Effect of Leech Therapy (*Irsal-e Alaq*) and Unani Formulation (*Itrifal Sagheer* with *Zanjabeel)* in the Management of Varicose Veins (*Dawali*): An open, randomized, standard controlled, three groups clinical trial

Varikoz venlerin tedavisinde sülük tedavisi *(Irsal-e Alaq)* ve Unani formülasyonun *(Itrifal Sagheer with Zanjabeel)* etkinliği: Randomize, standart kontrollü, üç gruplu klinik çalışma

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ABSTRACT

Aim: Varicose veins affect up to 5% or more of the adult population of western countries and 15 to 20% of general population. The inability to perform heavy and prolonged standing works affects the quality of life, and earning capacity of patients as well. Unani physicians have described this disease as Dawali and have been treating the disease since ancient times effectively on the principle of evacuation (Tanqiya), restoration (Ta'deel) and potentiation (Taqwiyat). The limitation of conventional treatment in the management of varicose veins paved the way to evaluate the efficacy and safety of leech therapy and a pharmacopoeial Unani poly herbal formulation in the management of varicose veins on scientific parameters.

Methods: The study was conducted as open, randomized, standard controlled, three groups clinical trial on 30 eligible patients. Leech therapy was selected as a treatment procedure in the test group 'A'. The combination of Unani formulation Itrifal Sagheer with Zanjabeel and leech therapy was selected as a treatment strategy in the test group 'B'. Compression stocking was selected as a standard treatment procedure in the control group 'C'.

Results: Significant statistical difference was observed in subjective and objective parameters. Almost all patients reported improvement in pain and heaviness. The more promising result was observed in group 'A' in pain (82%), where group 'B' showed more marked response (64%) in heaviness among all the groups. In intra group comparisons, statistically highly significant difference was observed from baseline to 14th day to 28th day ($P<0.001$) on Revised VCSS in both groups 'A' and 'B', But the mean difference was more in group 'B' (5.36) than in 'A' (4.53). In group 'C', the mean difference was (-1.60). Highly significant change was also observed in vein diameter below knee and above ankle in group 'A' and group 'B', while no significant change was demonstrable in group 'C'. No significant change was found in safety parameter.

Conclusion: The trial regimen of leech therapy and Unani formulation Itrifal Sagheer with Zanjabeel was found safe and effective in the treatment of varicose veins, predominantly in pain, heaviness, swelling, skin changes and vein diameter.

Keywords: Dawali; Irsal-e Alaq; Itrifal Sagheer; Varicose Veins; Leech therapy; Compression stocking.

ÖZET

Amaç: Variköz venler batı toplumundaki erişkin bireylerin %5, genel popülasyonun ise %15-20 kadarında görülmektedir. Ağır ve uzun süre ayakta kalmayı gerektiren işleri yapamamak, hastaların yaşam kalitelerini bozar. Unani hekimleri bu hastalığı Dawali olarak ifade etmişler ve eski zamanlardan beri bu hastalığı tahliye (Tanqiya), restorasyon (Ta'deel) ve güçlendirme (Taqwiyat) prensiplerine dayanan yöntemlerle etkili şekilde tedavi etmişlerdir. Variköz venlerin konvansiyonel tedavilerinin yetersizliği, sülük tedavisi ve Unani bitkisel tedavilerinin kullanılmasına kapı aralamıştır.

Yöntemler: Çalışma, randomize, standart kontrollü ve üç gruptan oluşan klinik çalışma olarak yapıldı. Çalışmaya 30 hasta dahil edildi. A grubuna sülük tedavisi uygulandı. B grubuna hem Unani formülasyon (Itrifal Sagheer ve Zanjabeel beraber) hem de sülük tedavisi verildi. C grubuna ise kompresyon çorabı standart tedavi yöntemi olarak uygulandı.

Sonuçlar: Subjektif ve objektif parametrelerde istatistiksel farklılıklar vardı. Hemen hemen bütün hastalar ağrı ve ağırlık hissinde hafifleme olduğunu belirtti. A grubundaki hastalar ağrı hissinin %82 oranında azaldığını, B grubundaki hastalar ise ağırlık hissinin %64 azaldığını ifade ettiler. Grup içi karşılaştırmalarda, A ve B gruplarının her ikisindede, 14 ve 28. günler başlangıca göre oldukça farklıydı ($P<0.001$). B grubunun ortalama farklılığı (5.36), A grubuna göre (4.53) daha yüksekti. C grubunun ise 1.60 idi. Diz altı ve ayak bileği üstündeki ven çapları A ve B gruplarında anlamlı şekilde farklı idi, fakat C grubunda bu farklılık yoktu. Güvenlik parametreleri açısından bir fark yoktu.

