

Current Trends and Advancements in the Management and Treatment of Varicose Veins - A Review

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Abstract: Varicose veins affect about 5% of the Indian Population and is one of the ubiquitous peripheral vascular diseases worldwide. Generally, they are neither life threatening nor disabling, however they cause morbidity among the patients. The Published research articles on the treatment of varicose veins were reviewed from the medical literature databases like Pubmed, European PMC and through a manual review of distinguished articles. Several clinical practice and recent progress in the management and treatment were reviewed in this article. And the distinct results and outcome of diverse treatment practices were also discussed.

Keywords: conservative management invasive management, eva, hirudotherapy, non-invasive management, varicose veins.

1. Introduction

Chronic lower extremity venous insufficiency is one of the most common vascular problems and badly affects the quality of people’s lives (Darvall KA et al, 2012; Kahn SR et al, 2004). About 10%–15% of men and 20%–25% of women suffers due to varicose veins in the lower part of the legs and is one of the most persistent vascular diseases of humankind. (T. Yamaki et al, 2002; Evans C.J. et al, 1998). Nearly one-third of adult males and females who are aged between 18 to 64 years have varicose veins. Every 1 out of 2 people have high incidence of this disease when they cross the age of 50 (Evans C.J. et al, 1999).

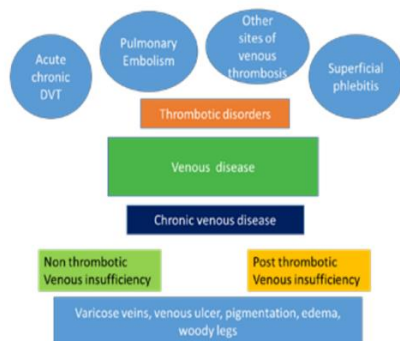


Fig. 1. Types of venous diseases (Source: Wikipedia)

The people tend to develop several risk complications which rapidly increase the occurrence of deep vein thrombosis,

varicose veins, leg edema, pulmonary embolism, varicose veins, Leg edema, Lipodermatosclerosis (LDS) and venous ulceration (Figure 1).

Varicose veins is a venous disorder and they look like “spider veins” ranging from a small, red or blue colored thread-like structure to large protruding veins of more than 1 cm in diameter. Sometimes the veins get distorted due to the reverse or unstable blood flow or at times the veins get dilated due to an underlying condition called edema. These conditions instigates the patients to seek prompt medical attention to ameliorate the associated symptoms of varicose veins (Figure 2).

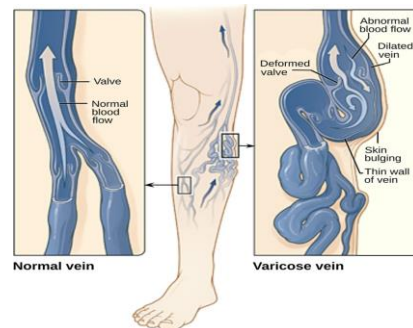


Fig. 2. Normal vs. Varicose Veins (Source: Wikipedia)

Almost for a century, the only practical treatment for varicose veins (VV) is surgery. However, the last decade has seen the inception of diverse non-surgical treatment modalities practiced by the clinicians of vascular surgery department. In 2014, the clinical practice regulatory guidelines for the management and treatment of varicose veins were developed conjointly by the American Venous Forum (AVF) and the Society for vascular surgery (SVS) (O'Donnell TF and Passman MA, 2014). The guidelines include conservatory treatments like modification of lifestyle like “exercise, diet management and weight control, keeping legs at an elevated place, wearing compression hosiery, open venous surgery, endovenous thermal ablation with laser or radiofrequency energy, and sclerotherapy” (Gloviczki P et al, 2011). In 2013, the UK National Institute for Health and Care Excellence (NICE) proposed Clinical Guidelines (CG, 168) for the treatment of

Varicose Veins. The treatments are Ultrasound Guided Foam Sclerotherapy (UGFS), Endothermal Ablation (ETA), Compression stockings and surgery (NICE, 2013).

