Early results of cyanoacrylate glue closure of the great saphenous vein in venous insufficiency

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Abstract:

Introduction: Chronic venous disease is a common clinical problem and an important health and social problem. Endovenous techniques have recently replaced the traditional open surgical methods for the treatment of venous insufficiency. The aim of this study is to present the early results of cyanoacrylate closure of the great saphenous vein in venous insufficiency

Patients and Methods: From November 2019 till March 2021 we treated 50 cases of venous insufficiency with endovenous embolization of the great saphenous vein with n butyl- cyanoacrylate adhesive (VenaSeal Closure System -Medtronic, Minneapolis, MN, USA). All patients were assessed preoperatively clinically and classified according to Clinical, Etiological, Anatomical and Pathophysiological (CEAP) classification and the revised Venous Clinical Severity Score (rVCSS) and examined with duplex ultrasound by two independent physicians. The mean preoperative rVCSS was 6.3 (SD: 2.3) Almost all patients 49/50 (98%) underwent local anesthesia. We didn't use compression stockings and patients were instructed to walk immediately after the operation. Patients were assessed postoperatively, both clinically and by duplex ultrasonography in 2 weeks, 3 months and 6 months.

Results: There was a 100% (50/50) successful obliteration of the target vein. All patients (100%) reported improvement of the symptoms, whereas 33 (66%) had complete elimination of symptoms. All patients improved their rVCSS, in a mean 82.5% decrease (postoperatively 1.1 -SD: 1.34). There were no major adverse effects, the only side effect being mild self-limited phlebitis.

Conclusion: Cyanoacrylate glue closure of the great saphenous vein, in our study, proved to be safe and effective method to treat venous insufficiency which provides improved patient comfort, rapid return to normal activities, and improved procedure time, without the need of perivenous tumescent anesthesia and postprocedure compression stockings

Keywords: cyanoacrylate; venous insufficiency; saphenous ablation; endovenous techniques; nontumescent nonthermal

INTRODUCTION

Chronic venous disease (CVD) with resultant varicose veins is a common clinical problem, especially in western countries and is responsible for substantial morbidity[1,2,3]. CVD can manifest a wide range of symptoms and signs that include limb heaviness, aching, soreness, fatigue, burning, edema, pigmentation, and venous ulcers.[4,5,6]. Chronic lower limb superficial venous disease affects approximately 35% of adults in the western world[7,8,9]. Symptoms of CVD affect the lifestyle of that population, while 1% to 4% presents serious complications at more advanced stages with a healed or active venous ulcer. The chronic character of the disease and the high prevalence make CVD an important health and social problem.

The treatment of CVD has changed dramatically during the past few years, as traditional surgical therapy has been supplanted by endovenous techniques. The standard open operation with ligation and stripping of the great saphenous vein (GSV) has been replaced with minimally invasive methods. Open surgery methods, such as ligation and stripping, are associated with more complications, including hematoma and paresthesia, with long recovery times and are considered risky and disfiguring[10]. As a consequence of the results of the newer techniques over the standard ones, the 2013 National Institute for Health and Care Excellence (NICE) guideline on diagnosis and management of varicose veins that was updated on March 2018, recommends thermal techniques as the first option for the treatment of insufficient veins, foam and liquid sclerotherapy as the second, and open surgery only if the previous methods are unsuitable[11].

More recently, a new technology for nonthermal vein closure has been introduced that involves the endovenous application of n-butyl cyanoacrylate (NBCA) glue for the closure of the incompetent great saphenous vein[12].

The aim of this study was to present our experience with this new endovenous technique for treatment of great saphenous vein insufficiency and to present anatomic and clinical early results of our 6-month follow up.

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PATIENTS AND METHODS

Patients

The study was a purely retrospective review of the record. We present the results of 50 cases in 49 patients treated with endovenous embolization of the GSV with (NBCA), during the period between November 2019 and March 2021. We used the VenaSeal Closure System™ (Medtronic Plc, Dublin, Ireland) with slowly polymerizing, high viscosity cyanoacrylate glue. All patients provided informed consent for the study.

