VDM Vascular Disease Management

REVIEW

PEER REVIEWED

Complications After Using Cyanoacrylate Glue in the Treatment of Venous Insufficiency

Dr. Ravi Suresh Manek[1]; Dr. Ashok Kumar[2]; Dr. Sushant Khurana[3]; Mitesh Mohan Hood[3]

[1]Pristyn Care, Mumbai, India; [2]Pristyn Care, Chennai, India; [3]Pristyn Care, Gurgaon, India

Keywords Varicose Veins
Vascular Closure Devices
Venous Insufficiency

May 2024
ISSN 2152-4343

VASCULAR DISEASE MANAGEMENT 2024;21(5):E33-E38

Abstract

Venous insufficiency consists of changes in the lower limb and discomfort associated with increased venous pressure. Based on the degree of severity, the condition can range from reticular veins to even an acute ulcer. The use of cyanoacrylate glue for treating this condition is increasingly becoming popular, but there are some complications associated with the method. This review article aims to summarize the information regarding the complications of using cyanoacrylate glue, along with their prevention and management, in detail to help clinicians make informed decisions while administering this treatment method.

Introduction

Venous insufficiency is typically manifested by swelling of the lower limbs, changes in skin condition, and discomfort resulting from increased venous pressure. Disorders associated with venous insufficiency can significantly reduce a patient's productivity and quality of life. In many cases, this condition is caused by ineffective functioning of the valve of the vein wall. The stages of venous insufficiency can be classified from C0 to C6, according to the clinical, etiological, anatomical, and pathophysiological (CEAP) classification, where C6 denotes the most severe stage. C0 indicates no obvious feature of venous disease, C1 represents the presence of reticular or spider veins, C2 represents obvious varicose veins, C3 represents the presence of edema but no skin changes, C4 represents skin discoloration or pigmentation, C5 denotes an ulcer that has healed, and C6 denotes an acute ulcer.[1]

Different treatment methods are available for each stage of venous insufficiency.[1] Treatments for spider veins include sclerotherapy, intense pulse light treatment, thermocoagulation, and microphlebectomy.[2] Treatments for varicose veins include conventional surgical stripping, endovenous thermoablation, radiofrequency ablation, foam sclerotherapy, ambulatory phlebectomy, and cyanoacrylate closure (CAC) procedures.[3-5] Treatments for edema include laser ablation, radiofrequency, and steam ablation.[6]

The CAC procedure involves the delivery of cyanoacrylate glue into the vein. This glue initiates an immediate inflammatory reaction in the vein wall through a polymerization process, which leads to the formation of a protective barrier and the development of fibrosis of the vein tissue. The increased thickness of the glue and the polymerization characteristics allow precise placement in the vein.[7] A low rate of complications has been reported.[8] These complications include extravasation of the glue, hypersensitivity reaction, septicemia, skin hyperpigmentation, and glue-induced thrombosis. Understanding these potential complications and their appropriate management is essential, especially as the use of cyanoacrylate glue for the treatment of venous insufficiency becomes more widespread.[9-14]

To our knowledge, there has been no review conducted in the past to summarize all the information available regarding the complications of this procedure. This review article aims to collate the available information and describe these complications, as well as their prevention and management, in detail.

Cyanoacrylate Glue

Cyanoacrylate glue is a liquid embolic material that polymerizes on contact with blood, resulting in blood vessel occlusion. It has found extensive use in the occlusion of cerebral venous and arterial anomalies and cerebral aneurysms, and in treating conditions involving the ovarian and spermatic veins.[14] Initial trials for its use in treating venous insufficiency were done in 2013, and by now, its use for the same has been established.[15]

Benefits of Cyanoacrylate Glue

The CAC procedure does not require the use of tumescent anesthesia and carries no risk of nerve damage from heat. Many studies have demonstrated the safety and efficacy of the CAC procedure for treating superficial venous insufficiency. In a randomized controlled trial comparing surgical stripping with the CAC procedure, both groups showed complete occlusion of the target veins at a 100% rate at 3 months. In addition, both groups showed similar improvements in quality of life, and the CAC group experienced significantly less pain and bruising.[14,16]

In another trial comparing the CAC procedure with radiofrequency ablation, the CAC procedure demonstrated a 99% closure rate at 3 months, compared with a 96% closure rate with radiofrequency ablation. There was a trend toward a preponderance in favor of the CAC procedure. Pain levels were comparable between the 2 methods, with less bruising observed in the CAC group.[14,17]

