Turkish Journal of Vascular Surgery 2022;31(2):78-85

DOI: 10.9739/tjvs.2022.1167
www.turkishjournalofvascularsurgery.org

Original Article

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Risk factors and management of phlebitis-like abnormal reaction after cyanoacrylate closure of the truncal varicose vein insufficiency

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ABSTRACT

Objectives: This study aims to evaluate the incidence of phlebitis-like abnormal reaction (PLAR), possible risk factors for the reaction, and the management of PLAR after cyanoacrylate closure (CAC) of great saphenous vein (GSV) or small saphenous vein (SSV) in patients with chronic venous insufficiency (CVI).

Patients and methods: Between June 2020 and March 2021, a total of 90 patients (35 males, 55 females; mean age: 47.6±6.0 years; range, 28 to 69 years) who underwent CAC procedure for GSV or SSV insufficiency were retrospectively analyzed. The patients were divided into two groups: those with PLAR (Group 1) and no PLAR (Group 2). Both groups were compared in terms of possible risk factors. The primary goal was to evaluate the incidence, onset time, duration, severity and possible risk factors for PLAR and Venous Clinical Severity Score (VCSS) and Visual Analog Scale-Pain (VAS-pain) scores of the patients and to compare the groups one week after the procedure. The secondary goal was to evaluate the technical success, recanalization, mortality, major adverse events, and other postoperative complications.

Results: No technical failure and device-related complications were encountered. Anatomic success rate was 100% after CAC procedures. The incidence of PLAR was 14 cases (15.5%). All mild or moderate PLARs occurred within a week of the procedures. During the six-month follow-up period, the target veins were completely occluded in all patients (100%) without any recanalization. Although older age (p=0.042), female sex (p=0.145), obesity (p=0.145), and history of drug allergy (p=0.131) were more common in the PLAR group, they did not reveal statistical significance. Logistic regression analysis revealed that no dependent variable was a risk factor associated with the development of PLAR. All PLAR cases were seen in the target GSV. Improvement in the VCSS scores were not statistically significant between baseline and the one-week control between two groups.

Conclusion: Although PLAR can be seen at high incidence rates, it is a preventable complication with various technical modifications applied during CAC procedure as treatment strategies. According to the present results, no dependent variable was found to be a risk factor for development of PLAR and a risk model could not be devised for the development of PLAR according to any dependent variable.

Keywords: Cyanoacrylate, hypersensitivity reaction, inflammation, phlebitis, varicose veins.

Endothermal ablation technique has supplanted over open high ligation and surgical stripping as the gold-standard treatment modality of chronic venous insufficiency (CVI) during the past two decades.[1,2] However, in the last decade, the use of non-thermal, non-tumescent (NTNT) endovenous ablation techniques such as cyanoacrylate closure (CAC) has become widespread use in the world for the treatment of CVI.[3] The CAC procedure, which does not cause thermal damage and does not require more than one tumescent injection, may be used on a daily basis under local anesthetic. It also played a significant role in the treatment of symptomatic patients, particularly during the novel coronavirus disease 2019 (COVID-19) pandemic.[2-5]

Many previous researches such as the eSCOPE trial and the VeClose study demonstrated the efficacy of

Received: October 17, 2021 ***Accepted:*** January 02, 2022 ***Published online:*** March 09, 2022

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Citation:
Yiğit G. Risk factors and management of phlebitis-like abnormal reaction after cyanoacrylate closure of the truncal varicose vein insufficiency. Turk J Vasc Surg 2022;31(2):78-85

CAC for the treatment of incompetent saphenous veins; however, the complications of CAC have not been well described.[6-8] Among them, phlebitis-like abnormal reaction (PLAR) is the most common complication and impairs the quality of life of patients.[9,10] This erythematous reaction is characterized by itching with pain, heating sensation, induration, erythema, and/or generalized hives.[11] The duration of these symptoms usually persist less than two weeks.[11] Furthermore, the Lake Washington Vascular VenaSeal™ Post-Market Evaluation (WAVES) trial reported that patients had no difficulty in returning to their daily activities after PLAR.[12] However, the risk factors, nature of the disease, and management of this reaction have not been clearly defined, yet.

In the present study, we aimed to evaluate the incidence, onset time, duration, severity, possible risk factors and the management of PLAR following CAC of great saphenous vein (GSV) or small saphenous vein (SSV) in patients with CVI.

