Regression of varicose veins after cyanoacrylate closure of incompetent great saphenous veins without a localized concomitant procedure

Jin Ho Hwang, MD, PhD,[a] Sang Woo Park, MD, PhD,[a] Ki Hyun Kim, MD,[a] Woo Young Yang, MD,[a] Jae Joon Hwang, MD, PhD,[b] Song Am Lee, MD, PhD,[b] Jun Seok Kim, MD, PhD,[b] Jae Bum Park, MD,[b] Hyun Keun Chee, MD, PhD,[b] *and* Ik Jin Yun, MD, PhD,[c] *Seoul, Republic of Korea*

ABSTRACT

Objective: The objective of this study was to evaluate the effectiveness and safety of endovenous cyanoacrylate closure (CAC) of incompetent great saphenous vein (GSV) and to assess the regression of varicose vein following CAC without a concomitant procedure.

Methods: A total of 63 limbs in 48 patients treated with CAC because of an incompetent GSV between December 2016 and November 2017 were retrospectively evaluated. In five limbs, incompetent GSV and small saphenous vein were treated simultaneously in the same session. Duplex ultrasound, Venous Clinical Severity Score, degree of regression of varicose veins, and adverse events were examined at intervals of 1 week, 1 month, 3 months, 6 months, and 12 months.

Results: In 63 limbs, of which 60 were available for follow-up, all treated GSVs showed complete closure during the follow-up period (8.4 ± 3.0 months). Venous Clinical Severity Scores at the time of all follow-up visits were significantly lower ($P < .001$) than those before CAC. Complete resolution of varicose veins was noted in 38 limbs (71.7%) after 3-month follow-up. The proportion of limbs showing >50% varicose vein regression reached 90.6%. The more that varicosity entry was covered ($P = .002$) and the farther down the leg the access site was located ($P = .024$), the more complete resolution of varicose veins was observed. Phlebitis occurred in 10 limbs (16.7%), and hyperpigmentation occurred in 8 limbs (13.3%).

Conclusions: CAC is safe and effective for the treatment of an incompetent GSV. It also shows a satisfactory result with the regression of varicose veins. Covering the entry of varicosities and accessing lower down the leg are associated with more complete resolution of varicose veins. (J Vasc Surg: Venous and Lym Dis 2019;7:375-81.)

Keywords: Cyanoacrylate; Great saphenous vein; Varicose vein; Regression

Endovenous thermal ablation has replaced varicose vein surgery (ligation and stripping) and has been proved to be effective and safe for the treatment of incompetent saphenous veins.[1-6] However, a main disadvantage of radiofrequency ablation (RFA) or endovenous laser ablation is the need for tumescent anesthesia to reduce the risk of potential thermal injury to the surrounding tissues, especially superficial nerves.[7] Tumescent anesthesia requires additional time for multiple needle sticks, and adverse events such as hematoma, pain, and ecchymosis may occur after the procedure.[8]

In recent years, cyanoacrylate closure (CAC) has emerged as a new nonthermal treatment of incompetent saphenous veins. CAC results in circumferential coaptation of the vein wall, followed by adhesion and encapsulation, causing permanent venous occlusion.[6] Several studies have reported comparable safety and efficacy of the CAC to endovenous thermal ablation.[1,3-6,8-11] CAC does not require tumescent anesthesia and is associated with less postprocedural ecchymosis and nerve injury. In addition, it has the advantage of not requiring compression stockings after the procedure.[4,5,9]

In a real-world setting, concomitant procedures to eliminate varicose tributaries at the time of CAC increase procedure time, postprocedure recovery time, and frequency of adverse events.[5] For these reasons, CAC is usually performed without concomitant treatment. Up to now, there have been only two studies of freedom from varicose veins after CAC without a concomitant procedure.[1,4] However, no specific research has considered the factors that affect freedom from varicose veins after CAC. In addition, there have been no reports observing the degree of regression of varicose veins after CAC.

The purpose of this study was to evaluate the safety and efficacy of CAC in the treatment of great saphenous vein (GSV) insufficiency. In addition, we investigated the factors associated with complete regression of varicose veins and the degree of regression of varicose veins after CAC without ancillary localized treatment.