Patients can usually return to regular activities just 1 hour after the procedure. In addition, the shorter duration of the procedure and the absence of tumescent anesthesia can allow the treatment to be performed in a clinic, which leads to time and cost savings.[14]

Complications of Cyanoacrylate Glue

The CAC procedure is a safe treatment method with potentially no immediate complications, and the patency of the deep venous system may remain intact after treatment has ended. However, some evidence suggests a minimal incidence of complications, including issues such as extravasation, complex hypersensitivity and irritation reaction (CHAIR), septicemia, skin hyperpigmentation, and endovenous glue-induced thrombosis (EGIT). These reported complications are generally mild. They can be effectively managed with noninvasive measures or on an outpatient basis. However, given its relatively recent introduction, health care professionals should exercise caution when using this procedure in clinical practice and watch for rare complications.[8-12,14] Patients should be educated about the potential adverse outcomes of the CAC procedure before undergoing treatment.

Endovenous Glue-Induced Thrombosis

EGIT is a common complication of the CAC procedure, which can sometimes prove to be worrisome.[11] EGIT is characterized by migrating glue-thrombotic mixture from the proximal part of the great saphenous vein (GSV) toward the sapheno-femoral junction (SFJ) with varying involvement.[18] Simply, it means a blood clot spreads into a deeper vein.[11]

Most cases of EGIT are identified within the first 1 to 2 weeks of follow-up.[18] Clinical studies show a variable incidence ranging from 0% to 21.1%. In a retrospective study, it was observed that 11 of 191 patients experienced EGIT, and each had a different pattern of extension of the thrombus into the deep vein. The most frequently observed shape was a slender, threadlike extension of the thrombus into the deep vein, which could be attributed to the pressure applied to prevent migration of the cyanoacrylate glue into the deep vein during the procedure.[11]

The incidence of EGIT is influenced by various factors, including the composition of the fluid in the vein, the type of vein, and the rate of insertion of the cyanoacrylate glue. This suggests that anatomic variables such as the diameter of the venous vessels, the length of the treated vein, and the mode of branching also contribute to the occurrence of EGIT. A retrospective study described risk factors such as older age, diabetes, hypertension, hyperlipidemia, and lack of anticoagulation.[18,19] Another study stated that a small saphenous vein under 5 mm in diameter is a risk factor for the development of EGIT. In addition, the study proposed creating a categorization system and therapeutic regimen for EGIT depending on the extent of thrombus expansion into the deep vein.[11] The Kabnick and Lawrence classification system can be used for the same, where level 6 denotes the most severe phase of EGIT. According to this categorization, level 1 means an extension of EGIT below the point where the epigastric vein is located. Level 2 indicates EGIT that extends to the same level as the origin of the epigastric vein. Level 3 means the extension of EGIT to the same level as the SFJ. Level 4 characterizes EGIT that extends into the common femoral vein (CFV). Level 5 describes EGIT that adheres to the adjacent wall of the CFV behind the SFJ. Finally, level 6 indicates the extension of EGIT into the CFV, which is consistent with deep vein thrombosis.[18,20]

To minimize the risk of EGIT, it is advisable to consistently administer the cyanoacrylate glue in the entire range of the target vein in a uniform concentration.[18,21] Although the treatment policy for EGIT has not yet been established, there is a low possibility that EGIT will naturally progress to hematoma expansion. In its initial stages, follow-up observation through ultrasound examination is required, and in an advanced stage, anticoagulant treatment is recommended. A retrospective study stated that usually, this complication does not require a separate treatment model. Instead, its conservative management is the way to cure it.[22] On average, its resolution can take up to 5 to 6 weeks after initial detection.[18]

Complex Hypersensitivity and Irritation Reaction

A significant complication after the CAC procedure is an inflammatory reaction, which results in symptoms such as pain, warmth, itching, localized tissue induration, redness, and widespread skin scarring. Although the exact cause of this complication has not been documented, clinical and pathological observations have suggested that it occurs due to glue injection during the procedure.[10] A prospective observational study termed this complication a phlebitis-like abnormal reaction.[9] Various terms have been used over the years for this complication until 2021, when a study finally used the term CHAIR to characterize this distinct complication based on the documented clinical manifestations.[10]

