A NEW MINIMALLY INVASIVE METHOD IN THE TREATMENT OF VARICOSE VEINS: CYANOACRYLATE BASED GLUE - LONG TERM RESULTS

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ABSTRACT

Introduction*: Varicose veins in the great saphenous vein (GSV) are common and have significant impact on the quality of life of the patients. Minimally invasive cyanoacrylate embolization, which uses a liquid biocompatible glue and compression in order to anneal the walls of the dilated vein, is a relatively recent approach for the treatment of the condition. Previously, we reported the six-month outcomes of a prospective study and herein we present the results of the two-year follow-ups for the procedures including those in the previous study and evaluate the long-term efficacy of the vein sealing system using VariClose®.*

Materials and methods*: The prospective study involved the treatment of a total of 73 patients for incompetent GSVs and their follow-up examinations. The site of reflux, patients' suitability for endovenous treatment, and closure of varicosities at the first week, the sixth month, and the first and second years after the procedure were determined with pre-operative duplex ultrasound. The status of veins was classified according to the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification. Clinical success of the treatment was evaluated with venous clinical severity score (VCSS).*

Results*: Total occlusion in the treated segment was achieved in all patients at week one but decreased to 93.2% at the end of postoperative sixth month and 90.4% and 87.7% at the end of first and second year, respectively. Varicosities of all the patients were resolved, and all of the patients experienced an improvement in their symptoms postoperatively as indicated by decreased CEAP classification and VCSS. Hematoma (in two patients, 2.7%) and phlebitis (in three patients, 4.1%) were observed as rare adverse events.*

Conclusion*: The system used in this study delivered comparable venous occlusion rates and clinical improvements to those of thermal ablation methods and other cyanoacrylate-based vein sealing systems available in the market.*

Keywords: *varicose veins, great saphenous vein, n-butyl cyanoacrylate, cyanoacrylate embolization.*

DOI: 10.19193/0393-6384_2019_6_479

Received *November 30, 2018;* ***Accepted*** *February 20, 2019*

Introduction

Varicose veins (VVs) are a relatively common condition characterized by dilation of superficial veins to various degrees, usually more than 3-4 mm in diameter[1,2]. Varicose veins are the most common result of chronic venous insufficiency/disease (CVI/D) with significant impact on the quality of life of the patients even though they are generally not life threatening. Varicose veins may develop in connection with the incompetence of veins at the junction of deep and superficial systems due to idiopathic valvular dysfunction or elasticity of walls, which lead to reflux and pooling of blood in and dilatation of superficial veins[1-3].

Less frequently, they may also develop secondary to pathologies of the deep venous system involving obstructions due to deep venous thrombosis (DVT), abdominal mass resulting in pressure on pelvic veins, obesity, or other reasons[1,2]. Most common sites of VVs are great saphenous vein (GSV) and small saphenous vein (SSV), which are associated with pathologies of the saphenofemoral junction (SFJ) and the saphenopopliteal junction (SPJ), respectively[1,3].

Incidence of VVs reported in literature ranges from 20 to 64%, being more common among older people, women, pregnant women, people with deep venous thrombosis or obesity, those who have family history of VVs or occupational predisposition due to posture (e.g. teachers standing for long periods of

time), and those of Caucasian origin[1-5]. Even though VVs are generally not life threatening, they may cause cosmetic concerns, significant pain, fatigue, limited mobility, edema, bleeding, or venous ulcerations, in the order of increasing severity[2]. Accordingly, untreated VVs incur significant economic and healthcare costs in the later stages of the disease; more severe consequences such as venous ulcerations lead to healthcare costs measured in billions of dollars[1,6].

Historically, treatment of VVs included the use of compression stockings and open surgery including high ligation and stripping, the former being a symptomatic treatment for simple VVs with no effect on their recurrence or progression[3]. As the historical gold standard and most commonly used method for the treatment VVs around the world, surgery has been shown to be an effective treatment for the prevention of leg ulcers due to VVs and reduce their recurrence rate[3,7,8].

However, frequency of open surgery declined rapidly with the advent of minimally invasive techniques such as sclerotherapy, radiofrequency ablation (RFA), and endovenous laser ablation (EVLA) by the end of the millennium[1,2]. These alternative methods are not without complications despite their increasing popularity in the recent years, especially related to thermal treatment[2]. Common complications include pain, hyperpigmentation, hematoma, bruising, and ecchymosis[2]. A more recent addition to the minimally invasive armamentarium for the treatment of VVs is the cyanoacrylate embolization (CAE), which uses biocompatible liquid glue and compression in order to anneal the walls of the dilated vein[9-11].

Initial studies on CAE indicated favorable outcomes with no requirement for tumescent anesthesia or the use of compression stockings in the post-treatment period and without the complications related to thermal effects although phlebitic reactions were commonly reported as a side effect[9,11,12].

Currently, two systems are available to apply the CAE procedure: VenaSealTM closure system (Medtronic, Minneapolis, USA), which uses a more viscous cyanoacrylate glue, and VariClose® vein sealing system (Biolas, Ankara, Turkey), which uses a slightly modified, less viscous cyanoacrylate glue with faster polymerization rate[11,13,14].