From the Department of Radiology,[a] Department of Thoracic and Cardiovascular Surgery,[b] and Department of Surgery,[c] Konkuk University Medical Center, Konkuk University School of Medicine.

Author conflict of interest: none.

Correspondence: Sang Woo Park, MD, PhD, Professor, Department of Radiology, Konkuk University Medical Center, Konkuk University School of Medicine, 120-1 Neungdong-ro, Hwayang-dong, Gwangjin-gu, Seoul 143-729, Republic of Korea (e-mail: psw0224@kuh.ac.kr).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

https://doi.org/10.1016/j.jvsv.2018.10.016

METHODS

Study participants. This is a retrospective study conducted at a single tertiary care hospital with Institutional Review Board approval. Between December 2016 and November 2017, there were 63 limbs among 48 patients that were treated for incompetent GSV. Varicose veins (3 mm in diameter or larger in a standing position) were found in 56 limbs. CAC was performed when the GSV demonstrated significant reflux (>0.5 second) in the standing position on duplex ultrasound examination using an iU22 (Philips, Bothell, Wash) with 12-5 MHz linear transducer. Preprocedural and postprocedural duplex ultrasound examinations were performed by interventional radiologists. The mean diameter of the GSV was 6.9 ± 1.8 mm (range, 4.0-13.0 mm). Demographic and baseline data of patients are summarized in Table I.

Varicose veins were found in 56 limbs. From seven limbs without visible varicose vein, two limbs were classified as C1 according to Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) classification with symptoms of fatigue, heaviness, and muscle cramping. The remaining five limbs were classified as C3. Epifascial GSV and below-knee GSV were not excluded. There was no limitation of the saphenous vein diameter. Fifteen patients were treated for bilateral incompetent GSVs. In five limbs, there was incompetence in both GSV and small saphenous vein, and both were treated at the same session.

Procedure. After providing written informed consent, the patient was brought to the procedure room, placed in a supine position, and draped in the usual sterile fashion from groin to ankle. Two practitioners (S.W.P. and J.H.H.) were involved in the CAC procedure. The targeted GSV was punctured under ultrasound guidance at the lowest level possible, and puncture was attempted below the knee, at the knee, or above the knee using a 21-gauge needle. After the GSV was successfully accessed, a 0.018-inch wire and a 4F or 5F microsheath (Cook Medical, Bloomington, Ind) were introduced into the access site.

CAC was performed with a VenaSeal Closure System (Medtronic Vascular Inc, Santa Rosa, Calif). A 0.035-inch J-wire guidewire was introduced into the vein. If passage of the J-wire guidewire was not achieved because of problems such as venous tortuosity, spasm, or repeated engagement into the entry of varicose vein tributaries, a 0.035-inch hydrophilic guidewire (Radiofocus angle type; Terumo, Tokyo, Japan) was used to advance into the saphenofemoral junction (SFJ).

A 5F delivery catheter in a 7F introducer was advanced into the SFJ and positioned 5 cm caudal to the SFJ. With compression of the GSV by an ultrasound probe at 2 cm proximal to the delivery catheter tip, double injections of cyanoacrylate were delivered 1 cm apart at this location, followed by a 3-cm pullback and 3-minute localized manual compression over the injected venous segment.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** In 60 of 63 limbs available for follow-up (mean follow-up, 8.4 ± 3.0 months) after cyanoacrylate closure of the incompetent great saphenous veins (GSVs), all GSVs demonstrated closure with resolution of varicose veins without an adjunctive procedure in 71.7% at 3 months. Resolution of varicose veins was associated with greater coverage of the varicosity entry point ($P = .002$) and more distal location of the access site ($P = .024$).
- **Take Home Message:** Cyanoacrylate closure of incompetent GSVs was effective in achieving GSV closure and resolution of varicose veins without associated varicosity-directed procedures. Covering the entry sites of varicosities and accessing the GSV more distally were associated with more complete resolution of varicose veins.

Then, a single injection and 30-second compression were repeated at every 3 cm until the whole length of the target GSV was closed. If puncture of the GSV was achieved below the entry of the varicose tributary, cyanoacrylate injection was performed twice (double injection) in some cases at the operator's decision when the delivery catheter reached the segment just above or at the entry of the varicose tributary. The closure was done throughout, even around the distal calf if the venous access was successful at that level. The sheath/catheter was removed, and manual compression was applied to the skin entry site until hemostasis was achieved. A small adhesive bandage was applied at the skin entry site. Occlusion of the GSV was verified by ultrasound examination immediately after the procedure.