Although first-in-human studies did not mention this complication, the studies conducted after that have reported this complication up to an extent. A study suggests that this complication rate could be substantially higher than previously documented in published research (0-25%).[9,15,23,24] Seventy-two percent of these complications are reported to be mild, 22% moderate, and 6% severe.[25]

A retrospective study reported that no patient who was treated for small saphenous veins was diagnosed with CHAIR. All CHAIR-diagnosed patients were from the group of patients who were treated for the GSV. In all of the CHAIR cases, the site chosen for introducing the glue was placed below the level of the knee joint. A research study documented an adverse event characterized as abnormal skin redness, which was believed to be a delayed hypersensitivity reaction to the cyanoacrylate glue. Despite the similarity to phlebitis, this reaction generally manifested as a more extensive skin disease, appearing 7 to 14 days after the procedure, with a tendency to occur at the GSV site, mainly in women. This condition is self-limiting, and treatment with anti-inflammatory drugs is considered only when patients experience discomfort. The research further clarified that this reaction originates from local inflammation following the injection of the cyanoacrylate glue.[10,26,27] The study found no identifiable patient procedural factors, or even a history of previous CAC procedures, as a predictive factor for these hypersensitivity reactions. The only notable observation was a lower risk of these reactions in patients falling into advanced clinical classes of the CEAP classification.[25]

To reduce the likelihood of CHAIR, it is advisable to refrain from using cyanoacrylate glue in individuals with known allergies to adhesive materials, including those associated with false eyelashes and nails.[25] In all cases, the delivery catheter should be removed carefully to avoid leaving adhesives in the subcutaneous tissue.[28] Patients affected by CHAIR should use nonsteroidal anti-inflammatory drugs and antihistamines to treat the complication.[10] In cases where a patient shows signs of suspected hypersensitivity, the initial course of action should include the administration of topical corticosteroids. Subsequently, oral corticosteroids and antihistamines should be considered. If a hypersensitivity reaction persists despite this treatment, it is advisable to refer the patient for hypersensitivity testing to confirm a specific reaction related to the performance of CAC.[24] A 6-day tapered course of oral steroids should be given for the treatment of patients with moderate hypersensitivity reactions; if the symptoms are not completely resolved by the end of the first 6-day course, the patient should be given additional 6-day steroid tapers in sequence.[25]

Septicemia

Septicemia refers to a bacterial infection that affects the bloodstream. It can manifest as increased body temperature and, in more severe cases, can lead to circulatory failure due to dilation of blood vessels, leakage from small blood vessels (capillaries), and a reduction in the heart's ability to contract effectively.[29] The occurrence of this complication after using cyanoacrylate glue is more common for bleeding gastric varices than for venous insufficiency. Still, it cannot be ignored as it can prove fatal if not treated in time.[2,30-33]

In 2022, Nishizawa and Kudo documented a case where a patient developed symptomatic septicemia after a CAC procedure, requiring surgical removal of the treated saphenous veins. Initially, after completing the CAC procedure, no anatomical abnormalities were observed, and postoperative hematoma did not develop. However, in the following days, the patient complained of pain and warmth in the left calf and redness and swelling of the left lower limb. The patient also presented with a fever ranging from 37°C to 38°C. A foreign body reaction, potentially triggered by the CAC procedure, was suspected as the cause. Oral steroids were initially administered for treatment, but 2 blood cultures later confirmed the presence of methicillin-sensitive *Staphylococcus aureus*. Subsequently, antibiotics were prescribed and surgery was performed under tumescent anesthesia for bilateral excision of both small saphenous veins. This complication can prove to be fatal if not treated in time.[12]

Skin Hyperpigmentation

Skin hyperpigmentation is a common dermatological condition resulting in a darkening skin tone. These changes in skin color can come from various internal and external influences, such as hormonal fluctuations, inflammation, trauma, acne, eczema, specific medications, exposure to ultraviolet radiation, and other factors.[34-37]

One of the complications reported after the use of cyanoacrylate glue for venous insufficiency is skin hyperpigmentation, though there is a lack of clinical studies with large patient cohorts.[8] This complication can occur in around 3% to 12% of treated patients and remain even after 12 months of the initial treatment.[15,38]

In 2019, Hwang et al conducted a study to evaluate the effectiveness and safety of CAC of an incompetent GSV and to assess the regression of varicose veins following CAC without a concomitant procedure on 48 patients. The result showed this procedure to be effective in treating varicose veins, but there were some complications as well. Skin hyperpigmentation occurred in 13.3% of the patients compared with CHAIR, which occurred in 16.7% of the patients. However, skin hyperpigmentation stayed longer than CHAIR, even after a 12-month follow-up.[39]

