Endovenous Sealing of Superficial Veins

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Clinical Pearls

1. Treatment of the saphenous vein using VenaSeal starts at 5 cm with the junction of the deep system.
2. Treatment of the saphenous vein using VariClose starts at 3 cm with the junction of the deep system.
3. Phlebitis is the most common complication with endovenous sealing of saphenous veins.

Introduction

Varicose vein disease affects approximately one third of the population [1], causing a variety of symptoms as well as negatively impacting the quality of life (QoL) of patients [2–5]. Treatment of the condition, however, has been shown to lead to improvement in patients' clinical condition and quality of life [6–8].

For a long time, such treatment took the shape of surgical ligation and stripping of the saphenous trunks. With time, though, the need for more minimally invasive interventions was felt, leading eventually to the advent of endothermal ablation, using radiofrequency ablation (RFA) and endovenous laser ablation (EVLA). This endovenous method of treating varicose veins using thermal energy has demonstrated its merits and has been adopted as the first-line treatment option by both the American Venous Forum and the National Institute for Health and Care Excellence (NICE, UK) [9, 10].

This status has come into question with the emergence of newer methods which enable faster and more comfortable procedures. This is of particular interest as endovenous thermal ablation can be associated with patient discomfort during tumescent infiltration as well as potential injury caused by the thermal ablation process itself. These newer techniques, namely, mechanochemical ablation (MOCA) [11] and cyanoacrylate glue injection (CAE) [12], are commonly referred to as

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non-thermal, non-tumescent (NTNT) interventions. There is a suggestion that MOCA might be equivalent to the endothermal treatment [13, 14].

In this chapter, the technique and outcomes of cyanoacrylate adhesive injection are discussed.

What is Cyanoacrylate?

The chemical adhesive used in this method is N-butyl cyanoacrylate (n-BCA), which was first introduced to medical practice more than 40 years ago [15]. It is a liquid monomer, which quickly polymerises and solidifies in contact with an anionic solution (e.g. with the hydroxyl groups in blood) [16]. In the beginning, it was found to have a low tensile strength and gave rise to features suggestive of both an acute and a chronic inflammatory process [15]. The polymerisation event leads to occlusion, a marked inflammatory endothelial response, and eventually leads to fibrosis [16].

Gradually, following the addition of plasticisers and stabilisers, the material was made more flexible and less toxic [15]. This rendered the chemical more appealing and expanded its use in ophthalmology, wound closure, dentistry and gastroenterology [17]. More than 10 years of cyanoacrylate use in the endoscopic sclerotherapy of gastric variceal bleeding confirmed that the chemical was safe [17].

In endovascular surgery, cyanoacrylates have been found indispensable in the treatment of type I and II endoleaks of abdominal aortic aneurysm repairs, arteriovenous malformations (AVM), varicoceles and pelvic congestion syndrome [17].

Given the efficacy and good safety profile of cyanoacrylates in these endovascular procedures, Dr. Raabe, an interventional radiologist from Washington (USA), considered using a similar technique in the treatment of varicose veins [18]. However, as the characteristics of the cyanoacrylate in use at the time were inappropriate for leg varicose veins, a team of chemical, biochemical and product engineers were assembled to produce a chemical with more suitable properties and develop a delivery system suited for leg veins [18].

Vein Sealing Devices and Technique Used

Two vein sealing devices are currently available. They are the VenaSeal™ closure system (Medtronic, Minneapolis, Minnesota, USA) and the VariClose® vein sealing system (Biolas®, Ankara, Turkey). The technique of cyanoacrylate injection as well as the makeup of the adhesive used differs.

