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International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Ann Int Med 1988;108:258-65.

- Both individual authors and organization as author Castelli E, Fazzi E; SIMFER-SINPIA Intersociety Commission. Recommendations for the rehabilitation of children with cerebral palsy. Eur J Phys Rehabil Med. 2016;52:691-703.

Issue with supplement

Lacarrubba F, Musumeci MI, Martorell A, Palmucci S, Petrillo G, Micali G. Role of the Imaging Techniques in the Diagnosis and Staging of Hidradenitis Suppurativa. G Ital Dermatol Venereol 2018;153 (3 Suppl 2), 20-5.

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 Congress proceedings
Novo S, Angelides N, Fletcher J, Roztocil K, editors. A multidisciplinary approach to cardiovascular diseases. Proceedings of the 1st Meeting of the Multidisciplinary Chapter of the International Union of Angiology (IUA); 2014 Oct 2-5; Palermo, Italy. Turin: Edizioni Minerva Medica; 2016.

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Supplementary Digital Material

Authors may submit supplementary material to support and enhance their article's text to be published in the online edition only. Supplementary material should be submitted online during the submission process and may include the following types of content: text files, tables, figures, audios and videos. Authors are requested to submit as supplementary material tables that are too long to fit on a single printed page of the journal and any appendices.

One or more files of supplementary material may be attached to the article. Such files must be submitted separately and cited in consecutive order in the text. There are no restrictions on the content of a file (it may include a text and a table, a single table, a figure and a table, two figures, a video, etc.).

Each in-text citation of supplementary material should be clearly labeled as "Supplementary Digital Material" followed by the relevant number and the description of the material submitted (Supplementary Digital Material 1: Supplementary Text File, Supplementary Figure 1, Supplementary Table I and Supplementary Table II online content only). Audio and video citations should also include the length and size of the file (Supplementary Digital Material 2: Supplementary Video 1, online content only, 5 minutes, 10MB). Text files, figures and tables of supplementary materials should be accompanied by the relevant title

Formats accepted for text files and tables: Word (.DOC and .DOCX) and RTF; formats accepted for figures JPEG set at 300 dpi resolution preferred; other formats accepted are TIFF and PDF (high quality); formats accepted for audio files: MP3, WAV; formats accepted for video files: MP4, AVI, WMV. To ensure a quality experience, it is suggested that authors submit supplementary audios and videos no larger than 10 MB each. If accepted, supplementary material will be published as submitted by the author without any correction and reformatting

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EDITORIAL

COVID-19, congresses and the dissemination of scientific information

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That do congresses represent for physicians and scientific societies? The congress is the expression of a variety of concepts: it is a time for catching up, or for conflict, but always a time for socializing and learning about what is new in research and pharmacology. It is a training ground where you can discuss and communicate your experiences directly, and not only ex cathedra, when your words have to be polished, communicated without too many upsets to tradition and in accordance with globalized international rules. It is a time for exchanging chat about emerging figures and forging bonds of friendship and interest institutionally and within the pharmaceutical industry. There is also an entertainment aspect to the congress. This is basically limited to the social dinner, another opportunity for members to get together and another observation post for noting who is sitting where, and whether spontaneously or according to the table plan.

In short, it is a curious world made up of scientific give and take and, above all, of social interaction. Generally speaking the congress has been an annual event although the tendency was to make it biennial, inserting a refresher course in between; although quite different from each other, both of these events, a bit for reasons of expediency a bit for lack of information, almost always overlapped in the way they were organized. At the end of the congress, everyone went back to their daily routine having tested the pulse of current knowledge and practice on a given subject and also with some diagnostic and therapeutic ideas picked up behind the scenes. In March 2020, this world was disrupted and swept away by a virus, they say just for the time being. To replace it the proposal is distance training and learning *via* the Internet and so-called webinars, with the argument that these digital events can more or less replace the congress, although, for all the reasons given above, there is no comparison. If we look closely, socialization is crucial to a scientific get together. It is not gossip, it is an emotive, interpersonal or at times group exchange of information where expression has free rein. The congress is a synchronization of different schools and currents of thought, it represents a stage for actors who are chosen for personal reasons or because they are recommended by the industry but largely on the basis of their historical and cultural background, otherwise the risk is that the public will abandon the proceedings; so, responsibility for the choice of actors and compulsory democracy on the basis of merit.

The so-called social distancing in our specific case coincides with distancing from communicated and shared culture. The present-day emergency is a socio-cultural middle age in which the holistic concept of the *ars medica* is forgotten in favor of the specific commitment to a circumscribed emergency that has nothing to do with a real knowledge of medicine. Today's virus is being studied not in its essence but in terms of the damage it produces, damage that varies depending on multiple variables such as age, comorbidities, the social environment in which it develops, climate, diet, type of work activity, social status, regionality, habits and so on; therefore, difficult to classify diagnostically and therapeutically.

When this so-called emergency moment comes to an end and we enter the post-medieval era, what will we be left with? The fear that is now part of us and is therefore almost irremovable, the globalization of behavior, the loss of sociability and responsibility in social and cultural relations. Will it be possible to restore congresses in the near future? Perhaps those at national level. Certainly not international ones because of the fear that international and intercontinental contagion has not gone away; suspicion and fear of one another will remain and we will invent cultural racism. We will therefore change, or risk changing from yesterday's congresses as unifying, socializing and responsible in their cultural honesty and in the shared choice of speakers, to restricted meetings, perhaps held at a distance, without social contact and without intellectual or critical dynamics. I believe that we will soon have to choose between dying culturally from COVID-19 or surviving and reintroducing as soon as possible that freedom of assembly and critical thinking that is communicated in words and face to face.

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THE ELOQUENCE OF SYMBOLS

From *Medicine* a call to the Community of the Phlebological World

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Phlebology includes not only chronic venous disease but venous thromboembolism, and diseases related to lymphatic vessels. The field of phlebology and lymphology today brings together basic scientists and clinicians to enhance our understanding of vascular disease and to improve health care delivery. The interdisciplinary exchange of information and opinions is considerable because venous and lymphological diseases comprise multiple pathophysiological disorders, which are expressed as basic disturbances in the integrative physiology and biochemistry of organ systems, and it is now evident that the SARS-Cov-2 produce high incidence of activation of coagulation and damage to vascular endothelium by the virus, while the ventilation in the intensive care units induces also a reduced lower limb blood flow and venous stasis. In other words, there is full activation of Virchow's triad (Andrew Nicolaides).

The attempt in consolidating the knowledge from all disciplines so to amplify our understanding of the mechanisms of the veno-lymphatic diseases and improve the diagnosis and treatment is the very crucial point to match during important congress, at the moment webinars, and classically within Journals as this one.

In 2020, for pandemic SARS-Cov-2, we need advances in our fields. An outstanding International Faculty of this Journal has been assembled to provide the most up-to-date best practice guidelines on venous and lymphatic topics.

Here we do not treat the innumerable actual literature on COVID and venous system¹ or also the lymphatic system: thoraco-mediastinal lymphatic circulation plays a basic role in the pathophysiology of inflammatory reaction consistent with interstitial pneumonia due to COVID-19 and consequent fibrosclerotic sequelae of lung parenchymatous tissue.²

To our mind the pandemic SARS-Cov-2 remembers a famous painting now destroyed: *Medicine* by Gustav Klimt.

Medicine was the second Ceiling Painting of the University of Vienna, presented in March 1901 at the tenth Secession Exhibition. It featured a column of nude figures on the right-hand side of the painting, representing the river of life. Beside it was a young nude female who floated in space, with a newborn infant at her feet, representing life. A skeleton represented death in the river of life. The only link between the floating woman and the river of bodies is two arms, the woman's and a man's as seen from behind. Figure of Hygeia, the mythological daughter of the god of medicine is shown at the bottom of the painting, all painted in marvelous gold (only a color photo of Hygieia also exist). Hygieia stood with the Aesculapian snake around her arm and the cup of Lethe in her hand, turning her back to mankind. Klimt conveyed an ambiguous unity of life and death, with nothing to celebrate the role of medicine or the science of healing.^{3, 4} At a time Vienna was leading the world in medical research thanks to the pioneering work of doctors such as Theodor Billroth (1829-94), Frantisek Chvostek (1835-84), and Ludwig Türck (1810-68), but Klimt was inspired by the ideas of composer Richard Wagner and philosopher Friedrich Nietzsche. However, he does not, celebrate the revolutionary goals of medical progress but, rather, is interested in humanity on a brink, victim of a social, political and psychological crisis. Today we would say — in COVID-19 era — ecological, economic, and gender crisis. The flow of naked bodies,

AGUS

GUSTAV KLIMT, MEDICINE



Figure 1.—Gustav Klimt, *Medicine* (1901) painting for the University of Vienna. Destroyed in 1945.

raw and real, worn down by disease and powerless against the inexorable force of time, and yet another virus, like us now. Klimt thus represents the succession of events of human existence, disrespectful of nature, which leads to the dissolution of life itself. It is undoubtedly a unique, radical, countercurrent painting, and for such reasons disputed not only for the nudes, but also for the distorted view of medical science understood as powerless. Today we must rethink it for its premonitory content; less for its beauty because it was impossible to admire it from the real and to see the use of gold with which Klimt had special affinity given his training and the work of his father, goldsmith and engraver.

In 1911 *Medicine* was owned by a different property, and in 1938 the painting was seized by Germany. In 1943, after a final exhibition, the painting was moved to Schloss Immendorf, a castle in the district of Hollabrunn in the northeast of Lower Austria, for protection. In May 7 1945 the painting was destroyed by retreating German SS forces that set fire to the castle to prevent it falling into enemy hands. All that remains now are preparatory sketches and a few photographs. Only one black &white photograph remains of the complete painting of *Medicine* (Figure 1), taken just before it was destroyed.

The knowledge of the medical profession is even before an invitation to a more humble attitude of medicine today so engaged by the pandemic that, as it is now known, it concerns greatly both phlebology and lymphology. Not last, full of suggestions, Gustav Klimt died in 1918 during the influenza pandemic.⁵

Now the Italian Phlebology is proud to meet in the same Journal *Acta Phlebologica* many Phlebological Societies from different parts of the world and opens a closer collaboration with them.

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Authors' contributions .--- The author read and approved the final version of the manuscript.

ORIGINAL ARTICLE

Outpatient treatment and prevention of acute hemorrhoids with sulodexide

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ABSTRACT

BACKGROUND: Vasoactive drugs are commonly used in the treatment of hemorrhoidal pathology due to its effect on the endothelium and the vascular component of inflammation. Sulodexide is of particular interest. It has angioprotective and anti-inflammatory effects, as well as an anticoagulant effect. The objective of the study was to examine the efficacy of sulodexide in treatment and prevention of acute hemorrhoids. METHODS: A prospective controlled study was conducted in 164 patients with acute hemorrhoids. Patients of the treatment group (N.=81) received diosmin, sulodexide, and used direct-acting anticoagulants (heparin ointments) twice a day for 7 days. Two capsules of sulodexide 250 ULS were taken twice a day for 30 days. Patients of the control group (N.=83) took only diosmin 1000 mg once a day for 30 days and direct-acting anticoagulants (heparin ointments) twice a day for 30 days and direct-acting anticoagulants (heparin ointments) twice a day for 30 days.

The efficacy of the treatment was determined by the physician's objective evaluation and the patient's subjective evaluation using the ColoRectal Evaluation of Clinical Therapeutics Scale (CORECTS) questionnaire. All patients also underwent measurements of blood flow in enlarged external hemorrhoids using a Samsung Medison SonoAce R7 ultrasound diagnostic device (Samsung, Taegu, South Korea). Patients were examined before starting the treatment and on days 5, 10 and 30 of the follow-up period.