2. Diagnosis

The symptoms of VV patients range from asymptomatic to manifestation of prominent symptoms like soreness, discomfort, irritation or eczema, and deep vein thrombosis (Ren S et al, 2005). The diagnosis of varicose veins is made by ultrasound imaging and superficial venous insufficiency is clinically diagnosed by duplex ultrasound. It is also used to assess the patients for suspected DVT before venous surgery; and also the significant guidance for the vascular blood flow examination which might guide in the diagnosis of vein valve function, proximal occlusion, and venous reflux. Brodie-Trendelenburg is a test that helps in differentiating between deep and superficial reflux.

Table 1

CEAP Classification (C- Clinical component)	
C0	No visible or palpable signs of venous disease
C1	Telangiectases (dilated interdermal venules <1 mm) or reticular veins (nonpalpable subdermal veins 1-3 mm)
C2	Varicose veins (diameter of vein >3 mm)
C3	Edema
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis
C5	Healed venous ulcer
C6	Active venous ulcer

Source: Vasquez MA, 2008

The gradation of the VV in patients were done by CEAP (clinical, etiology, anatomy, pathophysiology) (Table 1). It helps in elaborative diagnosis and to find the degree of severity of the venous disease (Vasquez MA, 2008; Lattimer CR et al, 2014). This article focuses on the various treatments in recent practice and the new trending advancements in the management of disease are reviewed.

3. Study Design

The research articles were retrieved from the medical literature databases like NCBI (Pubmed central) & Europe PMC and from Journals related to Vascular surgery that were published until 19th August, 2019 for writing this review article. The keywords used for searching the literature are management and treatment of varicose veins.

4. Management

Recent advancements in the technological development has led to the emergence of novel and minimally invasive treatments, such as endovenous radiofrequency ablation (ERFA), endovenous laser ablation (EVLA). This almost completely eliminates the disadvantages associated with conventional surgery that causes post-surgical complications like haematomas, scars, inguinal neovascularization, and a delayed recovery which interferes with the routine day to day

activities (Table 2).

Table 2
 Treatment options for VV (until 2005)

Compression hosiery	Below knee grade II (30-40 mmHg) compression stockings
Sclerotherapy	Direct injection of sclerosant into varicosities (outpatient); ultrasound guided LSV sclerotherapy (foam or liquid)
Minimally invasive:	
Radiofrequency ablation (VNUS [®])	Radiofrequency (thermal) ablation LSV ± phlebectomies or sclerotherapy: usually performed under general anaesthesia, day case or overnight in-patient stay
Endovenous laser treatment (EVL [®])	Laser (thermal) ablation LSV with pulsed diode laser ± delayed (6/52) sclerotherapy: local anaesthesia, out-patient ('Office') procedure
Surgical	
Sapheno-femoral ligation, LSV stripping and phlebectomies	Widely available, day case or overnight in patient stay, general anaesthesia. Variations include length of vein stripped and method of stripping
Ambulatory conservative haemodynamic management (ACTM or CHIVA)	Identification of sites of deep to superficial reflux and elimination of these sites only, general anaesthesia, day case or overnight in-patient stay
Transilluminated powered phlebectomy (TIPP, TriVex [®])	An alternative to phlebectomies using tumescent peri-venous infiltration and illumination to allow 'resection' of varicosities resulting in fewer incisions. Conventional surgery for reflux still required: general anaesthesia, day case or overnight in-patient stay
Endovenous diathermy	Endovenous diathermy: general anaesthesia, usually day case procedure
Cryosurgery	Endovenous cryoprobe: general anaesthesia, usually day case procedure

(Source: Beale R.J. and Gough M.J., 2005)

The systematic approach for the management of VVs has changed due to recent knowledge of cosmesis among people since they have an impact in deteriorating the quality of life; and due to the recent advancements in new treatment practises such as foam sclerotherapy echo-guided sclerotherapy, endovascular obliteration and ambulatory care practices. The ideal VV management requires exact identification of the cause of superficial venous insufficiency and also include the successive treatment modalities for eliminating the venous reflux, amelioration of symptoms, forbid associated venous complications, improve the state of being morbid, decrease the recurrence rates, and quick recovery time.