VenaSeal™ Closure System

The VenaSeal™ closure system was the first device available, and the technique of vein sealing involves segmental pullback. The method of cannulation is similar to other current endovenous methods: truncal vein cannulation and insertion of a 0.035 in. J-guidewire, followed by placement of a 7Fr introducer sheath/introducer [12]. A 3 mL syringe containing the cyanoacrylate adhesive is connected to the delivery catheter. This latter system possesses hydrophobic properties, thereby preventing adhesion to the vessel wall, and air-filled microchannels, which allow for better visibility when using an ultrasonic device [12]. The dispenser gun is then fired, thus priming the catheter. Each trigger pull delivers 0.1 mL of cyanoacrylate. In order to prevent premature contact between the cyanoacrylate and blood during introduction into the venous lumen, the distal 3 cm of the catheter tubing is kept empty. The catheter is then connected to the introducer sheath, and under ultrasound guidance, the tip is positioned 5 cm from the saphenofemoral junction (SFJ). With extrinsic pressure applied over the SFJ (above the tip of the catheter) using the ultrasound transducer, 0.2 mL of cyanoacrylate is delivered (two trigger pulls). The catheter is pulled back 3 cm, and pressure is applied to the treated segment for 3 min. Again, the ultrasound probe is positioned above to the tip of the catheter, 0.1 mL of CAE (one trigger pull) is injected and 30 s of pressure is applied to the vein. This cycle is repeated until the whole vein is treated. At the end, the catheter is removed and additional pressure is exerted onto the entry

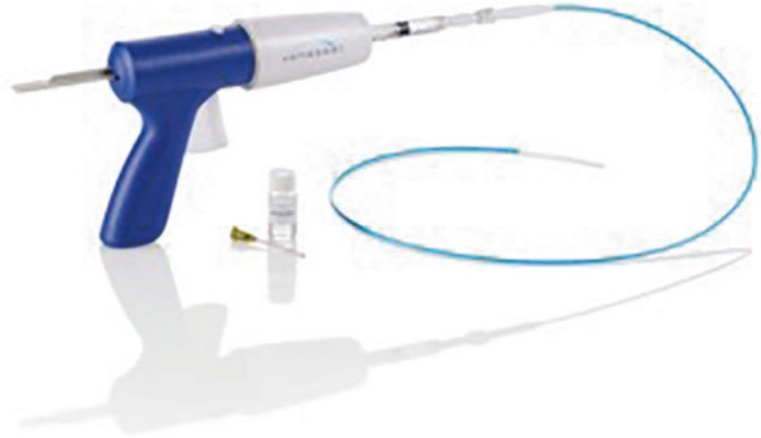

Fig. 11.1 The VenaSeal™ closure system

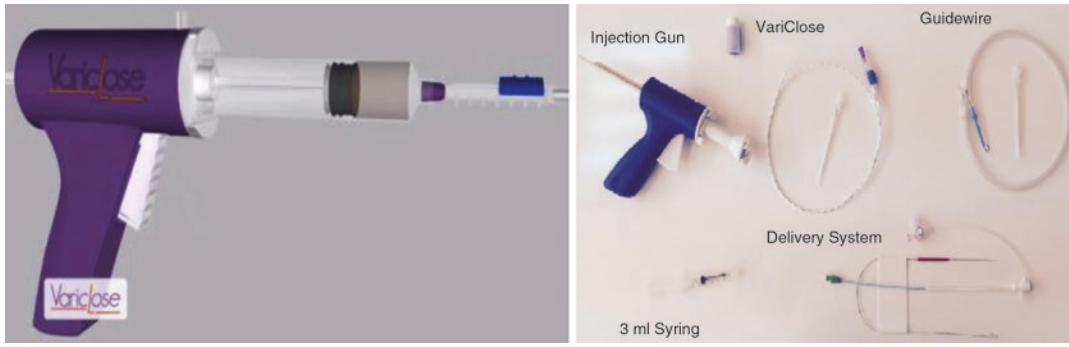

Fig. 11.2 The VariClose® vein sealing system

site. If no further treatment is necessary, a wound dressing is applied on the entry site. There is no requirement to wear compression stockings or bandaging afterwards.

Patients are discharged shortly after their treatment, with the recommendation to return to their normal activities as soon as they are able to (Fig. 11.1).

VariClose® Vein Sealing System

The VariClose® vein sealing system is similar to the VenaSeal™ closure system but uses a cyanoacrylate with a faster polymerisation rate. The process of venous access is as for other conventional endovenous methods. The delivery catheter has been designed with hydrophobic properties and features enabling easy visualisation under ultrasound. A 3 mL cyanoacrylate-containing syringe is connected to this 4Fr catheter, which is primed by slowly pulling the trigger gun over 5 s (delivering 0.3 mL of cyanoacrylate) [19]. The catheter tip is exposed and positioned 3 cm distal from the SFJ. Pressure is applied over the SFJ with the ultrasound transducer. Treatment of the saphenous vein involves injecting 0.3 mL for every 10 cm of vein length. External compression is applied for 5 s following treatment of the first 10 cm of vein. The catheter is pulled back continuously at a rate of 2 cm per second with pressure from the ultrasound probe moving down the leg at the same rate. This carries on until the full length of the vein is ablated (Fig. 11.2).