RESULTS: Within three months after the end of treatment, 2 (2.5%) patients in the treatment group and 11 (13.3%) patients in the control group experienced exacerbations of hemorrhoids. No clinical signs of acute hemorrhoids were revealed in patients of the study groups during the examination on day 30 of the treatment. The measurement of blood flow in the external hemorrhoids by ultrasound showed 8.1 ± 1.2 cm/s and 7.9 ± 1.3 cm/s in patients of the treatment. The measurement of blood flow in the external hemorrhoids by ultrasound showed 8.1 ± 1.2 cm/s and 7.9 ± 1.3 cm/s in patients of the treatment. The measurement of blood flow in the external hemorrhoids by ultrasound showed 8.1 ± 1.2 cm/s and 7.9 ± 1.3 cm/s in patients of the treatment group and the control group, respectively. Three months later, a significant difference in the subjective evaluation of the impact of hemorrhoids on daily activities was identified, which is associated with exacerbations of hemorrhoids. In three months after starting the treatment, the CORECTS score of all signs analyzed by a physician significantly decreased (P<0.05) in the suldexide group *versus* the control group. Such symptoms as swelling decreased from 5.3 ± 3.1 to 0, bleeding from 0.5 ± 2.3 to 0, discomfort from 6.5 ± 3.3 to 0, pain from 4.5 ± 3.3 to 0, the impact on daily activities from 7.5 ± 3.3 to 0. In the control group, itching decreased from 1.7 ± 1.2 to 0 ± 0.3 and the impact on daily activities from 7.3 ± 3.4 .

CONCLUSIONS: Sulodexide is an effective and pathogenetically substantiated drug for the conservative treatment of patients with acute hemorrhoids. It significantly reduces the severity of clinical symptoms of hemorrhoids and improves the results of objective examinations. It has good tolerability, no adverse effects, and a better long-term effect than the standard treatment regimen.

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KEY WORDS: Hemorrhoids; Glucuronyl glucosamine glycan sulfate; Therapeutics.

The most common coloproctological disease is hemorrhoids. It affects hemorrhoidal veins of the terminal rectum and the perianal region. The true prevalence is unknown; however, according to various authors, hemorrhoids affect between 15% and 90% of adult patients.^{1, 2}

This is a chronic condition with possible exacerbations. Acute hemorrhoids can be both external and internal.^{2, 3} Exacerbations of internal hemorrhoids are treated using conservative methods, including oral phlebotropic drugs, local anticoagulants (ointments), and surgical interventions, as indicated.³

Conservative or surgical treatment can be used for acute external hemorrhoids. Drug therapy should be the first choice in less severe cases (grade I-II) and used as a support for surgical treatment in more severe cases (grade III). Conservative treatment in acute internal hemorrhoids includes oral phlebotropic drugs and local anticoagulants. Surgical treatment included thrombectomy from a thrombosed hemorrhoid or excision of the entire thrombosed hemorrhoid.³

Anticoagulants are currently formulated as ointments, parenteral and oral drugs. Vasoactive drugs are of great interest as a conservative treatment because they can contribute to the relief of signs and symptoms by affecting the endothelium and the vascular component of inflammation in hemorrhoids. Sulodexide, glycosaminoglycan (GAG), is of particular interest. It has angioprotective and antiinflammatory effects, as well as an anticoagulant effect.⁴⁻⁷ This drug is recommended for the treatment of different angiopathies with an increased risk of thrombosis. These include varicose veins of the lower extremities and microand macro angiopathies in diabetes mellitus.⁵ Sulodexide is commonly used to treat chronic venous diseases and venous ulcers of the lower extremities.8,9 Sulodexide modulates the activity of matrix metalloproteinases (MMPs), which are markers of inflammation most extensively involved in the degradation of connective tissue surrounding renal venous plexuses.10, 11

The objective of our study was to examine the efficacy of sulodexide in the conservative treatment and prevention of hemorrhoids.

Materials and methods

In 2016 to 2019, a prospective comparative study, including 164 patients with acute hemorrhoids, was conducted at teaching hospitals of Samara State Medical University. All patients signed informed consent to participate in the study, which was carried out under the applicable Russian laws, protocols, and ethical principles of the World Medical Association Declaration of Helsinki (Seoul, 2008) and Good Clinical Practice (ICH GCP).

The following inclusion criteria were used: grade I-II external and internal hemorrhoid thrombosis; 18 years and older; no confirmed pregnancy during the study period; signed informed consent; and normal complete blood counts.

The following exclusion criteria were used: withdrawal at any stage of the study; lost to follow-up; poor compliance; diagnosis of acute or decompensated somatic pathology; confirmed pregnancy during the study.

All patients were recommended to reduce the intensity and regularity of physical activity (lifting of weights not more than 5 kg), abstinence from sports during and within a month after the end of treatment.

All patients underwent complete blood count tests before starting the treatment. During the follow-up, a splitmeal, high-fiber diet (at least 4 times a day) low in spicy, salty and pickled food and alcohol was recommended to patients.

All patients were randomized into two comparable groups. The treatment group included 81 patients (47 male and 34 female) at the of 31-61 (50.1 ± 6.3) years old. The duration of the disease was 10 ± 9.5 years.

The control group consisted of 83 patients (45 male and 38 female) at the age of 33-63 (51.1 \pm 4.3) years old with the disease duration of 10 \pm 8.2 years.

The statistical processing of the findings identified no significant differences between the groups in age (t=0.8; P=0.4), nosology (χ^2 =0.102; P=0.39), and sex (χ^2 =0.636; P=0.43).

Before starting the treatment, all patients underwent a routine proctological examination (visual inspection, digital investigation, anoscopy, rectoscopy), screening, randomization, and complete blood count testing, on the first day of treatment.

The first day of treatment was the day of the first administration of medicines in both study groups. Patients of the treatment group took diosmin 1000 mg once a day for 30 days and used direct-acting anticoagulants (heparin ointments) twice a day for 7 days. Two capsules of sulodexide (Alfasigma, Bologna, Italy) 250 ULS were taken twice a day for 30 days. The daily dose of sulodexide was 1000 ULS.

Patients of the control group took diosmin 1000 mg once a day for 30 days and used direct-acting anticoagulants (heparin ointments) twice a day for 7 days.

Patients were examined on days 5 and 30, and in 3 months after the end of conservative treatment. Physician's objective evaluation and the patient's subjective evaluation of the severity of hemorrhoids using the CORECTS score was performed before starting the treatment and three months after the end of the treatment.¹² Patients evaluated symptom severity using a scale of 1 to 10 (Table I).

During the treatment, all patients also underwent measurements of blood flow in enlarged external hemorrhoids using a Samsung Medison SonoAce R7 ultrasound diagnostic device (Samsung, Taegu, South Korea). Patients were examined before starting the treatment and on days 5, 10, and 30.

After the end of the conservative treatment regimen, patients of both groups were followed up for three months

TABLE I.—CORECTS score.

Before and after treatment	
How much pain do you experience?	0-10 points
How much itching do you experience?	0-10 points
How much swelling do you experience?	0-10 points
How much bleeding do you experience?	0-10 points
How much discomfort do you experience?	0-10 points
How much impact does your condition have on your	0-10 points
daily activities?	-

to identify the number of exacerbations after the end of treatment.

The comparison of the efficacy of conservative treatment was based on the following criteria:

• dynamics of changes in the clinical picture of acute hemorrhoids;

• number of exacerbations of acute hemorrhoids;

• duration of the temporary incapacity to work;

• dynamics of changes in blood flow velocity in the external hemorrhoids;

• number of exacerbations of hemorrhoids within three months after the end of conservative treatment;

• results of the evaluation of hemorrhoid severity using the CORECTS score.

Statistical analysis

The results were processed and presented as the mean and standard deviation, absolute and relative values. The statistical significance of differences in the quantitative data was estimated using the Student's *t*-test. The critical level of statistical significance for a test of zero hypothesis was $P \leq 0.05$.

Results

The clinical picture in patients of both groups was characterized by a significant intensity of clinical manifestations of acute hemorrhoids. All patients had thrombosed external and internal hemorrhoids accompanied by the inflammation. The treatment group and the control group included 19 (23.5%) and 18 (21.7%) patients with grade I hemorrhoid thrombosis, respectively. The treatment group and the control group included 62 (76.5%) and 65 (78.3%) patients with grade II hemorrhoid thrombosis, respectively.

Within three months after the end of treatment, 2 (2.5%) patients in the treatment group and 11 (13.3%) patients in the control group experienced exacerbations of hemorrhoids. All exacerbations of hemorrhoids were treated conservatively.

TABLE II.—The results of the subjective evaluation of hemorrhoids in patients of the study groups using the CORECTS score before starting the treatment and three months after the treatment.

Parameter	Treatment group	Control group	Significance level (P)
Before starting the treatment			
Pain	4.5±3.3	4.3±3.2	< 0.05
Itching	1.5±1.3	1.7±1.2	0.05
Swelling	5.3±3.1	4.9±3.2	< 0.05
Bleeding	0.5 ± 2.3	0.1±2.0	< 0.05
Discomfort	6.5±3.3	6.1±3.7	< 0.05
Impact on daily activities	7.5±3.3	7.3±3.6	< 0.05
Three months after the end of treatment			
Pain	0	0	< 0.05
Itching	0	0±0.3	< 0.05
Swelling	0	0	< 0.05
Bleeding	0	0	< 0.05
Discomfort	0±0.3	0	< 0.05
Impact on daily activities	0	1±3.4	< 0.05

The subjective evaluation of hemorrhoids in patients of the study groups using the CORECTS score before starting the treatment and three months after the treatment are summarized in Table II.

Three months later, a statistically significant difference in the subjective evaluation of the impact of hemorrhoids on daily activities was identified, which may be associated with exacerbations of hemorrhoids in patients of the study groups.

In three months after starting the treatment, the COR-ECTS score of all signs analyzed by a physician significantly reduced (P<0.05) in the sulodexide group *versus* the control group. Such symptoms as swelling reduced from 5.3 ± 3.1 to 0, bleeding from 0.5 ± 2.3 to 0, discomfort from 6.5 ± 3.3 to 0, pain from 4.5 ± 3.3 to 0, the impact on daily activities from 7.5 ± 3.3 to 0. In the control group, itching decreased from 1.7 ± 1.2 to 0 ± 0.3 and effect on daily activities from 7.3 ± 3.6 to 1 ± 3.4 .

The ultrasound measurement of the blood flow rates in the external hemorrhoids before treatment recorded 2.4±1.0 cm/s and 2.5±0.9 cm/s in the control group and the treatment group, respectively. There were no statistically significant differences in the blood flow rates in the external hemorrhoids between the study groups ($\chi^2=0.008$; P=0.5). All patients were treated under the planned conservative regimen.

No clinical signs of acute hemorrhoids were revealed in patients of the study groups during the examination on day 30 of the treatment. The measurement of blood flow in the external hemorrhoids by ultrasound showed 8.1 ± 1.2 cm/s and 7.9 ± 1.3 cm/s in patients of the treatment group and the control group, respectively. There were no complications of acute hemorrhoids in either group.

The study showed that the inclusion of Sulodexide (1000 ULS, 2 capsules twice a day for 30 days) in the combination therapy of patients with grade I and II acute hemorrhoids significantly reduces clinically objective signs (swelling, bleeding, prolapse [P<0.05]).

The efficacy of sulodexide was also confirmed by patients (CORECTS) who experienced an improvement in all parameters analyzed (swelling, bleeding, discomfort, pain, and impact on daily activities [P<0.05]).

Discussion

All patients were examined in a similar manner, using the same program, and were randomized into two groups comparable by sex, age, and nosology. In both groups, the clinical picture was characterized by severe clinical signs of acute hemorrhoids.