Yorumlar: Sülük tedavisi ve Unani formülasyonu varikoz venlerin tedavisinde etkili ve güvenli bulundu. Bu tedaviler özellikle ağrı, ağırlık hissi, şişme, deri değişiklikleri ve ven çapı üzerine etkili idi.
Anahtar kelimeler: Dawali; Irsal-e Alaq; Itrifal Sagheer; Varikoz venler; Sülük tedavisi; Kompresyon çorapları.

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INTRODUCTION

The word varicose vein is derived from 'varix', a Latin word, means twisted. [1] The varicose vein is defined as "dilated tortuous and elongated superficial vein of lower limb." [2] Varicose veins is one of the commonest categories of primary venous insufficiency. [3] It affects 5% or more of adult population in western countries. The gender prevalence was found nearly equal as mentioned in Bailey & Love's Short Practice of Surgery with reference to Edinburgh Vein Study. Pathophysiology of varicose veins is probably related to defective connective tissue and smooth muscle in the wall of veins leading to a secondary incompetence of the valves rather than to a primary defect in the valves. The common symptoms of varicose veins are leg aching ankle swelling, itching, bleeding and complications like eczema, superficial thrombophlebitis, lipodermatosclerosis and ulceration, [4] The patients with symptomatic varicose veins commonly report heaviness, discomfort and extremities fatigue. [3] Diagnosis is based on clinical examination [5] and standard Doppler test. [4] Till date, no curative treatment for varicose veins is available; however, elastic compression stocking, sclerotherapy and different types of surgeries are recommended in conventional system of medicine. The surgical intervention is effective in varicose vein treatment, But after surgery bruising and sensory nerve injury are common. Recurrence is the most common complication of varicose vein surgery. [4]

In Unani system of medicine, "*Dawali",* described in almost all classical books of Unani medicine, is synonymous with varicose veins. Unani physicians claim that black bile (*Khilt-e Sauda*) and phlegm *(Balgham*) are responsible for genesis of this disease. People engaged in professions requiring prolonged standing are more prone to develop varicose veins. [6, 7] Many single and compound drugs along with bloodletting regimens are described for the treatment of *"Dawali*". [6, 7, 8, 9, 10] Leech therapy is an important and effective method of bloodletting in the treatment of varicose veins. [8, 9, 10] Leech therapy and evacuation of black bile from the body (*Tanqiya-e Sauda*) [6, 7, 8, 9,10] by drugs are being successfully used for the management of varicose veins in Unani system of medicine. In order to evacuate morbid matter, *Itrifal Sagheer* with *Zanjabeel* [6, 11] is one of the effective compounds Unani formulation used for the treatment of varicose veins. Efficacy of leech therapy alone in the management of varicose vein has been already established by some studies, but no comparative study of leech therapy and Unani formulation has been carried out on scientific basis. The common prevalence of varicose veins and non-availability of safe and effective treatment, were two important causes to embark upon a credible and rational clinical trial.

In view of the above facts, a comparative, three groups, Randomised, open, standard controlled clinical study was carried out to evaluate the efficacy of leech therapy and Unani formulation *Itrifal Sagheer* with *Zanjabeel* in the management of varicose veins**.**

METHODOLOGY

Study design

The study was designed as Randomised, open, standard controlled clinical study conducted at National Institute of Unani Medicine (NIUM) Hospital, Bangalore, Karnataka, India from February, 2013 to December, 2013. The study was approved by Institutional Ethical Committee of NIUM and conducted according to the Declaration of Helsinki and the GCP guidelines issued by Indian Counsil of Medical Research (ICMR). Ethical clearance: IEC No: NIUM/IEC/2011-12/007/Moal/07, University Registration No: 07_U006_33071

Participants

Patients of both genders, age group of 20-60 years, with varicose veins and confirmed by venous colour Doppler, willing to give written informed consent and follow the protocol were enrolled in the study. Pregnant and lactating women, Patients of diabetes, severe hypertension, secondary varicose veins, Deep

Venous Thrombosis (DVT), coagulopathy and severe systemic diseases were excluded from the study.