Much advancement is observed in clinical studies that currently fulfil the standards of evidence and research based medicine. The progressive therapy for the complex VV includes initial clinical findings of symptoms and ultrasound imaging, followed by rapid meticulous diagnosis, and then to direct the patients for an appropriate and effective treatment procedures.

5. Conservative Management

It is basically the initial line of therapy provided to treat symptomatic varicose veins. There are numerous conservative management options like compression therapy, leg elevation, weight loss, and pharmacotherapy. Compression therapy is not advised to patients with conditions of saphenous vein as the first line treatment (Gloviczki P et al, 2011). Numerous interventional modalities are beneficial in the treatment of varicose veins, nevertheless the recurrence rates are high (Murad MH et al, 2011).

In 2016, Rajiv Mallick et al, conducted a retrospective study among the newly diagnosed VV patients and evaluation of therapy among different cohorts and the post treatment outcomes were also studied. The results showed that the majority of patients with VV complaints underwent conservative treatment. Various factors such as age, gender, and burden of morbidity has a prominent role to play in opting the conservative management against interventional treatment. Amongst the patients who were treated with interventional therapies, successful outcomes were observed in the group that received surgery and the most favorable outcomes were observed in the study cohort that received an extra

interventional treatment; additionally, the costs for the management of varicose veins possibly resulted in the least price for the extra interventions. The minimal degree of disease advancement is seen in sclerotherapy and it might reflect some unmeasured patient selection in that traditional sclerotherapy is often used for visible varicosities. Sustained benefits were present in all the interventional study groups even during the successive years of post-treatment. Contrarily, the initial and continued high costs in the observation and compression therapy cohorts also showed that the costs associated with other associated medical conditions were also more thereby counteracting the low varicose vein-specific treatment costs.

6. Minimally Invasive Surgery

Conventional ligation and removing of the saphenous vein has been indispensably displaced by endovenous thermal procedures for removing the valvular reflux within the saphenous veins.

Endovenous ablation (EVA) is an ambulatory percutaneous technique which involves less-invasive catheter that employs heat energy (laser or radiofrequency) to block the inefficient vein, thereby eliminating reflux and restoring the abnormal venous hemodynamics (Liu P et al, 2011). In Endovenous laser ablation (EVLA), after giving local anaesthesia (by perivenous tumescent technique), a catheter tube is inserted at 2 cm underneath the saphenofemoral or saphenopopliteal junction and heat waves are delivered onto the incompetent vein, thereby triggering the inflammation followed by fibrosis and clots of the vein (Rasmussen LH, 2011). Quicker recovery is seen in the patients who underwent this procedure and instant resumption of their daily activities are observed in this medical procedure. However, there are some postoperative complications like hematoma, thrombophlebitis, infection at the site of procedure, bruising and infiltration of tumescent fluid also causes discomfort (van den Bos RR, 2009).

1) *Complications: In a case report by Damar (2019), a case in which the guidewires which were used during invasive procedures were unknowingly left in the intravascular area itself and it was then removed by hybrid technique through probing into jugular vein and percutaneous intervention of femoral vein. The principal reasons for leaving a guidewire in the vascular area are inattentiveness, ignorance, hastiness, fatigue of the surgeon, and insufficient surveillance of an experienced surgeon (Taşoğlu, 2007).*

2) *Laser Ablation: One of the most commonly used new minimally invasive techniques is Endovenous laser ablation (ELA). Fibrotic sealing of the treated vein lumen is the end result. The removal of vein is achieved under local - tumescent anesthesia and the patients can be given treatment even in a small setting with instant resumption to routine activity. Clinical Safety and efficacy appear to be the significant features and advantages as well. EVLA provides significantly reduced postoperative pain and discomfort and appears to be cost effective solution.*