The study analyzed the objective and subjective efficacy of oral sulodexide 1000 ULS (2 capsules twice a day for 30 days) in the group of patients with grade I-II acute hemorrhoids. The findings showed a significant improvement and absence of exacerbations in a 3-month followup period in 97.5% of patients taking sulodexide, and no exacerbations were identified in 86.7% of patients in the control group. We believe that this is due to the systemic angioprotective action of sulodexide.

Clinically evaluated objective data collected during the proctological examination showed that sulodexide was effective in treating all signs and symptoms analyzed by the physician (swelling, bleeding, prolapse, and pain). Patients reported a significant reduction of symptoms (pain and itching) and signs (swelling, bleeding), with decreased discomfort and improved wellbeing.

Our findings are consistent with the literature. Particularly, Lizza *et al.*⁷ showed that sulodexide reversed such symptoms as swelling, bleeding, and prolapse of hemorrhoids in more than 88% of patients with hemorrhoids.

Sulodexide is a natural component of endothelial glycocalyx proven as beneficial for restoring the physiological function of the vascular wall through the reintegration of the damaged layer of glycosaminoglycans in acute hemorrhoids, which can explain a significant reduction of swelling and observed bleeding episodes.^{13, 14}

Finally, sulodexide is a controlled agent in its oral form with an excellent efficacy and safety profile,¹⁵ which was also confirmed in this study since no significant side effects were observed.

In our opinion, the inclusion of sulodexide in the conservative combination treatment of patients with acute hemorrhoids results in a faster resolution of inflammation of hemorrhoids through to the improvement of peripheral circulation and microcirculation. Patients treated with sulodexide experienced a prolonged angioprotective effect for up to 3 months. This effect is ensured by a comprehensive action on the blood vessel walls, blood viscosity and lipid levels. Owing to this, hemodynamic is normalized, especially in the microcirculatory bed. Furthermore, sulodexide affects blood clotting, platelet adhesion and aggregation, fibrinolysis.⁴ All the above profibrinolytic, antithrombotic, anti-inflammatory, and protective properties show that sulodexide can be used for the treatment of acute hemorrhoids. At the same time, further studies of the use of sulodexide in patients with acute hemorrhoids are required.

Conclusions

Sulodexide is an effective and pathogenetically substantiated drug for the conservative treatment of patients with acute hemorrhoids. It significantly reduces the severity of clinical symptoms of hemorrhoids and improves the results of objective examinations. It has good tolerability, no adverse effects, and a better long-term effect than the standard treatment regimen.

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ORIGINAL ARTICLE

Effect of four-layer dressing on venous ulcer

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ABSTRACT

BACKGROUND: Venous ulcer is a chronic disease and has periods of exacerbation and remission. It takes a long time to heal, resulting in physical and psychological discomfort thereby negatively affecting the functional status of the patients. Various bandage systems, single layered, double layered and multiple layered with elastic and non elastic components have been commercialized. A requirement of sustained pressure brought the four-layer bandage into picture. We tried to study the bacteriology of the venous ulcers and the effect of our layer bandage on the healing of the ulcer.

METHODS: Sixty patients were recruited for the study. However, 4 patients had a bilateral disease and so a total of 64 limbs were taken into consideration in the study. Clinical details of all patients with wound size measurement by gauze piece, wax paper and scale was done. The wounds were initially debrided and photographic records of all patients was maintained. Patients were followed up every week and the dressing was changed every week.

RESULTS: 93.8% had complete healing while 1.6% had partial healed ulcer and 4.7% had non healing ulcer. After excluding the four ulcers that did not heal, 16.6% had recurrence while 50 out 60 had no recurrence in the follow-up for one year. There was a significant correlation (P<0.001) between ulcer size and the number of dressings.

CONCLUSIONS: Compression therapy is the mainstay of treatment of venous ulcer. Compression in the range of 30 mmHg to 40 mmHg is the most effective level for uncomplicated venous ulcers with adequate arterial competency.

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KEY WORDS: Varicose ulcer; Varicose veins; Wound and injuries.

The majority of leg ulcers are secondary to chronic venous insufficiency (CVI), the vascular insufficiency caused by valvular insufficiency in either deep system or superficial system. The venous hypertension leads to leakage of fluid and fibrinogen out of the stretched veins into the tissues forming a pericapillary fibrin cuff which leads to reduced diffusion of oxygenated blood to the tissues resulting in ulceration. Also, there is reduced pressure gradient between the arteriolar and venular end of the capillaries resulting in sluggish movement of the blood within them and adherence of blood cells to the endothelium. Inflammatory mediators and reactive oxygen species are released which lead to obliteration of functioning capillary loops, thus, aggravating ischemia and result in ulceration. Capil-

laries can also be occluded by microthrombi and exhibit long intra-capillary stasis which in turn reduce nutrition and oxygenation of the skin and lead to ulceration.

Venous ulcer is a chronic disease and has periods of exacerbation and remission. It takes a long time to heal, resulting in physical and psychological discomfort thereby negatively affecting the functional status of the patients. These chronic ulcers are susceptible to microbial invasion and this probably contributes to the non-healing nature of the ulcer. These secondarily infected ulcers pose a challenge for the clinicians and the patients. Regular dressings or antimicrobial bandages have been effective to control to some extent. However, the results are not satisfactory.

Various treatment modalities have been introduced.

Compression dressing is the cornerstone of the treatment of venous ulcer. The compression reestablishes normal transluminal venous pressure for it increasing extravascular pressure higher than pressure within the venous system. Various bandage systems, single layered, double lavered and multiple lavered with elastic and non-elastic components have been commercialized. A requirement of sustained pressure brought the four-layer bandage into picture. It has been designed uniquely to provide a pressure of 40 mmHg at the level of ankle and 17 mmHg at the level of knee. This elastic bandage provides a graduated, sustained pressure by working on the principles of Laplace. The four lavers of the bandage are consecutively applied from toes to knee. While layer 3 in all 4-layer systems is highly elastic, with a wide extensible range, the outer cohesive layer has a much shorter extension; this could contribute to the short-stretch effect.

Materials and methods

The patients were selected from Department of General Surgery, Institute of Medical Sciences, Banaras Hindu University and included both inpatients and outpatients. The period of study for this prospective cohort study was from June 2016 to July 2019. The following patients were included: The Patient/Guardian must have the ability to give consent, Older than 18, Diagnosis of Venous Ulcer, Ankle brachial pressure index >0.8, Ulcer present \geq 1 months, Ulcer area 1-100 cm², No immunosuppressant (including systemic corticosteroids), cytotoxic chemotherapy or topical steroids to the wound surface within 1 month prior to enrolment.

Sixty patients were recruited for the study. However, 4 patients had a bilateral disease and so a total of 64 limbs were taken into consideration in the study. Clinical details of all patients with wound size were measurement by gauze piece, wax paper and scale was followed with initial debridement of the ulcer and photographic records. Patients were followed up every week with a change of dressing. Ethical approval was taken from Ethical Review Committee, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

Method of four-layer dressing

After cleaning the ulcer with normal saline, gauze is applied followed by four layers of bandage from toes to knee. First layer- cotton padding was rolled gently starting from just proximal to toes to two cm below the knee. It was rolled without stretch with a 50% overlap in a spiral

fashion. Similarly, the second layer, short stretch, cotton roll was wrapped with 50% overlap and 50% stretch. The third layer, the long stretch crepe bandage was wrapped with a 50% stretch and 50% overlap, in a spiral manner, following the green lines of bandage. It was taken care that the bandage is not too tight from third layer onwards. The fourth cohesive bandage was wrapped in a spiral fashion, with 50 percent stretch and 50 percent overlap. Again, it was taken care that the fourth layer was not too stretched and the wrinkles of this bandage are visible.

The toes were examined for color, warmth and mobility. If at all, there was any difficulty or discoloration of the toes or impaired mobility or pain, the fourth layer (if required third layer also) was opened and again wrapped. The compression was such that it was tolerated well by the patient with comfortable toes movement.

All cases were advised to continue with his daily activities and to elevate his limb while resting. In case of intolerable discomfort, patients were advised to open all layers of his bandage and consult the doctor.

Patients were followed weekly with ulcer size tracings and photographs. Any change in size of ulcer was recorded. Bandages were changed every week. Patients were followed up at least for 24 weeks or till the ulcer heals, whichever is earlier.

Primary outcome was the time to heal and ulcer healing and secondary outcome was complications. Ulcer healing is defined as complete when there is full epithelialization, partial when there is more than 50% epithelialization, nonhealing when there is less than 50% epithelialization. Recurrence is defined when there is ulcer formation at the same site after healing.

Statistical analysis

Data were documented and stored in a proper database format. At the end of data collection from the samples, data analysis was done using SPSS 23 software and appropriate tests of significance were applied. Data were checked for the assumption of normality. For categorical data χ^2 test was used. For comparing two groups of mean Student's *t*-test was used. For paired samples, Paired *t*-test was used. To correlate more than two continuous data Pearson and Spearman Correlation Coefficient was used. P value <0.05 is considered as statistically significant.

Results

This is a prospective study which included 60 patients with venous ulcer and 64 limbs (four patients had bilateral

ulcers). A four-layer dressing was done and the change in size of ulcer bandaging was studied.

In this study the youngest patient was 19 years and oldest was 68 years and maximum patients were between 21-40 years of age, *i.e.* in the productive age group. 95% of the patients were male and 5% were female. Maximum patients (26.7%) were government servants, 25% were shopkeeper while 8.3% patients were farmer, followed by barber, conductor, housewife, cook, student, butcher, laborer and teacher. Maximum (31.2%) limbs had ulcer from 2-4 months while 25% had ulcer from 6 to 12 months and 23.4% had ulcers from 4-6 months. The longest duration of ulcer was 6 years. Heaviness, a common symptom, was present in 87.5%. History of bleed was present in 7 limbs (10.9%).

Ulcer was present in right leg in 56.2% and in left leg in 43.8%. 4 patients had bilateral disease. All limbs had tortuous veins, pain at the time of presentation and 21.8% had pigmentation. Mean size of ulcer at presentation was 8.406 cm. with standard deviation of ± 7.1197 . The median size of ulcer at presentation was 6.00 with interquartile range between 4.00-11.50.

On studying the history of intervention in these patients, 64.1% had history of no intervention, while 14.1% had history of RFA alone and 9.4% had history of RFA with sclerotherapy and 10.9% had stripping done. EVLT was done in 1 of 64 (1.6%) cases.

Varicose veins were present in all patients, dermatitis and edema was present in 95.3% and 68.7% cases, respectively. Lipodermatosclerosis was present in 21.8%, erythema was present in 18.7%, scaling and atrophie blanche in 15.6% each.

The largest ulcer was present on medial side in 50%, whereas on lateral side in 25% cases, on anterior aspect in 15.6% and posterior aspect in 6.2% and on foot in 3.1% cases. Depth of ulcer was <3 mm in 92.2% and 3-6 mm in rest of the cases.

SFJ incompetence was present in 84.4% limbs and SPJ incompetence was in 31.2%. On studying the incompetence of perforators, four limbs had no incompetent perforator and one perforator incompetence was seen in 6.2%. Two perforators were incompetent in 35.9%, three perforators were incompetent in 31.2%, four perforators were incompetent in 14.1% limbs, 5 perforators were incompetent in 6.2% limbs.

After weekly dressings, 39.1% ulcers healed by 8 weeks, 67.1% ulcers healed by 12 weeks 60 93.8% had complete healing by 24 weeks. 1 out 64 (1.6%) had partial healing and 3 out of 64 patients (4.7%) had non healing ulcer.



Figure 1.—Correlation between the size of ulcer at presentation and the number of dressings done. It shows that number of dressings depended on the size of ulcer. P value is <0.001 which shows highly significant correlation between ulcer size and the number of dressings done.