Age		
25-35	6	12%
36-45	9	18%
46-55	16	32%
56-65	11	22%
>65	8	16%
Medical History		
Hypertension	10	20%
Hyperlipidemia	8	16%
Diabetes	2	4%
Mild heart failure	2	4%

Table1. Demographics

All patients who had full follow-up were selected. The study involved 29 women (59.2%) and 20 men (40.8%) with a mean age of 51 years (range 27-80) (Table 1). All patients were diagnosed with either unilateral or bilateral symptomatic GSV incompetence. Preoperatively, patients were assessed with clinical examination and were classified according to 2004 CEAP (Clinical, Etiological, Anatomical and Pathophysiological) classification and the revised Venous Clinical Severity Score (rVCSS)[13]. All patients were examined with a deep and superficial vein duplex ultrasound with the patient both in supine and upright positioning, which was conducted by an independent certified radiologist. All patients were also subjected to a second duplex ultrasound, performed by the lead author, using a General Electric LOGIQ V2 (General Electric Healthcare) prior to any decision making. Reflux times and the mean diameters of the great saphenous vein were recorded at 4 points in the GSV, in the proximal thigh, mid-thigh, distal thigh, and below the knee. The patients were enrolled without a trial of compression stockings before treatment.

Study eligibility inclusion criteria were:

1. Age >18 years and ability to give informed consent
2. CEAP class C2 or above (visible varicosities)
3. Symptomatic venous insufficiency with reflux > 0.5 sec on color Duplex. Symptoms include: aching, heaviness, fatigue, soreness, burning, pruritus, discomfort and edema
4. Initial trunk diameter in standing position > 5.5 mm at 2-3 cm distal to the saphenofemoral junction (SFJ)
5. Ability to attend follow up visits
6. Ability to walk unassisted

Study exclusion criteria were:

1. Previous interventions
2. Deep vein disease
3. Incompetent tributaries of the GSV within 3cm distance from the SFJ
4. Recent (3 months) superficial venous thrombosis (SVT) or venous thromboembolism (VTE)
5. Peripheral arterial disease (PAD)
6. Allergy/hypersensitivity reaction to cyanoacrylate
7. Severe comorbidities

Primary end points (in 6 months) were:

1. Anatomical success as indicated by GSV occlusion rate on ultrasound examinations, defined as no segments of patency longer than 3 cm
2. Clinical success as assessed by the quality of life (QoL) using the revised Venous Clinical Severity Score

Secondary end points were:

Any kind of complication during and after the operation and all adverse events

Patients were assessed postoperatively after 2 weeks, 3 months and 6 months. Follow up included clinical examination and repetition of the rVCSS, as well as duplex ultrasound to ensure successful target vein closure and exclude the presence of deep vein thrombosis.

Methods and Procedural protocols

We used the Vena Seal Closure System™ (Medtronic Plc, Dublin, Ireland) which is an innovative technology. The delivery system consists of two sets which separates flushable vs non-flushable components. The first set consists of components that remain dry before and during the procedure: a 5F delivery Catheter, a Dispensing Gun, an Adhesive (bottle), a 3-mL Syringe and a Dispenser Tip. The 5F delivery catheter has a hydrophobic coating to prevent adhesion to delivered NBCA and air-filled micro channels for better sonographic visibility. The second set consists of components that are exposed to fluids before or during the procedure and include a 7F Introducer sheath/dilator and a J-tip guidewire. Each pull of the trigger delivers approximately 0.1 ml of NBCA.