3) *Ultrasound-guided foam sclerotherapy (UGFS)* is a non-thermal, non-tumescent method and, regardless of having a lower occlusion rate, it has also been shown to enhance the quality of patients' lives. The two recently launched non-thermal, non-tumescent methods, mechanochemical ablation and cyanoacrylate glue, have also been found to provide promising results (Bootun, R et al, 2016). In a swine model, the injection of *Cyanoacrylate (CA)* in the blood vessel initiates polymerization, led by a chronic foreign-object-type inflammatory response followed by the closure of venous walls, segmental wall thickening, and fibrosis. The injection of CA is feasible for closure of superficial veins in animal models (Almeida J I et al, 2011). The effectiveness of *mechanochemical ablation (MCA)* to endothermal techniques was studied by Kim, P. S. et al, 2017. This study involved patients with reflux in the great saphenous vein involving the sapheno-femoral junction and who had no previous history of venous interventions were included. Venous closure rates were found to be 100% at first week, 98% at three months, 95% at 12 months, and 92% at 24 months. Early high occlusion rate associated with mechanochemical ablation showed significant clinical improvement at 24 months, making it to be a very good option for the treatment of great saphenous vein incompetence. They also found a marked betterment in CEAP and venous clinical severity score.

4) *Ambulatory phlebectomy* is a procedure that doesn't require any hospital stay for the VV patients. Under local anesthesia, the superficial veins are removed through a tiny 2-3 mm incisions on the skin over the varicose veins. The instruments used for this technique is the vein retractor or phlebectomy hook to grasp the veins, extracted and are pinned with a clamp and finally vein is stripped out. Using standardized compression stockings or bandages are tied at the site of procedure for upto 1 to 2 weeks. This procedure can also be used as an addition to EVLA or Radiofrequency Ablation. The complications are unexpected however may include paresthesia, bruising, bleeding, and blood clotting. Preferring compression stockings to the bandage may decrease the complications of skin contusion. EVLA with with both treatments achieves excellent results at 5 years. Additional treatment of varicosities often provides an optimal improvement in both quality of life and the degree of clinical severity (Harlander, 2013; Carroll C et al, 2014).

Under tumescent anesthesia, *Transilluminated powered phlebectomy (TIPP)* is performed by the combination of a supersonic mechanical resector with fiber optic transillumination endoscopy for the removal of superficial varicose veins through micro-incisions with exceptional results. which combines irrigated illumination with for ablation of superficial varicosities and venous resection.

7. Non-Invasive Management

An additional benefit is that varicose veins frequently regress followed by the EVA procedure, so in order to attain maximal

cosmetic improvement, some patients may even opt to undergo additional minimally invasive treatment options later. Recently, numerous novel alterations of endovenous ablation are commonly available which are even less invasive and promises lower risk of complications. Techniques such as mechanochemical vein ablation or the use of cyanoacrylate “glue” may prove to be equally effective at “closing” the faulty vein(s) with yet an even lower incidence of potential minor side effects.

8. Sclerotherapy

Under the supervision of Duplex ultrasound, sclerosing foam is introduced through a cannula in the affected vein where in the sclerosing foam replaces the blood. The endothelium and its sub endothelial layers of the venous wall gets inflamed because of the irritant nature of the foam, leading to fibrosis and followed by the occlusion of the vein. It can even be performed in the basic hospital setting, and use of compression stockings is prescribed straightaway after FS (Gloviczki P et al, 2011). The success rate ranges from 82% to 100% in the observational studies. The recovery was quick following foam sclerotherapy than the conventional surgical vein stripping. It takes only about 1 hour to carry out FS, patients do not even need to take follow up medicines or hospital stay after the treatment (Telling SS et al, 2011). It is mandatory that the axial vein reflux be wholly eliminated by EVA before sclerotherapy for effective results. In recent years, the use of newer sclerosing agents and techniques (including foam sclerosants) has led to markedly enhanced results. Stab avulsion is a surgical technique performed under local anesthesia to surgically remove the varicose veins through numerous tiny incisions (<1 cm). This is performed when the saphenous vein is normal or had been previously removed, and is especially helpful for patients who have complaints of large veins that cannot be treated by sclerotherapy.