Localized concomitant treatment, such as phlebectomy or sclerotherapy, was not performed. If varicosities remained after the 3-month follow-up, we further evaluated the need for additional localized treatment. The entire procedure was carried out under local anesthesia, and sedation was not applied to all patients. Neither compression stockings nor compression bandages were applied, and patients were instructed to ambulate frequently and to resume their normal activities immediately. All patients were prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) for 5 days, and they were instructed to take the medicine if they had pain in the treated limb.

Clinical assessment and follow-up. Procedure time, access site (above the knee, knee joint level, proximal calf, mid calf, and distal calf), use of hydrophilic guidewire, length of treated segment, number and total volume of cyanoacrylate injections, coverage of the entry

Table I. Demographic and baseline data of patients

Characteristics	Mean ± SD (range) or No. (%)
Age, years	49.5 ± 11.0 (26-68)
Female sex	30 (62.5)
Body mass index, kg/m^2	23.9 ± 3.0 (17.3-31.8)
Primary symptoms	
Fatigue	44 (69.8)
Pain	30 (47.6)
Edema	22 (34.9)
Heaviness	48 (76.2)
Muscle cramping	29 (46)
Burning	3 (4.8)
Tingling	10 (15.9)
Itching	4 (6.3)
CEAP clinical class	
C1	2 (3.2)
C2	37 (58.7)
C3	21 (33.3)
C4	3 (4.8)
VCSS	4.0 ± 1.2 (2-8)
GSV diameter, mm	6.9 ± 1.8 (4.0-13.0)
Epifascial GSV	15 (23.8)

CEAP, Clinical, Etiology, Anatomy, and Pathophysiology classification; *GSV,* great saphenous vein; *SD,* standard deviation; *VCSS,* Venous Clinical Severity Score.

of varicose tributaries, double injection of cyanoacrylate, and rate of pain during venous access and closure were assessed. Pain was assessed using a numeric rating scale of 0 to 10 (0, no pain; 10, worst imaginable pain), and it was checked just before the patient left the procedure room.

Patients revisited the hospital at 1 week, 1 month, 3 months, 6 months, and 12 months after the procedure for clinical assessment and duplex ultrasound evaluation. Complete closure of the GSV after CAC was defined as closure along the entire treated GSV segment without a patent segment >5 cm in length.[12] Preprocedural and postprocedural Venous Clinical Severity Score (VCSS), adverse events such as phlebitis (redness of the overlying skin and pain on palpation), pain without phlebitis, hyperpigmentation, ecchymosis, deep venous thrombosis, pulmonary thromboembolism, paresthesia, and infection were recorded by physicians at each visit.

The degree of regression of varicose veins after CAC was evaluated by taking serial pictures in a standing position at each visit. Loss of varicose veins on the treated limb was evaluated by two practitioners (S.W.P. and J.H.H.) who were involved in the procedure on a scale ranging from 1 to 4: grade 1, no change; grade 2, residual varicose veins >50%; grade 3, residual varicose veins <50%; grade 4, complete resolution. Both practitioners independently graded the degree of regression of varicose veins after treatment, and any discordance was resolved by consensus.

Statistical analysis. Categorical variables are expressed as percentages, and continuous variables are expressed as means and standard deviations. The paired *t*-test was used to compare baseline and outcome VCSSs. The level of interobserver agreement for the degree of regression of varicose veins after CAC was determined by calculating κ coefficient.

Coverage and double injection of cyanoacrylate at the entry of varicose tributaries and location of access site were analyzed to investigate the relationship with complete resolution of varicosities using a χ^2 test, Fisher exact test, and linear-by-linear association test, respectively. All statistical analyses were performed using SPSS software version 17.0 (SPSS Inc, Chicago, Ill).

RESULTS

Procedure characteristics. A total of 63 limbs (100%) were successfully treated in the 48 patients. Procedural characteristics are summarized in Table II. The mean length of the targeted GSV was 38 ± 13.4 cm, and the average duration of the procedure was 23.3 ± 7.3 minutes. The level of access was as follows: distal thigh (n = 8), knee joint level (n = 15), proximal calf (n = 14), mid calf (n = 18), and distal calf (n = 8).