Extravasation

In rare cases, the CAC procedure may result in extravasation, which may further lead to persistent foreign body reactions requiring surgery. This problem can cause extensive inflammation in the outer layer of the skin and the tissue just below it, characterized by lymphoid clusters, eosinophils, and foamy histiocytes around the leaked glue. This pattern is consistent with a foreign body-like response.[8] A study reported the occurrence of subcutaneous granuloma in a patient at the site of vein cannulation in the upper calf as a mildly painful lump with skin erythema around. A duplex ultrasound revealed the glue extravasation with a skin inflammatory reaction. To cure it, glue extraction was done distantly from the cannulation point.[40]

This complication can occur even when there have been no immediate complications or difficulties after the initial treatment. It has been reported that it can occur up to 9 months after the initial treatment. The etiology of such delayed extravasation remains elusive. However, cases have been documented suggesting a plausible mechanism involving a chronic immunological response to cyanoacrylate glue, leading to subsequent damage to the vessel wall. Another possible explanation could be that when pressure is applied after the glue is installed per the manufacturer's instructions, the glue may be forced into the small branch, causing it to rupture, leak, and subsequently trigger a foreign body reaction. As a result, it is advisable to be careful and apply moderate pressure during this compression process.[8]

This complication is particularly significant due to the inflammation extending into the nearby skin, necessitating surgery, its unexpected occurrence several months after treatment, and its adverse impact on aesthetic outcomes and patient satisfaction. Studies suggest that doctors should inform patients about this complication before the treatment and include it in the consent form.[8,41]

Conclusion

The occurrence of complications after the CAC procedure is coming to light more as its use has increased over recent years. These complications cannot be completely ignored because many of them can have long-lasting effects on the quality of life of the patient, even proving to be fatal. CHAIR is the most common complication, with a possible occurrence rate of above 25%. However, the most serious complication is septicemia, as it can prove to be fatal if not cured in time. With proper knowledge and awareness about these complications, many can be treated in the early stages or even prevented from occurring. ■

The authors report no financial relationships or conflicts of interest regarding the content herein.

Manuscript accepted April 24, 2024.

Corresponding Author: Mitesh Mohan Hood, Pristyn Care, Capital The Cityscape, Badshahpur, Sector 66, Gurgaon, Haryana, India 122102. Email: mitesh.hood@pristyncare.com

References

1. Patel SK and Surowiec SM. Venous Insufficiency. [Updated 2023 Jul 18]. In: *StatPearls* [Internet]. StatPearls Publishing, 2023. https://www.ncbi.nlm.nih.gov/books/NBK430975

2. Sandean DP and Winters R. Spider Veins. [Updated 2023 Jul 4]. In: *StatPearls* [Internet]. StatPearls Publishing, 2023. https://www.ncbi.nlm.nih.gov/books/NBK563218

3. Andercou O, Stancu B, Coman HF, Cucuruz B, Noppeney T, Marian D. Radiofrequency thermal ablation for the treatment of chronic insufficiency of the saphenous vein—a comparative retrospective study. *Int J Environ Res Public Health*. 2023;20(4):3308. doi:10.3390/ijerph20043308

4. Beyaz MO, Urfalı S, Koyuncu O, Fansa İ. Thermal ablation, nonthermal ablation and surgical striping applications: 1-year single center early results. *MKÜ Tıp Dergisi.* 2022;13(47):417-424. doi:10.17944/mkutfd.1121446

5. Almeida JI. Treatment of varicosed tributary veins. In: Almeida JI, ed. *Atlas of Endovascular Venous Surgery.* 2nd ed. Elsevier; 2019:285-306.