The GSV is accessed at the distal point of reflux percutaneously with direct puncture or with a micropuncture introducer kit. When this approach is not feasible, a small incision (3mm) is made to facilitate open access to the vein. Usually this distal point is just above the internal malleolus, but it can be in every point along the saphenous vein path. An insertion of a 7F introducer sheath/dilator catheter follows (Figure 2). A 0.035-inch J-tip guidewire is advanced to the saphenofemoral junction (SFJ) under ultrasound guidance and the introducer catheter is inserted and positioned approximately 5 cm caudal to the SFJ. (Figure 3)

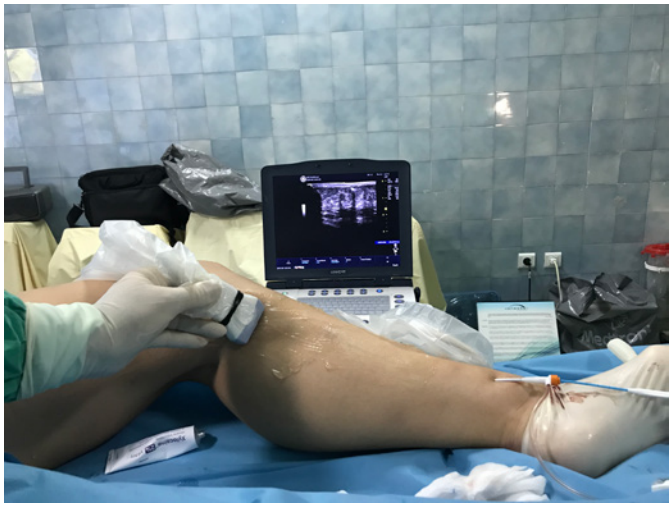

Figure 2 Endovenous technique set up

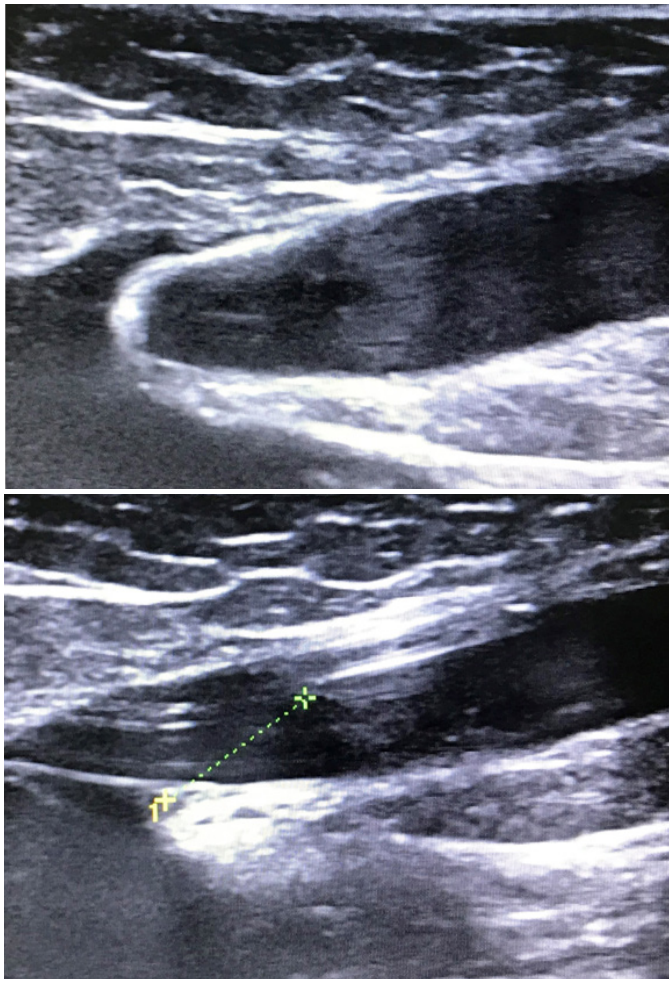

Figure 3. The J-tip guide wire at the Sapheno-femoral junction (SFJ) (left image) and the delivery catheter near SFJ before withdrawal (right image)

The delivery catheter (preloaded with NBCA glue) is inserted into the introducer catheter, secured, advanced up to the SFJ and connected to the dispenser gun. At that time, 6 cm of the catheter tip is exposed distal to the sheath tip because the catheter is longer than the sheath, so it reaches the SFJ. After 6 cm pullback the catheter is now finally repositioned 5 cm from the SFJ. This distance of 5 cm is necessary for safety reasons as it protects from glue propagation toward the SFJ and serves as space for the exertion of external pressure.