A percentage of 93.8% had complete healing while 1.6% had partial healed ulcer and 4.7% had non healing ulcer. After excluding the four ulcers that did not heal, 16.6% had recurrence while 50 out 60 had no recurrence in the follow-up. 7 out of 10 patients had a single recurrence while rest of the three had recurrence twice, thrice and four times each. The incidence of recurrence that occurred within 1 month was (30%) patients and within 6 months in 50% patients and within 12 months in 2 out of 10(20%) patients.

There was highly significant correlation (P<0.001) between ulcer size and the number of dressings done (Figure 1).There was statistically significant change (P<0.05) in ulcer with each dressings, *i.e.* the ulcer healed with subsequent dressings.

On studying the other effects/ side effect of bandaging, it showed pigmentation increased from 21.6% to 90.6% after dressing. Tenderness was seen to decrease; it was present initially in all patients and gradually decreased and was present in 6.2%. Skin scaling increased from 1.6% to 98.4%. Also, itching increased from 20.3% to 81.25% after the dressing.

Discussion

Venous ulcer has a prevalence rate of 1% and accounts for 80% of lower extremity ulcerations. The compression therapy remains the mainstay of treatment and of which, the four-layer bandage system is the gold standard for treatment.

Our study is a prospective study in which the effect of four-layer bandage on healing of ulcer was studied. The study included 60 patients of which 4 had a bilateral ulcer. Therefore, a total of 64 limbs have been studied. Youngest patient was 19 years old and eldest was 68 years and maximum patients were between 21-40 years of age. In the study by Kota *et al.*, from India, most of the patients were in the productive age group of 36 to 45 years.¹ This disease is the disease of young and most active population.

We had 57 (95%) males and 3 (5%) females. In other studies from India by Kota *et al.*, out of 170 patients 79% were men and 21% were female and by Alamelu, out of 29 patients 86.2% were male and female were $13.8\%.^2$ A review by Jennifer *et al.* stated that the prevalence of varicose veins varies widely, from 2% to 56% in men and from1% to 73% in women.

The ergonomics and physical activity of an occupation has been seen to have contributing factor in varicose ulcers. In our study, 16 out of 60 (26.7%) patients were government servants, 15 out 60(25%) were shopkeeper while 5 out of 60 (8.3%) patients were farmer, followed by barber, conductor, housewife, cook, student, butcher, laborer and teacher. Most of them were indulged in activities where prolonged standing (>4 hours) was required.

Venous ulcer was present in right leg in 36 cases out of 64 (56.2%) and left leg 28 out of 64 (43.8%) and 4 patients had bilateral disease. In a study by Baker *et al.*, of the 163 limbs with chronic venous ulcers, 43.6% were ulcerated on the right side and 56.4% on the left and in 25 patients the ulcers were bilateral.

Duration of ulcer varied, 31.2% from 2-4 months, 25% from 6 to 12 months and 23.4% from 4-6 months.12.5% of them were affected by it for over one year. Maximum patients had ulcers within one year and were non-responding to any other form of treatment. The longest duration of ulcer was 6 years.

Nine out of 64 (14.1%) had Radio frequency ablation (RFA) of varicose veins and 6 out of 64 (9.4%) had RFA with sclerotherapy and 7 out of 64 (10.9) had stripping done. RFA with foam sclerotherapy was done in 6 out of 64 (9.4%). EVLT was done in 1 of 64 (1.6%) cases. In the study by Baker *et al.* 30% had a primary procedure for varicose veins, in 17.8% patients the long saphenous vein had been stripped and in 7.4% the communicating veins had been divided.³ Individual ligation of varicosities was performed in 1.2% patients, with sclerotherapy in

3.6% others. 0.6% patient underwent thrombectomy of the iliofemoral vein.

Compression therapy is the mainstay of treatment of venous ulcer. Compression in the range of 30 mmHg to 40 mmHg is the most effective level for uncomplicated venous ulcers with adequate arterial competency. Lorimer *et al.* concluded that a high degree of compression (30 mmHg to 40 mmHg) was better than low compression (<20 mmHg) with no specific bandage system recommended.⁴

Compression therapies are broadly categorized into bandages, stockings (hosieries) and intermittent pneumatic compression. Further, bandages may be either elastic and inelastic or single or multi-layered. The four-layer bandage is elastic and a onetime use, multilayer bandage. Partsch *et al.* stated that when multiple layers of elastic bandages are applied, the top layer becomes inelastic as a result of alteration of the friction capacity. Thus, it is an elastic bandage with properties of inelastic bandages. The short stretch bandage on other hand is inelastic, reusable bandage. These are examples of high compression (ankle sub-bandage pressure 35-40 mmHg).

Several studies compared different elastic and inelastic bandages. A RCT by Polignano *et al.* concluded that the four layer bandage (elastic) was as effective as Unna's boot (inelastic) for healing of venous ulcers.⁵ In a randomized control trial (RCT) of 387 adults to compare a four-layer system and short-stretch compression bandages comprised of one layer of padding and one to two layers of compression bandages). Nelson *et al.* found a statistically significant increase in the probability of healing with the four-layer bandage system.⁶ Meta-analysis by O'Meara *et al.*, which included five RCTs (797 patients). It concluded that multilayer bandage systems are superior to shortstretch bandages as they result in more rapid healing of leg ulcers.⁷

Another randomized controlled trial by Mofatt *et al.* concluded that the four-layer bandage offers advantages over the two-layer bandage in terms of reduced with-drawal from treatment, fewer adverse incidents, and lower treatment cost.⁸ However, there are studies suggesting two layerbandages to have similar efficacy as four-layer bandage.⁹ The various randomized controlled trials (Harrison *et al.*, Scriven *et al.*, Partsch *et al.*)¹⁰⁻¹² showed no differences in healing between short-stretch and multilayer bandages.

Also, Dolibog *et al.* compared the compression options and concluded the most effective treatment of venous leg ulcers is the use of intermittent pneumatic compression, stockings and multi layer compression bandaging (similar efficacy) and two layer compression therapy with bandages proved to be the least effective.¹³

After weekly dressings, 39.1% ulcers healed by 8 weeks, 67.1% ulcers healed by 12 weeks 60 93.8% had complete healing by 24 weeks. 1 out 64 (1.6%) had partial healing and 3 out of 64 patients (4.7%) had non healing ulcer. Of the 170 patients studied by Kota *et al.*, healing was seen in 87.6%. 69 and 74 per cent of the ulcers healed by 12 weeks, as seen in different studies.^{1, 14-17}

Recurrence is one of the major complications of fourlayer bandage. Here, in our study, after excluding the four ulcers that did not heal, 10 out of 60 (16.6%) had recurrence while 50 out 60 (84.3%) had no recurrence in the follow-up. The incidence of recurrence that occurred within 1 month is 3 out of 10 (30%) patients and within 6 months in 5 out of 10 (50%) patients, within 12 months in 2 out of 10 (20%) patients.

Seven out of 10 patients (70%) had a single recurrence while 1 each patient had recurrence twice, thrice and four times each. In a similar study by Thomson *et al.*, of the 318 ulcers that were completely healed, 19.5% (62) recurred; 41 of these were healed again. Recurrence still remains a challenge and a prophylactic, lifelong, class III compression stockings was advised to all the patients when the ulcer healed.¹⁸

Apart from healing of the ulcer, the dressing has other effects on the patient and the limb. In our study, the periulcer pigmentation/ lipodermato-sclerosis increased from 21.6% to 90.6%, after the dressings. Pain and tenderness were seen to decrease, it was present initially in all patients and gradually decreased and was eventually present in 6.2% patients. Skin scaling during the treatment increased from 1.6% to 98.4%. Itching increased from 20.3% to 81.25%. Kota *et al.* noted pain, itching, bleeding as the complications of four-layer bandage. One unpublished study from UK by Iglesias *et al.* studied maceration, allergic reaction, eczema of periulcer skin in relation to four-layer bandage.⁹ Nelson *et al.* mentioned other complications like, maceration, excoriations, skin damage and deterioration, new ulcer formation.⁶

However, four-layer bandaging results are dependent on the bandaging skills, application technique. Hopkins *et al.* considered the application of compression bandaging to be a specialist skill and in literature.¹⁹ Feben *et al.* estimated that many practitioners are failing to apply bandages in an effective and competent manner.²⁰ As stated by Callam *et al.*, poor bandaging techniques can lead to tissue damage, necrosis, pain, chronic skin changes and edema in unbandaged areas, such as the toes and knees.²¹ Also, the four consecutive layers tend to be heavy and there are chances of slippage of bandage. The foul smellingexudates from a grossly infected ulcer further affect the quality of life.

Conclusions

Compression therapy is the mainstay of treatment of venous ulcer. Compression in the range of 30 mmHg to 40mmHg is the most effective level for uncomplicated venous ulcers with adequate arterial competency.

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ORIGINAL ARTICLE

Study of quality of life in patients with varicose vein after radiofrequency ablation and ultrasound guided foam sclerotherapy

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ABSTRACT

BACKGROUND: Chronic venous insufficiency manifests most commonly as varicose veins affecting quality of life in significant way due to morbidity, recurrence and economic burden. This study was done in varicose veins to assess the quality of Life in varicose vein patients after treatment with radiofrequency ablation (RFA) and ultrasound guided foam sclerotherapy (UGFS) in great saphenous vein (GSV) in selected patients.

METHODS: In our study, in 30 patients UGFS and in another 30 patients RFA therapy in GSV was done. After these procedures, health related quality of life (HRQOL) was assessed with help of SF-36 and Venous Clinical Severity Score (VCSS). At pretreatment SF-36 and VCCS scoring was assessed and then reassessed all the parameter at 1 month, 6 months and 1 year. Higher the score, good is the quality of life.

RESULTS: The pretreatment scoring in both the group was comparable but not significant. But in subsequent follow-up HRQOL is better in RFA group patients than the USGFS group and statistically significant (P<0.05). The eight domain of SF-36 denoting different dimension of HRQOL were insignificant and comparable (P>0.05) in pretreatment level, but attained higher scoring in follow-up more than the UGFS group and significant (P<0.05).

CONCLUSIONS: Higher scores of SF36 and VCSS found in RFA group patients along with low recurrence of varicose veins, less complications related to RFA denotes that the HRQOL is much better in patients undergoing RFA as compared to UGFS.

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KEY WORDS: Varicose veins; Quality of life; Radiofrequency ablation; Sclerotherapy.

The term "varicose vein" is defined as a dilated and tortuous vein of diameter >4 mm, and most frequently refers to the superficial veins in the leg.

Varicose veins have incompetent valves causing increased venous pressure which may lead to progressive vessel dilatation and tortuosity, skin changes and sometimes to ulceration. Venous disease is often the cause of discomfort, pain, loss of working days, and deterioration of health-related quality of life.^{1, 2} The treatment of symptomatic varicose veins imposes a high burden on health care budgets. In European countries venous disease consumes 1-2% of the health care budgets.³ For the Radiologist, it is possible to assess the flow pattern in the venous system and subsequently treatments could become endovenous, minimally invasive, as they could now be performed intraluminally under ultrasound guidance. These therapies have quickly gained popularity and are used with increasing frequency including chemical and thermal ablation of the treated vessel.

Chemical ablation is performed by using ultrasound guided foam sclerotherapy (UGFS), and thermal ablation by endovenous laser ablation (EVLA) and radiofrequency ablation (RFA). All these treatments have single aim in obliterating veins with reflux. Now a days minimally invasive techniques are favored by both physicians and patients with limited role in selected few cases remains for surgical methods. The rapid development towards frequent use of these alternative treatments of varicose veins warrants evaluation of efficacy, safety and costs when compared with surgery.

Consequently, the treatment of varicose veins has witnessed a change from being performed under general anesthesia in the operation theatre to treatment in an outpatient setting under local or tumescent anesthesia.

