

# Hypersensitivity reaction after cyanoacrylate closure of incompetent saphenous veins in patients with chronic venous disease: A retrospective study

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## ABSTRACT

**Purpose:** The objective of this study was to evaluate the incidence of, the risk factors for, the nature of the disease, and the management of hypersensitivity reaction (HSR) after cyanoacrylate closure (CAC) of incompetent saphenous veins in patients with chronic venous disease.

**Methods:** Data consisting of all incompetent saphenous veins, including great saphenous veins, anterior accessory saphenous veins, and small saphenous veins, treated with CAC at Siriraj Hospital (Bangkok, Thailand) from January 2017 to December 2018 were retrospectively evaluated.

**Results:** A total of 126 saphenous veins, including 106 great saphenous veins (84.1%), 7 anterior accessory saphenous veins (5.6%), and 13 small saphenous veins (10.3%) of 126 limbs from 101 patients were included. A HSR occurred in 16 of 101 patients (15.8%), in 19 of 126 limbs (15.0%), and in 19 of 126 treated saphenous veins (15.0%). HSR-related erythema, itching, swelling, and pain occurred in 100.0%, 95.0%, 68.4%, and 52.6%, of HSR patients, respectively. HSR occurred 1 week after CAC. All HSR symptoms were mild, could be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and antihistamine, and were resolved within 1 week. The risk factors for HSR were suprafascial saphenous vein with a depth <1 cm from the skin, and saphenous vein diameter of  $\geq 8$  mm.

**Conclusions:** A HSR occurred in 15.8% of patients and in 15.0% of limbs after CAC. Risk factors for HSR were a suprafascial saphenous vein located close to the skin and a large saphenous vein. All HSR symptoms were mild in severity, occurred at 1 week after CAC, and were resolved within 1 week after treatment with nonsteroidal anti-inflammatory drugs and antihistamines. To prevent HSR, CAC should be avoided in suprafascial saphenous veins that are located close to the skin, and CAC in saphenous veins with a size of  $\geq 8$  mm should be performed with caution. (*J Vasc Surg Venous Lymphat Disord* 2021;9:910-5.)

**Keywords:** Cyanoacrylates; Chronic venous disease; Varicose vein; Hypersensitivity reaction; Phlebitis-like abnormal reaction

Nonthermal, nontumescent endovenous treatments were introduced as a minimally invasive surgery to eliminate the need for tumescent injection in endovenous thermal ablation to treat superficial venous reflux.<sup>1</sup> Cyanoacrylate closure (CAC) is a nonthermal,

nontumescent ablation technique in which cyanoacrylate functions as a medical adhesive to close the vein.<sup>2</sup> Several previous studies demonstrated the effectiveness of CAC for treatment of incompetent saphenous veins, but the complications of CAC have not been clearly described.<sup>3-7</sup> A hypersensitivity reaction (HSR) or phlebitis-like abnormal reaction is a common complication after CAC.<sup>8-10</sup> HSR is defined as a red, itchy dermal reaction that is sometimes painless, but that can also be associated with pain and/or localized swelling.<sup>9,10</sup> The risk factors for this reaction, the nature of the disease, and the management of HSR are not yet well-established. Accordingly, the aim of this article was to evaluate the incidence of HSR, the onset and course of the disease, the risk factors for the reaction, the duration of symptoms, and the management of HSR after CAC of saphenous veins in patients with chronic venous disease.

## METHODS

This retrospective study included patients aged >18 years who were diagnosed with chronic venous

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disease with superficial venous incompetence in the great saphenous vein (GSV), small saphenous vein (SSV), or anterior accessory saphenous vein (AASV), 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 our university's institutional review board (COA no. Si710/2019) with a waiver of need to obtain informed consent.

All patients had undergone duplex ultrasound examination before saphenous vein ablation. Evaluation of the lower limb veins was performed using a GE LOGIC 9 system (GE Healthcare, Chicago, Ill) 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. GSV and AASV were measured 3 cm below the saphenofemoral junction, and the SSV diameter was measured 3 cm from the saphenopopliteal junction.<sup>11</sup>

Ablation of saphenous veins with CAC was performed using a VenaSeal Closure System (Medtronic Vascular, Inc., Santa Rosa, Calif). Patients were treated per manufacturer's instructions for use for treatment of saphenous veins, as described previously.<sup>2,12,13</sup> 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 CEAP (Clinical-Etiological-Anatomical-Pathophysiological 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 did 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 treated vein, total volume of cyanoacrylate injections, and the presence of 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 an HSR occurred, the onset, duration of symptoms, and severity of HSR were collected and

## ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective observational study
- **Key Findings:** Hypersensitivity reaction after cyanoacrylate closure occurred in 16 of 101 patients (15.8%), and in 19 of 126 limbs (15.0%). Risk factors for a hypersensitivity reaction were suprafascial saphenous vein with a subcutaneous distance between the anterior vein wall and skin of <1 cm, and a saphenous vein size of  $\geq 8$  mm.
- **Take Home Message:** Risk factors for hypersensitivity reaction after cyanoacrylate closure were suprafascial saphenous vein located close to the skin and large saphenous vein size.

recorded. HSR severity was defined as mild if the patient required no treatment or nonsteroidal anti-inflammatory drugs (NSAIDs) and/or antihistamine, moderate if the patient required oral steroids, and severe if the reaction was prolonged >30 days or required vein excision.<sup>10</sup> Treatment of HSR was per physician discretion.

**Statistical analysis.** PASW Statistics version 18.0 (SPSS, Inc., Chicago, Ill) was used to perform all statistical analyses. Qualitative demographic data are presented as frequency and percentage, and normally distributed quantitative data are presented as mean  $\pm$  standard deviation. Non-normally distributed quantitative data are shown as median and range. In univariate analysis, qualitative data were analyzed using either  $\chi^2$  test or Fisher's exact test. For univariate analysis of quantitative data, unpaired *t*-test was used for normally distributed data, and the Mann-Whitney *U* test was used for non-normally distributed data. A multivariate analysis for risk factors for HSR was performed using a multiple logistic regression model. A receiver operating characteristic curve analysis was employed to assess the cutoff value of saphenous vein diameter. A *P* value of <.05 was regarded as being statistically significant.

## RESULTS

**Study subject characteristics.** A total 126 legs from 101 patients that underwent CAC were included in this study. The mean age and BMI of patients was  $64.1 \pm 12.2$  years and  $27.7 \pm 6.3$  kg/m<sup>2</sup>, respectively. There were 71 female (70.3%) and 30 male (29.7%) patients. Bilateral CAC was performed in 25 patients (24.8%). The 126 treated saphenous veins included 106 GSV (84.1%), 7 AASV (5.6%), and 13 SSV (10.3%). 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  $7.8 \pm 2.3$  mm, and the mean length of treated veins was  $28.1 \pm 12.7$  cm. The mean volume of adhesive glue

**Table I.** Patient demographic and clinical characteristics

Characteristics	Values
Patients	(N = 101)
Age, years	64.1 ± 12.2
Sex	
Male	30 (29.7%)
Female	71 (70.3%)
BMI, kg/m <sup>2</sup>	27.7 ± 6.3
Treated side	(n = 126)
Right side	59 (46.8%)
Left side	67 (53.2%)
CEAP clinical classification	
C2	56 (44.4%)
C3	19 (15.1%)
C4	29 (23.0%)
C5	2 (1.6%)
C6	20 (15.9%)
Treated saphenous veins	(n = 126)
GSV	106 (84.1%)
AASV	7 (5.6%)
SSV	13 (10.3%)
Saphenous vein diameter, mm	7.8 ± 2.3
Suprafascial saphenous vein with depth <1 cm from skin	18 (14.3%)
VCSS score	5.7 ± 3.8 (2-15)
<small>AASV, Anterior accessory saphenous vein; BMI, body mass index; C2, varicose veins; C3, edema; C4a, pigmentation or eczema; C4b, lipodermatosclerosis or atrophie blanche; C5, healed venous ulcer; C6, active venous ulcer; CEAP classification, Clinical-Etiological-Anatomical-Pathophysiological classification; GSV, great saphenous vein; SD, standard deviation; SSV, small saphenous vein; VCSS, Venous Clinical Severity Score.</small>	

used for CAC was  $0.96 \pm 0.58$  mL. There were 18 suprafascial saphenous veins (14.3%) with a subcutaneous distance between the anterior vein wall and skin of <1 cm. The mean operative time was  $36.6 \pm 4.2$  minutes (Table I).

**Vein closure.** At the 1-week follow-up, the ablated veins were completely occluded in 126 of the 126 veins (100%). At the 1-month follow-up, the ablated veins were occluded in 119 of the 120 veins (99.2%). At the 1-year follow-up, the ablated veins were completely occluded in 90 of the 92 veins (97.8%). At 3 months after CAC, 7 patients (6.9%) who had persistent venous symptoms from tributary varicosity were treated with foam sclerotherapy.