The leg is elevated approximately 15 degrees and the glue delivery starts with an initial double injection spaced 1 cm apart, followed by a 3 cm pullback. Then a 3-minute localized compression is applied directly over the SFJ and the first segment of the GSV. In a similar manner, 3 repeated injections of CA followed by pullbacks of 3 cm each and 30-second localized compressions of the treated vein segment take place. The process is repeated until the entire targeted vein segment is treated. A 3 second trigger hold delivers 0.10 ml (range 0.06-0.12) of adhesive. When finished, the catheter is removed, and compression is applied to the catheter entry site. Successful occlusion of the entire treated vein was confirmed by on-table duplex ultrasound (Figure 4). There was no post-operative use of bandages or compression stockings.

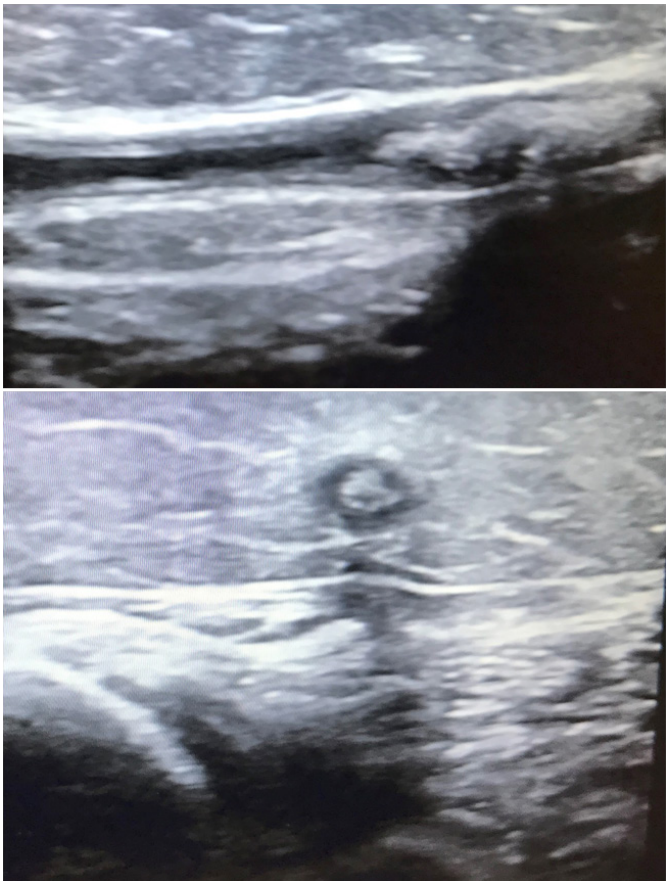

Figure 4. Postoperative image of the polymerized glue into the Saphenous vein

Postprocedural management

Patients were instructed to walk mildly and stay in the hospital area for 45 minutes before being discharged. They were encouraged to walk and were instructed to resume normal activities within a day. Postoperative ultrasound examination was performed immediately after surgery, at 15 days, at three and six months.