6. Thomis S, Verbrugghe P, Milleret R, Verbeken E, Fourneau I, Herijgers P. Steam ablation versus radiofrequency and laser ablation: an in vivo histological comparative trial. *Eur J Vasc Endovasc Surg.* 2013;46(3):378-382. doi:10.1016/j.ejvs.2013.06.004

7. Tang TY, Rathnaweera HP, Kam JW, Chong TT, Choke EC, Tan YK. Endovenous cyanoacrylate glue to treat varicose veins and chronic venous insufficiency—experience gained from our first 100+ truncal venous ablations in a multi-ethnic Asian population using the Medtronic VenaSeal™ Closure System. *Phlebology*. 2019;34(8):543-551. doi:10.1177/0268355519826008

8. Langridge BJ, Onida S, Weir J, Moore H, Lane TR, Davies AH. Cyanoacrylate glue embolisation for varicose veins—a novel complication. *Phlebology*. 2020;35(7):520-523. doi:10.1177/0268355520901662

9. Jones AD, Boyle EM, Woltjer R, Jundt JP, Williams AN. Persistent type IV hypersensitivity after cyanoacrylate closure of the great saphenous vein. *J Vasc Surg Cases Innov Tech.* 2019;5(3):372-374. doi:10.1016/j.jvscit.2019.05.004

10. Lee S, Cho S, Joh JH. Risk factors for complex hypersensitivity and irritation reactions after an ultrasound-guided cyanoacrylate closure. *J Surg Ultrasound.* 2021;8(1):19-24. doi:10.46268/jsu.2021.8.1.19

11. Cho S, Gibson K, Lee SH, Kim SY, Joh JH. Incidence, classification, and risk factors of endovenous glue-induced thrombosis after cyanoacrylate closure of the incompetent saphenous vein. *J Vasc Surg Venous Lymphat Disord.* 2020;8(6):991-998. doi:10.1016/j.jvsv.2020.01.009

12. Nishizawa M, Kudo T. Septicemia after cyanoacrylate glue closure of varicose veins. *J Vasc Surg Cases Innov Tech.* 2022;8(4):653-656. doi:10.1016/j.jvscit.2022.09.008

13. Sumarli SA, Lee QWS, Yap HY, Tay HTL, Chong TT, Tang TY. Exit site complications following cyanoacrylate glue endovenous ablation of incompetent truncal veins for chronic venous insufficiency. *J Vasc Surg Cases Innov Tech.* 2020;6(4):500-504. doi:10.1016/j.jvscit.2020.08.010

14. Falvo N, Latreche A, Chevallier O, et al. Cyanoacrylate glue for treating chronic saphenous vein insufficiency: a retrospective observational single-center study. *Diagnostics (Basel).* 2023;13(14):2313. doi:10.3390/diagnostics13142313

15. 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(2):174-180. doi:10.1016/j.jvsv.2012.09.010

16. Joh JH, Lee T, Byun SJ, et al. A multicenter randomized controlled trial of cyanoacrylate closure and surgical stripping for incompetent great saphenous veins. *J Vasc Surg Venous Lymphat Disord.* 2022;10(2):353-359. doi:10.1016/j.jvsv.2021.08.012

17. Morrison N, Gibson K, McEnroe S, et al. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). *J Vasc Surg.* 2015;61(4):985-994. doi:10.1016/j.jvs.2014.11.071

18. Pillutla A, Hendrix MP, Ha J. Endovenous glue-induced thrombosis in nonthermal glue closure therapy for greater saphenous vein insufficiency: a single-center experience. *J Vasc Interv Radiol.* 2019;30(7):1075-1080. doi:10.1016/j.jvir.2018.12.730

19. Kailasnath P, Chaloupka JC. Quantitative assessment of polymerization-binding mechanics of cyanoacrylates: model development and validation. *AJNR Am J Neuroradiol*. 2002;23(5):772-778.

20. Lawrence PF, Chandra A, Wu M, et al. Classification of proximal endovenous closure levels and treatment algorithm. *J Vasc Surg.* 2010;52(2):388-393. doi:10.1016/j.jvs.2010.02.263

21. Yavuz T, Acar AN, Aydın H, Ekingen E. A retrospective study of a new n-butyl-2-cyanoacrylate glue ablation catheter incorporated with application guiding light for the treatment of venous insufficiency: twelve-month results. *Vascular*. 2018;26(5):547-555. doi:10.1177/1708538118770548

22. Ko H, Min S, Ahn S, Han A, Kim J, Min SK. Stump length changes after endovenous cyanoacrylate closure or radiofrequency ablation for saphenous vein incompetence. *Vasc Specialist Int.* 2021;37(1):14-21. doi:10.5758/vsi.210006

23. 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(2):149-156. doi:10.1177/1708538116651014

24. Jones AD, Boyle EM, Woltjer R, Jundt JP, Williams AN. Persistent type IV hypersensitivity after cyanoacrylate closure of the great saphenous vein. *J Vasc Surg Cases Innov Tech.* 2019;5(3):372-374. doi:10.1016/j.jvscit.2019.05.004