PATIENTS AND METHODS

This single-center, single-arm, retrospective study was conducted at Yozgat City Hospital, Department of Cardiovascular Surgery, between June 2020 and March 2021. A total of 90 patients (35 males, 55 females; mean age: 47.6±6.0 years; range, 28 to 69 years) who underwent CAC procedure for GSV or SSV insufficiency were included. All clinical, demographic, and perioperative data were obtained through review of original hospital and physician records.

Demographic, clinical, and procedural data including age, sex, comorbid factors, Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP) clinical classification,[13] Visual Analog Scale-Pain (VAS-pain) scores, Venous Clinical Severity Score (VCSS),[14] type of veins treated, mean diameter of the treatment segment, length of the treated vein, duration of the procedure, concomitant phlebectomy and perforating vein excisions were recorded. This study included CVI patients diagnosed by color Doppler ultrasonography (CDUS) performed by a single radiologist. The CDUS procedure was performed in the standing position in all patients. Patients over the age of 20 with CEAP Class C2-C4b varicose veins, GSV diameter of ≥5.5 mm, SSV diameter of ≥4 mm, and venous reflux of ≥2 sec were eligible. Patients with a GSV diameter of <5.5 mm, SSV diameter of <4 mm, chronic or acute thrombophlebitis, deep venous insufficiency or thrombosis, systemic infection, hypercoagulability condition, pregnancy or lactation, previous treatments using other procedures, bilateral leg CAC, congenital vascular malformations, symptomatic peripheral arterial disease, and pulmonary embolism were excluded.

Prior to the procedure, all patients were also assessed using CDUS by a single cardiovascular surgeon. The CAC procedures were performed in the operating room under sterile conditions using local anesthesia. The efficacy of the vein ablation was immediately assessed by the same surgeon using CDUS after CAC. The patients were invited to return one week later for a follow-up examination. Subsequent follow-up visits were conducted three and six months after the CAC, throughout which clinical and CDUS evaluations were performed. The CDUS examination was performed by a radiologist at three and six months of follow-up. The same cardiovascular surgeon compared clinical outcomes using the CEAP, VCSS, and VAS-pain scores before and one week after the procedure.

The PLAR was defined as the presence of pain, heating sensation, itching, and erythema located at the ablated target vein segment (Figure 1a, b). If a PLAR occurred, the time from treatment to onset, duration of symptoms and severity of the reaction

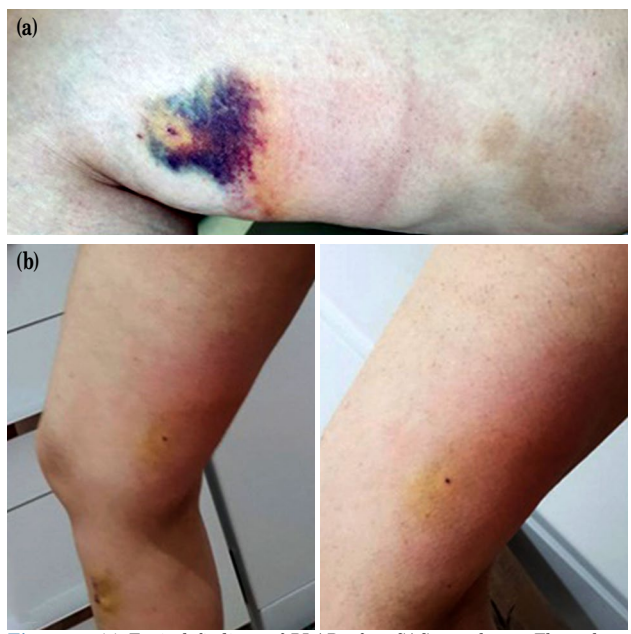

Figure 1. **(a)** Typical findings of PLAR after CAC are shown. Throughout the target vein segment, the patient experienced pain, itching, and a localized heating sensation, as well as erythema and ecchymosis. **(b)** The other patient experienced pain, localized heating sensation, and as well as erythema.
PLAR: Phlebitis-like abnormal reaction; CAC: Cyanoacrylate closure.

were all recorded. The patients were advised to consult to the hospital in case of experiencing these symptoms or any potential complications. Depending on the severity of the patient's symptoms, PLAR treatment was administered and monitored by the same cardiovascular surgeon.