A total of 30 patients were randomly allocated into three groups, comprising 10 patients in each of test group 'A' test group 'B' and control group, respectively. The random allocation was based on computer generated randomization table. One patient was lost to follow up from group 'C' (compression stocking group) but was compensated by enrolling one more patient in that group.

The treatment period was as certained as 28 days for each group. The patients were treated in the out patient department and in patient department and followed up at 14 days intervals for the assessment of disease till the completion of study. Concomitant treatment in any form was not allowed to patients other than test drug and regimen of study.

The **Test group A**, comprised of 10 patients, was treated by application of 2-3 leeches twice weekly for 28 days only. The **Test group B,** comprised of 10 patients, and was treated by application of 2-3 leeches twice weekly and oral administration of *Itrifal Sagheer*, 7 gm with powder of *Zanjabeel*, 1.75 gm both once in a day for 28 days. **The Standard Control group,** comprised of 10 patients, and was treated by class II elastic compression stocking. The subjects were advised to wear compression stocking during the day time hours for 28 days.

Investigations

Certain investigations were carried out focusing on four important objectives:

(a) To exclude other patients as a part of exclusion criteria (b) Diagnosis of the disease

(c) To establish the safety of the test drug (d) Pre-procedure for leech therapy

Ø Haemoglobin Percentage (Hb %) , Total Leucocytes Count (TLC), Differential Leucocytes Count (DLC) Erythrocytes Sedimentation Rate (ESR) Ø Urine routine & microscopic Ø Blood Sugar random Ø Kidney Function Test (Blood urea & serum creatinine) Ø Liver Function Test (SGOT, SGPT, S. Bilirubin), Venous Colour Doppler of leg Ø HIV I & II, HBsAg.