**Clinical outcome measures.** 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 (all  $P < .001$ ).

**Fig.** Hypersensitivity reaction (HSR) after cyanoacrylate closure (CAC) of the great saphenous veins (GSV).

**HSR.** HSR occurred in 16 of 101 patients (15.8%), in 19 of 126 limbs (15.0%), and in 19 of 126 treated saphenous veins (15.0%). All HSR occurred at 1 week after CAC. HSR-related erythema, itching, swelling, and pain occurred in 100.0%, 95.0%, 68.4%, and 52.6% of HSR patients, respectively. The mean saphenous vein diameter in legs with HSR was  $9.2 \pm 1.5$  mm compared with  $7.62 \pm 2.41$  mm in legs without HSR. HSR after CAC is shown in the Fig.

Univariate analysis revealed CEAP classification (CEAP C2 vs C3-6;  $P = .026$ ), vein diameter ( $P = .004$ ), and suprafascial saphenous vein with a subcutaneous distance between the anterior vein wall and the skin of <1 cm ( $P < .001$ ) to be factors significantly associated with HSR (Table II).

A multivariate analysis revealed suprafascial saphenous vein with a subcutaneous distance between the anterior vein wall and the skin of <1 cm and saphenous vein diameter  $\geq 8$  mm to be the independent factors associated with HSR (Table III). There was no significant difference in age, BMI, sex, leg side, total volume of cyanoacrylate injections, length of treated vein, or procedure time between those with and without HSR. All patients with HSR had mild symptoms and were treated with NSAIDs and antihistamine for 5 to 7 days. All HSR resolved within 1 week.

## DISCUSSION

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. The clinical parameters and the VCSS score were all significantly improved. The observed effectiveness of CAC in our study is comparable with the results reported from previous studies.<sup>6,12,14</sup> All patients in our study underwent CAC without concomitant procedures for varicose tributaries. At 3 months after CAC,

**Table II.** Patient, limb, and operative characteristics compared between those with and without a hypersensitivity reaction (HSR)

Characteristics	HSR	No HSR	P value
Patients	16	85	
Age, years	67.5 ± 11.5	63.5 ± 12.3	.181
BMI, kg/m <sup>2</sup>	26.4 ± 5.9	27.9 ± 6.37	.347
Male sex	1 (8.3%)	29 (32.6%)	.103
Legs	19	107	
Leg side			.804
Right leg	8 (42.1%)	51 (47.7%)	
Left leg	11 (57.9%)	56 (52.3%)	
CEAP clinical classification			.026
C2	13 (68.4%)	43 (40.2%)	
C3-6	6 (31.6%)	64 (59.8%)	
Diameter of saphenous vein, mm	9.2 ± 1.5	7.6 ± 2.4	.004
Suprafascial saphenous vein with depth <1 cm from skin	14 (73.7%)	4 (3.7%)	<.0001
Adhesive volume, mL	0.8 ± 0.2	1.00 ± 0.6	.278
Length of treated vein, cm	21.9 ± 7.14	26.6 ± 13.3	.264
Operative time, min	36.0 ± 4.2	36.7 ± 4.8	.362

BMI, Body mass index; C2, varicose veins; C3, edema; C4a, pigmentation or eczema; C4b, lipodermatosclerosis or atrophie blanche; C5, healed venous ulcer; C6, active venous ulcer; CEAP classification, Clinical-Etiological-Anatomical-Pathophysiological classification.  
Data presented as mean ± standard deviation or number (%).  
A P value of less than .05 indicates statistical significance.

only 7% of the patients had persistent venous symptoms from varicose tributaries, and those residual varicose tributaries were treated with foam sclerotherapy.

In our study, an HSR occurred in 15.8% of patients, and in 15.0% of limbs after CAC. Park et al<sup>9</sup> reported an incidence of HSR of 25.4% in Korean patients. Tang et al<sup>15</sup> found HSR in 18% of Singaporean patients. Gibson et al<sup>10</sup> reported HSR in 6% of US patients. Proebstle et al<sup>16</sup> reported HSR in 11% of European patients. There seems to be a higher incidence of HSR in Asians when compared with Caucasian patients.