Procedural details

A single cardiovascular surgeon performed all procedures under ultrasound supervision using the VenaBlock® (Invamed, Ankara, Turkey) system. The procedure was carried out in the supine or prone position. After applying local anesthetic, a 6-Fr introducer sheath was placed into the targeted vein. The catheter was advanced to the saphenofemoral (SFJ) or saphenopopliteal junction (SPJ) and was located 3 cm distal to the SFJ or SPJ. Compression to the target vein and the junction side was applied, 2 cm proximal to the delivery catheter tip using the ultrasound probe. Following a total of 1.5 to 2 mL of cyanoacrylate injection into the catheter, the procedure consisted of segmental pullback and vein compression. A final pressure was applied onto the ablated target vein segment about 30 sec. Normal blood flow in the SFJ or SPJ level and deep veins with occlusion in the target vein was confirmed by CDUS. Following CAC, a simultaneous mini-phlebectomy and/or perforating vein excisions was performed following local anesthetic. The index leg was wrapped in a full-length elastic bandage, and the patient unwrapped the bandage after 24 h. All patients were advised to wear compression stockings (30 to 40 mmHg) for the first three days in case phlebectomy was performed.

Follow-up and study outcomes

The follow-up intervals for all patients were one week, three months, and six months, and CDUS examination was performed to obtain the outcome data. One week following the CAC, CDUS was performed to confirm target vein closure and to evaluate any complications. The CDUS evaluation of the treated veins were performed by the same radiologist and same cardiovascular surgeon, before the procedure and one week, three and six months after the procedure. The primary goal was to evaluate the incidence, onset time, duration, severity and possible risk factors for PLAR and VCSS and VAS-pain scores of the patients and to compare one week after the procedure between the groups. The patients were divided into two groups as follows: those with PLAR (Group 1) and no PLAR (Group 2). Both groups were compared in terms of possible risk factors. In addition, in Group 1, oral non-steroidal anti-inflammatory drugs (NSAIDs) and topical antihistamine therapy were initiated, and their clinical response was assessed. The secondary goal was to evaluate the technical success, recanalization, mortality, major adverse events, and other postoperative complications. Total occlusion or nearly complete occlusion (defined as <5-cm segment of flow in the treated vein) of the treated vein was described as technical success. A >5-cm segment of patency in the treated vein was described as recanalization or treatment failure.[15]

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 21.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to analyze normally distributed continuous variables. Continuous variables were expressed in mean ± standard deviation (SD) and median (min-max), while categorical variables were expressed in number and frequency. A two-tailed Fisher exact test was used for categorical values. A paired t-test was used to calculate statistical significance for continuous variables. The groups were compared using the independent t-test and chi-square test to evaluate the risk factors. Development of PLAR was identified as the target variable. Multivariate analysis was performed using the binary logistic regression model to identify the risk factors with independent variables. Age, occluded target vein length, duration of procedure and concomitant phlebectomy were incorporated into the model. A p value of <0.05 was considered statistically significant.

RESULTS

Of the 90 treated saphenous veins, 81 (90%) were GSV and nine (10%) were SSV. The mean duration of procedure was 10.4±3.2 (range, 4 to 12) min. The mean diameter of the treated target veins was 8.6±1.7 (range, 5 to 13) mm and the mean length of the treated target veins was 210.7±58.3 (range, 120 to 320) mm. Procedures were performed for the right leg in 41 and for the left leg in 49 patients. Concomitant phlebectomy of calf varicosities was performed in 36 (40%) patients. In addition, concomitant perforating vein excision of calf varicosities was performed in 26 (28.9%) patients. Baseline demographic, clinical characteristics, and intraoperative details of the patients are given in Table 1 and Table 2, respectively. No technical failure and device-related complications were encountered. Anatomic success rate was 100% after CAC procedures.

Table 1. Baseline demographics and clinical characteristics of patients

	n	%	Mean±SD	Min-Max
Age (year)			47.6±6	28-69
Sex				
Female	55	61.1		
Male	35	38.8		
Diabetes mellitus	8	8.9		
Hypertension	17	18.9		
History of cardiovascular disease	2	2.2		
Obesity	5	5.6		
Drug allergy	2	2.2		
Smoking	12	13.3		

SD: Standard deviation.