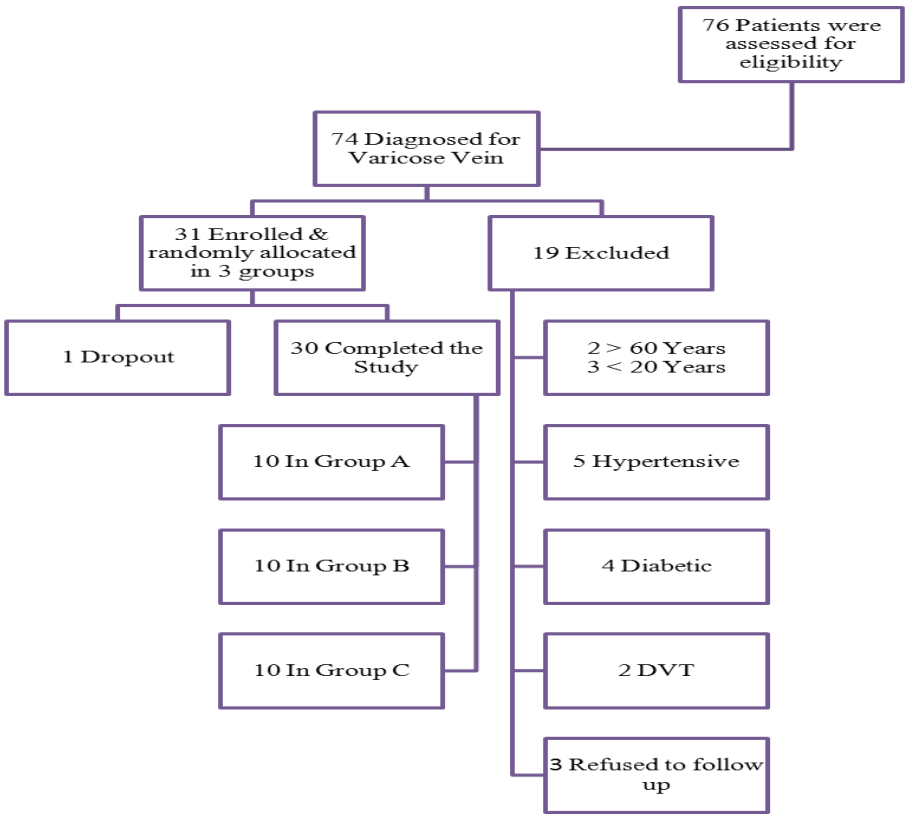

Figure No. 1. Study patients flow chart

Preparation of treatment material

The ***Itrifal Sagheer*** consisted of *Emblica officinalis* dried (*Amla khushk*), *Terminalia belerica* fruit rind *(Poast bahera)*, *Terminalia chebula* fruit rind *(Poast halaila zard)* and *Terminalia chebula (Halaila Siyah)*. The ingredients of *Itrifal Sagheer* and *Zanjabeel* were procured from licensed drug dealers of Bangalore city. The dried components for *Itrifal Sagheer* were pulverized and passed through sieve no. 50 to prepare powder. The powder was mixed with Butter (Ghee). The sugar syrup (*(Qiwam*) was prepared and powder added slowly and steadily into sugar syrup, heated gently and kept on stirring throughout the process of mixing to avoid any lumping of drug material. On cooling, *Itrifal* was packed and stored in air tight container. Identification of ingredient and preparation of *Itrifal* was done under the guidance of chief pharmacist of NIUM, Bangalore. The *Zanjabeel* was also powdered and stored in air tight container.

The leeches were procured from leech suppliers and were sent for identification to The New College (Autonomous) PG & Research Department of Zoology, Chennai. Dr. M. Asrar Sheriff, PhD, associate professor & Head of the Department identified leeches as *Hirudinaria granulosa.* The leeches were stored in regimenal therapy unit as per ideal condition.

Leech application procedure:

Before the application of leeches, all the necessary investigations such as Bleeding Time (BT), Clotting Timing (CT), Haemoglobin percentage (HB %), HBsAg and HIV were carried out. Before leeching, the application part was thoroughly washed with soap and water. The leeches were cleaned by sponge before application. The site was rubbed till appearance of redness followed by application of leeches. If the leeches seemed averse to bite, a small needle prick was made on the target site to surface a tiny droplet of the blood to attract them. The leeches, on sucking the target part to their fill, usually detach after 30 minutes; if not so, they were separated by sprinkling turmeric powder on their heads. The used leeches were placed in separate container duly labelled with patient's name to avoid any confusion in case they were used again. The oozing from wound usually stops itself within three hours. The dressing of wound was done with sterile pad and antiseptic lotion. The leech bite area was routinely observed for any swelling or infection. Patients were asked to avoid any strenuous physical activity on the day of leech application and contact the investigator in case of any adverse effect. To prepare the leech for reuse in same patient, emesis was induced in the leech by turmeric or forced to disgorge by squeezing it between fingers. These disembogued leeches were used again in same patient. On the day of leech application, the Patients were advised not to use any cream or perfume at the site of leech application, since the leeches are very sensitive to smell and refuse to bite.

Assessment of the efficacy

The assessment of efficacy of treatment in test and control groups was carried out on the basis of "Revised venous clinical severity score" (Revised VCSS) especially designed for evaluation of chronic venous diseases. The Revised VCSS contains 10 items. Each item of scale has a definite activity. Each attribute has a definite score on ground of history and clinical examination. The score ranges from 0-4. 0 is for none, 1 for mild, 2 for moderate and 3 for severe, as per guidelines of Revised VCSS. Scores were recorded in a prescribed proforma. The efficacy assessment was made on total score in each group. Assessment was carried out on 0 day, 14th day and 28th day of the treatment.

Patients were also assessed for the girth of leg; the girth was recorded in centimetre just below tibial tuberosity and 1cm above the ankle joint of affected leg. It was recorded in record form on base line (0 day) and after treatment (28th day) in each group. Venous colour Doppler findings were taken into account for assessment of efficacy of treatment in each group. Assessment was carried out on 0 day and 28th day.

The presence of pain and heaviness in leg was recorded as none, mild, moderate and severe category as subjective parameter at every follow up and was analyzed accordingly. The scores were analyzed in all three groups and subjected to comparison and analysis statistically to evaluate the efficacy of the treatment.

Descriptive and inferential statistical analyses were carried out in the study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Repeated Measures ANOVA has been used to find the significance of study parameters between three or more measurement of patients (Within group analysis); Analysis of Variance has been used to find the significance between three groups. Student 't' test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale within each group. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1,Systat 12.0 and R environment

ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs and tables etc**.**

RESULTS

Clinical observations

Seventy four patients were assessed for eligibility, of whom31 enrolled and allocated randomly in three groups. Out of 31 randomized patients 30 completed the study and one dropped out due to unknown reason. Out of completed 30, the male female ratio was19:11. 26 out 30 patients had a history of prolonged standing. BMI score was > 25 in 21out of 30 patients. Age wise 19 patients out of 30 belong to 31-40 year of age group as shown in table-1.