Eighteen procedures (28.6%) required use of an additional separate hydrophilic guidewire (spasm, n = 8; tortuosity, n = 6; repeated engagement into the varicose vein tributaries, n = 4). The frequency of use of the hydrophilic guidewire according to the puncture site was 35.7% (5/14) at the proximal calf level, 44.4% (8/18) at the mid calf level, and 62.5% (5/8) at the distal calf level. Although not statistically significant, the frequency of use of the hydrophilic guidewire tended to increase as the puncture site was lowered.

From the total of 56 limbs having varicose veins, coverage of the entry of varicose vein tributaries connected to the treated GSV during CAC was obtained in 36 limbs. In the remaining 20 limbs, GSV access was achieved above the entry of varicose vein tributaries. Double injections at the segments of varicose vein tributary entry were performed in 9 of 36 limbs in which the entry of varicose vein was covered and treated.

Procedural outcomes and follow-up. All the treated GSVs showed complete closure on immediate postprocedure duplex ultrasound evaluation. Pain ratings during venous access and closure were 2.1 ± 1.6 and 1.3 ± 1.7, respectively.

Of the 63 limbs among 48 patients, three limbs in two patients did not have a follow-up. As a result, a total of 60 limbs (95.2%) among 46 patients and 24 limbs (38.1%) among 19 patients were available at the

Table II. Procedural characteristics

Characteristics	Mean ± SD (range) or No. (%)
Access site	
Distal thigh	8 (12.7)
Knee level	15 (23.8)
Proximal calf	14 (22.2)
Mid calf	18 (28.6)
Distal calf	8 (12.7)
Total length of treated GSV, cm	38 ± 13.4 (11-70)
No. of CA injections	12.5 ± 4.8 (3-24)
Total volume of delivered CA, mL	1.3 ± 0.4 (0.3-2.3)
Procedure time, minutes	23.3 ± 7.3 (11.1-38.8)
Use of hydrophilic guidewire	18 (28.6)
Coverage of VV entry	36 (64.3)
Double injection at VV entry	9 (25)
Pain during procedure	
Endovenous access	2.1 ± 1.6 (0-7)
GSV closure	1.3 ± 1.6 (0-5)

CA, Cyanoacrylate; *GSV*, great saphenous vein; *SD*, standard deviation; *VV*, varicose vein.

6-month and 12-month visits, respectively. During the mean follow-up period (8.4 ± 3.0 months), recanalization was not observed in any of the limbs.

VCSS and regression of varicose veins. VCSS improved from a mean of 4.0 ± 1.2 at baseline to 2.2 ± 0.8, 1.2 ± 0.6, 0.8 ± 0.6, 0.5 ± 0.5, and 0.4 ± 0.3 at 1 week, 1 month, 3 months, 6 months, and 12 months after CAC, respectively. VCSSs at the time of all follow-up visits were significantly lower ($P < .001$) than those before CAC.

Follow-up of varicose vein regression was performed in 53 of 56 limbs in which a varicose vein was present, and the results are shown in the Fig. There was substantial interobserver agreement ($\kappa = 0.794$; $P < .001$) for the degree of regression of varicose veins after CAC. Complete resolution of varicose veins was achieved in 24.5% (n = 13) of limbs at 1 week, 58.5% (n = 31) of limbs at 1 month, and 71.7% (n = 38) of limbs after 3 months. There was no change in the degree of varicose vein regression at follow-up after 3 months.

From the 35 limbs covering the entry of varicosities, complete resolution was achieved in 30 limbs (85.7%). However, only 8 of 18 limbs (44.4%) not covering the entry of varicosities showed complete resolution. A more complete resolution of varicose veins was observed as varicosity entry was covered ($P = .002$).

There was complete resolution in all nine limbs (100%) under double injection of cyanoacrylate at varicosity entry. However, complete resolution was obtained in 21 (80.8%) of 26 limbs under single injection of cyanoacrylate at varicosity entry. Double injection did not show a significant association with complete resolution of varicose veins ($P = .297$).