The World Health Organization issued a summary statement in 2002 that in part defined QoL as 'a multidimensional construct relating to symptoms, impairments, functional status, emotional states and health domains'.

UGFS is gaining popularity as a minimally invasive technique for treating varicose veins, but its effects on health-related quality of life (HRQOL) are unknown. The aim of this study was to determine the effect of UGFS for varicose veins on generic and disease-specific HRQOL.

In this study, two questionnaires were used, one is generic that is SF-36 and another is disease specific that is Venous Clinical Severity Score (VCSS), for anatomical outcome great saphenous vein (GSV) diameter was compared in subsequent follow-up.

Materials and methods

This study was carried out in Department of General Surgery, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University. The patients were selected from department of General Surgery and included both inpatient and outpatients. Total 60 patients were included in study. In 30 patients, RFA of GSV and in another 30 patient UFGS was performed.

All enrolled patients and their identification data followed by detailed history related to sign and symptoms and their duration were taken. Patients were examined clinically, color Doppler accomplished of venous system as well as arterial system.

Truncal as well as non-truncal varicose veins were identified and patients were selected and subjected for treatment according to inclusion and exclusion criteria of RFA and UFGS as given below.

After these procedures, HRQOL was assessed with help of SF 36 and VCSS. At pretreatment SF36 and VCCS scoring was assessed and then reassessed all the parameter at 1 month, 6 month and 1 year. Higher is the score, good is the quality of score.

The Short Form-36 (SF36) from the Medical Outcomes Survey is the most common generic HRQL measure used to demonstrate improvement after SVS.⁴⁻⁷ It consists of 36 questions assessing eight health status domains, and also provides two summary scores; the physical component summary score (PCS) which represents what a person can do, and the mental component summary score (MCS) which represents how a person feels. The SF36has been widely used in many languages in many different clinical conditions and norms' have been created to allow comparisons with the general population. The mean PCS and MCS of the general population are 50 with a standard deviation of 10: the higher the score, the better the HRQL.

Another score to define HRQOL assessed by VCSS. It was designed by a committee to include nine hallmarks of venous disease scored on a scale of severity ranging from 0 to 3. To avoid confusion with the CEAP scale and to generate a dynamic score, the categories of the VCSS are presented on an elemental basis to add emphasis to the most severe sequelae of venous disease that are likely to show the greatest change in response to therapy. These include skin changes (which were expanded to include pigmentation), inflammation and induration, and ulcers (including number, size and duration).

Results

For the measurement of Health-Related Quality of life (HRQOL) We took two scoring one is generic (SF-36) and another is disease specific score, VCSS. In our study, 60 cases were registered in age group 15 to 75 years during 1st September 2016 to 31 July 2019.

Patients registered in our study were studied on the basis of dilated veins, ulcer, eczema, lipodermatosclerosis, paresthesia, pain, pigmentation and C grading of CEAP classification. A reference group of patients without varicose veins was defined by selecting patients in class 0 (no physical signs of venous disorders) or class 1 (presence of telangiectasias or reticular veins only on either leg) of the international CEAP classification.⁸

UGFS is gained popularity as a minimally invasive technique for treating VVs, but its effects on HRQOL are unknown. The aim of this study was to determine the effect of USGFS for VVs on generic and disease-specific HRQOL.

In this study, two Questionnaire were used, one is generic that is SF-36 and another is Disease specific that is VCSS, for anatomical outcome GSV diameter was compared in subsequent follow-up. Total 60 patients were taken, 30 underwent RFA and 30 underwent UGFS. SF-36 and VCSS were used in both.

The majority of the patients were in the age group of 18 to 30 years in both the group which was comparable and

insignificant (P=0.734) we took total 60 patients in this study, 30 in RFA group and 30 in UGFS group.

In our study, multiple parameters were taken preoperatively which were not found in other studies, like dilated veins present in 27 patients (90%) in RFA group which is statistically significant (P<0.005) 16 patients (53.3%) in UGFS group (Table I).

TABLE I.—Comparison of sign and symptoms at pretreatment level of patients underwent RFA and USGFS.

		RFA		USGFS		Develue
		No.	%	No.	%	P value
Dilated veins	Yes	27	90.0	16	53.3	0.007
	No	3	10.0	13	43.3	
Pain	Yes	12	40.0	12	40.0	1.000
	No	18	60.0	18	60.0	
Tiredness feeling heaviness	Yes	11	36.7	18	60.0	0.071
-	No	19	63.3	12	40.0	
Throbbing	Yes	4	13.3	13	43.3	0.010
-	No	26	86.7	17	56.7	
Itching	Yes	11	36.7	9	30.0	0.584
-	No	19	63.3	21	70.0	
Swollen limb	Yes	10	33.3	25	83.3	< 0.001
	No	20	66.7	5	16.7	
Bleeding	Yes	3	10.0	8	26.7	0.095
	No	27	90.0	22	73.3	
Ulceration	Yes	6	20.0	13	43.3	0.052
	No	24	80.0	17	56.7	
Redness	Yes	5	16.7	19	63.3	< 0.001
	No	25	83.3	11	36.7	
Exercise intolerance	Yes	15	50.0	11	36.7	0.297
	No	15	50.0	19	63.3	
Restless legs	Yes	8	26.7	9	30.0	0.774
-	No	22	73.3	21	70.0	
Night cramp	Yes	14	46.7	11	36.7	0.432
	No	16	53.3	19	63.3	
Paraesthesia	Yes	5	16.7	9	30.0	0.222
	No	25	83.3	21	70.0	
Previous surgery	Yes	3	10.0	0	0.0	0.237
	No	27	90.0	30	100	
Treatment received for VV	Yes	9	30.0	6	20.0	0.371
	No	21	70.0	24	80.0	
Smoking	Yes	14	46.7	24	80.0	0.007
	No	16	53.3	6	20.0	
Prolonged standing	Yes	12	40.0	3	10.0	0.007
	No	18	60.0	27	90.0	
Varicosities	Yes	24	80.0	15	50.0	0.015
	No	6	20.0	15	50.0	
Limb edema	Yes	16	53.3	7	23.3	0.017
	No	14	46.7	23	76.7	
Pigmentation	Yes	7	23.3	7	23.3	1.000
	No	23	76.7	23	76.7	
Eczema	Yes	6	20.0	0	0.0	0.024
	No	24	80.0	30	100	
Lipodermato sclerosis	Yes	4	13.3	5	16.7	0.718
	No	26	86.7	25	83.3	
Healed ulcers	Yes	10	33.3	5	16.7	0.136

Pain was increased from pretreatment level to 1, 6 months and at 1 year (P<0.001) which is significant. The domain of SF36 known as general health was significantly improved (<0.001) from pretreatment to post treatment level in subsequent follow-up, and highest (79.55 \pm 8.87) in 3rd follow-up in patient underwent RFA in comparison of patients underwent UGFS (Table II).

Tiredness was present in 11 patients (36.7%) in RFA group and 18 patients (60%) in UGFS group which is comparable. Paresthesia present in 5 patients (16.7%) in RFA and in 9 patients (30%) in UGFS group however this relation is not significant.

Recurrence developed in 3 patients (10%) out of 30 after RFA at 1 month, 1 patient (3.3%) at 6 months which is statistically significant (Table III). At two years, 92% of visible varicosities were successfully treated, 69% had complete sclerosis, and 97% had no reflux.

The diameter of GSV at pretreatment and at follow-up of 1 month and at 6 months patient was comparable and insignificant, but significant (<0.05) and decrease in diameter at 1 year (P-0.005) and required 3 session to occlude the vein lumen, found no DVT (Table IV).

TABLE II.—Pain.

	Me	an±SD	(Duoluo
	RFA	UGFS		r value
PAIN_0 (0 month)	53.77±9.10	48.56±7.28	2.413	0.019
PAIN_1 (1 month)	64.97±9.23	51.26±7.32	6.314	< 0.001
PAIN_2 (6 month)	76.77±9.03	54.16±7.46	10.561	< 0.001
PAIN_3 (1Yr)	88.29±9.17	57.26±7.76	14.481	< 0.001

TABLE III.—*Recurrence of varicose vein in terms of recanalization in both groups.*

	1-Yes/	R	FA	USGFS		
	2-No	Ν	%.	N	%.	- P value
Recurrence at 1 month	1	3	10.0	15	50.0	< 0.001
	2	27	90.0	15	50.0	
Recurrence at 6 months	1	1	3.3	15	50.0	< 0.001
	2	29	96.7	15	50.0	
Recurrence at 1 year	1	1	3.3	15	50.0	< 0.001
	2	29	96.7	15	50.0	

TABLE IV.—Great saphenous vein diameter (anatomical outcome) variation with treatment in both groups.

	RFA	UGFS	<i>t</i> -value	P value
GSV_0	6.600±1.2487	6.227±.9490	1.304	0.197
GSV_1mo	4.700±1.3062	$4.497 \pm .9852$	0.681	0.499
GSV_6mo	3.407±1.2953	3.187±.8932	0.766	0.447
GSV_1yr	2.647±1.3101	1.713±1.1805	2.899	0.005

In our study, maximum number 16 out of 30 (53.3%) patients who underwent RFA were male and underwent UGFS 18 out of 30 (60%) were female, which is insignificant because of less no of patients. The patients 23 out of 30 (76.7%) who underwent RFA were of BMI>23.9 and students (13 out of 30 [43.3%] in UGFS 20 out of 30 [66.6] were of BMI>23.9 and laborer [13] out of 30 [43.3%]) which is comparable and insignificant.

The SF-36 has been developed over time with questions in the following two categories: physical health (assessed as the patient's level of functioning) and mental health (assessed as an indication of well-being). These two groups have been broken down into eight domains that include evaluation of physical and social functioning, role limitations due to physical or emotional problems, mental health, pain, vitality and health perception. Then these domains again divided into group Physical summary component (PCS) and mental component summary (MCS).

In our study, physical functioning of the patient was insignificant (P>0.483) at pretreatment level but gradually improved in subsequent follow-up. Physical health was insignificant at 0 month but gradually became improved and significant (P<0.001) in follow-up at 1, 6 months and at 1 year more than the USGFS group (Table V, VI).

Role limitation due to emotional problem was insignifi-

cant at 0 month but gradually increased in subsequent follow-up and (P<0.001), and highest at 1 year (79.11 \pm 10.12) and significant in comparison to UGFS group. The scoring of emotional wellbeing of both the group was insignificant at pretreatment level but at 1 month 6 months and 1-year follow-up the emotional wellbeing score of RFA group was higher than USGFS group and significant (P<0.001). Social Functioning Score in both the group was comparable at the pretreatment. After 1-month follow-up the SF 36 Score of RFA group higher as compare to UGFS group. On 6 month and 1-year follow-up there was also significantly higher score was present in RFA group as compared to UGFS group.

Energy was insignificant at pretreatment level, after 1-month follow-up the energy /fatigue score of RFA group was higher as compared to UGFS group. At 6 months and 1-year follow-up there was also significantly higher score present in RFA group as compared to UGFS group.

The SF36 domain described as of above further divided into PCS and MCS.