Almost all patients reported improvement in pain and heaviness. The more promising result was observed in group 'A' in pain (82%), where group 'B' showed more marked response 64% in heaviness among all the groups as shown in table-2. It is also observed that there was no positive family history in 90% of patients. 96% were married and 86% patients were non vegetarian. No positive history was observed regarding use of OCP in females.

Statistical Result

Statistically highly significant difference was observed from baseline to 14th day and to 28th day ($P<0.001$) on Revised VCSS in group 'A' and group 'B'. But the mean difference was more in group 'B' (5.36) than in 'A' (4.53). In group 'C' the mean difference was (-1.60). Highly significant difference was observed in girth measurement below knee and above ankle, in group 'A' and group 'B', while in group 'C' it was relatively less. No significant changes were found in Venous Doppler Study of any group except in vein diameter. Highly significant change was also observed in vein diameter below knee and above ankle in group 'A' and group 'B', while no significant change was in group 'C'. No significant change was found in safety parameter except increase in RBS in group 'B' and BT in group 'C' as shown in table-3.

Adverse events: Mild to moderate itching was observed in few patients of group 'A' and group 'B' after leeching. Only in one patient, redness, swelling and pain developed around the biting point of leech, which was relieved by application of *Roghan- Gul* within 48 hours.

Table 1. Demography of patients

Attribute	Group A (n=10)	Group B (n=10)	Group C (n=10)
Age (Mean years)	37.7	40.4	36.7
Gender (Male: Female)	6:4	7:3	6:4
Prolonged standing (Yes: No)	10:0	7:3	9:1
BMI (>25: < 25) {kg/m^2}	8:2	4:6	9:1
Mizaj (Temperament)(B:D:S)	5:4:1	8:2:0	7:3:1

B=Balghami (Phlegmatic), D=Damvi (Sanguineous), S=Safravi (Bilious)

Table 2. Subjective parameters

Attribute (improvement)	Group A(n=17 legs)	Group B(n=14 legs)	Group C(n=15 legs)
Pain (% change)	82.40	57.10	20.00
Heaviness (% change)	58.80	64.30	40

DISCUSSION

Study Design

Keeping in view the previous studies done on leech therapy, the comparison between compression stockings, leech therapy alone and leech therapy along with a Unani formulation was selected as a design of the study. In Unani system of medicine, leech therapy alone is not advised for treatment [7, 8, 9]; therefore, a combination of evacuation regimen leech therapy with *Itrifal Sagheer* and *Zanjabeel* was holistically tested in the patients of *Dawali* for the validation of a safe and effective alternative treatment.

Demography

The total number of patients in the study was 30. It was so less to comment and discussed on.

Obesity, *Mizaj* (Temperament), Oral Contraceptives

The BMI of most of the patients was above 25, favouring the Unani concept of excessive lipids (*Kasrat-e Shahm*) [12] and modern concept where Lindsey Robertson study suggests that increased weight is associated with the increased incidence of chronic venous disease (varicose veins), where the risk was 3.6 fold higher in obese participants. [13]

Unani system of medicine believes that *Dawali* occurs due to viscid humour (*Ghaleez Khilt*) [6, 7] or dominance of any humour (*Khilt*), qualitatively or quantitatively, except pure bile (*Safra Khalis*). [8, 14] Therefore, the temperament of the patients in the study was found in accordance with the observations of ancient physicians.

Venous function is undoubtedly influenced by hormonal changes. [3] The oral contraceptive pills alter the viscosity of blood, level of progesterone and dilate vessel. [2] In the present study, no positive history was observed regarding use of OCP in females. It is supported by the findings of *Tiina Ahti* study, where she did not find any relation between Oral contraceptives or hormone replacement therapy and varicose veins. [15]

Assessment

Pain and Heaviness

Pain and heaviness as subjective parameters and limb girth measurement as objective parameter were included for the assessment of varicose veins. Though, pain and heaviness was also the part of Revised VCSS, but it was needed to assess the effect of compression therapy as studies suggest that it has role in relieving the symptoms specially pain, heaviness and swelling.