An adhesive bandage is applied over the entry site, and as for the VenaSeal™ closure system, no compression stocking or bandage is necessary. Patients are advised to return to their normal

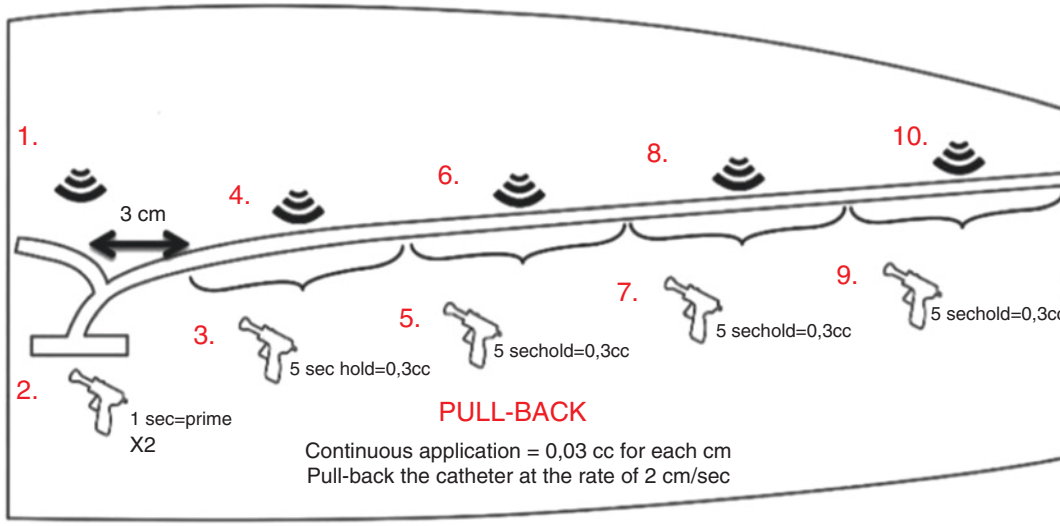

Fig. 11.3 The VariClose® vein sealing system involves positioning of the catheter 3 cm distal from the saphenofemoral junction, injection of 0.03 mL/cm of cyanoacrylate and continuous pullback of the catheter at a rate of 2 cm per second along with simultaneous application of pressure using the ultrasound probe

Table 11.1 Comparison of the VenaSeal™ closure and VariClose® vein sealing systems

	VenaSeal™	VariClose®
Country of origin	USA	Turkey
Venous access	Vein cannulation and sheath insertion	Vein cannulation and sheath insertion
Chemical used	Cyanoacrylate	Cyanoacrylate
Delivery catheter	Connected to delivery gun	Connected to delivery gun
Catheter pullback	Segmental	Continuous
External compression	Segmental	Continuous
Speed of polymerisation	Slow	Fast
Distance from SFJ	5 cm	3 cm
Post-intervention compression	None	None

activities as soon as possible but to wait until 1 day after their intervention before they start exercising (Fig. 11.3) (Tables 11.1 and 11.2).

Table 11.2 Comparison of the cyanoacrylate characteristics of the two vein sealing systems

	VenaSeal™	VariClose®
Colour	Clear	Blue
Consistency	Viscous (like 'honey')	Runny (like 'water')
Polymerisation	Slow	Fast
Texture post-polymerisation	Soft	Hard

Cyanoacrylate in the Treatment of Varicose Vein Disease

Animal Studies

A plastic and a tissue model (common carotid artery of a swine) were used to investigate the process of polymerisation of cyanoacrylates, and three distinct stages were noted [20]. An initial stage (phase I), lasting less than 10 s, showed a linear rate of increasing tensile forces, while a second stage (phase II), lasting up to 1 min, was found to have a constant strength of tensile

forces. Finally, the third and final step (phase III) follows phase II and involves complete polymerisation of the compound, characterised by an exponential rise in the tensile forces [20]. The strength of the binding forces as well as the rate of polymerisation is variable and dependent on the type and formulation of cyanoacrylate used [17, 20].