For patients with veins that are very large can be successfully treated only with sclerotherapy, also several other techniques of vein excision (phlebectomy) are also available. Recent novel trends in clinical practices enable more veins to be removed through smaller incisions, all on an ambulatory basis and with minimal scarring at the site of VV.

9. Venaseal System

It is the latest innovative treatment for the inefficient saphenous vein by performing the Cyanoacrylate closure. And this method was successfully employed to treat a larger great saphenous vein (GSV) which measured about 2.84 cm in diameter. With the help of ultrasound guidance, delivery catheter was introduced into the inguinal area and was posited 5.0 cm distal to the GSVs proximal end. By pressing the end of saphenous vein with the ultrasound probe, two CA glue injections of roughly 0.10-mL were given, followed by a repeated single injections and compression of 30 seconds. Extra glue injection was permitted with caution for regions having larger diameter, or regions with interfacing or perforated veins.

If the GSV veins are larger with a diameter of 2.84 cm, sealing is done by double glue injections in every 2 cm. And the remaining GSV was treated in the formerly described manner, with repeated cycle single injections followed by a 30-second compression for every 3 cm distally. And then the catheter was removed and compression was given at the site, until there are no signs of bleeding. A bandage was applied and closure was finally confirmed by ultrasound (Park Insoo, 2018).

Concomitant phlebectomy is not performed, but concomitant sclerotherapy with sodium tetradecyl sulfate is carried out after completing the above described procedure. Liquid type solution (0.2%) is used for the procedure of telangiectasia in the middle part of thigh region and foam type solution (1.0%) is used when there are two penetrating veins in the sides of calf region and in the back of the calf area. The treated patients are recommended to wear a thigh high compression hosiery for about 1 week due to the concomitant sclerotherapy. During the follow-up after one month, duplex sonogram is done to confirm the closure of the vein and the maximal vein diameter was reduced from 2.84 cm to 2.31 cm (Park Insoo, 2018).

10. Pharmacological Therapy

Numerous clinical trials and a Cochrane review of research articles evaluated that a diversified group of phyto-based venous drugs helps in treating patients with symptomatic varicose veins (Pittler MH and Ernst E, 2012; Martinez MJ et al, 2005). Management of symptoms of VV and amelioration of achiness, cramps, restless legs, swelling sensation, and paresthesia were identified through clinical studies. Mechanism of action of the studied plant based drugs have proven to increase coordination of veins by intensifying the noradrenaline pathway, amplifying the capillary resistance, and depleting the capillary filtration. Micronized purified flavonoid fraction (MPFF) has been proven to enhance the lymphatic flow, reduce blood viscosity, and diminish the release of inflammatory mediators. These plant based medications should be taken as a supplement in combination with other therapies such as surgery, ablation techniques, compression therapy, sclerotherapy, and surgery. Pentoxifylline is a phytodrug generally used for patients with arterial diseases, but is also proven to increase the healing of venous ulcers (Jull A et al, 2012), by impeding the activation of neutrophils and minimizing the liberation of free radicals. Presently, the American Venous Forum practice guidelines (Gloviczki P et al, 2011) allotted a slight advice for the usage of venoactive drugs along with combined therapies for symptomatic VV patients, and a strong suggestion for the usage of pentoxifylline as adjuvant therapy when advising compression for patients who had venous ulcers.