Physical Component Summary (PCS) Score of SF-36was insignificant at pretreatment level, after 1-month follow-up this score of RFA was higher (51.82 ± 7) as compared to UGFS group. At 6 months and 1-year follow-up, there was also significantly (P<0.001) higher

	Pretreatment	(1 month)	(6 month)	(1 year)	P value
Physical functioning	53.06±9.71	63.06±9.81	74.06±9.75	85.56±9.71	< 0.001
Role limitations due to physical health	48.09±11.39	58.29±11.45	68.65±11.59	79.49±11.44	< 0.001
Pain	53.77±9.10	64.97±9.23	76.77±9.03	88.29±9.17	< 0.001
General health	44.19±9.06	55.13±9.76	67.13±9.46	79.55±8.87	< 0.001
Role limitations due to emotional problem	46.65±16.10	58.65±16.05	70.65±16.63	79.11±10.12	< 0.001
Emotional well-being	57.56±6.98	70.06±6.96	83.63±6.18	92.09±4.15	< 0.001
Social functioning	48.75±15.52	61.70±15.57	73.27±14.08	82.54±10.00	< 0.001
Energy fatigue	54.46±10.21	66.05±10.25	78.45±10.01	89.38±7.07	< 0.001
Physical component summary	51.82±7.92	63.83±7.90	76.92±6.93	87.62±5.60	< 0.001
Mental component summary	51.39±6.34	63.39±6.47	75.89±6.40	88.17±5.25	< 0.001

	0 (0 month)	1 (1 month)	2 (6 month)	3 (1 year)	P value
Physical functioning	51.55±6.77	54.30±6.57	57.30±6.47	60.50±6.59	< 0.001
Role limitations due to physical health	42.05±18.67	44.55±18.25	47.15±18.75	50.05±18.66	< 0.001
Pain	48.56±7.28	51.26±7.32	54.16±7.46	57.26±7.76	< 0.001
General health	38.83±7.32	41.78±7.58	44.83±7.41	48.03±7.67	< 0.001
Role limitations due to emotional problem	45.44±13.22	47.70±13.14	50.40±13.18	52.40±13.43	< 0.001
Emotional well-being	54.00±6.56	57.00±6.52	59.70±6.50	62.60±6.56	< 0.001
Social functioning	45.33±14.43	48.33±14.58	50.93±14.40	53.83±14.51	< 0.001
Energy/fatigue	51.25±12.45	53.77±12.72	56.60±12.32	58.67±12.02	< 0.001
Physical component summary	47.60±7.41	50.04±7.49	53.14±7.79	56.64±7.40	< 0.001
Mental component summary	49.33±9.78	52.23±9.47	54.63±9.40	57.23±9.08	< 0.001

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(63.83±7.90) score present in RFA group as compared to UGFS group.

Mental Component Summary Score of SF 36was insignificant at pretreatment level, after 1-month follow-up this score of RFA was higher as compared to UGFS group. After 6 months (75.89 ± 6.40) and 1-year (88.17 ± 5.25) follow-up, there was also significantly higher (P<0.001) score present in RFA group as compared to UGFS group.

The next disease specific scoring deciding quality of life is VCSS. It includes nine hallmarks of venous disease scored on a scale of severity ranging from 0 to 3. Higher is the scoring higher is the quality of life.

In our study, 60 limbs were examined with CEAP C2 to C6 were examined in which C2 was 44%, C3 was 24%, C4 was18%, C5 was 8% and C6 was 6%. The initial VCSS mean score was 9.17 which decreased to 2.60 at 1 year.

The CEAP clinical class breakdown was 37% C3, 30% C4, 12% C5 and 20% C6. The initial VCSS mean score was 11.5, which decreased to a mean score of 4.4 within three months of USGFS or RFA. No significant difference was noted between the VCSS values in patients undergoing USGFS *vs.* RFA. Long-term follow-up is planned to evaluate the outcome of the procedure and the symptomatic progress over time.

There is significant improvement (Table VII) of VCSS from pretreatment level (9.17 ± 2.119) to 1 month (5.60 ± 2.159) but less significant at 6 month (3.57 ± 2.144) and again increased at 1 year and at significant level (P<0.001). The Quality of life in the form of VCSS improved in subsequent follow-up.

In this study, the anatomical outcome was measured by the occlusion of the lumen of the GSV not the reflux in patients underwent both the intervention separately.

Recurrence was developed in 3 patients (10%) out of 30 after RFA at 1 year, and in 15 patients (50%) after UGFS at 1 year. Recurrence is much less common in the patients undergoing RFA as compared to USGFS.

Discussion

The pretreatment scoring in both the group was comparable but not significant. But in Subsequent follow-up

TABLE VII.—Venous Clinical Severity Score.

	RFA	UGFS	<i>t</i> -value	P value
VCSS_0	9.17±2.119	7.13±2.300	3.561	0.001
VCSS_1mo	5.60±2.159	4.00±1.114	3.607	0.001
VCSS_6mo	3.57±2.144	2.77±1.406	1.709	0.093
VCSS_1yr	2.60±1.476	$1.73 \pm .640$	2.950	0.005

HRQOL is better in RFA group patients than the USGFS group and statistically significant (P<0.05).

Kaplan *et al.* studied 2404 patients for the presence of venous disease and application of the SF-36, finding that 'even modest venous disease translates into functional limitations and limitations in daily activities. Venous disease does not appear to affect emotional aspects of HRQOL.⁹

Another large epidemiological study using the SF-36 is the Bonn Vein Study. This population survey was undertaken in Germany with 3072 participants and was designed to determine the rate of occurrence and severity of chronic venous disease among the general public.¹⁰

To assess the outcome of HRQOL multiple scoring were used in different studies. But we used SF36 and VCSS scoring.

UGFS was found to be a safe and effective treatment for both primary and recurrent GSV and small saphenous vein (SSV) incompetence, assessed by occlusion of treated veins on duplex ultrasound (DUS), and by disappearance of visible varicose veins (VV) on clinical examination. There was some evidence that healing of chronic venous ulcers (CVU) may be improved by UGFS when combined with compression bandaging.

In our study, significant (P=0.005) occlusion was found after RFA and USGFS group but more in RFA group. In a similar study, early results show complete occlusion of treated veins in over 90% of cases, and 85- 100% occlusion at two-year follow-up.¹¹

The eight Domain of SF36 denoting different dimension of HRQOL were insignificant and comparable (P>0.05) in pretreatment level, but attained higher scoring in follow-up more than the USGFS group and significant (P<0.05).

In our study, recanalization developed in 50% patients underwent USGFS and <5% in patients of RFA. The range of diameter of GSV took into study was of 3 to 6 mm but in similar study treatment is limited to veins of <12 mm diameter, meaning that up to 50% of patients are unsuitable for this technique.¹²

In similar study, Cabrera *et al.* published the outcome of 500 GSV treated with a foam. At three years they found that 81% of GSV were obliterated and 96.5% of superficial branches were obliterated. This required one session of sclerotherapy in 86% of patients, two in 11% and three sessions in 3% of patients. They found no serious complications and no DVT in their series.¹³

Physical Functioning of the patient was insignificant (P>0.483) at pretreatment level but gradually improved

in subsequent follow-up and significant (P < 0.001) at 1, 6, months and at 1 year.

Physical Health was insignificant at 0 month but gradually became improved and significant (P<0.001) in followup at 1, 6 months and at 1 year more than the USGFS group.

General health was significantly improved (<0.001) from o month to subsequent follow-up, and highest (79.55 ± 8.87) in 3rd follow-up in patient underwent RFA in comparison of patients underwent UGFS.

Social Functioning Score in both the group was comparable at the pretreatment. After 1-month follow-up the SF 36 score of RFA group higher as compare to UGFS group. On 6 month and 1-year follow-up there was also significantly higher score was present in RFA group as compared to UGFS group.

Energy/fatigue insignificant at pretreatment level, after1 month follow-up the energy/fatigue score of RFA group higher as compare to UGFS group. On 6 month and 1-year follow-up there was also significantly higher score was present in RFA group as compare to UGFS group.

Physical Component Summary (PCS) Score of SF-36was insignificant at pretreatment level, after 1 month follow-up this score of RFA was higher as compared to UGFS group. 6 month and 1-year follow-up there was also significantly higher (P<0.001) score was present in RFA group as compare to UGFS group.

Mental Component Summary Score of SF 36was insignificant at pretreatment level in both groups. After 1-month follow-up, this score of RFA was higher as compare to UGFS group. On 6 month and 1-year follow-up, there was also significantly higher (P<0.001) score in RFA group as compared to UGFS group.

Recurrence was developed in 3 patients (10%) out of 30 after RFA at 1 month, 1 patient (3.3%) at 6 months and at 1 year which is significant (P<0.001) and in 15 patients (50%) after UGFS at 1 month, 6 month and at 1 year of follow-up which is also significant (P<0.001).

Conclusions

HRQOL was measured by the SF 36 and VCSS at pretreatment and post treatment level in patients undergoing RFA and USGFS. Higher scores of SF36 and VCSS found in RFA group patients along with low recurrence of varicose veins, less complications related to RFA denotes that the HRQOL is much better in patients undergoing RFA therapy as compared to UGFS group.

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CASE REPORT

Takotsubo Syndrome induced by sclerotherapy with polidocanol

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ABSTRACT

Takotsubo Syndrome or stress cardiomyopathy is reversible cardiomyopathy characterized by a sudden onset reversible episode that mimics an acute coronary syndrome; it presents with acute left ventricular dysfunction, ventricular dilation and contractility alteration, but there is no identifiable coronary artery compromise in the angiogram. It usually occurs in post-menopausal women and in some cases might be triggered by an emotional or physical stress episode; this allowed to call it "the broken heart syndrome." We present an unexpected event in the course of treating a patient with polidocanol foam sclerotherapy, a 71 year-old woman with a sudden onset of chest oppression sensation, dyspnea, nausea and diminishment of visual acuity that began 5 minutes after a session of sclerotherapy while lying on the procedure bed at an ambulatory vascular surgery center. Polidocanol foam was injected in the left lower limb below the knee, to treat varicosities in the context of chronic venous insufficiency. The symptoms resolved spontaneously shortly after the episode and the patient was released. Five hours later, while being lying on her bed at home, a similar but more intense episode occurred. At the ER, the EKG showed sinus tachycardia with no other alterations, Troponin I level in blood showed a frankly positive result. She was diagnosed with non-ST elevation myocardial infarction (NSTEMI) and received the initial management. The percutaneous coronary intervention (PCI) was normal and showed no arterial abnormalities, an echocardiogram revealed left ventricular dysfunction which confirmed the diagnosis of Takotsubo Syndrome. The patient had history of several previous well tolerated sclerotherapy sessions, with no complications. Additionally, the patient was grieving due to the passing of a beloved one two months before.

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KEY WORDS: Takotsubo cardiomyopathy; Sclerotherapy; Polidocanol.

S clerotherapy is a widely demonstrated, safe, effective and well tolerated treatment strategy for ectatic veins and telangiectasias seen in chronic venous disease; the incidence of sclerotherapy induced cardiomyopathy is still unknown. Three case reports of Takotsubo Syndrome (TS) are found in the literature. TS is an acute coronary syndrome with reversible severe left ventricular dysfunction due to exaggerated sympathetic response that takes place in 90% of the cases in post-menopausal woman.¹ It is usually related to a severe stress trigger such as unexpected deaths, natural disasters, or extreme physical activity. Some cases have been related to drugs administration with 1/5 of patients having no identifiable stress trigger.² The symptoms such as chest pain and dyspnea, signs and

echocardiographic and electrocardiographic findings suggest an acute coronary syndrome. Patients have increased creatine kinase-MB and cardiac troponin concentrations, but angiography show normal coronary arteries with no obstruction. The EKG might show ST-segment elevation, which resolves after a few hours. Although most patients fully recover after a few weeks, cardiac arrest, cardiogenic shock, and serious ventricular arrhythmias may occur, giving a mortality rate in hospitalized patients of 4-5%.³

Case report

A 71 year-old woman was brought by an ambulance to our institution Emergency Room (ER), after a second episode of

acute onset of chest pain, followed a session of sclerotherapy with 1 cc of polidocanol with 3 cc mix of CO_2/O_2 70/30% in the enlarged superficial veins of the left lower limb earlier the same day. The first episode was milder and took place 5 hours before, while being in supine position 5 minutes after the procedure at a private vascular surgeon's office. She experienced acute chest pain and dysautonomia symptoms, such as diaphoresis, nausea, disturbances in the visual field, tremors, and weakness that lasted less than 5 minutes. She was released after 30 minutes of observation and sent home shortly after.