Evaluation of cyanoacrylate as a vein sealing method was conducted in the superficial epigastric veins (SEVs) in a swine model [21]. The SEVs were treated with the cyanoacrylate, and the swines were euthanised 60 days later. There were no sections of the SEVs which were patent. The segment treated was shown to be occluded with histological sections showing the presence of both inflammatory cells and fibrous tissue. This was consistent with a chronic foreign-body-type inflammatory reaction. No undesirable migration of the chemical or recanalisation of the treated veins was found.

Human Studies

VenaSeal™ Closure System

In the first clinical trial of CAE in the treatment of varicose veins, Almeida et al. (2013) recruited 38 patients [12]. They used the Sapheon closure system (Sapheon, Santa Rosa, California, USA) (eventually acquired by Medtronic, Minneapolis, Minnesota, USA) in which the catheter tip is placed 4 cm away from the SFJ. The incompetent GSV was treated, and patients were reviewed up at different time points over 24 months. Seventy-six percent of them were females, and the median age of patients was 51 years (range, 26–77 years) [12]. The mean length of GSV treated was 33.8 cm (standard deviation (SD), 9.1 cm), and the mean GSV diameter at the SFJ was 8.0 mm (SD, 2.2 mm). The complete occlusion rates were 100% at 2 days and 92.1% at the 12-month follow-up (three veins had recanalised). Using a Kaplan-Meier life table analysis, the occlusion rate was found to be 92% at the 24-month point [22]. Commonly encountered complications included post-operative thrombophlebitis (seven patients), thrombus extension into the common femoral vein (eight patients), cellulitis (one patient) and hyperpigmentation (one patient) [12].

A multicentre study in seven European centres looked at the use of CAE in the treatment of incompetent GSVs, but the distance of the catheter tip from the SFJ was modified to 5 cm [23]. This distance was thought to be more suitable as it could allow for glue propagation proximally towards the SFJ following cyanoacrylate injection and, at the same time, would provide for enough space to exert external pressure between the tip of the delivery catheter and the SFJ. As per Almeida et al. study, no compression hosiery was prescribed following treatment. In addition, no tributary treatment or reintervention was undertaken until after 3 months of post-ablation. Seventy patients were recruited in total, 78.6% of whom were females. The mean age was 48.4 years (range, 22–72 years). The mean length of GSV treated was 37.6 cm (range, 7–72 cm), and the mean GSV diameter at the SFJ was 7.8 mm (SD, 2.1 mm). The mean ablation time was 18.6 min (range, 8–74 min). At the 12-month follow-up, the complete occlusion (defined as no patent segment of more than 10 cm) rate using a life table method was 92.9% [23]. The Venous Clinical Severity Score (VCSS) improved from a mean of 4.3 at the baseline to 1.1 at the 12-month follow-up ($p < 0.0001$). The disease-specific Aberdeen Varicose Vein Questionnaire (AVVQ) also showed improvement from 16.3 at the baseline to 6.7 at 12 months ($p < 0.0001$). Phlebitis was noted in eight legs, and a single patient had thrombus extending into the common femoral vein. Treatment of this complication with 2 weeks of low molecular weight heparin led to resolution of the thrombus.

The efficacy of the VenaSeal™ device in the treatment of varicose veins was compared to endothermal ablation techniques in a multicentre randomised controlled trial (the VeClose trial), with patients randomised to receiving either radiofrequency ablation (RFA) or cyanoacrylate injection [24]. Two hundred and twenty-two patients were recruited, randomised and treated. Since the instruction for the use of RFA recommends compression stockings, these were prescribed for 7 days for all patients (3 days

continuous wear and 4 days for daytime wear only). The primary end-point was a successful closure of the entire treated vein with no discrete patent segments of more than 5 cm. The most common CEAP clinical class recorded was 2 and 3. Three months post-intervention, the occlusion rate for the cyanoacrylate group was found to be 99% compared to 96% in the RFA group [24]. Clinical scores (VCSS) and QoL (AVVQ and EQ-5D) showed significant improvement from the baseline, with no difference between treatment groups. There were more cases of phlebitis noted in the cyanoacrylate group, but this was not statistically significant. The degree of ecchymosis was found to be significantly less in the cyanoacrylate group ($p < 0.01$). The mean intra-procedural pain scores for CAE was 2.2, compared to 2.4 for RFA ($p = 0.11$). This study demonstrated that cyanoacrylate was not inferior to RFA and that it was a safe and highly effective method of varicose vein treatment.