11. Ayurvedic Management

According to ayurveda VV can be linked with *Siraja Granthi*. VV occurs due to occurs as a result of rakta-pitta dosha and also due to accumulation of blood within venous walls as a

result of damaged or weakened venous valves (Wickramasingha M and Ediriweera E, 2018). The dosha can be removed by employing either any one of the following two mechanisms 1) By prescribing blood purifiers to purify the polluted blood or by prescribing blood thinners and 2) By eradicating the dosha (also called as inflammation). Laxative use is advised in order to remove the pitta dosha. The blend of nanosized particle ashes of pearl, mollusc shell, oyster shells, cowries, coral mixed with latex of *Calotropis procera* are used to achieve the laxative effect (Emmi et al, 2015).

Hirudotherapy: (Medicinal leech therapy) is used to treat a number of diseased conditions characterized by manifestation of pain. Saliva of leech contains vital components like hirudin and calin which possess anti-inflammatory agent, anticoagulant (inhibit acetylcholine), thrombolytic agent and blood/lymph circulation improving properties. In this therapy, saliva of leech is injected into patient while withdrawing blood from the patients. As it has analgesic property as well, the leech therapy is fast, effective and long-lasting in many painful conditions. Review of Case reports compilation provides clinical evidence for leech therapy's analgesic effects (Koeppen D et al, 2014).

Herbal Therapy: The drug Gotu kola is known to treat skin ailments and also to promote healthy veins. It has also been listed in the Indian Pharmacopeia in the 19th century since it possesses the ability to cure various skin ailments like leprosy, varicose ulcers, psoriasis, eczema, etc. The permeability of the veins gets increased due to hyperplasia which gets provoked by the phyto active constituents of the plant. This plant drug provides relief from the symptoms of varicose veins and helps in the management of VV (Tiwari S et al, 2011; Gohil K et al, 2010). *Tagetes erecta* are also scientifically proven to exhibit antioxidant, healing properties, analgesic and antibacterial properties. This treatment regimen is found to be effective in the treatment of *Siraja Granthi* (varicose veins).

Varicose veins are treated by *Raktamokshana* also termed as bloodletting therapy which is performed using leeches, paste of fresh leaves of Dahaspathiya (*Tagetes erecta*) and *Maduruthala Koththamalli Wandu Thambuma* (*Ocimum sanctum* and *Coriandrum sativum*) which are utilised by Sri Lankan traditional physicians to VV effectively with positive outcome (Wickramasingha M and Ediriweera E, 2018).

12. Comparison of Therapies

There are various randomized trials that comparatively analysed the venous surgery with other types of endovenous ablation procedures. In 2015, Van der Velden and his team examined at five year results that comparatively assessed the surgery, EVLA, and foam sclerotherapy in VV patients with GSV reflux disease. As a result, they found conventional surgery and EVLA to be better than foam for occlusion of the saphenous veins.

In 2016, O'Donnell and his team mates performed a meta-analysis of randomized clinical trials that compared surgery and endovenous ablation (either EVLA or RFA) of the saphenous

vein reflux and observed no variations in varicose vein recurrence. In 2017, Koramaz and his co-researchers performed a retrospective comparative study from the follow-up data retrieved from patients who underwent n-butyl-2 cyanoacrylate closure and EVLA. The results showed that there were not any noticeable variations in efficacy between the two treatment modalities except a few adverse events like pigmentation and phlebitis after n-BCA compared with EVLA. In a randomized clinical trial comparing MOCA and RFA, Bootun and his colleagues (2016), found no difference in the degree of closure or quality of life, but early results indicated MOCA is the less painful of the two procedures (Bootun R et al, 2016). In general, these studies suggest that endovenous procedures are equally effective for treating VV patients with GSV or SSV reflux when compared with surgery.

13. Conclusion

Varicose veins can be successfully managed with a broad range of treatment facilities. Outpatient clinic based ultrasound imaging procedure has upgraded the diagnosis, clinical assessment and various options for therapy to choose. Not just one treatment is advised for all the symptomatic and asymptomatic VV patients. Occasionally, varied treatment modalities are required to diagnose and treat accordingly to the different veins in the same patient. On the basis of anatomy of vein, pathophysiology of venous disease, existing symptoms, comorbidities, and preferences of patients the treatment modalities become varied.