Complete resolution of varicose veins according to the access site was as follows: 2 of 5 limbs (40%) at the distal thigh; 7 of 12 limbs (58.3%) at the knee level; 8 of 11 limbs at the proximal calf (72.7%); 14 of 17 limbs at the mid calf (82.4%); and 7 of 8 limbs at the distal calf (87.5%). As the access site level was located more caudally, a more complete resolution of varicose veins was observed ($P = .024$).

At the 6-month follow-up, sclerotherapy was performed on the legs showing varicose vein regression of grade 2 and grade 3 in two patients. Another 13 patients who had remaining varicose veins did not require additional treatment until their final follow-up visit.

Adverse events. Adverse events after CAC are summarized in Table III. Ten limbs (16.7%) had phlebitis along the treated segment. Phlebitis occurred within a week after CAC and was resolved within a month in all but one

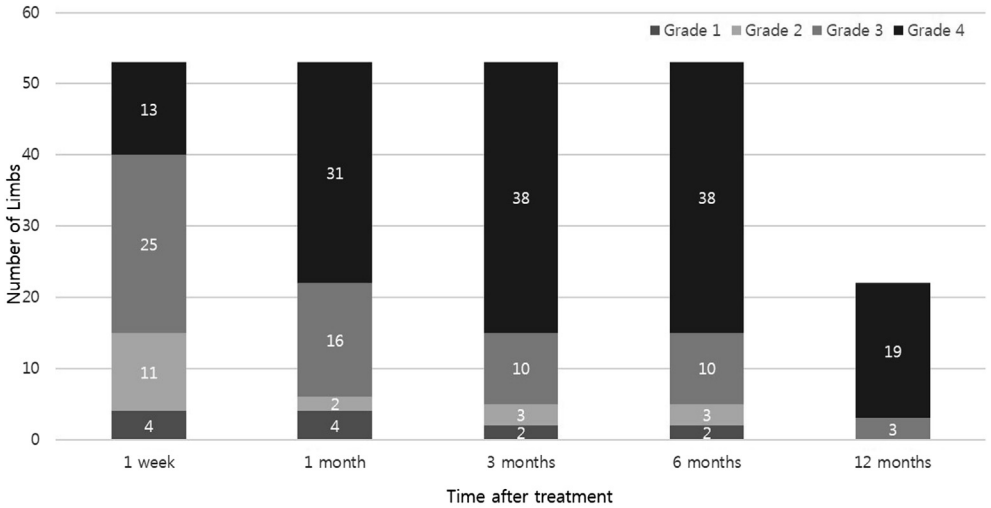

Fig. Regression of varicose veins during follow-up: grade 1, no change; grade 2, residual varicose veins >50%; grade 3, residual varicose veins <50%; grade 4, complete resolution.

Table III. Adverse events

	Limbs, No. (%)
Phlebitis	10 (16.7)
~1 week	9 (15)
1 week-1 month	1 (1.7)
After 1 month	0 (0)
Pain without phlebitis	6 (10)
Hyperpigmentation	8 (13.3)
Above the knee	6 (10)
Below the knee	2 (3.3)
Ecchymosis	0 (0)
Access site infection	1 (1.7)
Paresthesia	0 (0)
Deep venous thrombosis	0 (0)
Pulmonary thromboembolism	0 (0)

limb. In one limb, phlebitis developed 2 weeks after CAC but was resolved at the 1-month follow-up. All patients with phlebitis received NSAIDs within 5 days. Pain without phlebitis was noticed in six limbs (10%) at the 1-week follow-up and disappeared by the 1-month follow-up in all limbs.

Hyperpigmentation occurred in eight limbs (13.3%). Of the 15 limbs with an epifascial GSV at the distal thigh, 12 limbs underwent CAC including an epifascial segment, of which 6 limbs had hyperpigmentation. The other two cases of hyperpigmentation occurred in the proximal calf GSV, which were among four cases of proximal calf GSV closure with bulging of GSV that were easily detected on visual inspection at preprocedural assessment. Follow-up was achieved in eight limbs within 6 months and in three limbs within 12 months, and hyperpigmentation remained in all eight limbs.