RESULTS

In consonance with medical history, 2 patients had mild heart failure and one patient was a former intravenous drug user with a malformation in the index leg due to injury (open fracture) caused by a car accident. All patients were between C2 and C4a according to CEAP classification. More specifically, 19 patients had varicose veins C2 (38%), 21 patients were in stage C3 (42%) with venous edema and 10 patients in C4a (20%), presenting pigmentation or venous eczema. (Table 2) (Figure 1). The majority of patients (64%) had an rVCSS ≥6, while 30% of patients had an rVCSS≥9. The mean preoperative rVCSS was 6.3 (SD: 2.3). Specifically, the VCSS for this cohort of patients was 3: 5pts, 4: 10pts, 5: 3pts, 6: 12pts, 7: 2pts, 8: 3pts, 9: 9pts, 10: 4pts, 11: 2pts (Table 3)

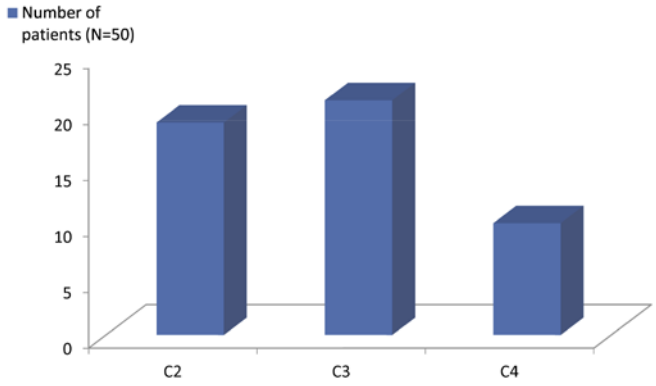

Figure 1. CEAP classification

Symptoms	Number of patients (N=50)	Percentage
Heaviness	43	86%
Fatigue	41	82%
Soreness	39	78%
Burning	34	68%
Edema	31	62%
Aching	17	34%
Pruritus	10	20%

Table 2. Symptoms

VCSS	Number of patients (N=50)	Percentage
1	0	0
2	0	0
3	5	10%
4	10	20%
5	3	6%
6	12	24%
7	2	4%
8	3	6%
9	9	18%
10	4	8%
11	2	4%

Table 3. Pre-operative Venous Clinical Severity Score

Almost all patients 49/50 (98%) underwent local anesthesia and only one received general anesthesia, after patient's request due to her anxiety. In 28 patients (56%) there was a percutaneous approach via direct puncture (in 24 of them w used micropuncture), 2 of them (4%) needed a double puncture, whereas 22 patients (44%) had a short 3 mm cut down exposure of the target vein. The access point was near the ankle in 36 cases (72%), below the knee in 8 cases (16%) and the thigh in 4 cases (8%), while 2 cases (4%) needed a double puncture. To reduce the operative time, after a few minutes of unsuccessful percutaneous puncture, regardless of the cause (e.g. small diameter of the vein, spasm), we proceeded to cut down. All patients underwent an on-table completion ultrasound to verify successful ablation closure of the treated venous segment and to inspect the common femoral vein for deep venous thrombosis via compressibility test.

There was a 100% (50/50) successful obliteration of the target vein in day 0, 2 weeks, 3- and 6-month follow up. All patients (100%) reported improvement of the symptoms, whereas 33 (66%) had complete elimination of symptoms. Forty-six patients (92%) improved the appearance of their varices without any need for complementary plhebectomies. Twenty-four patients (48%) presented complete obliteration of varicose veins in the follow up period, while 22/50 (44%) showed significant improvement of the appearance of the varicose veins (Table 4). All patients improved their rVCSS, in a mean 82.5% decrease (postoperatively 1.1 -SD: 1.34) (Table 5).