Table 2. Vein characteristics and operative details

	n	%	Mean±SD	Min-Max
Treated target vein	90			
Vena saphena magna	81	90		
Vena saphena parva	9	10		
Treated leg side	90			
Right side	41	45.6		
Left side	49	54.5		
Diameter of the vein (mm)			8.6±1.7	5-13
Occluded target vein length (mm)			210.7±58.3	120-320
Duration of procedure (min)			10.4±3.2	4-12
Concomitant phlebectomy	36	40		
Concomitant perforating veins excision	26	28.9		

SD: Standard deviation.

The ultrasonographic evaluation performed by the surgeon immediately after the procedure revealed complete occlusion in all the treated target vessel segments. There was no mortality or major adverse events such as pulmonary thromboembolism related to the procedure during the follow-up. Moreover, deep vein thrombosis, thrombophlebitis, paresthesia, skin necrosis and infection, which are important potential complications, were not encountered in any of the patients. The incidence of PLAR was 14 (15.5%) cases. All mild or moderate PLARs occurred within a week following the procedures. Erythema and itching were limited to the skin overlying the treated target vein, in all the patients with mild or moderate reactions. No severe reactions were encountered. Typical findings of Group 1 patients after CAC was shown in the Figure 1. All patients in Group 1 were treated with NSAIDs and/or topical antihistamines for five to seven days. None of the patients required systemic or oral steroid treatment.

Table 3. Patient and procedural data

	Group 1 (n=14)			Group 2 (n=76)			
Characteristics	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			52.3±11.2			46.7±10.0	0.042
Sex							0.145
Female	11	78.6		44	57.9		
Male	3	21.4		32	42.1		
Patients comorbidities							
Diabetes mellitus	1	7.1		7	9.2		0.221
Hypertension	2	14.3		15	19.7		0.104
History of cardiovascular disease	0	0		2	2.6		0.462
Obesity	3	21.4		2	2.6		0.145
Drug allergy	1	7.1		1	1.3		0.131
Smoking	1	7.1		11	14.5		0.364
Treated target vein							0.202
Vena saphena magna	14	100		67	88.2		
Vena saphena parva	0	0		9	11.8		
Treated leg side							0.825
Right side	6	42.9		35	46.1		
Left side	8	57.1		41	53.9		
Diameter of the vein (mm)			8.2±1.5			8.7±1.8	0.352
Occluded target vein length (mm)			274.1±27.1			199.4±55.3	0.001
Duration of procedure (min)			10.4±1.1			8.04±2.5	0.001
Concomitant phlebectomy	2	14.3		34	44.7		0.033
Concomitant perforating veins excision	2	14.3		24	31.6		0.190
Preoperative VCSS			8.0±2.4			7.4±2.2	0.370
Postoperative VCSS			3.9±1.6			3.8±1.3	0.811
Preoperative pain score			2.4±1.4			2.4±1.5	0.989
Postoperative pain score			6.1±1.4			1.2±1.1	0.001

SD: Standard deviation; VCSS: Venous Clinical Severity Score.

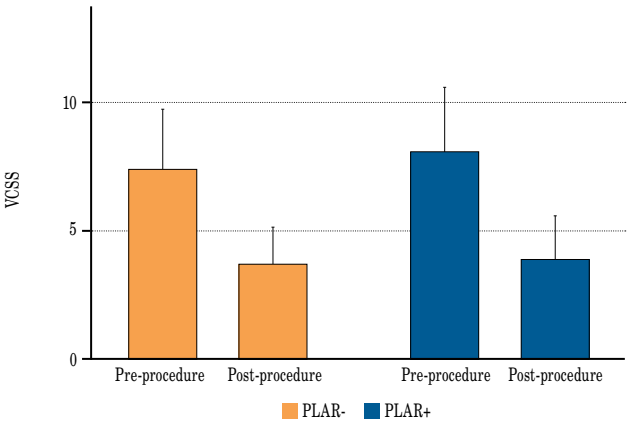

Figure 2. Venous Clinical Severity Score changes between PLAR and no PLAR groups during one week.

VCSS: Venous Clinical Severity Score; PLAR: Phlebitis-like abnormal reaction.