There was a localized infection in one limb (1.7%) at the access site at the 1-month follow-up, and the patient received oral antibiotics. Infection was improved within 2 weeks. Paresthesia, ecchymosis, deep venous thrombosis, and pulmonary thromboembolism were not observed.

DISCUSSION

In the early swine model, a chronic foreign body type of inflammatory reaction followed by venous closure, segmental venous wall thickening, and fibrosis was observed 60 days after cyanoacrylate delivery.[13] Several clinical studies based on this experimental pilot study reported the complete closure rate of the GSV after CAC as 92% to 100%.[1,3-5,10,11,14] In particular, a first-in-human study demonstrated the high efficacy and safety of CAC for the treatment of GSV incompetence during 36 months, and the occlusion rate reached 94.7%.[6] In this study, the complete closure rate was 100% during the mean follow-up period of 8.4 months. The VenaSeal Sapheon Closure System Pivotal Study (VeClose)[8] suggested that incomplete occlusion and recanalization appeared to be caused by continued flow of blood from GSV tributaries into the treated GSV. In our study, we tried to close the targeted GSV as low as possible, covering the GSV tributary entry, which is presumed to be related to a desirable closure rate. Further study will be needed to evaluate the factors affecting recanalization after CAC.

The main reason for treating varicose veins is symptomatic and cosmetic improvement. Therefore, many physicians prefer concomitant phlebectomy or sclerotherapy, or both, in conjunction with endovenous thermal ablation.[15] However, a concomitant procedure increases the procedure time, the postprocedure recovery time, and the frequency of adverse events.[5] Accordingly, questions have been raised about whether concomitant treatment is indispensable. In a study by Monahan,[2] 28.4% of varicose veins spontaneously resolved and 62.8% of varicose veins had decreased in size at the 6-month follow-up after RFA for GSV insufficiency without concomitant treatment. The evaluation of varicose vein regression after CAC for treatment of saphenous vein incompetence was well described in the first-in-human studies. The proportion of limbs free of varicose veins after CAC was 47%, 50%, 35%, and 41% at 6 months, 12 months, 24 months, and 36 months, respectively.[1,6,9] Furthermore, 36% and 25% of legs showed limited varicosities at 6 months and 12 months, respectively. Therefore, there was spontaneous complete or partial regression of varicose veins without concomitant treatment in 83% at 6 months and 75% at 12 months.[9] In the European multicenter study,[4] the proportion of patients whose target limbs were free from visible varicosities ranged from 1.4% at baseline to 41.4% at the 3-month follow-up. In this study, complete resolution of varicose veins was noted for 71.7% of limbs at the 3-month follow-up after CAC. In particular, the proportion of limbs showing >50% of varicose vein regression reached 90.6%. These are better outcomes for varicose vein regression than in the previous RFA study[2] or CAC studies[1,4,6,9] under the same condition of absence of a concomitant procedure. Our study differs from the previous RFA study[2] in that venous access was performed as far down the leg as possible because there was less concern for nerve injury. Compared with the first-in-human CAC studies[1,6,9] with a good result for varicose vein regression, the GSV access site was even lower in our study, as follows: above the knee, 38% vs 12.7%; knee level, 12% vs 23.8%; and below the knee, 50% vs 63.5%. We found that as varicosity entry was covered and as the access site level was located more caudally, a more complete resolution of varicose veins was observed. Approaching at a lower GSV as an access site implies that there may be more varicosity entries communicating with truncal GSV, and cyanoacrylate

would also flow into the varicosity as well as into the GSV during injection. In this process, cyanoacrylate flowing into the varicosity seems to have an additional therapeutic effect like that of the concomitant procedures.

Postprocedural compression stockings are inevitable for patients who undergo endovenous thermal ablation, sclerotherapy, or phlebectomy. However, patients' compliance with compression stockings is low because of cost, sweating, itching, cosmetic reason, and wearing discomfort.[16] In a few CAC studies,[10,17,18] phlebectomy or sclerotherapy was performed in the same session. Consequently, postprocedure compression stockings were inevitable for patients in those studies, and the advantage of CAC to avoid wearing compression stockings was obscured. According to the Lake Washington Vascular VenaSeal Post-Market Evaluation (WAVES) study,[5] closure rates after CAC were high even without the use of compression stockings. Some other studies also have shown good closure rates without use of postprocedural compression stockings.[4,9,11,19] Furthermore, in our study, a closure rate of GSV in 100% of limbs and complete resolution of varicose veins in 71.7% of limbs were obtained at the follow-up without use of compression stockings. Not having to wear compression stockings after CAC treatment is a great advantage, and considering the results of our study and previous studies, satisfactory treatment outcomes for occlusion rate or varicose vein regression can be obtained without use of postprocedural compression stockings.