	Number of patients (N=50)	Percentage
Vein occlusion	50	100%
Varicose veins obliteration	24	48%
Symptom obliteration	17	34%
Varicose veins improvement	22	44%
Symptom improvement	33	66%

Table 4. Results

VCSS	Number of patients (N=50)	Percentage
0	14	28%
1	13	26%
2	9	18%
3	9	18%
4	5	10%
5	0	0
6	0	0
7	0	0
8	0	0
9	0	0
10	0	0
11	0	0

Table 5. Post-operative Venous Clinical Severity Score

There were no major adverse effects observed during follow-up (pulmonary embolism, skin necrosis, TIA, nerve injury,

infection). A percentage of 42% (21 patients) presented erythema and tenderness along GSV during the first postoperative days, which was self-restricted. This was observed between second and seventh post-operative day, lasting one or two weeks and gradually getting better. From those who presented erythema the majority (18/21 patients - 85.7%) had a superficially placed GSV, out of the saphenous compartment, with very limited distance from the skin. Thirteen of those patients (13/21 - 26%) were treated with anti-inflammatory drugs (Ibuprofen). (Figure 5)

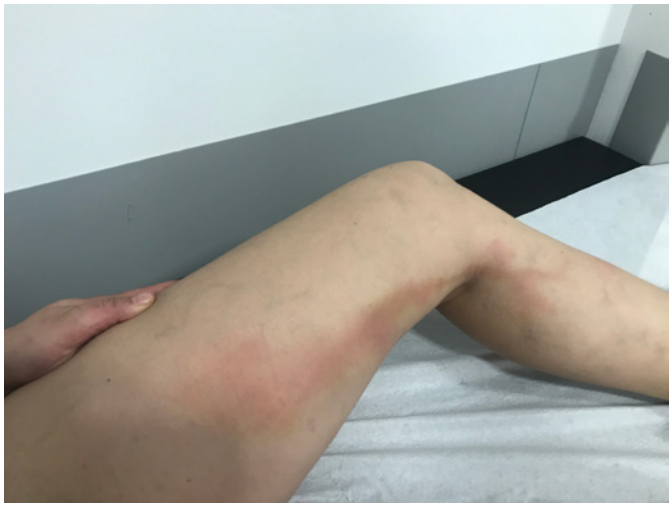

Figure 5. Postoperative phlebitis

DISCUSSION

Endovenous techniques are nowadays recommended as first-line treatment for venous trunk reflux, both in the USA and the UK. These techniques include thermal ablation by laser or radiofrequency and non-thermal ablation by foam sclerotherapy or mechano-chemical obliteration of the insufficient venous trunks. Although endovenous thermal ablation has many advantages and is currently the treatment of choice for GSV insufficiency, it has also some limited drawbacks. Firstly, it requires perivenous tumescent anesthesia which causes pain and disturbance to the patient during application, as well as post-operative annoyance and bruising[14,15]. Moreover, after thermal ablation there is a possibility of sensory nerve damage due to the tumescent anesthesia or heat damage following endothermal treatment. On the other hand, foam sclerotherapy, has low success rates (75.8%) for the treatment of GSV and frequently needs repetition[16]. In addition, sclerotherapy is sometimes complicated by inflammation and staining[17,18] and, rarely, with paradoxical air embolism and stroke.[19,20,21]. Non-thermal, nontumescent (NTNT) techniques have also become available, like mechanochemical ablation (84% success at 5 years) and proprietary endovenous microfoam (PEM), which have relatively good clinical results, but high possibility of pigmentation[22].

Finally, these techniques require the use of post-operative graduated compression stockings, which patients often find uncomfortable, especially in warm countries like Greece. This discomfort can also lead to poor compliance. More recently, a new technique for truncal vein closure has been approved by the Food and Drug Administration in the United States in February 2015 which involves the endovenous application of n-butyl cyanoacrylate glue for the closure of the incompetent GSV.

Almeida et al first announced the use of cyanoacrylate adhesive for the treatment of venous incompetence. The method proved to be safe and effective and suggested some possible advantages in comparison to thermal techniques[23,24]. The first advantage was the freedom from a time consuming and disturbing tumescent anesthesia, as well as decreased post-procedural ecchymosis. The second advantage was the avoidance of heat damage. Finally, there was no need for post-operative graduated compression stockings. The early results showed non-inferior efficacy and safety when compared to radiofrequency ablation, which was an established treatment for great saphenous vein insufficiency. The two-year and thirty-six-month follow-ups of the patients reconfirmed this conclusion. In sum, the method was fast, painless and effective.

