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Cyanoacrylate Granuloma After Cyanoacrylate Closure of Incompetent Saphenous Veins

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BACKGROUND Cyanoacrylate closure (CAC) is a minimally invasive surgery to treat incompetent saphenous veins.

OBJECTIVE To evaluate the incidence, the risk factors for, and the management of cyanoacrylate granuloma (CAG) after CAC of incompetent saphenous veins in patients with chronic venous disease.

MATERIALS AND METHODS Data specific to incompetent saphenous veins, including great saphenous veins, anterior accessory saphenous veins, and small saphenous veins, that were treated with CAC were retrospectively evaluated.

RESULTS A total of 126 saphenous veins from 101 patients were included. Recapture of the delivery catheter before withdrawal was not performed in all patients. Cyanoacrylate granuloma occurred in 3 of 101 (2.9%) patients, and in 3 of 126 (2.3%) treated saphenous veins. All patients with CAG presented with granuloma and abscess at the puncture site 3 to 5 months after CAC. All patients were treated with incision, drainage, and removal of the glue foreign body. No recurrent granuloma was observed during the study period. No patient or procedural predictive factor for CAG was identified.

CONCLUSION Cyanoacrylate granuloma is not a rare complication after CAC when recapture of the delivery catheter is not performed. Patients should be advised of the possibility of CAG after CAC.

Cyanoacrylate closure (CAC), which is a nonthermal, nontumescent endovenous treatment, was introduced as a minimally invasive surgery to treat superficial venous reflux.[1,2] Cyanoacrylate closure produces vein closure by introducing a cyanoacrylate adhesive agent that polymerizes in tissue fluids and creates a chemical bond between the coapted vein walls.[2,3] Several previous studies demonstrated the effectiveness of CAC for treatment of saphenous vein reflux, but cyanoacrylate granuloma (CAG), which is one of the complications of CAC, has not been clearly described.[4–8] Cyanoacrylate granuloma was defined as cyanoacrylate extravasation with chronic foreign body reaction after CAC.[9] The risk factors for, the nature of the disease, and the management of CAG are not yet well understood or established. Accordingly, the aim of this article was to evaluate the incidence of CAG, the onset and course of disease, and the risk factors for, the duration of symptoms, and the management of CAG after CAC of saphenous veins in patients with chronic venous disease.

Material and Methods

This retrospective observational study included patients older than 18 years who were diagnosed with chronic venous disease with superficial venous reflux in the great saphenous vein (GSV), anterior accessory saphenous vein (AASV), or small saphenous vein (SSV) and who were treated with CAC at the Division of Vascular Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, during the January 2017 to December 2018 study period. This study was approved by the authors' university's institutional review board (COA no. Si978/2020) with a waiver of need to obtain informed consent.

All patients had undergone duplex ultrasound scanning before saphenous vein ablation. Evaluation of the lower-limb veins was performed using a GE LOGIC 9 system (GE Healthcare, Chicago, IL) using 5- to 10-MHz linear transducers in standing position with standard protocol. Saphenous vein reflux was defined as retrograde flow of >0.5 seconds with distal compression and release. Vein diameters were measured in standing position. Great saphenous vein and AASV were measured 3 cm from the saphenofemoral junction, and the SSV diameter was measured 3 cm from the saphenopopliteal junction.[10]

Ablation of saphenous veins with CAC was performed using a VenaSeal Closure System (Medtronic Vascular, Inc., Santa Rosa, CA). Patients were treated per the manufacturer's instructions for use (IFU) for treatment of saphenous veins, as previously described.[2,11,12] Recapture of the

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delivery catheter before withdrawal was not performed in all patients.

Occlusion of the saphenous vein was verified by ultrasound examination immediately after the procedure. Neither compression stockings nor compression bandages were applied in patients with Clinical–Etiological–Anatomical–Pathophysiological (CEAP) classification C2 (varicose vein). In patients with CEAP C3-C6 (C3, edema; C4a, pigmentation or eczema; C4b, lipodermatosclerosis or atrophie blanche; C5, healed venous ulcer; and C6, active venous ulcer), patients were asked to continue using compression stockings or compression bandages the same as they had been using them before surgery. Patients were instructed to ambulate frequently and to resume their normal activities at their own discretion.

Patients were followed up at the hospital at 1 week, 1 month, 3 months, and 12 months after the procedure for clinical assessment. Duplex ultrasound evaluation was performed at 1 week, 1 month, and 12 months after CAC.

Demographic data and clinical information, including age, sex, body mass index (BMI), and CEAP classification, were recorded. Procedure time, length of the treated vein, total volume of cyanoacrylate injections, and the presence of the suprafascial saphenous vein with a subcutaneous distance between the anterior vein wall and the skin of <1 cm were recorded.

Complete closure of the saphenous vein after CAC was defined as closure along the entire treated saphenous vein without a patent segment >5 cm in length. Preprocedural and postprocedural Venous Clinical Severity Score (VCSS) and complications were recorded by physicians at each visit.