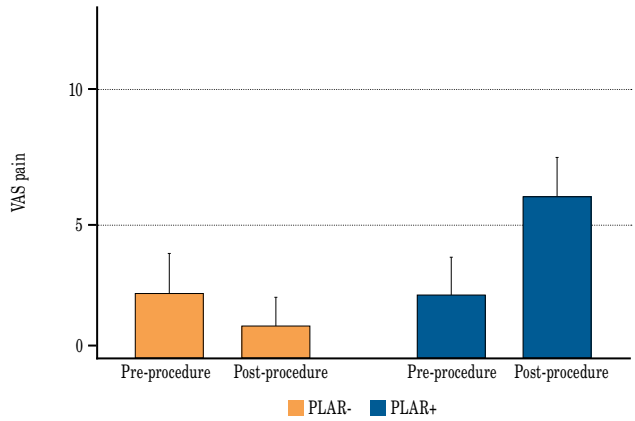

Figure 3. Pain score changes between PLAR and no PLAR groups during one week.

VAS-pain: Visual Analog Scale-Pain; PLAR: Phlebitis-like abnormal reaction.

All PLAR cases resolved within an average of one week.

During the six-month follow-up period, the treated target veins were completely occluded in all patients (100%) without any recanalization. A dramatic improvement was observed in the symptoms of the patients, immediately after the procedure and for six months during the postoperative follow-up period. We compared the baseline demographics, treated veins, and procedure details of the groups (Table 3). The mean occluded target vein of patients with PLAR (Group 1) was significantly longer (274.1±27.1 mm *vs.* 199.4±55.3 mm, respectively; p<0.001). In addition, the mean duration of the procedure in Group 1 was significantly longer (10.4±1.1 min *vs.* 8.04±2.5 min, respectively; p<0.001). Cases with concomitant phlebectomy was significantly higher in Group 2 (44.7% *vs.* 14.3%, respectively; p=0.033). The other factors including sex, age, comorbid factors, target vein diameter, treated target vein, concomitant perforating vein excision, preoperative VCSS and CEAP scores were similar in both groups. Although older age (p=0.042), female sex (p=0.145), obesity (p=0.145), and history of drug allergy (p=0.131) were more common in Group 2, it did not reach statistical significance. No PLAR developed after SSV treatment. On the contrary, all PLAR cases were seen in the target GSVs. Improvement in the VCSS scores were not statistically significant between baseline and the one-week after treatment between the two groups (Table 3, Figure 2). The mean VAS-pain scores of patients in Group 1 was significantly higher (6.1±1.4 *vs.* 1.2±1.1, respectively; p<0.001) (Table 3, Figure 3). Binary logistic regression model was performed for PLAR development according to age, occluded target vein length, duration of procedure and concomitant phlebectomy (Table 4). Logistic regression analysis revealed that no dependent variable was a risk factor associated with the development of PLAR.

DISCUSSION

Cyanoacrylate closure has been used extensively as a novel method for the treatment of CVI in

Table 4. Binary logistic regression model for PLAR development according to age, occluded target vein length, duration of procedure, and concomitant phlebectomy

						95% CI	
	Estimate	SE	Wald	df	Sig.	Lower limit	Upper Limit
Age	0.244	0.037	0.000	1	0.999	-0.729	0.729
Occluded target vein length	0.001	0.0006	0.000	1	1.000	-0.125	0.125
Duration of procedure	0.929	0.093	0.000	1	0.999	-1.827	1.829
Concomitant phlebectomy	-7.513	5.031	0.000	1	0.999	-9.869	9.854

PLAR: Phlebitis-like abnormal reaction; SE: Standard error; CI: Confidence interval.

recent years.[2] It has several benefits over thermal ablation, including the avoidance of tumescent anesthesia, the lack of nerve injuries, and the ability of patients to return to regular activities with no restrictions.[10] Cyanoacrylate closure has played a major role in the treatment of symptomatic patients under local anesthesia and with the option of outpatient therapy, particularly during the COVID-19 pandemic.[4,5] However, the most common side effect of CAC is PLAR, which is characterized by erythema, swelling, pruritus, pain, and tenderness over the treated vein. In the literature, Park et al.[9] published an incidence of 25.4% in an Asian population. This is higher than the incidence reported in the American (16 to 20%) and European literature (11.4%).[2,6,7] In the present study, PLAR occurred in 15.5% of patients, similar to other studies. The benefit-risk ratio should be well considered in patients at high risk for PLAR following CAC procedure.