25. Gibson K, Minjarez R, Rinehardt E, Ferris B. Frequency and severity of hypersensitivity reactions in patients after VenaSeal™ cyanoacrylate treatment of superficial venous insufficiency. *Phlebology*. 2020;35(5):337-344. doi:10.1177/0268355519878618

26. Tang TY, Tiwari A. The VenaSeal™ abnormal red skin reaction: looks like but is not phlebitis! *Eur J Vasc Endovasc Surg*. 2018;55(6):841. doi:10.1016/j.ejvs.2018.02.003

27. Korkmaz Ö, Göksel S, Gül M, Başçil H, Yildir Y, Berkan Ö. Does the use of N-butyl-2 cyanoacrylate in the treatment of lower extremity superficial varicose veins cause acute systemic inflammation and allergic reactions? *Cardiovasc J Afr.* 2018;29(4):213-217. doi:10.5830/CVJA-2018-012

28. Sermsathanasawadi N, Pruekprasert K, Chinsakchai K, Wongwanit C, Ruangsetakit C. Cyanoacrylate granuloma after cyanoacrylate closure of incompetent saphenous veins. *Dermatol Surg.* 2021;47(10):1372-1375. doi:10.1097/DSS.0000000000003183

29. Waller DG, Sampson AP. Chemotherapy of infections. In: Waller DG, Sampson AP. *Medical Pharmacology and Therapeutics*. 5th ed. Elsevier; 2018:581-629.

30. Nawrot I, Cieciura Tomasz, Morawski B, Malkowski P, Żurakowski J, Durlik M. Pulmonary embolism with septicemia after N-butyl-2-cyanoacrylate injection for bleeding gastric varices. *Chin Med J (Engl).* 2014;127(16):3030-3031.

31. Chang CJ, Shiau YT, Chen TL, et al. Pyogenic portal vein thrombosis as a reservoir of persistent septicemia after cyanoacrylate injection for bleeding gastric varices. *Digestion*. 2008;78(2-3):139-143. doi:10.1159/000175360

32. Liu CH, Tsai FC, Liang PC, Lee CZ, Yang PM. Splenic vein thrombosis and Klebsiella pneumoniae septicemia after endoscopic gastric variceal obturation therapy with N-butyl-2-cyanoacrylate. *Gastrointest Endosc.* 2006;63(2):336-338. doi:10.1016/j.gie.2005.08.025

33. Tan YM, Goh KL, Kamarulzaman A, et al. Multiple systemic embolisms with septicemia after gastric variceal obliteration with cyanoacrylate. *Gastrointest Endosc.* 2002;55(2):276-278. doi:10.1067/mge.2001.118651

34. Alexis AF, Sergay AB, Taylor SC. Common dermatologic disorders in skin of color: a comparative practice survey. *Cutis*. 2007;80(5):387-394.

35. Tunzi M, Gray GR. Common skin conditions during pregnancy. *Am Fam Physician.* 2007;75(2):211-218.

36. Lawrence E and Al Aboud KM. Postinflammatory hyperpigmentation. [Updated 2022 Oct 3]. In: *StatPearls* [Internet]. StatPearls Publishing, 2023. https://www.ncbi.nlm.nih.gov/books/NBK559150

37. Hassan S, Zhou XA. Drug-induced pigmentation. [Updated 2023 Jul 10]. In: *StatPearls* [Internet]. StatPearls Publishing, 2023. https://www.ncbi.nlm.nih.gov/books/nbk542253

38. 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(8):545-549. doi:10.1177/1538574417729272

39. Hwang JH, Park SW, Kim KH, et al. Regression of varicose veins after cyanoacrylate closure of incompetent great saphenous veins without a localized concomitant procedure. *J Vasc Surg Venous Lymphat Disord.* 2019;7(3):375-381. doi:10.1016/j.jvsv.2018.10.016

40. Murzina EL, Lobastov KV, Bargandzhiya AB, Laberko LA, Popov IB. Mid-term results of cyanoacrylate embolization of saphenous veins. *Flebologiya*. 2020;14(4):311-321. doi: 10.17116/flebo202014041311

41. Tüzün H, Recep E. Does size matters for the treatment of varicose veins with cyanoacrylate glue. *J Phlebol Lymphol.* 2020;13(1):8-9.