If CAG occurred, the onset, duration of symptoms, and management were collected.

Statistical Analysis

PASW Statistics version 18.0 (SPSS, Inc., Chicago, IL) was used to perform all statistical analyses. Qualitative demographic data are presented as frequency and percentage, and quantitative data are presented as mean ± SD. Non-normally distributed data are shown as median and range. In univariate analysis, qualitative data were analyzed using either the chi-square test or Fisher exact test. For univariate analysis of quantitative data, the unpaired *t*-test was used for normally distributed data, and the Mann-Whitney *U* test was used for non-normally distributed data. Multivariate analysis for risk factors for CAG was performed using a multiple logistic regression model. A p value of less than 0.05 was regarded as being statistically significant.

Results

Study Subject Characteristics and Clinical Outcome Measures

A total of 126 legs from 101 patients who underwent CAC were included in this study. The mean age and BMI of patients was 64.1 ± 12.2 years and 27.7 ± 6.3 kg/m^2, respectively. There were 71 (70.3%) female and 30 (29.7%) male patients. Bilateral CAC was performed in 25 (24.8%) patients. The 126 treated saphenous veins included 106 (84.1%) GSV, 7 (5.6%) AASV, and 13 (10.3%) SSV. The CEAP classification (C2, C3, C4, C5, and C6) of 126 limbs was 56 (44.4%), 19 (15.1%), 29 (23.0%), 2 (1.6%), and 20 (15.9%), respectively. The mean diameter of treated saphenous veins was 7.8 ± 2.3 mm, and the mean length of treated veins was 28.1 ± 12.7 cm. The mean volume of adhesive glue used for CAC was 0.96 ± 0.58 mL. There were 18 (14.3%) suprafascial saphenous veins with a subcutaneous distance between the anterior vein wall and skin of <1 cm. The mean operative time was 36.6 ± 4.2 minutes. The occlusion rate was 100%, 99.2%, and 97.8% at the 1-week, 1-month, and 1-year follow-up, respectively. Seven (6.9%) patients who had persistent venous symptoms from tributary varicosity were treated with foam sclerotherapy at 3 months after CAC. The median (min, max) VCSS score was 4 (2, 15), 2 (0, 21), 2 (0, 14), and 1 (0, 13) at baseline, 1 week, 1 month, and 1 year after surgery, respectively. Improvement in the VCSS score was statistically significant between baseline and the 1-week, between baseline and the 1-month, and between baseline and the 1-year visits ($p < .001$).

Cyanoacrylate Granuloma

Cyanoacrylate granuloma occurred in 3 of 101 (2.9%) patients, in 3 of 126 (2.3%) limbs, and in 3 of 126 (2.3%) treated saphenous veins. Patients with CAG presented with granuloma and abscess at the puncture site at 3, 4, and 5 months after CAC. All CAG occurred after CAC of GSV. There was no significant difference in age, BMI, sex, leg side, vein diameter, total volume of cyanoacrylate injections, length of the treated vein, procedure time, and the presence of the suprafascial saphenous vein with a subcutaneous distance between the anterior vein wall and the skin of <1 cm between limbs with and without CAG (Table 1).

All patients were treated with incision, drainage, and removal of the glue foreign body. All patients received amoxicillin and clavulanic acid 1 gram twice daily for 7 days. Pus cultures showed no growth for bacterial infection. No recurrent granuloma was observed during the study period. Clinical presentation of CAG is shown in Figure 1A. Ultrasound of CAG is shown in Figure 1B. Cyanoacrylate granuloma that was excised and removed is shown in Figure 1C.

Discussion

Cyanoacrylate closure is a nonthermal nontumescent method that is growing in popularity. This study showed CAC to be an effective treatment for incompetent saphenous veins. The occlusion rate was 97.8% at the 1-year follow-up in this study. The clinical parameter, the VCSS score, was significantly improved. Cyanoacrylate closure also seems to be a safe method of treatment. Although hypersensitivity reaction or phlebitis-like abnormal reaction is the most commonly reported complication,[13,14] more rarely observed complications, such as CAG, have not been clearly evaluated.

TABLE 1. Patient, Limb, and Operative Characteristics Compared Between Those With and Without Cyanoacrylate Granuloma (CAG)

Characteristics	CAG	No CAG	*p* value
Patients, *n*	3	98	
Age, yrs, mean ± SD	74.3 ± 3.1	63.9 ± 12.3	.760
Body mass index, kg/m^2, mean ± SD	32.2 ± 10.7	27.6 ± 6.2	.462
Male sex, *n* (%)	0 (0.0)	30 (30.6)	.553
Legs, *n*	3	123	
Leg side, *n* (%) Right leg Left leg	 1 (33.3) 2 (66.7)	 66 (53.7) 57 (46.3)	.599
CEAP classification, *n* (%) C2 C3-6	 1 (33.3) 2 (66.7)	 55 (44.7) 68 (55.3)	1.000
Diameter of the truncal vein, mm, mean ± SD	9.3 ± 2.11	7.8 ± 2.36	.291
Suprafascial saphenous vein with depth <1 cm from skin, *n* (%)	0 (0.0)	18 (14.6)	1.000
Adhesive volume, mL, mean ± SD	0.92 ± 0.15	0.96 ± 0.58	.683
Length of the treated vein, cm, mean ± SD	26.7 ± 4.0	25.9 ± 12.8	.531
Operative time, min, mean ± SD	36.8 ± 4.76	36.61 ± 4.7	.573