The exact mechanism of PLAR has not been yet well-described. However, it was hypothesized as a type IV delayed hypersensitivity reaction caused by a foreign material, rather than localized inflammation, and was alleviated in over 85% of patients by antihistamines and steroids.[9,16,17] The exact incidence and severity of type IV hypersensitivity reactions of CAC remain unclear. In preclinical investigations, the predominant histopathological feature was an acute inflammatory reaction that proceeded to subacute vasculitis at three weeks and, then, to a chronic granulomatous foreign body reaction at four weeks.[10,18] Moreover, in chronic phases, the vein had fibrotic structures with partial recanalization.[19] In the present study, all mild or moderate PLARs occurred within a week after the procedures. In addition, no severe reactions were encountered. During the six months of follow-up period, the treated target veins were completely occluded in all patients without any recanalization.

The risk factors for this complication have been described variably in the literature. According to their experience, Tang and Tiwari[16] highlighted the GSV location and female sex as possible risk factors. Park et al.[9] reported that PLAR was more common in suprafascial GSV after CAC. Similar to previous research, in the present study, no PLAR developed after SSV treatment; however, all PLAR cases were seen in the target GSVs. Another critical point, as Chung et al.[20] proposed is that, if glue was injected across the joint, an inflammatory response would occur in both the vein wall and the surrounding tissue. Abnormal skin findings following CAC can be caused by active movement. Avoiding injections around the knee joint, particularly after GSV ablation, may minimize the risk of developing PLAR. The mean occluded target vein of patients with PLAR was significantly longer in the present study. This finding supports that particularly for GSV glue ablation procedures, which are performed around the knee-joint and the length of the injections, may increase the incidence of PLAR. However, binary logistic regression (used for further evaluation, since the number of patients between the groups was dissimilar) revealed that no dependent variable was a risk factor for development of PLAR. Therefore, a risk model could not be devised for the development of PLAR according to any dependent variable.

Another crucial issue is to perform CAC to the target GSV or SSV located below the superficial fascia to prevent PLAR. Thus, treatment should be avoided in suprafascial veins with a subcutaneous distance of 1 cm between the anterior vein wall and the epidermis, and performed carefully in saphenous veins larger than 8 mm.[21] To ensure minimal glue leakage into the subcutaneous space, Sumarli et al.[22] and Jones et al.[17] applied the method of removing the glue catheter by pulling it into the sheath 3 cm before the last dose was given to the puncture site. Possible excessive leakage of glue into the subcutaneous space may trigger a large number of immune cells there, causing a hypersensitivity reaction.[23] In line with the findings of the present study and the discussions in the literature, we may recommend some modifications with regard to the use of CAC. Attention should be paid to technical details: applying CAC to veins of 10 mm below diameter, keeping the distance of the ablated target vein short, avoiding the procedure close to the knee joint, applying the procedure uninterruptedly, providing minimal liquid adhesive contact with the skin and subcutaneous tissues, and target vessel compression for a minimum of 30 sec after the CAC. These applications may lead to significant reduction of this complication.

Phlebitis-like abnormal reaction differs from typical post-endothermal ablation phlebitis in a way that the use of prophylactic NSAIDs after the treatment does not reduce its frequency.[22] It is self-limiting or can be treated with oral NSAIDs and antihistamines, and usually resolves within one to two weeks.[7,8] The clinical course of PLAR in the study patients was mild or moderate and a well-tolerated event, erythema and itching were limited to the skin overlying the treated

saphenous vein. Management with NSAIDs and antihistamine treatment was sufficient for resolution of these symptoms. None of the patients received systemic or oral steroid treatment. No severe reactions were encountered. All PLAR cases resolved within an average of one week. However, the point that needs to be emphasized and questioned is whether a prophylactic treatment can be applied to prevent PLAR. The use of topical antihistamine and oral NSAIDs after CAC may be effective for prophylaxis. However, studies with larger patient populations are required to elaborate on the risk factors and prophylaxis of PLAR.

This study has certain limitations such as its single-center and retrospective nature with a limited number of patients.

In conclusion, it is critical that cardiovascular surgeons should be aware of PLAR as a complication of CAC, which may cause morbidity in patients. Although PLAR can be seen at high incidence rates, it is a preventable complication with various technical modifications applied during CAC procedure as treatment strategies. According to the present results, no dependent variable was found to be a risk factor for development of PLAR and a risk model could not be devised for the development of PLAR according to any dependent variable. Further prospective, randomized studies with larger number of patients may further identify the risk factors and prophylaxis for PLAR.

Ethics Committee Approval: The study protocol was approved by the Yozgat City Hospital and Yozgat Provincial Health Directorate Commitee (Date: 21.12.2020, No: 92198657-000-7080). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest: The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The author received no financial support for the research and/or authorship of this article.

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