All the groups showed statistically significant improvement in the subjective parameters, but the more promising improvement for pain was observed in leech group 'A'. This may due to decongestion of morbid material as per Unani concept and analgesic activity of leech enzymes as per conventional concept. The significant improvement in heaviness in leech therapy and *Itrifal Sagheer* with *Zanjabeel* group 'B' may be due to the evacuation of extravasated morbid matter from the surroundings of the varicose veins, which is a cause of heaviness in *Dawali* as mentioned in Unani literature. [14] The observed effect in group 'C' is supported by the statement that use of compression stocking provides only symptomatic relief. [5, 16]

Table 3. Objective parameters

Attribute	Group A (n=17 legs)		Group B (n=14 legs)		Group C (n=15 legs)	
	BT	AT	BT	AT	BT	AT
REVISED VCSS (Mean±SD)	8.53±3.59	4.00±2.52	10.21±3.79	4.86±2.28	6.40±3.14	8.00±3.00
SFJ COMPETENCY	5(29.4%)	6(35.3%)	5(35.7%)	5(35.7%)	8(53.3%)	8(53.3%)
Number of perforators	1.76±1.52	1.76±1.39	3.36±2.50	2.93±2.34	2.62±2.29	2.38±2.29
Vein diameter (above ankle) cm	5.12±1.65	3.96±1.20	5.40±3.22	4.69±2.47	5.18±1.76	4.73±1.42
Vein diameter (below knee) cm	5.87±2.28	5.00±1.87	6.65±3.02	6.04±2.26	5.44±1.68	5.33±1.43
Vein diameter (mid thigh) cm	6.06±2.20	6.24±2.20	7.26±3.57	6.40±2.13	5.68±1.96	5.35±2.02
Girth (below knee) cm	34.65±2.73	33.62±2.78	37.21±4.48	36.11±4.90	36.90±3.97	36.10±4.43
Girth (above ankle) cm	21.85±1.40	21.12±1.15	23.07±3.53	22.04±3.21	24.03±2.90	23.60±2.90

AT= After treatment, BT= Before treatment, Cm= centimetre, VCSS=venous clinical severity score SFJ= sapheno femoral junction

Limb girth measurement

The statistically significant reduction was observed in limb girth, below knee and above ankle in all of the groups. The more pronounced result was observed in group 'B' i.e. leeches with *Itrifal Sagheer* and *Zanjabeel* group. It also proves the additional effect of *Itrifal Sagheer* with *Zanjabeel.*

The conclusion of previous study on varicose vein done to evaluate the effect of leech therapy was safe, well tolerated, and effective and has potential to treat the complication of the varicose veins. [17] The scale adopted in previous study was arbitrary one. They also mentioned that improvement was evaluated on pain, limb girth measurement and pigmentation, but study was silent on induration, extent of varicose vein, venous oedema, inflammation and ulceration. The findings of another clinical trial where they used the leech therapy along with *kaishor guggul* (an Ayurvedic formulation) in management of varicose vein found significant effect, but they assessed patients only on pain, swelling, itching and varicosity. They reported that the minimum of benefit was in varicosity and the maximum in itching. [18]

Revised VCSS

The American Venous Forum committee developed the venous severity scoring system in 2000, based upon initial experiences with the VCSS, they revised the VCSS. [19] So the Revised VCSS was taken for assessment in present study. Highly significant difference was observed from baseline to 14th day and to 28th day (P<0.001) on Revised VCSS in group 'A' and group 'B', But the mean difference was more in group 'B' (5.36) than in 'A' (4.53). In group 'C' the mean difference was (-1.60). The statistically significant improvement was found in leech group (A) and in leech with *Itrifal Sagheer* and *Zanjabeel*, group (B).The change in compression stocking group was in negative, indicating increase in VCSS scores. The more promising result was observed in group (B) than in group (A). The significant difference in leech group (A) is supported by the findings of previous studies. [17,18] The more promising result of leech along with *Itrifal Sagheer* and *Zanjabeel* (group B) suggests additional effect of *Itrifal Sagheer* and *Zanjabeel* over the leech therapy alone. Another important observation was that the significant improvement was found at 28th day than at 14th day. It indicates that prolonged treatment may have shown more promising result. It was also observed that in 10 attributes of Revised VCSS, the least improvement was in appearance of varicose vein. The significant improvement in group A & group B was in pain, venous oedema, inflammation and skin pigmentation. Furthermore, group 'B' showed better improvement in induration also.

Though compression stocking group showed improvement in pain and venous oedema, but the mean difference remained ineffective due to the inclusion of item of compressive therapy in Revised VCSS. In Revised VCSS, inclusion of compressive therapy is most controversial element. The American venous forum is still discussing the issue and possibly they will amend the VCSS in their next modification.

