	1 ulcer	12 (60.0)
	2 ulcers	6 (30.0)
	3 ulcers	2 (10.0)
Ulcer Location	Medial	11 (55.0)
	Lateral	4 (20.0)
	Middle	4 (20.0)
	Anterior	3 (15.0)
	Posterior	7 (35.0)
	Middle	9 (45.0)
	Below Knee - Upper	0 (0)
	Below Knee - Middle	3 (15.0)
	Below Knee - Lower	17 (85.0)
Ulcer Size	Average Size (mm2)	695.99 +/- 1382.6
Ulcer Duration	Median days (IQR)	641.5 (158, 1571)

Procedure Characteristics: All 20 subjects underwent the study CAC intervention between Nov 2019 and May 2021. Procedures duration on average was 73.6 +/- 20.9 minutes, with a range of 30-120 minutes. The great saphenous vein was the target vein for all subjects, and the small saphenous vein was additionally treated in three subjects (15%). Both retrograde and antegrade injections were performed on 16 subjects (80%), with four subjects undergoing retrograde-only treatment.

Clinical Outcomes: These were recorded in terms of Vein Closure and Ulcer Healing.

Vein Closure

Target vein closure was confirmed immediately post-procedure for 94.4% of subjects (17/18). (See Table 4.) Target vein closure rates were 88.9% and 84.6% at three and 12 months, respectively (16/18 subjects; 11/13 subjects). Two subjects had incomplete closure of the target veins. In the first subject, both antegrade and retrograde injections were performed from below knee access sites. Post-procedure, the retrograde segment was partially thrombosed but the antegrade segment was fully occluded. In the second subject, the device maldeployed, leading to incomplete delivery of glue and partial occlusion of the target vein.

Table 4: Target Vein Closure

	% fully ablated	#/total
Post-Procedure	94.4	17/18
1 Week	80.0	16/20
1 Month	93.3	14/15
2 Months	93.8	15/16
3 Months	88.9	16/18
6 Months	83.3	10/12
12 Months	84.6	11/13

Ulcer Healing

By three months post-CAC, 52.6% of subjects were ulcer-free (10/19), 50.0% of ulcers had healed (14/28) and the average reduction in ulcer size was 88.1% +/- 25.3. (See Figure 1.) At 12 months, 79.2% of ulcers had healed (19/24) and 68.8% of subjects were ulcer-free (11/16). Average rVCSS scores had significantly improved by three months (17.65 +/- 3.01 to 9.47 +/- 5.66, p<0.00005). (See Figure 2.) Ulcer recurrence was observed for two ulcers (6.7%), with one recurrence at two months

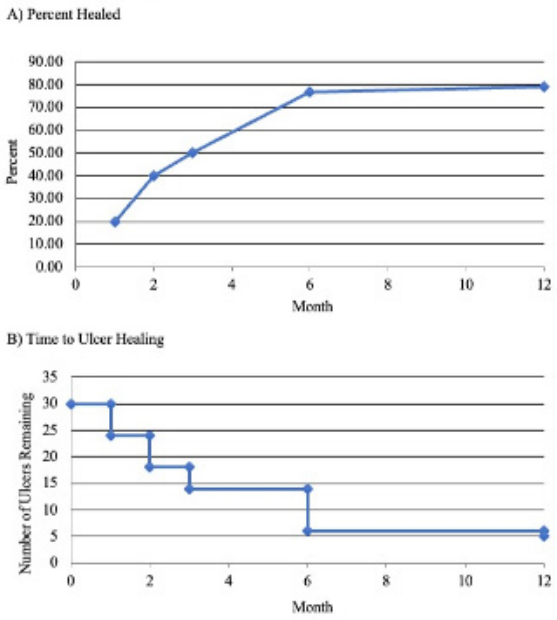

Figure 1A: Percent Healed: The percent of ulcers healed at each post-procedure follow-up (1 week, 2, 3, 6, and 12 months).
Figure 1B: Time to Ulcer Healing: The total number of open ulcers at each time point (baseline, 1 week, 2, 3, 6, and 12 months).

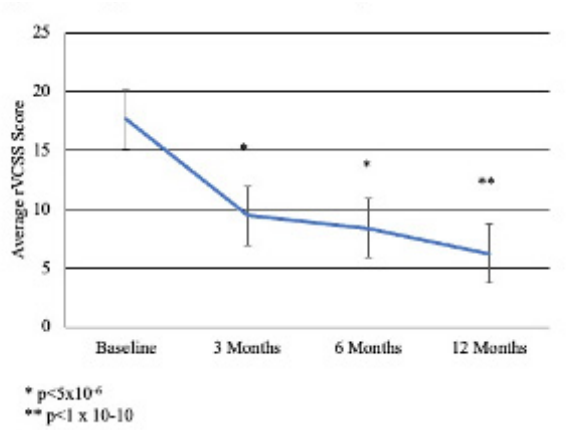

Figure 2: Average rVCSS scores at baseline, 3, 6, and 12 months.

and subsequent rehealing at six months, and the other ulcer recurring at 12 months.
Three subjects (15%) developed new ulcers post-procedure: one subject developed an ulcer at two months that subsequently healed by six months, and another subject developed two new ulcers at one month, both of which healed by two months.