References

- [1] Almeida, Jose I., et al. "Cyanoacrylate adhesive for the closure of truncal veins: 60-day swine model results." *Vascular and endovascular surgery* 45.7 (2011): 631-635.
- [2] Beale, R. J., and M. J. Gough. "Treatment options for primary varicose veins—a review." *European journal of vascular and endovascular surgery* 30.1 (2005): 83-95.
- [3] Bootun, Roshan, Tristan RA Lane, and Alun H. Davies. "The advent of non-thermal, non-tumescent techniques for treatment of varicose veins." *Phlebology* 31.1 (2016): 5-14.
- [4] Carroll, C., et al. "Systematic review, network meta-analysis and exploratory cost-effectiveness model of randomized trials of minimally invasive techniques versus surgery for varicose veins." *British Journal of Surgery* 101.9 (2014): 1040-1052.
- [5] Işık, Mehmet. "Removal of the splitted guidewire forgotten during the treatment of varicose veins via radiofrequency ablation." *Turkish Journal of Vascular Surgery* (2019).
- [6] Darvall, K. A. L., et al. "Generic health-related quality of life is significantly worse in varicose vein patients with lower limb symptoms independent of CEAP clinical grade." *European Journal of Vascular and Endovascular Surgery* 44.3 (2012): 341-344.
- [7] Darvall, K. A. L., et al. "Generic health-related quality of life is significantly worse in varicose vein patients with lower limb symptoms independent of CEAP clinical grade." *European Journal of Vascular and Endovascular Surgery* 44.3 (2012): 341-344.
- [8] Emmi S V, Singh R, Rajput N: Ayurvedic Management of Varicose Vein and Varicose Ulcer. *Int. J. Res. Ayurveda Pharm.* 2015; 6(2).
- [9] Evans C.J., Allan P.L., A.J. Lee, A.W. Bradbury, C.V. Ruckley, F.G. Fowkes. Prevalence of venous reflux in the general population on duplex scanning: the Edinburgh vein study. *J Vasc Surg*, 28 (1998), pp. 767-776.
- [10] Evans C.J., Fowkes F.G., C.V. Ruckley F.G., Lee. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general