VariClose® Vein Sealing System

Bozkurt and Yilmaz (2016) investigated the VariClose® vein sealing system, by comparing the cyanoacrylate injection device to endovenous laser ablation (EVLA) in patients attending for treatment of their GSV incompetence [19]. Three hundred and fourteen patients were recruited and followed up for 1 year. The mean age was 40.2 years for the EVLA group and 42.5 years for the CAE group. The mean GSV length was 29.7 ± 8.1 cm for EVLA and 29.8 ± 5.4 cm for CAE, and the mean vein diameter was 7.1 ± 1.6 mm and 7.2 ± 1.8 mm for EVLA and cyanoacrylate, respectively. Pain scores were recorded as 6.5 ± 2.3 for EVLA, compared to 3.1 ± 1.6 for CAE ($p < 0.001$). The procedure time was significantly faster with cyanoacrylate (15 min for CAE vs 33.2 min for EVLA; $P < 0.001$). At 12 months, the occlusion rate was found to be 95.8% for CAE and 92.2% for EVLA [19]. Both the clinical scores (using VCSS) and QoL scores (AVVQ) showed significant improvement compared to the baseline, and there were no significant differences between the two groups. Seven cases of paraesthesia were noted in the EVLA group compared to none in the cyanoacrylate group. This study, therefore, showed that both endothermal ablation and cyanoacrylate injection were equivalent.

Complications of Cyanoacrylate

The most commonly recorded complication after cyanoacrylate injection seems to be ecchymosis and phlebitis. Extension of thrombus into the common femoral vein was noted in the first human trial, and this was believed to be secondary to the catheter being placed too close from the SFJ and not providing enough room for the glue to propagate along the vein [12]. This distance was, therefore, increased in ensuing studies with a resultant improvement in the rate of this complication. The acceptable distance for the VenaSeal™ closure system catheter tip from the SFJ is now 5 cm [23, 24]. The VariClose® vein sealing system, however, still uses a distance of 3 cm, and no thrombus extension into the deep venous system has been described. Another potential problem with the technique is the possibility of the adhesive getting stuck in the delivery sheath, thereby making movement and retrieval of the catheter difficult.

Other possible complications from cyanoacrylate come from other medical usage of the chemical. In the treatment of gastric varices, CAE is at the risk of systemic embolisation. This can cause pulmonary embolism, multi-organ infarction via a patent foramen ovale, stroke and recurrent sepsis caused by the embolised cyanoacrylate glue acting as a septic focus [25]. These latter adverse events have, thus far, not been reported with cyanoacrylate use in varicose veins.

Conclusion

Varicose vein management is fast evolving with endovenous ablation now the accepted new norm. Endothermal ablation is recommended as first-line treatment by a number of venous societies, but its use is associated with complications related to the thermal ablation process as well as discomfort from tumescent infiltration. The new

non-thermal, non-tumescent methods have been launched with the aim of avoiding these undesirable effects while maintaining a high effectiveness rate. Vein sealing, using the cyanoacrylate injection devices, seems promising and has shown equivalence when compared with the endothermal methods. There is currently no set limit on the amount that can be used, and, therefore, this might be more advantageous than some of the other non-thermal interventions (e.g. the European Phlebological Societies guidelines recommend a maximum of 10 mL of foam sclerosant to be used per session [26]).

Based on available evidence, the endothermal technologies remain the favoured choice for endovenous ablation in many European centres. NICE guidelines on the use of cyanoacrylate glue occlusion for varicose veins have also highlighted that current evidence on the safety and efficacy of the technique is limited and advocates its use with special arrangements only [27]. Further randomised comparative studies will hopefully shed more light onto the longer-term efficacy of the technique.