Safety and QoL Outcomes: These were noted as Procedure and Device Events and Qualify of Life.

Procedure and Device Events
Adverse events related to the procedure within three months post-treatment included self-limiting thrombophlebitis (2, 10.0% [See Table 5]) and deep venous thrombosis (10.0%) at four days (n=1) and two months (n=1). Adverse events unrelated to the procedure within three months post-treatment included fever (5.0%), respiratory infection (5.0%), wound infection (5.0%) and new ulceration (2, 10.0%).

Attempted vein access was aborted during the procedure for three subjects due to a vein spasm during antegrade access (n=1, 5.0%), small veins size prohibiting antegrade access (n=1, 5.0%), or vein anatomy precluding retrograde access from GSV to SFJ from below the knee (n=1, 5.0%).
A maldeployment of the injection device during treatment of one subject's GSV resulted in aborted proximal treatment (n=1, 5.0%).

Table 5: Rates of Adverse Events

Adverse Event	n (%)
Related	
Thrombophlebitis	2 (10.0)
Deep vein thrombosis	2 (10.0)
Vein spasm	1 (5.0)
Vein size or anatomic limitation	2 (10.0)
Maldeployment of device	1 (5.0)
Unrelated	
Wound infection	1 (5.0)
New ulceration	3 (15.0)
Fever	1 (5.0)
Respiratory Infection	1 (5.0)

Quality of Life
No significant improvement in average EuroQoL EQ-5D scores was observed (data not shown).

Discussion

The purpose of this study was to examine the role of CAC in the management of chronic venous leg ulcers that are refractory to standard wound care. Our results demonstrate that CAC is a safe and successful treatment modality for this patient population and can help expedite healing.

The procedure was successful in completely occluding the target vein in all but two subjects. The first subject's great saphenous vein was large, measuring 1.41cm at the saphenofemoral junction, 1.03cm in the proximal thigh, and 1.02cm at the knee. He also received chronic anticoagulation therapy for a cardiac arrhythmia. Despite the large calibre of the vein and the anticoagulation therapy, however, the majority of his great saphenous vein was fully ablated and his wound healed entirely. The second subject experienced a device maldeployment and received an insufficient dose of the CAC therapy. We were not aware of this maldeployment during the procedure because the glue dispenser gun and delivery catheter appeared to function normally. We experienced similar issues with CAC packages from the same batch that were used with non-study patients and requested that the packages from that batch be replaced. We did not have any other application issues after this was done.

Most of the study subjects had no adverse complications or issues post-procedure. Two subjects experienced an episode of thrombophlebitis that resolved with a short course of over-the-counter oral anti-inflammatory therapy, with no recurrence or other complications. One subject developed a partial common femoral DVT that was noted on the first post-procedural ultrasound. This subject was morbidly obese and the procedure was technically challenging due to limited groin visualization. He was treated with oral anticoagulation therapy and remained asymptomatic and did not experience any further complications from his CAC treatment. A second

subject was noted to have a partial DVT in the left femoral vein at two months follow-up. The DVT was not visualized on any of his earlier post-procedural ultrasound studies and the patient was entirely asymptomatic. The subject was treated with oral anticoagulation and the DVT resolved with close follow-up. The subject's venous ulcer healed within two months post-procedure.

Our study is retrospective in nature and our sample size is small. Nonetheless, we observed a high success rate that confirms the importance of endovenous ablation for the management of venous leg ulcers. This study was mostly conducted during the COVID-19 pandemic and as such there were numerous subjects lost to follow-up due to an inability to adequately contact or see patients in person.

There are many advantages to using CAC for the management of venous leg ulcers. Most importantly, CAC offers a durable option for treating the infra-geniculate saphenous venous segments of the great saphenous vein and the small saphenous vein all the way to the malleoli, where most venous ulcers occur. This is a distinct advantage compared to thermal endovenous ablation modalities, which are more limited due to concern about injuring the saphenous and sural nerves that travel closely with the saphenous veins below the knee. Practitioners have addressed this limitation in the past by ablation the supra-geniculate and proximal small saphenous vein segments with thermal energy and injecting the more distal segments with foam, but this is not as durable as CAC therapy.

Conclusion

In conclusion, we have demonstrated that cyanoacrylate closure of an incompetent saphenous vein is safe and effective for treating patients with chronic venous leg ulcers. Further studies in a randomized controlled fashion are needed to compare this treatment with compression therapy alone.

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