The second episode presented with similar symptoms, but with more intense chest oppression sensation and pain localized in the left side of the chest. On her way to the hospital by an ambulance, an electrocardiogram (ECG) was performed and showed sinus tachycardia at 127 beats per minute with no other alterations. At the hospital her symptoms had diminished and completely disappeared 1 hour after arrival. The initial laboratory tests revealed troponin I levels of 645.8 ng/L with a troponin I control of 1.209 ng/L (upper limit: 40 ng/L).⁴ As a result of the biomarkers elevation, the patient was transferred to the Intensive Care Unit for further evaluation. The patient had history of controlled hypertension, with no other relevant medical background. She underwent 3 sclerotherapy sessions one year ago.

Chest X-ray, echocardiography and catheterization were performed. The chest X-ray was normal. The transthoracic echocardiogram showed left ventricular and septal akinesia associated with a 45% ejection fraction, ventricular dilation and a thrombus of 1.7×0.7 cm in the apex of the left ventricle (Figure 1). A diagnostic arteriography revealed no significant obstruction in the epicardial coronary arteries (Figure 2), which confirmed the diagnosis of Takotsubo Syndrome. She received supportive treatment and anticoagulation for the left ventricular thrombus. The next day she was transferred to hospitalization and released 2 days later. After a total of three days hospitalized, the patient was evaluated after 4 weeks at a follow-up session, where an echocardiogram showed no thrombus, with resolution of the low ejection fraction, ventricular ballooning and the contractility defect (Figure 3A, B).

Discussion

In the literature there are three cases reported of sclerotherapy induced Takotsubo Syndrome.⁵⁻⁷ Out of which 1 occurred after sodium tetradecyl sulphate injections and





Figure 1.—Transthoracic echocardiogram showing an apical thrombus of 1.7×0.7 cm and apical ballooning.

Figure 2.—Coronary arteriography showing patent coronaries with no signs of obstruction.



Figure 3.—A) Corresponds to the echocardiogram of the day of the event, showing ventricular dilation (ballooning) and an apical thrombus; B) corresponds to the echocardiogram taken after 4 weeks with complete resolution.

2 following polidocanol injections. All cases were women older than 65 years old, who developed symptoms a few minutes after the injections. They all had left ventricular contractility dysfunction and ejection fraction reduction; none of them had an identifiable stress trigger and were fully recovered a few weeks after the event. Despite that our patient went through the loss of a beloved one 3 months ago, she denied still having deep sadden feelings and did not relate the episode to an emotional situation. Given the low incidence of TS (100 new cases per million per year⁸) the differential diagnosis should include life threatening conditions such as pulmonary embolism and myocardial infarction.

The mechanism by which TS occurs is not fully understood yet, the most accepted hypothesis stands that multivessel epicardial spasm takes place in response to emotional or physical stress-induced catecholamine release,⁹ hence, most cases of pharmacologically-induced TS are secondary to epinephrine, dobutamine, or beta adrenergic enhancing drugs.¹⁰ TS occurs more frequently in postmenopausal women due to the lack of sympatholytic effect exhibited by estrogens, which centrally regulate the sympathetic tone and decrease the expression of beta-adrenoreceptors.¹¹ Therefore, as soon as the systemic estrogen concentration lowers after menopause, tissues expressing beta-adrenoreceptors become more prone to sympathetic hyper response, increasing cardiovascular reactivity to catecholamines.

Polidocanol is a safe and broadly used sclerosing agent, consists of a synthetic fatty alcohol with detergent activity that cause endothelial cell death and produce vessel fibrosis.¹² Polidocanol is used in concentrations of 0.25-5% to sclerose lower limb varicose veins and telangiectasias.¹³ The most common adverse events include hyperpigmentation and matting, with an incidence ranging from 10-30%, with complete resolution in 99% of cases after one year.14 Isolated cases of severe complications such as anaphylactic shock, stroke, paradoxical embolism, and cardiac toxicity have also been reported¹⁵⁻¹⁷ attributing polidocanol's negative inotropic, chronotropic, and dromotropic effects as the possible cause.¹⁸ The case presented does not allow to establish a causality relationship between the polidocanol injection and the development of TS; however, the short time between the two events, just as in the other three cases reported until now, remains highly suggestive of some possible association, and should motivate to develop more studies assessing the physiological response of the heart to sclerosing agents. This new case report of TS after polidocanol sclerotherapy should increase the vascular surgeon's awareness of this disease and identify the type of patients who might be at risk of developing it to take the needed precautions and warn the patients about its presentation. Variables such as, the polidocanol concentration, the type of gas that it is mixed with and the ratio between CO_2 and O_2 and the site of injection should be taken into account for further studies in order to identify if they might affect or not the incidence of adverse events.

Conclusions

Takotsubo syndrome post-sclerotherapy is an adverse event that occurs with a very low incidence, and despite it can be life threatening in some cases, most of them resolve completely after a few weeks. Vascular surgeons should be aware of post-menopausal women who undergo sclerotherapy, since they are the age group most prone to develop TS, therefore, they should be warned about this possible complication. Since a clear mechanism of cardiac toxicity has not been elucidated, further studies need to be carried out assessing variables such as the concentration of the drug, site of injection and the ratio of gases that is used on the foam preparation and their influence in TS appearance.

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CASE REPORT

Recurrent thrombosis: a case report of young patient JAK2+ without myeloproliferative disease and other risk factors. The role of sport activity

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ABSTRACT

In the pathogenesis of thrombotic events, especially those of unknown origin, the role of the *JAK2-V617F* mutation have been underestimated so far. Commonly, *JAK2* mutations are associated with chronic myeloproliferative neoplasms (MPNs). This paper reports the clinical events occurred to a woman positive for *JAK2-V617F* mutation and no MPNs, who experienced three episodes of thrombosis, without other risk factor. Only a few studies have so far described cases of thrombophilia exclusively related to a JAK2 in the absence of MPN, but none of them presented a severe clinical history like that of the patient described here. It is advisable in clinical practice, to search for the JAK2 mutation in all cases of unexplained venous thrombosis. A 46-year-old Caucasian woman was first observed at our clinic in January 2018, after an episode of partial thrombosis of the transverse sigmoid of the venous central axis still under oral treatment with warfarin. After the thrombotic episode, the patient ensured self-sufficiency, but she was unable to drive, had memory disorders and sometimes slight space-time disorientation. The patient reported other episodes of thrombosis occurred in 2000 and in August 2013. The major concern of patients who have undergone numerous thrombotic events is a further recurrence or a new episode. We searched for all thrombophilic mutations and for all of all other indicative parameters of mg, one tablet twice a day. The general situation gradually improved and after 2 months of treatment, the patient completely recovered their autonomy, was well oriented and started driving again. This patient achieved a stable excellent clinical condition, free of thrombotic events for a two-years follow-up. It is advisable in clinical practice, to search for the JAK2 mutation in all cases.

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In the pathogenesis of thrombotic events, especially those of unknown origin, the role of the JAK2-V617F mutation have been underestimated so far.¹ Commonly, JAK2mutations are associated with chronic myeloproliferative neoplasms (MPN).² The observation of thromboembolic events in patients with MPN, even if in the early stages of the disease or in asymptomatic subjects, has raised the question of whether the JAK2-V617F mutation is related to a higher incidence of these events.³ Indeed, it has been shown that aberrant activation of JAK2 is associated with hyperproliferation of myeloid progenitor cells with abnormal release of inflammatory cytokines, hyper-agglutination and thrombosis. Therefore, the thrombophilic condition in JAK2 patients is due not only to the increase in blood viscosity due to hypercellularity, as it occurs in MPN, but also to changes in plasma coagulation, in vessels' wall and in platelet adhesion, all JAK-induced. The activation of JAK2-V617F mutations in MPNs results in an increased sensitivity to thrombopoietin (Tpo) stimulation for megakaryocytes, with increased pro-platelet formation and increased possibility of thrombus formation.³⁻⁵ Neutrophils also appear to be involved in these mechanisms, since a higher expression of beta1-integrins on granulocyte wall of mutated patients has been described compared to unmutated patients. In these patients, the activation of integrin is greater, and this could cause an accumulation of myeloid cells in the spleen, favoring thrombotic events in this district. International guidelines include regular physical activity as one of the main methods of venous thromboembolism prevention. Indeed, a modest physical activity involving long walks is recommended after a thrombotic event.⁶⁻⁹ This paper aimed to report the clinical events in a JAK2 mutated young woman with relapsing thrombosis, without any risk factors and no evidence of MPN who achieved a stable excellent clinical condition with a long-term specific anti-thrombotic treatment associated with regular physical activity with prevented new thrombotic events during a two-years follow-up. The patient signed an informed consent for the use of her data in clinical investigation, according with the Italian laws on privacy.

Case report

A 46-year-old Caucasian woman was first observed at our clinic in January 2018, after an episode of partial thrombosis of the transverse sigmoid of the venous central axis; still under oral treatment with warfarin. After the thrombotic episode, the patient ensured self-sufficiency, but she was unable to drive, had memory disorders and sometimes slight space-time disorientation. She had never been a smoker, did not use oral contraceptive or other drugs, had normal lipid profile, absence of metabolic diseases, heart rhythm disorders, hypertension, arteriovenous malformations in the system of brain spraying and portal. Adult woman in excellent physical shape, Body Weight 55 kg, Height 1.70 m, Body Mass Index (BMI) 18.3 kg/ m². There are no reports of thrombosis, spontaneous abortion, stroke or heart attack at a young age in the family. The patient declared an episode of spontaneous right femoral deep vein thrombosis occurred in 2000, treated for 6 months with heparin with good recanalization and an episode of portal thrombosis occurred in August 2013, and treated with an oral therapy with warfarin. International Normalized Ratio (INR) value was kept in an interval between 2 and 3. Previously there had been no thrombotic episode in the limb and no symptoms that could suggest episodes of this type. She was not affected by liver disease or portal hypertension. In 2003 she reported a spontaneous abortion in the first trimester of pregnancy, but later she had carried to term regularly two pregnancies in the following 4 years. The new thrombotic episode occurred in 2018 during warfarin therapy with an INR interval within the recommended limits. We searched for all thrombophilic mutations: factor V (G1691A, H1299R), factor II, methylenetetrahydrofolate reductase (MTHFR) (A1298C, C677T), plasminogen inhibitor1 (PAI1); for anticardiolipin antibodies, antiphospholipid antibodies, protein C, S, antithrombin III, homocysteinemia, immunophenotyping for paroxysmal nocturnal hemoglobinuria, INR, blood count, fibrinogen, C-reactive protein.¹⁰⁻¹⁶ We also determined serum markers of HBV, HCV and HIV infections¹⁷⁻²¹ in relation to previously episode of portal thrombosis. Only one heterozygosity was found for the C677T mutation for MTHFR, with homocysteine always in the normal values, fibrinogen was 520 mg/dL, C-reactive protein was 1.5 mg/dL, INR: 2. All other biochemical exams were within normal limits (Table I). Mutation of the JAK2-V617 gene was searched and found present. No diagnostic criteria for chronic myeloproliferative disease was present, nor mutations for Philadelphia chromosome was detected. Warfarin therapy was modified while keeping INR values between 3 and 4. In the following two

TABLE I.—Blood count, biochemical tests,	INR,	fibrinogen,	С-
reactive protein, and homocysteine of a 46	6-year	-old Caucas	sian
woman at the first observation at our clinic	in Ja	nuary 2018.	