However, limited number of studies have investigated the short and long-term outcomes of the new method, especially of the latter system. Previously, we reported the six-month outcomes of a prospective study including 62 patients[15]. Here we present the results of the two-year follow-ups for 73 procedures including those in the previous study and evaluate the long-term efficacy of vein sealing system using VariClose® to treat varicose veins in the GSV.

Material and methods

This prospective study involved a total of 73 patients (41 male, 32 female) who were treated for incompetent GSV using VariClose® vein sealing system (Biolas, Ankara, Turkey) at Kayseri Research and Training Hospital between January - June 2014. The site of reflux and patients' suitability for endovenous treatment were determined with pre-operative duplex ultrasound examination operated by the same radiologist using an Aplio500 ultrasonography device (Toshiba, Tokyo, Japan). In ultrasonography, the patency of deep veins, the extent and severity of the reflux in the superficial veins in the standing position, and the competence of the leg perforators were determined. The diameter of GSV was measured 3 cm below the SFJ. An experienced vascular surgeon classified the status of veins according to the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification.

Inclusion/exclusion criteria

Patients over 18 years of age with symptomatic incompetent GSV, a GSV diameter of more than 5.5 mm with or without visible varicosities, and CEAP classification of >2 were included. Patients with asymptomatic incompetent GSV or SSV with a GSV diameter of <5.5 mm or >13 mm, pregnancy, deep venous thrombosis (DVT), superficial thrombophlebitis, non-healing ulcers, or non-palpable pedal pulses were excluded. Patients with very superficial or tortuous GSV and those with ancillary procedures like phlebectomy or sclerotherapy after vein sealing system were also excluded. Informed consents of all patients were obtained in writing.

Procedure

Procedure for the CAE treatment was as previously published[15]. All procedures were carried out with local anesthesia under ultrasound guidance; tumescent anesthesia was not used. A 6F introducer sheath was inserted into the vein at an appropriate point near or below the knee. After insertion of 0.035-inch J-tip guidewire, the 4F micro delivery system was inserted and moved to 5 cm below the SFJ. High-density NBCA glue was continuously injected (3 mL) with the dispenser gun while withdrawing micro delivery system and pressuring on to the SFJ

so that 0.05 mL NBCA glue was injected per cm of GSV; mean volume of the injected glue was 1.5 mL. After the procedure, elastic bandage was wrapped around the operated leg and patients were asked to walk for 20 minutes; the patients were discharged on the same day. Patients were advised to wear elastic bandages for one day but not compression stockings, and they were not prescribed non-steroid anti-inflammatory drugs. They were recommended to walk at least one hour a day and warned to avoid intense exercise or standing for a long period of time. All of the patients were followed-up for clinical evaluation of venous clinical severity score (VCSS) and underwent post-procedural duplex ultrasound examination for recanalization at the first week, the first, third, and sixth months, and the first and second years after the procedure[16]. Total occlusion was defined as lack of patency more than 5 cm length in the treated segment of varicose GSV.

Results

The study included a total of 73 patients (41 (56%) male and 32 (44%) female) with an average age of 45.1 years (±2.8, range 29-70 years). Key indicators for the procedure and its outcome were presented in Table 1. The following premorbid conditions were present in the patients: hypertension (11%) and diabetes mellitus (5%). Average duration of procedure was 14 min (range 9-33 min).

Procedure	**Mean/(Median)**	**±SD**	**Min-Max**
Age (years)	45.1	±2.8	29 - 70
Treated GSV length (cm)	(27.8)	±2.3	20 - 40
Treated GSV diameter (mm)	7.5	±1.5	5.5 - 13
Duration of procedure (min)	14	±1.9	9 - 33
Occlusion	**Total (%)**	**Subtotal (%)**	**None (%)**
Week 1	73 (100%)	-	-
Month 6	68 (93.2%)	2 (2.7%)	3 (4.1%)
Year 1	66 (90.4%)	3 (4.1%)	4 (5.5%)
Year 2	64 (87.7%)	4 (5.5%)	5 (6.8%)
CEAP classification			
Pre-treatment (mean ±SD)	3 ±0.4	P <0.005	
Post-treatment (mean ±SD)	0.8 ±0.16		
VCSS			
Pre-treatment (mean ±SD)	5.1 ±1.7	P<0.05	
Post-treatment (mean ±SD)	2.1 ±1.4		
Adverse events			
Thrombophlebitis	3 (4.1%)		
Hematoma	2 (2.7%)		

Table 1: Key indicators for the procedure and its outcome. *Abbreviations: SD, standard deviation; GSV, great saphenous vein; CEAP, Clinical-Etiology-Anatomy-Pathophysiology; VCSS, venous clinical severity score.*

The follow-up period was 26 months. The rate of total occlusion decreased from 93% at the end of postoperative sixth month to 88% postoperative second year. For the three patients who had no occlusion, the GSV diameter was greater than 11 mm. Varicosities of all the patients were resolved, and all of the patients experienced an improvement in their symptoms postoperatively as indicated by decreased CEAP classification and VCSS after the treatment. Mortality rate throughout the study was 0%. Reported adverse effects after the procedure were thrombophlebitis (4.1%) and hematoma (2.7%); none of the patients developed DVT or pulmonary embolism.