The first documented case of CAG in the literature was reported by Langridge and colleagues.[9] The authors' study found an incidence of CAG of 2.5%. All CAG occurred at the access site. Although the authors could not identify any risk factors for CAG in the authors' study because of the small sample size, the authors hypothesize that the potential mechanism is residual polymerized cyanoacrylate inadvertently deposited in the subcutaneous tissue during withdrawal of the delivery catheter from the vein or deposition of cyanoacrylate at the access site.

According to the original manufacturer's IFU, the delivery catheter was removed from the skin after last injection. There is a chance that subcutaneous tissue and dermis were contaminated with polymerized cyanoacrylate from the white delivery catheter during withdrawal from the vein.

To reduce the risk of contaminating the subcutaneous tissue and dermis with polymerized cyanoacrylate, Gibson and colleagues[14] suggested recapturing the white delivery catheter into the blue 7 French sheath before removal from the skin. Recapture of the white delivery catheter should be performed by advancing the blue sheath forward over the white delivery catheter while the white delivery catheter is still inside the vein.[14,15]

The recapture technique described in the new manufacturer's IFU that was published in 2020 is different from the technique described by Gibson and colleagues.[14] After applying 30 seconds of compression after the final injection within the target vein, the delivery catheter is recaptured by retracting it through the introducer until the delivery catheter's proximal laser mark is visible 1 cm to 5 cm outside of the introducer hub,

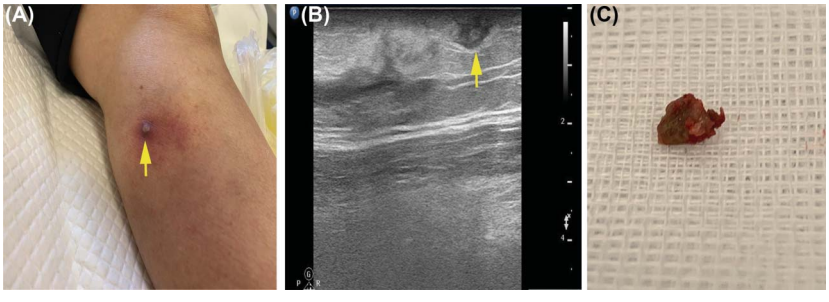

Figure 1. (A) Cyanoacrylate granuloma with redness and abscess at puncture site (yellow arrow). (B) Ultrasound image showing subcutaneous fluid collection and granuloma (yellow arrow). (C) Glue cast excised and removed.

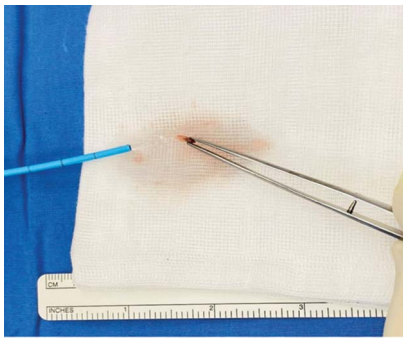

Figure 2. Retained cyanoacrylate glue was detected in the blue sheath after the white delivery catheter was recaptured.

after which the introducer and catheter are removed together.[16]

In this study, recapture of the delivery catheter before withdrawal was not performed in all cases because CAC was performed during 2017 to 2018, which is before the new IFU was published in 2020. After release of the new IFU in 2020, the authors recaptured the delivery catheter before withdrawal. Retained cyanoacrylate glue was detected in the blue sheath after the white delivery catheter was recaptured (Figure 2). However, the benefit of recapture of the white delivery catheter before withdrawal should be evaluated in further study. Moreover, chronic immunological reaction to cyanoacrylate with subsequent damage to the vessel wall has been reported. Foreign body granuloma formation inside the treated vein may progress to necrosis, ulceration, and foreign body extrusion from the treated vein.[17] As such, patients should be advised of the possibility of CAG after CAC, and fully informed patient consent should be obtained before treatment.

This study has some mentionable limitations. First and consistent with the retrospective nature of this study, some patient data may have been missing or incomplete. Second, the size of the study population was relatively small. As a result, the authors' study may have lacked sufficient power to identify all significant differences and associations. Third, the data for this study were collected from a single center.

Conclusions

Cyanoacrylate closure is safe and effective treatment for saphenous reflux. Cyanoacrylate granuloma was not found to be a rare complication after CAC when recapture of the delivery catheter was not performed. Patients should be informed of the risk of CAG before treatment.

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