0	2
Data	January 2018
BMI, kg/m ²	18.3
Red blood cells, 106/uL	4.5
White blood cells, 10 ³ /uL	7.6
Hemoglobin,g/dL	12
Hematocrit, %	44
Platelets, 10 ³ /uL	300
INR	2
Fibrinogen, mg/dL	520
C-reactive protein, mg/dL,	1.5
Homocysteine, mcmol/L	8
Creatinine, mg/dL,	0.6
Glucose, mg/dL,	50
Bilirubin, mg/dL	0.5
AST, IU/L	13
ALT, IU/L	10
Triglycerides, mg/dL	70
Total cholesterol, mg/dL	150

INR: international normalized ratio; AST: serum glutamic oxaloacetic transaminase; ALT: serum glutamic pyruvic transaminase.

months, the neurological symptoms were struggling to improve. Memory disturbances, disorientation and lack of autonomy made the patient more and more afraid of facing everyday life. The INR values during this period were consistently held between 3 and 4. The anticoagulant therapy was changed by introducing apixaban 5 mg, one tablet twice a day. The general situation gradually improved and after 2 months of treatment, the patient completely recovered their autonomy, was well oriented and started driving again. Despite her challenging clinical history, the patient, being was in good physical condition, started practice regularly pilates, aerobic gymnastics, and long walks. Subsequently, she increased her physical activity with 3 weekly sessions at a high rate and long walks regularly. Regular physical activity improved health-related quality of life. Currently, after a 2-year follow-up, she is in full wellbeing, in good clinical condition and, thanks to the physical training program, she has achieved an enviable physical condition.

Discussion

Physical activity is very helpful in preventing and thrombosis recurrence.²²⁻²⁵ Accordingly, early mobilization is recommended after post-thrombotic period, in order to avoid recurrence, whereas an intense physical activity is not recommended since it could facilitate the mobilization of thrombus during the disaggregation. Physical training benefits patients who have had deep vein thrombosis controlling body weight gain, favoring cardiovascular fitness and strengthening muscles. In addition, strengthening the muscles by improving their functionality beneficial effects on venous return and on and typical skin dehydration.²⁶⁻³¹ In our case, the mutation of the JAK2-V617F was the only cause of thrombophilic condition and of the episodes of thrombotic events. Only a few studies have so far described³² cases of thrombophilia exclusively related to a JAK2 in the absence of MPN, but none of them presented a severe clinical history like that of the patient described here. The pathogenetic mechanisms associated to this mutation have not been fully elucidated at present. An increased incidence of cerebral and splanchnic venous thrombosis in patients with JAK2 mutation without MPN has been previously reported. In addition, JAK2-V617F mutant liver endothelial cells have been described in patients with Budd-Chiari Syndrome, even in the absence of MPN, suggesting that the JAK2-V617F expression may favor splanchnic venous thrombosis even in the absence of hematopoietic cells.

Conclusions

In conclusion, besides hyperproliferation of myeloid progenitor cells, the mechanisms favoring venous thrombosis most likely includes an abnormal release of inflammatory cytokines and hyper-agglutination. It would be interesting to search for the JAK2 mutation in all cases of unexplained venous thrombosis, because this mutation can involve a thrombotic risk regardless of the evidence of a concomitant myeloproliferative disease. At present, specific therapies (JAK inhibitor) are not used for these patients, due to insufficient knowledge of the link between this mutation and thrombotic events, and for the few cases described in the literature not associated with myeloproliferative disease. Therefore, adequate conventional therapy with anticoagulants and early mobilization represent the firstchoice treatment of acute thrombosis of unknown origin, followed by regular physical activity to prevent further thrombotic episodes.

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CASE REPORT

Foot acrosyndromes in patients with COVID-19: the podiatrist's approach

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ABSTRACT

Acrocyanosis is a permanent dystonic vascular acrosyndrome. Vascular acrosyndromes often occur with changes in temperature and skin color. They can also be associated with paresthesia or hypoesthesia as well as ischemic damage and necrosis in the worst cases. Often the acrosyndromes can also be the manifestation of other pathologies, as is the case of viral infections, where they could favor early diagnosis. On March 29, 2020, five weeks after the first Italian case of COVID-19, the first report of acro-ischemic lesions appeared in asymptomatic positive children, the confirmation of which was common throughout Italy with the report of some dozens of cases and still new cases are reported every day. From these data, acrosyndromes manifestations occurs in healthy children and adolescents; often mistaken for chilblains or allergic dermatitis for erythematous patches. Three recent studies conducted in Wuhan show that hypertension is often associated with people with COVID-19 and increases the risk of pathological complications. The new coronavirus responsible for acute and severe respiratory syndrome (SARS-CoV-2) binds to target cells through the angiotensin 2 converting enzyme, which is expressed on the epithelial cells of the lungs, intestine, kidney and blood vessels. Our hypothesis is that the podiatrist, in his clinical practice, could consider the possible dermoscopic differences in the vascular aspect of the nail capillaries and their association with the clinical state of the disease. Education, prevention, compliance are the keywords of the operator/user relationship within the podiatry study.

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KEY WORDS: Podiatry; Foot; COVID-19; Education.

A crocyanosis is a permanent dystonic vascular acrosyndrome. Vascular acrosyndromes often occur with changes in temperature and skin color. They can also be associated with paresthesia or hypoesthesia as well as ischemic damage and necrosis in the worst cases. Causes of these dysfunctions are commonly associated with environmental factors such as exposure to low temperatures or heat sources and stress, but often the acrosyndromes can also be the manifestation of other pathologies, as is the case in viral infections, where they could favor early diagnosis.

From the beginning of the spread of COVID-19 it was clear that its severity was related to age and comorbidity: reporting the data of a Chinese study on 44,672 confirmed cases of positivity, subjects from 0 to 10 years were represented by 0.9% and those from 10 to 19 for 1.2%.¹

Half of the children in this group had no obvious symptoms, making it difficult to identify them for epidemiological and preventive purposes. This further leads us to think that upstream podiatry screening can be an effective tool for the community.

On March 29, 2020, five weeks after the first Italian case of COVID-19, the first report of acro-ischemic lesions appeared in asymptomatic positive children,² the confirmation of which was common throughout Italy with the report of some dozens of cases and still new cases are reported every day. From these data, acrosyndromes manifestations occurs in healthy children and adolescents; often mistaken for chilblains or allergic dermatitis for erythematous patches, they can be red-violet in color, rounded with a diameter of a few millimeters and with blurred limits. They mainly affect the feet and sometimes the hands.

Clinical series

To begin this evaluation on some cases we examined 3 patients received at our podiatry clinics during this period. Although the age range was wide, the clinical signs and discomfort complained by the patients were superimposable on each other. As a standard of treatment, immediately after clinical podiatry treatment, all patients had laser treatment with the following settings: frequency 645 nm, 90 seconds on the dorsal side of the foot and 60 seconds on the erythematous areas. All subjects were considered COVID-19 positive suspects at the visit time.

Case 1

A 17-year-old female underwent the medical examination. The family physician suspected chilblains and prescribed topical vasodilators without effect. The patient came to clinic due to pain in the legs (thighs) VAS 7, itching and hypersensitivity of the erythematous areas; she reported absence of systemic pathologies. The pain worsens at rest. Laboratory analyses (blood count and urine culture) were in the norm. The subject did not have a complete diet and presented menstrual cycle disorders. She never went to vascular MD before (Figure 1). Regarding the local foot symptomatology, laser treatment was chosen as standard. At the end of this treatment, there was no change in pain perception compared to the previously indicated value. Forty-eight hours later the patient no longer had itching.

Case 2

A 16-year-old female underwent the medical examination. The family physician suspected allergies and prescribed antihistamine without results. The patient comes



Figure 1.—Acro-ischemic lesion V MTP.

to clinic due to foot and legs pain VAS 6, itching and hypersensitivity of the erythematous areas; she reported absence of systemic pathologies and never went to vascular MD before. The pain worsens at rest, especially during the night. Laboratory analyses (blood count and urine culture) showed nothing relevant (Figure 2). The subject had menstrual cycle disorders. Concerning the local foot symptomatology, laser treatment was chosen as standard. At the end of this treatment, there was no change in pain perception compared to the previously indicated value. Forty-eight hours later the patient had no improvement in symptoms.

Case 3

A 93-year-old female underwent the medical examination. The patient presented type II diabetes treated with metformin and bilateral MTP structural alterations. He came to clinic due to a single foot pain which she described as small cramps VAS 5 in correspondence of the erythematous areas. The patient showed signs of acro-ischemia of



Figure 2.—Acro-ischemic lesion V MTP.



Figure 3.—Acro-ischemic lesion II MTP with onychodystrophy.

II and III MTP of the right foot, which were painful to the touch. About the local foot symptomatology, laser treatment was chosen as standard (Figure 3). She presented regular peripheral pulses. Laboratory analysis (blood count and urine culture) showed nothing relevant. At the end of the laser treatment, there were improvements (VAS 3) in pain perception compared to the previously indicated value. Forty-eight hours later the patient had no more pain. As for COVID-19, the patient was asymptomatic at the time of the visit, but she will be positive after the swab requested by the family doctor, 4 days later.

Discussion

The foot areas, usually most affected, are situated near the distal metatarsophalangeal joint, but in some cases, they can be found even in the plantar region. The lesions do not affect all the toes uniformly – on average they are three on five; they may have blackish crusts in the subsequent evolution – usually painful, they evolve within two weeks and do not leave any aftermath. This syndrome may be associated with muscle pain and intense itching with burn-

ing pain in the foot. However, acrocyanosis may not be the only obvious clinical sign.

The lower limbs can manifest symptoms such as pain or dyschromia, which are sometimes associated with hypoxia, metabolic alterations in the microcirculation, or acrocyanosis.³

Three recent studies⁴ conducted in Wuhan showed that hypertension is often associated with people with COV-ID-19 and increases the risk of pathological complications.

The new Coronavirus – responsible for acute and severe respiratory syndrome (SARS-CoV-2) – binds to target cells through the angiotensin 2 converting enzyme – which is expressed on the epithelial cells of the lungs, intestine, kidney and blood vessels.

Angiogenesis is closely related to onychodystrophy based on the activity of fibroblasts (FGF);^{5, 6} the evaluation of the skin appendages, such as the altered regrowth of the nail (onychopathy) – in addition to factors related to traumatism – varies according to nutraceutical factors, oxygenation of the matrix and systemic diseases. The low angiogenic activity causes damage to the tissues followed by ischemia or heart failure caused by COVID-19.

Our hypothesis is that the podiatrist, in his clinical practice, could consider the possible dermoscopic differences in the vascular aspect of the nail capillaries and their association with the clinical state of the disease. Recent studies in HCV and HBV patients⁷ have shown how nail capillary abnormalities are or could be a sign of endothelial tissue damage in chronic viral hepatitis.

Education, prevention, compliance are the keywords of the operator/user relationship within the podiatry study.

Synergic and interdisciplinary work would be appropriate; working with outpatient archives and summary sheets reported the following data:

- name and surname, gender, age;
- fever states;
- · medical diagnosis;
- · clinical signs, onychopathies;
- acrocyanosis.

Although the Spanish guidelines of the General Council of the College of Podiatrists advise not to go to the hospital for the sole appearance of symptoms, outpatient management through memoranda of understanding between public and private health professionals through the use of these means and telemedicine, would allow greater speed in differential diagnosis and therapeutic administration.

Conclusions

In conclusion, we cannot fail to take into consideration some evidence, in support of what has been said so far. "If it is true that heparin reduces the severity of COVID-19 symptoms, can we really think that an immune complex microangiopathy occurs?" On the basis of these considerations that are currently the topic of scientific debate, one should think about the contribution that podiatrists can give from a clinical point of view. In his clinical practice, the podiatrist who works on the territory, both at an outpatient and at home level, visits and independently treats multi-pathological subjects who very often escape public health. By considering a pandemic event, as in the case of COVID-19, the podiatry study can act as a sentinel on the territory for preventive purposes and for reporting the patient with suspected positivity to the competent reference bodies.

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