Discussion

In the last decade, endovenous thermal ablation techniques using radio frequency or laser beam started to replace open surgery for the treatment of varicose veins (VVs)[1]. Even though thermal ablation methods have satisfactory occlusion rates and are minimally invasive, quicker, associated with less complications, and require less extensive anesthesia and less time to heal, they still have the risk of causing serious adverse reactions such as pain, hyperpigmentation, hematoma, bruising, and ecchymosis[2]. Novel embolization interventions involving cyanoacrylate glues for the treatment of varicosities of the great saphenous vein (GSV) promise similar outcomes with even more patient-friendly procedures and even less adverse effects[11,13,14].

Currently, there are two alternative medical products using the cyanoacrylate-based embolization technique for VVs, and the studies on the efficacy and other aspects of VariClose®, which uses a less viscous glue mixture with a faster polymerization rate, are limited[17]. This study followed up a total of 73 patients who underwent the cyanoacrylate embolization (CAE) procedure for varicosities in the GSV for two years.

In the first study on the use of CAE in humans, complete occlusion (defined as the absence of patency or recanalization in any treated segment of >5 cm in length) was achieved in all of the patients immediately after the procedure and declined to 92% after one year, which remained the same after two years (38 patients)[11,18,19]. The three-year follow up in the same study reported an occlusion rate of 95% (29 patients[20]. Subsequent studies using the commercialized VenaSeal® reported comparable rates of complete occlusion in the GSV: a decrease from 97.1% shortly after the procedure to

92.7% after one-year (complete occlusion defined as patency segment <10 cm, 68 patients)[21], a decrease from 100% one-month after the procedure to 97.2% after one-year (patency segment <5 cm, 95 patients)[22,23], a decrease from 98.2% one-week after the procedure to 78.5% after one-year (patency segment <5 cm, 57 legs in 29 patients)[24], 99% three or six months after the procedure (patency segment <5 cm, 104 or 101 patients, respectively) [25], and 100% one week or one month after the procedure (patency segment <5 cm, includes 48 GSVs, 14 accessory saphenous veins, and 8 SSVs)[26].

In a limited number of studies using VariClose®, the alternative glue, comparable closure rates were found: 100%, 96.6%, and 94.1% closure rates immediately and 5.5 months, 12 months, and 30 months after the procedure, respectively (patency criteria not disclosed, 180 patients)[27,28]; %, 96.7% and 95.8% closure after one and twelve months (patency segment <5 cm, 310 patients)[29]; and 98.6% closure after one year (patency segment <5 cm, 150 patients)[14].

In the present study, total occlusion of varicose GSV was achieved in all of the patients shortly after the procedure; however, this rate gradually decreased to 90.4% in one-year and to 87.7% in two-year after the procedure. The decrease in closure rates was similar to the pattern observed in previous reports, and the vein closure outcomes were comparable. Some of the abovementioned studies involved head-to-head comparison of CAE with established ablation methods such as EVLA or RFA[14,22,23,29] and were reviewed by Lam et al. and Radak et al.[11,13]. In those studies, the closure rates by the CAE approach were comparable to if not better than these ablation techniques.

In our study, we have also evaluated the clinical improvement in patients' condition through Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification and venous clinical severity score (VCSS)[16], both of which indicated a clear improvement after the procedure ($p<0.05$and $p<0.05$, respectively). Significant improvements in VCSS were also reported in previous studies utilizing the CAE approach[18-29]; in those comparing CAE to thermal ablative approaches, improvements in VCSS were comparable[14,22,23,29].

Adverse effects of the procedures are an important aspect in the treatment of varicose veins as these procedures are carried out quite often for cosmetic reasons or for better quality of life. In thermal ablation methods, some serious adverse reactions as thermal injury, deep venous thrombosis (DVT), or pulmonary embolism have been reported[2].

In individual studies or head-to-head comparisons, adverse events were nonexistent, not related to the procedure, or significantly less in the CAE procedures although phlebitis and post-procedural pain were also observed in patients treated with the CAE approach[11,14,23,29]. In our study we observed hematoma and phlebitis as rare adverse reactions.

This prospective study carries some limitations especially related to the use of a limited set of tools to assess the clinical success. Here we used VCSS to evaluate the improvements in patients' venous health, additional tools such as Aberdeen Varicose Vein Questionnaire could provide more depth to the analysis. Since there are slight differences in approaches, procedures, and inclusion criteria, it is not possible to directly compare various aspects of treatment outcomes of the two cyanoacrylate products available.

Our study investigated the treatment outcomes of VariClose® vein sealing system for the patients with varicosities in great saphenous vein. In conclusion, this system provided venous occlusion rates and clinical improvements comparable to those of thermal ablation methods and the other cyanoacrylate-based vein sealing systems available in the market. Future studies might be directed towards the comparing the two systems in a standardized setting especially in terms of adverse reactions associated with the procedure.

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