- population: Edinburgh Vein Study. *J Epidemiol Comm Health*, 53 (1999), pp. 149-153
- [11] Głowiczki P, Comerota AJ, Dalsing MC, et al; for the Society for Vascular Surgery; American venous Forum. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2011; 53(5 suppl):2S-48S.
- [12] Gohil K, Patel J and Gajjar A: Pharmacological review on Centella asiatica: A potential herbal cure-all. *Indian Journal of Pharmaceutical Sciences*. 2010; 72(5), 546.
- [13] Harlander LM, Jimenez JC, Lawrence PF, Derubertis BG, Rigberg DA, Gelabert HA. Endovenous ablation with concomitant phlebectomy is a safe and effective method of treatment for symptomatic patients with axial reflux and large incompetent tributaries. *J Vasc Surg*. 2013; 58(1):166–172.
- [14] https://en.wikipedia.org/wiki/Varicose_veins
- [15] Jull A, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. *Cochrane Database Syst Rev* 2012; (12):CD001733.
- [16] Kahn SR, M'Lan CE, Lamping DL, for the VEINES Study Group, et al. Relationship between clinical classification of chronic venous disease and patient-reported quality of life: results from an international cohort study. *J Vasc Surg* 2004; 39:823–8.
- [17] Kim, Pamela S., et al. "Mechanochemical ablation for symptomatic great saphenous vein reflux: a two-year follow-up." *Phlebology* 32.1 (2017): 43-48.
- [18] Koepfen, D., Aurich, M. & Rampp, T. *Wien Med Wochenschr* (2014) 164: 95.
- [19] Koramaz I, Kilic H, Gokalp F, et al. Ablation of the greater saphenous vein with non-tumescent n-butyl cyanoacrylate versus endovenous laser therapy. *J Vasc Surg Venous Lymphat Disord* 2017; 5: 210-215.
- [20] Lattimer CR, Kalodiki E, Azzam M, Geroulakos G. The Aberdeen varicose vein questionnaire may be the preferred method of rationing patients for varicose vein surgery. *Angiology*. 2014; 65(3):205–209.
- [21] Liu P, Ren S, Yang Y, Liu J, Ye Z, Lin F. Intravenous catheter-guided laser ablation: a novel alternative for branch varicose veins. *Int Surg*. 2011; 96(4):331–336.
- [22] Martinez MJ, Bonfill X, Moreno RM, et al. Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev* 2005;(3):CD003229.
- [23] Murad MH, Coto-Yglesias F, Zumaeta-Garcia M, et al. A systematic review and meta-analysis of the treatments of varicose veins. *J Vasc Surg*. 2011; 53(5 suppl):49S-65S.
- [24] National Institute for Health and Clinical Excellence. Varicose veins in the legs. NICE guidelines CG168 www.nice.org.uk/guidance/cg168 (2013).
- [25] O'Donnell TF, Balk EM, Dermody M, et al. Recurrence of varicose veins after endovenous ablation of the great saphenous vein in randomized trials. *J Vasc Surg Venous Lymphat Disord* 2016; 4: 97-105.
- [26] O'Donnell TF Jr and Passman MA. Clinical practice guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF)--Management of venous leg ulcers. Introduction. *J Vasc Surg*. 2014 Aug; 60 (2):1S-2S.
- [27] Park Insoo. "Successful use of VenaSeal system for the treatment of large great saphenous vein of 2.84-cm diameter." *Annals of surgical treatment and research* vol. 94, 4 (2018): 219-221.
- [28] Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database Syst Rev* 2012; (11):CD003230.
- [29] Rajiv Mallick, Aditya Raju, David Wright, Kimberly Boswell. Treatment Patterns and Outcomes in Patients with Varicose Veins. *Am Health Drug Benefits*. 2016 Nov; 9(8): 455–465.
- [30] Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. *Br J Surg*. 2011; 98(8):1079–1087.
- [31] Ren S, Liu P. Initial clinical experiences in treating 27 cases of varicose veins with EVLT plus TRIVEX. *J US China Med Sci*. 2005; 2(1):4–8.
- [32] T. Yamaki, M. Nozaki, O. Fujiwara, E. Yoshida. Comparative evaluation of duplex-derived parameters in patients with chronic venous insufficiency: correlation with clinical manifestations. *J Am Coll Surg*, 195 (2002), pp. 822-830
- [33] Taşoğlu İ, Özgül H, İmren Y, Gokgoz L. A rare complication after central venous catheterization: a retained guide wire in the subclavian vein. *Turkish J Thorac Cardiovasc Surg* 2007; 15: 174-5.
- [34] Telling SS, Ceulen RP, Sommer A. Surgery and endovenous techniques for the treatment of small saphenous varicose veins: a review of the literature. *Phlebology*. 2011; 26 (5):179–184.
- [35] Tiwari S, Gehlot S, Gambhir IS: Centella asiatica: A concise drug review with probable clinical uses. *Journal of Stress Physiology and Biochemistry*. 2011; 7(1), 38-44.
- [36] Van der Velden, S. K., et al. "Five-year results of a randomized clinical trial of conventional surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins." *British Journal of Surgery* 102.10 (2015): 1184-1194.
- [37] Vasquez MA, Munschauer CE. Venous Clinical Severity Score and quality-of-life assessment tools: application to vein practice. *Phlebology*. 2008; 23(6):259–275.
- [38] Wickramasingha, M.A.P., and Ediriweera, E. (2018). Effect of Rakthamokshana (bloodletting therapy) and Sri Lankan traditional medicine on Siraja Granthi (varicose veins) - A case study. *International Journal of AYUSH Case Reports*, 2(1), 6-13.