One of the independent risk factors for HSR in our study was suprafascial saphenous with a depth of <1 cm from the skin. This finding is somewhat comparable to that from a study by Park et al<sup>9</sup> that found that HSR occurred more frequently in limbs with a suprafascial GSV with a length of >10 cm. We think that the symptoms of HSR are much more easily observed when HSR occurs in the suprafascial area closer to the skin than when it occurs in the subfascial area. The higher incidence of HSR

in Asian population might be due to a higher incidence of suprafascial GSV compared with a Caucasian population.<sup>17</sup> We also found a vein diameter of ≥8 mm to be an independent risk factor for HSR, which may be due to a more pronounced HSR to the larger amount of cyanoacrylate needed to close larger veins.

Gibson et al<sup>10,13</sup> reported that HSR differs from the phlebitis that occurs after endothermal ablation, and from the definition of typical phlebitis. HSR is thought to be a type IV HSR.<sup>9,18</sup> The main clinical feature of HSR is redness or pruritus over the treated vein that is sometimes painless; however, it is sometimes associated with localized pain and/or swelling.<sup>10,19</sup> In contrast, the clinical feature of typical phlebitis after thermal ablation was reported to be localized pain and swelling.<sup>10</sup>

HSR is self-limiting or managed by oral NSAIDs and antihistamine, and usually resolves within 1 to 2 weeks.<sup>5,20</sup> The clinical course of HSR in our patients was a mild and well-tolerated event, and management with NSAIDs and antihistamine was sufficient for resolution of symptoms.

**Table III.** Multivariate analysis for risk factors contributing to hypersensitivity reaction (HSR)

Factors	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Suprafascial truncal vein with depth <1 cm from skin	72.1 (17.2-300.8)	<.001	365.7 (32.2-4144.5)	<.001
CEAP clinical classification C2 vs C3-6	3.2 (1.1-9.1)	.028	0.57 (0.1-6.1)	.641
Size of saphenous vein ≥8 mm	5.6 (1.5-20.4)	.009	16.2 (5.6-802.3)	.001

CI, Confidential interval; C2, varicose veins; C3, edema; C4a, pigmentation or eczema; C4b, lipodermatosclerosis or atrophie blanche; C5, healed venous ulcer; C6, active venous ulcer; CEAP classification, Clinical-Etiological-Anatomical-Pathophysiological classification; OR, odds ratio.  
A P value of less than .05 indicates statistical significance.

It was reported that aggressive treatment with a combination of NSAIDs, antihistamines, and steroids could improve symptoms in severe cases of HSR.<sup>21</sup>

Although HSR cannot be avoided, preventive intravenous dexamethasone or oral antihistamine medication has been reported to significantly reduce its severity.<sup>9</sup> The prevention protocol for HSR after CAC is being investigated.<sup>9</sup>

To prevent an HSR, CAC should be performed when the saphenous vein is located below the superficial fascia, avoided in suprafascial saphenous veins with a subcutaneous distance between the anterior vein wall and the skin of <1 cm, and with caution in saphenous veins with a size of  $\geq 8$  mm.

CAC offers several advantages, including the avoidance of tumescence anesthesia and postprocedural compression. Although an HSR occurred in approximately 15% of patients, the HSR is usually mild and self-limiting, with a good response to NSAIDs and antihistamine. A severe HSR requiring systemic steroid or surgical excision of the treated vein is rare.<sup>18,21</sup> An HSR is a risk that is unique to CAC treatment, and its risk must be balanced against the benefits of the procedure, especially in patients at high risk for an HSR.

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, our study may have lacked sufficient power to identify all significant differences and associations. Third, HSR might occur after 1 week with mild symptom, but with subsequent spontaneous resolution, so some patients may not have reported HSR at the 1-month follow-up.

## CONCLUSIONS

CAC is a safe and effective treatment for saphenous reflux. HSR is frequently found in suprafascial saphenous veins with a subcutaneous distance between the anterior vein wall and the skin of <1 cm, and in saphenous veins with a size of  $\geq 8$  mm. All HSR in this study were mild severity, occurred at 1 week after CAC, and resolved within 1 week after treatment with NSAIDs and antihistamine. To prevent HSR, CAC should be avoided in suprafascial saphenous veins located close to the skin, and CAC in saphenous veins with a size of  $\geq 8$  mm should be performed with caution.

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## AUTHOR CONTRIBUTIONS

Conception and design: NS, PH, CR  
Analysis and interpretation: NS, CR

Data collection: NS, PH, KP, TP, NP, KH, SH, KC, CW, CR  
Writing the article: NS, CR

Critical review of the article: NS, PH, KP, TP, NP, KH, SH, KC, CW, CR

Final approval of the article: NS, PH, KP, TP, NP, KH, SH, KC, CW, CR

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