A 0.035-inch J-wire guidewire included in the VenaSeal Closure System is not directional because of its shape, and it may not be able to overcome difficult situations, such as venous tortuosity, spasm, or repeated engagement into the entry of the varicose vein. Even the first-in-human study has excluded a tortuous GSV from the study participants.[9] In our study, a hydrophilic guidewire with an angled tip was used in 18 cases (28.6%), and all accesses were achieved below the proximal calf. We tried to solve these situations by changing the direction of the tip of the hydrophilic guidewire while watching real-time ultrasound. The lower the location of the puncture site, the more frequently a hydrophilic guidewire was used. Because it is undesirable to repuncture at the upper part of the site experiencing the difficulty of the J-wire, the use of a hydrophilic guidewire could improve the success rate of the procedure, especially when accessing from below the proximal calf.

Phlebitis is the most common complication associated with CAC, and the frequency reported in previous studies ranged from 11.4% to 20%.[1,4,5,8,10] The incidence of phlebitis in our study (16.7%) was similar to that of the previous studies, and all patients showed improvement with only NSAIDs. Cyanoacrylate itself is known to cause a nonspecific, mild inflammatory reaction that promotes venous closure, resulting in phlebitis.[3] In most CAC studies, phlebitis was mild, self-limited, and simply treated with NSAIDs alone for a short time.[1,3,10] In two previous reports, the frequency of hyperpigmentation after CAC has been reported to be 2.6% and 11.8%.[9,10] In one of these studies,[9] hyperpigmentation occurred in one patient along the treated saphenous vein coursing close to the skin. In another study,[10] all four patients had hyperpigmentation in the epifascial saphenous segment. In our study, hyperpigmentation occurred in eight limbs (13.3%), and the incidence was slightly higher than in previous reports, probably because CAC was performed without exclusion of the epifascial GSV segment or calf GSV close to the skin. It would be better to keep in mind that if the epifascial segment is long in the distal thigh GSV on preprocedural ultrasound evaluation or if the calf GSV is bulging and readily detected on visual inspection, hyperpigmentation may occur after CAC.

This study has several limitations. First, the number of patients included in the study is small, and this is a retrospective review from a single institute. Second, the long-term outcome of the closure rate of the GSV and regression of varicose veins could not be assessed. Almeida et al[6] reported that freedom from varicose veins was 47% at 6 months but decreased to 41% at 36 months, presumably owing to the progression of underlying disease. The long-term outcome of varicose vein regression is yet to be investigated as an extension of this study or in another large-scale study. Third, regression of varicose veins was assessed by using a gross comparison of serial photographs of each patient, which has a subjective aspect. Because of the limitation, each degree interval was set wide and evaluated by two practitioners.

CONCLUSIONS

CAC is safe and effective for the treatment of an incompetent GSV. CAC also shows satisfactory results for the regression of varicose veins. Covering the entry of varicosities and accessing lower down the leg are associated with a more complete resolution of varicose veins.

AUTHOR CONTRIBUTIONS

Conception and design: SP
Analysis and interpretation: JHH, SP, KK, WY, JJH, SL, JK, JP, HC, IY
Data collection: JHH, SP, KK, WY
Writing the article: JHH, SP
Critical revision of the article: JHH, SP, KK, WY, JJH, SL, JK, JP, HC, IY
Final approval of the article: JHH, SP, KK, WY, JJH, SL, JK, JP, HC, IY
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: SP