References

1. Evans CJ, et al. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh vein study. J Epidemiol Community Health. 1999;53(3):149–53.
2. Kurz X, et al. Do varicose veins affect quality of life? Results of an international population-based study. J Vasc Surg. 2001;34(4):641–8.
3. Kaplan RM, et al. Quality of life in patients with chronic venous disease: San Diego population study. J Vasc Surg. 2003;37(5):1047–53.
4. Beebe-Dimmer JL, et al. The epidemiology of chronic venous insufficiency and varicose veins. Ann Epidemiol. 2005;15(3):175–84.
5. Shepherd AC, et al. A study to compare disease-specific quality of life with clinical anatomical and hemodynamic assessments in patients with varicose veins. J Vasc Surg. 2011;53(2):374–82.
6. Durkin MT, et al. Long saphenous vein stripping and quality of life--a randomised trial. Eur J Vasc Endovasc Surg. 2001;21(6):545–9.
7. MacKenzie RK, et al. The effect of long saphenous vein stripping on quality of life. J Vasc Surg. 2002;35(6):1197–203.
8. Darvall KA, et al. Changes in health-related quality of life after ultrasound-guided foam sclerotherapy for great and small saphenous varicose veins. J Vasc Surg. 2010;51(4):913–20.
9. Gloviczki P, Gloviczki ML. Guidelines for the management of varicose veins. Phlebology. 2012;27(Suppl 1):2–9.
10. National Institute for Health and Care Excellence, NICE Clinical Guideline Centre. Varicose veins in the legs – the diagnosis and management of varicose veins (clinical guideline 168). UK: NICE; 2013.
11. Elias S, Lam YL, Wittens CH. Mechanochemical ablation: status and results. Phlebology. 2013;28(Suppl 1):10–4.
12. Almeida JI, et al. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. J Vasc Surg Venous Lymphat Disord. 2013;1(2):174–80.
13. van Eekeren RRJP, et al. Mechanochemical endovenous ablation for the treatment of great saphenous vein insufficiency. J Vasc Surg Venous Lymphat Disord. 2014;2(3):282–8.
14. Lane T, et al. A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins – final results of the Venefit versus Clarivein for varicose veins trial. Phlebology. 2016;32(2):89–98.
15. Idle MR, et al. N-butyl-2-cyanoacrylate (NBCA) tissue adhesive as a haemostatic agent in a venous malformation of the mandible. Br J Oral Maxillofac Surg. 2013;51(6):565–7.
16. Linfante I, Wakhloo AK. Brain aneurysms and arteriovenous malformations: advancements and emerging treatments in endovascular embolization. Stroke. 2007;38(4):1411–7.
17. Min RJ, et al. Novel vein closure procedure using a proprietary cyanoacrylate adhesive: 30-day swine model results. Phlebology. 2012;27(8):398–403.
18. Morrison N. Is cyanoacrylate safe for peripheral venous applications? Endovascular Today. 2015: pp. 78–79.
19. Bozkurt AK, Yilmaz MF. A prospective comparison of a new cyanoacrylate glue and laser ablation for the treatment of venous insufficiency. Phlebology. 2016;31(1 Suppl):106–13.
20. Kailasnath P, Chaloupka JC. Quantitative assessment of polymerization-binding mechanics of cyanoacrylates: model development and validation. AJNR Am J Neuroradiol. 2002;23(5):772–8.
21. Almeida JI, et al. Cyanoacrylate adhesive for the closure of truncal veins: 60-day swine model results. Vasc Endovasc Surg. 2011;45(7):631–5.
22. Almeida JI, et al. Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. Phlebology. 2015;30(6):397–404.
23. Proebstle TM, et al. The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins. J Vasc Surg Venous Lymphat Disord. 2015;3(1):2–7.
24. Morrison N, et al. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation

for incompetent great saphenous veins (VeClose). J Vasc Surg. 2015;61(4):985–94.
25. Bhat G, Suvarna D, Pai CG. Symptomatic portal biliopathy following cyanoacrylate injection for a bleeding duodenal varix. Trop Gastroenterol. 2013; 34(2):108–9.
26. Rabe E, et al. European guidelines for sclerotherapy in chronic venous disorders. Phlebology. 2013; 29(6):338–54.
27. National Institute for Health and Care Excellence. Interventional procedure guidance: cyanoacrylate glue occlusion for varicose veins. 2015.