Venous Doppler Study

No significant change was found in Venous Doppler Study of any group except in vein diameter. Highly significant change was also observed in vein diameter below knee and above ankle in group 'A' (P 0.027* and 0.002**) and group 'B', (P 0.021* and 0.052+) while no significant change was observed in group 'C'. (P 0.394 and 0.059+). However, more promising result was in group A than group B. It is very difficult to explain as to why group 'A' responded better than group 'B'. The *Zarnigar et al*. study showed significant result on perforator, [17] which is not found in this study, due probably to short period of this study.

Compression stocking

The use of compression stocking provides only symptomatic relief.[5,16] The compression stocking group shows similar result in present study where it is observed that relief is limited to pain, heaviness and a little on oedema.

The overall statistical observations showed highly significant improvement in group A & group B, but more promising result was observed in group B than group A. It may due to additional effect of *Itrifal Sagheer* and *Zanjabeel.*

The effect of therapy achieved in present study is being discussed on two prospect, Unani (ancient) and conventional (Modern).

Unani Aspect

The pathology of *Dawali* in Unani system of medicine is dilation of veins due to excess of blood, (Dominance of Khilt-e- Dam) [8, 20] stasis of matter, [20] infiltration of viscid blood in vessels.[6] The viscid nature of morbid matter makes impossible to extravasate excess morbid matter from vessels resulting in congestion of vessels (*Imtila-e- Urooq*) and dilation of veins as well. Evacuation, restoration and potentiation of the involved organ is the principle of management in Unani system of medicine. The treatment was done on this basic principle. The emphasis on elimination of excess blood and morbid

matter is the key in the management of *Dawali*. Self elimination is not possible, so regimen should be applied. [21] Leech therapy is the means of elimination of blood and morbid matter as well. [22] The observed effect was possibly due to evacuation of morbid matter (*Tanqiya-e Madda*) by leech therapy. Detoxification of diseased organ *(Tanqiya of Uzoo'-e Khas)* is recommended in *Dawali*. [6, 21] This was achieved by leech and observed effect proved the role. The temperament of *Itrifal Sagheer* is opposite to the temperament of disease. The generalised evacuation property of *Itrifal Sagheer* and its usefulness especially in varicosities played a vital role in reverting the pathology. The *Zanjabeel* also has ability to produce long lasting hotness (*Hararat*) in human being and evacuation of viscid *khilt* by its mucolytic (*Qate'e Balgam*) activity. [23] It has detergent (*Jaali)* property [24] and used in piles and filariasis. [23] The *Itrifal Sagheer* and *Zanjabeel* are highly recommended in piles independently, but together they are recommended in varicose vein. It is possibly due to the concept that the organs, away from heart are colder and need high dosage and intensive treatment is requisite. The combination of *Zanjabeel* with *Itrifal Sagheer* potentiates the activities of each other to make them effective treatment strategy for *Dawali*. The more promising result observed in leech and *Itrifal Sagheer* with *Zanjabeel* group may be due to above mentioned properties of *Itrifal Sagheer* and *Zanjabeel*. The use of potent astringent paste (*Quabiz and Muqavvi Zimad*) is also suggested as a part of treatment after evacuation in varicose veins in classical texts, [8] however, it is not used in this study. This may be the possible reason behind insignificant change in the extent of varicose vein and vein valves.

In Unani system of medicine *Ratoobat-e Fasida*, *Hararat-e Mizaji*, or *Hararat-e Arzi* are responsible for development of ulceration. [6, 8, 9] The *Itrifal Sagheer* has *Jazib-e-Rutoobat* property [25] and leeches suck the morbid blood and therefore, instrumental in removal of the coagulated and stagnant blood. [23] All these properties, perhaps, played effective role in reversion of the pathology of venous ulcer formation.

Modern Aspect

In conventional system of medicine, the pathogenesis of varicose veins formation is not clear but certain possible pathology has been discussed. The new evidences suggesting that the occurrence of changes in anatomy and physiology are due to increased venous pressure and cause dilation of veins especially in leg. The recent studies clearly stated that it is the defect of vein wall, further leading to defect in vein valve due to matrix metalloproteinases (MMPs) activation, Inflammation and fibrosis. [26] Another study reported that the mechanical stretch in human tissues leads to over expression of MMPs in endothelial cell and smooth muscles. [27] It is also found that activation and infiltration of leukocyte in venous wall cause tissue fibrosis which further leads to wall degeneration and valve degradation. Type III