REFERENCES

1. Almeida JI, Javier JJ, Mackay EG, Bautista C, Cher DJ, Proebstle TM. Two-year follow-up of first human use of cyanoacrylate adhesive for treatment

of saphenous vein incompetence. Phlebology 2015;30:397-404.
2. Monahan DL. Can phlebectomy be deferred in the treatment of varicose veins? J Vasc Surg 2005;42:1145-9.
3. Morrison N, Gibson K, Vasquez M, Weiss R, Cher D, Madsen M, et al. VeClose trial 12-month outcomes of cyanoacrylate closure versus radiofrequency ablation for incompetent great saphenous veins. J Vasc Surg Venous Lymphat Disord 2017;5:321-30.
4. Proebstle TM, Alm J, Dimitri S, Rasmussen L, Whiteley M, Lawson J, et al. The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins. J Vasc Surg Venous Lymphat Disord 2015;3:2-7.
5. Gibson K, Ferris B. Cyanoacrylate closure of incompetent great, small and accessory saphenous veins without the use of post-procedure compression: initial outcomes of a post-market evaluation of the VenaSeal System (the WAVES Study). Vascular 2017;25:149-56.
6. Almeida JI, Javier JJ, Mackay EG, Bautista C, Cher DJ, Proebstle TM. Thirty-sixth-month follow-up of first-in-human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. J Vasc Surg Venous Lymphat Disord 2017;5:658-66.
7. Vos CG, Unlu C, Bosma J, van Vlijmen CJ, de Nie AJ, Schreve MA. A systematic review and meta-analysis of two novel techniques of nonthermal endovenous ablation of the great saphenous vein. J Vasc Surg Venous Lymphat Disord 2017;5:880-96.
8. Morrison N, Gibson K, McEnroe S, Goldman M, King T, Weiss R, et al. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). J Vasc Surg 2015;61:985-94.
9. Almeida JI, Javier JJ, Mackay E, Bautista C, Proebstle TM. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. J Vasc Surg Venous Lymphat Disord 2013;1:174-80.
10. Park I. Initial outcomes of cyanoacrylate closure, VenaSeal system, for the treatment of the incompetent great and small saphenous veins. Vasc Endovascular Surg 2017;51:545-9.
11. Bozkurt AK, Yilmaz MF. A prospective comparison of a new cyanoacrylate glue and laser ablation for the treatment of venous insufficiency. Phlebology 2016;31(Suppl):106-13.
12. Khilnani NM, Grassi CJ, Kundu S, D'Agostino HR, Khan AA, McGraw JK, et al. Multi-society consensus quality improvement guidelines for the treatment of lower-extremity superficial venous insufficiency with endovenous thermal ablation from the Society of Interventional Radiology, Cardiovascular Interventional Radiological Society of Europe, American College of Phlebology and Canadian Interventional Radiology Association. J Vasc Interv Radiol 2010;21:14-31.
13. Almeida JI, Min RJ, Raabe R, McLean DJ, Madsen M. Cyanoacrylate adhesive for the closure of truncal veins: 60-day swine model results. Vasc Endovascular Surg 2011;45:631-5.
14. Yasim A, Eroglu E, Bozoglan O, Mese B, Acipayam M, Kara H. A new non-tumescent endovenous ablation method for varicose vein treatment: early results of N-butyl cyanoacrylate (VariClose). Phlebology 2017;32:194-9.
15. Mekako A, Hatfield J, Bryce J, Heng M, Lee D, McCollum P, et al. Combined endovenous laser therapy and ambulatory phlebectomy: refinement of a new technique. Eur J Vasc Endovasc Surg 2006;32:725-9.
16. Ziaja D, Kocelak P, Chudek J, Ziaja K. Compliance with compression stockings in patients with chronic venous disorders. Phlebology 2011;26:353-60.
17. Chan YC, Law Y, Cheung GC, Cheng SW. Predictors of recanalization for incompetent great saphenous veins treated with cyanoacrylate glue. J Vasc Interv Radiol 2017;28:665-71.
18. Chan YC, Law Y, Cheung GC, Ting AC, Cheng SW. Cyanoacrylate glue used to treat great saphenous reflux: measures of outcome. Phlebology 2017;32:99-106.
19. Koramaz I, El Kilic H, Gokalp F, Bitargil M, Bektaş N, Engin E, et al. Ablation of the great saphenous vein with non-tumescent n-butyl cyanoacrylate versus endovenous laser therapy. J Vasc Surg Venous Lymphat Disord 2017;5:210-5.

Submitted Jul 2, 2018; accepted Oct 22, 2018.