The intravascular use of CA is not new at all[25.26,27,28,29]. In fact, it has more than two decades of history in treating arteriovenous malformations. Monomeric cyanoacrylate compounds, when in contact with anionic compounds of the plasma, polymerize and begin to solidify, which creates an inflammatory effect over the vein wall. This process is completed in three phases: a first initial rapid polymerization with linear increase in tensile forces (10 seconds), a second phase with stable tensile forces, lasting about 60 seconds, and finally a third phase with more rapid rise of tensile forces. In the third stage, final polymerization and bonding to the endothelium occurs[30]. This, in general, is followed by a subacute inflammatory tissue response, a typical foreign body reaction, leading to a fibrotic transformation. This process following glue injection, takes several weeks before it becomes permanent[31].

Shortly after completion of the feasibility study on first in-man use of CA for GSV embolization[23], many studies were set up to obtain anatomic and clinical data regarding the use of the technique and to compare it with other endovenous treatments[9,32,33]. Potential benefits of the method, as far as procedural and post-procedural experiences of the patients must be balanced with long-term results[34,35,36,37,38].

The technique is considered to be easy for all surgeons with endovascular experience and especially for those with previous expertise in endothermal treatments of GSV reflux. The CA delivery system requires skill sets familiar to those who perform thermal vein ablation.

In our study we tried to evaluate the effectiveness of the method, based on anatomic and clinical data and its safeness, estimated by the rate of all side effects. The primary study endpoint was to assess the GSV occlusion rate at 6-month follow-up and the quality of life (QoL) using the Venous Clinical Severity Score. The secondary endpoints included the periprocedural pain and all types of complications after the intervention and during the follow-up period.

Each patient was examined by ultrasound at two weeks,

three months and 6 months post-operatively and the anatomic criterion for success was the complete occlusion of the target vein at the 6-month follow-up on duplex ultrasound evaluation. Complete occlusion of the treated vein was defined as no segments of patency longer than 3 cm, whereas in the literature this segment is defined usually as less than 5 or even 10cm. Although our definition of vein occlusion was even stricter, the closure rate in our study was excellent (50/50), similar or even better than that observed in similar studies. This anatomic result remained stable during the 6-month follow-up. Clinical improvement was estimated with clinical examination and the standard rVCSS evaluation after the operation. All patients showed significant improvement of venous symptoms postoperatively. Interestingly, this clinical improvement, and especially the absence of limb heaviness, in many cases was reported by the patients immediately after standing up from the operating table, whereas in others it was clear after their first post-operative visit.

However, even more remarkable in our study was the proportion of patients whose target limbs were free from visible varicosities at 6-month follow-up, as was reported by the examiner and the patient himself. That fact was also depicted in the decrease of the rVCSS score. In our study, per protocol, we chose not to treat the varicose veins during the initial procedure. Instead, we let them shrink without reflux supply, and treated them only if they were visible after three months. Adjunctive treatments like phlebectomies or sclerotherapy at the time of operation are routinely used in most clinical trials. In our study we followed a different routine. The rationale behind this decision was to minimize the discomfort of our patients, as all procedures were done under local anesthesia, and secondly to treat fewer varicose veins when needed, as most of them could have been reduced in size and number, due to the absence of reflux- derived supply. This hypothesis proved to be valid as 24 patients (48%) presented complete obliteration of their varicose veins, while 22 (44%) showed significant improvement of the appearance of varicose veins. As a result, only 4 (8%) needed complementary treatment.