Collagen is important for distensibility and elasticity of blood vessel. The ratio of Type I & Type III collagen and alteration in collagen synthesis are responsible for early vein wall changes which lead to varicose veins formation. [26] Deficiencies of collagen and collagen of venous wall enter into pathogenesis of varicose veins. Increased collagen content and decreased elastin content have been postulated to enhance the dilatation of the veins. [3] The sustained venous pressure results in extravasation of cells, specially RBCs. The heamosiderin deposition in the subcutaneous plane from lysed RBC's is responsible for production of free radical. These free radicals cause tissue destruction and ulceration. [2, 28] The pathogenesis of varicose veins is thought to include increased venous and capillary Pressures, increased capillary permeability, chronic oedema, repeated inflammation, and Stasis. [29] As per Unani system of medicine the basic pathogenesis of varicose veins is congestion of varicose vein, increased level of morbid matter, its deposition and infiltration in and around vessels. In view of above reports and findings of leech saliva makes it an ideal treatment modality for varicose veins treatment. The possible mechanism of action behind the overall observed effects in leech group may be due to the bioactive substances such as Hirudin, Hyaluronidase and Eglin etc. present in leech saliva. The Hirudin retards the coagulation and is used for prevention of phlebitis and inflammation. [30] A study reports that destabilase dissolves blood clot; Hyaluronidase modifies the connective tissue permeability and reduces the viscosity of blood; calin suppresses collagen induced platelet aggregation and inhibits the direct platelet- collagen interaction; Eglin prevents neutrophil infiltration into inflamed vessels. Guamerin is new type of human leukocyte elastase inhibitor; fibrinase and collagenase reduce the scar tissue density and adhesion. [31] In another study unheated extract of leech shows analgesic effect. [31] *Zaidi SMA et al* reported that plastic surgeons use leeches to aid salvage of compromised venous engorged tissue. [32] This amalgamation of bioactive substances of leech saliva suggests that it has the capability to reduce or revert the pathology of varicose veins. In view of above reports and findings of leech saliva, this becomes an ideal treatment modality for varicose veins. Obesity is one of the risk

factors for varicose vein development. [12, 13] The study on *Itrifal Sagheer* reported that it helps to reduce weight and possesses anti hypercholesterolemic activity. [33] The *Itrifal Sagheer* (*Triphala*) has good amount of antioxidant which may be used for the treatment of high oxidative stress and also in scavenging of free radicals. [34, 35] Possibly, due to this property of *Itrifal Sagheer*, additional effect in group B was observed. The ingredients of *Triphala* have also nearly same properties as *Triphala* as a formulation, but it is found that *Triphala* as a formulation proves more effective than individual ingredients of *Triphala*, possibly due to synergistic activity.36 The exact mechanism of *Itrifal Sagheer* is not fully understood by modern medicine, though polyphenols and flavonoids present in it are thought to be responsible for many of its effects. Gallic acid, a major polyphenol in *Triphala*, has antioxidant property. [37] The ginger stimulates the circulation [38] which is useful in correction of stasis of blood due to dilation and can prevent the extravasation of RBCs. It is mucolytic. [23]

CONCLUSION

It may be concluded that the trial regimen comprising leech therapy and *Itrifal Sagheer* with *Zanjabeel* is effective in reducing symptoms and signs of varicose veins; particularly, pain, heaviness, swelling, skin changes and vein diameter. The employment of leech therapy and *Itrifal Sagheer with Zanjabeel* based on the principles of evacuation and restoration is safe and effective for the treatment of varicose vein. Experimental studies are necessary to find out further pharmacological actions of test regimen. Having no major side effect, this treatment may be preferred over conventional treatment comprising compression stocking, oral drug, injectable sclerosants and even over surgery, as a first line treatment. The limitation of this study was smaller sample size and short duration of therapy; hence, controlled clinical trials with large sample size are required to further prove the efficacy and safety of this treatment regimen in comparison to other prevalent treatment options. Incorporation of paste of potent astringent drugs (*Qabiz wa Muqavvi Zimad*) should also be taken into account by future researchers as this is also strongly recommended in all classical text after evacuation of morbid substance. Hence, it can be concluded that the test regimens used in present study have all the potential properties which seem to have positive effects not only in controlling the pathological changes but reverting them to normal state to restore the venous functions.

COMPETING INTERESTS

None

AUTHORS' CONTRIBUTIONS

Mohammad Shahid Khan was the principal investigator and Dr. Abdul Nasir Ansari was the supervisor of the study.

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