This number of actual adjunctive plhebectomies at three months was significantly lower than the preoperative prediction. Moreover, this low rate of complementary intervention was the same even in patients with larger varicosities. This is reflected in the improvement in QoL scores after the treatment. Even more, as a consequence of this routine, we had the opportunity to evaluate the results of the cyanoacrylate closure method in treating reflux by itself, without any assistance of any type of surgical intervention. The concomitant complementary surgical interventions may create potential confounding of the outcome measurements compared with other studies, as adjunctive procedures may improve the results of the method itself[39,40,41,42,43,44,45,46].

In our study we did not use graduated compression stockings. The reason behind this decision is the knowledge that obliteration is succeeded very early, as 80% of the cyanoacrylate polymerization is completed in just three minutes, so the vein walls adhere to each other. However, we cannot predict what benefit compression stockings could add under special circumstances like CA use in very large diameter veins.

The side effects were mild. No neurological complications or deep vein thrombosis was observed. This observation seems quite logical, since by protocol the tip of the catheter is positioned 5 cm away from the superficial to deep vein junction. The most common side effect in our study was post-procedural phlebitis of the treated vein which occurred in 21 patients. In our study this inflammatory response was very common and ranged from mild (16%) to disturbing (26%) but in all cases proved to be benign. We informed all patients preoperatively about this potential side effect and about its short and self-limited duration, in order to reduce the anxiety of the patient if this were to happen. The superficial veins were more prone to this visible phlebitic reaction, which presented with redness and pain. In more pronounced cases (13 patients) there was a need for ibuprofen for some days once or twice daily, but in almost all cases it was limited after 10 days (20 days in one case). There was not any permanent pigmentation or stagnation of the skin. Some patients with very superficial saphenous vein also described some mild discomfort during the periprocedural catheter manipulation, as nearly all procedures were performed under local anesthesia.

The risk of recanalization is the main problem of all endovenous techniques. Several randomized trials and meta-analyses have shown that the risk of recanalization depends on many factors, one of them being the method used for treatment[47,48]. The endovenous methods of treatment for vein reflux initially produce thrombosis of the target vein. Thrombosis is associated with recanalization. As a result, to achieve permanent occlusion, there must be -in addition to the thrombosis- chemically or thermally induced vein wall destruction. On the other side, cyanoacrylate glue acts in a different way: the application of external compression, in the presence of the adhesive, makes the vein walls to come together without significant thrombosis, so the process is more inflammatory and eventually fibrotic rather than thrombotic.

Another cause of recanalization is untreated tributaries with high blood flow or reflux. In our study, patients with large insufficient collaterals originating less than 3cm from the SFJ, were excluded from the study, as for safety reasons the first 5 cm of the GSV remain untreated. This might be one reason for the excellent obliteration results we observed in our patients.

As cyanoacrylate glue closure is a relatively new technique there are not many data in the literature reporting the long-term results of the method. Almeida et al[34] first revealed an occlusion rate of 94.7% at 36 months, Eroglu et al[44] reported 94.1% occlusion rates at 30 months, while Morrison et al[40] estimated 91.4% freedom from recanalization at five years. In most studies comparing the cyanoacrylate closure to other endovenous treatment modalities such as laser ablation and RF ablation, no differences were observed in occlusion rates between the three modalities, but NBCA appeared superior with respect to peri-procedural pain, return to work and decreased VCSS[39,40,42,43,45,46].

The current trial has several limitations. It is a purely retrospective study of a single center database. There is a lack of

objective measures for postoperative pain, discomfort and reduction in size and number of the residual varices. Even more, we focused only in the early -six months- closure rates of the technique. We keep a close follow-up of the treated patients in order to obtain long term data and estimate the efficacy of the technique over time.

CONCLUSION

In our study, endovenous cyanoacrylate closure of the GSV proved to be safe and efficient treatment for symptomatic venous insufficiency. It has many advantages because it provides improved patient comfort, rapid return to normal activities, and reduced procedure time, without the use of perivenous tumescent anesthesia with multiple needle sticks and without post-procedural compression stockings. Phlebitis is mild and self-limiting. Failure rates are extremely low, but long-term data are required to affirm this over time.

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