International Journal of Biomedicine 11(1) (2021) 87-91
http://dx.doi.org/10.21103/Article11(1)_OA15

ORIGINAL ARTICLE

Surgery

INTERNATIONAL JOURNAL OF BIOMEDICINE

Clinical and Pathogenetic Aspects of Complex Treatment of Decompensated Forms of Chronic Venous Insufficiency of the Lower Extremities

Vladimir V. Izosimov, MD, PhD; Serhiy H. Hryvenko, MD, PhD, ScD*; Yuriy G. Baranovskiy, MD, PhD; Yuriy V. Artemov, MD, PhD; Andrej A. Dovgan MD, PhD; Elizaveta V. Izosimova

Medical Academy named after S.I. Georgievsky of Vernadsky CFU
Simferopol, Crimea

Abstract

The article presents a clinical assessment of the effectiveness of the author's method of pharmacological correction in the complex treatment of patients with trophic ulcers of venous origin in the lower extremities. Based on the analysis of the data obtained, we found that the use of the proposed method of drug correction in the complex treatment of chronic venous ulcer ensures the effectiveness of treatment, a reduction in the duration of inpatient treatment, and the reliability of rehabilitation in the postoperative period.(**International Journal of Biomedicine. 2021;11(1):87-91.**)

Key Words: chronic venous insufficiency • chronic venous ulcer • chronic venous disease

For citation: Izosimov VV, Hryvenko SH, Baranovskiy YuG, Artemov YuV, Dovgan AA, Izosimova EV. Clinical and Pathogenetic Aspects of Complex Treatment of Decompensated Forms of Chronic Venous Insufficiency of the Lower Extremities. International Journal of Biomedicine. 2021;11(1):87-91. doi:10.21103/Article11(1)_OA15

Abbreviations

CVD, chronic venous disease; **CVI**, chronic venous insufficiency; **DHS**, dioctahedral smectite; **CVU**, chronic venous ulcer

Introduction

Chronic venous disease (CVD) of the lower extremities is one of the most prevalent disorders worldwide.[1] The steadily progressive course of CVD of the lower extremities leads to the development of complications in 15%-25% of patients with varicose veins and in more than 80% of patients with post-thrombotic disease.[2] As chronic venous insufficiency (CVI) progresses, persistent severe microcirculation disorders develop, ultimately leading to the appearance of an ulcer.[3] Trophic ulcers are a complication of CVI of the lower extremities and occur in 2% of the working-age population of industrialized countries.[4] Every year in the United States, 2.2 million cases of chronic venous ulcers (CVU) are diagnosed.[5] In Russia, from 1.5 to 5 million people suffer from this severe pathology.[1,6] The high prevalence of CVU and its tendency to recur dictate the need to use an optimal complex of various modern methods of treatment.[1]

Modern strategy and tactics to treat CVU suggest a differentiated approach and a combination of different methods of conservative and surgical interventions.[3,7] Only an integrated approach to the treatment of this category of patients—a combination of CVU sanitation, competent compression, and drug therapy in an indispensable combination with corrective operations on the venous system—makes it possible to obtain a good, persistent clinical result and subsequent

***Corresponding author:** Serhiy H. Hryvenko, MD, PhD, ScD. Medical Academy named after S.I. Georgievsky of Vernadsky CFU, Simferopol, Crimea. E-mail: hryva@mail.ru*

long-term, relapse-free course of the disease.[1] Therefore, the development and implementation of modern methods of CVU treatment, their inclusion in the complex of preoperative preparation and their combination with various methods of surgical correction of CVI is an urgent problem of modern phlebology.[7] In addition, it should be clearly remembered that even in cases of successful surgical correction, patients with CVI need a long-term and sometimes lifelong maintenance therapy aimed at leveling the known risk factors for CVI and its key pathogenetic mechanisms.[8] Unfortunately, to date a clear, comprehensive, step-by-step approach has not yet been developed for the treatment of patients with CVU.

The variety of the proposed methods for treating CVU indicates dissatisfaction with the results of each of them. In this regard, the search for new pathogenetically substantiated methods for the treatment of CVU remains relevant in order to correct general disorders and normalize the condition of tissues, enhance their regeneration, fight ischemia, normalize lymph circulation, and correct body hemostasis.[9] A number of recent studies have indicated the positive role of enterosorbents in the treatment of complicated forms of varicose veins. [10] The therapeutic effectiveness of enterosorption also depends on a number of factors, including the direction of the therapeutic effect of the sorbent that is used. In our opinion, dioctahedral smectite (DHS) is of particular interest. DHS is one of the sorbents highly standardized for the raw materials from which it is obtained. DHS has a strong polymeric organosilicon base containing aluminum and magnesium as heteroatoms coordinating OH-groups around themselves. The porous structure provides "softness" of the DHS action and compatibility in contact with biological media.[11] Magnesium contained in DHS is also important for the repair processes. The feasibility of using magnesium preparations has been confirmed in patients with varicose veins, including those who have undergone phlebectomy, from the standpoint of their influence on the level of matrix metalloproteinases and their inhibitors.[12]

The aim of this study was to improve the immediate, long-term and functional results of complex treatment of CVI patients with CVU of the lower extremities on the basis of the development and implementation of new pathogenetically substantiated methods of pharmacotherapy.

Materials and Methods

The presented clinical study is based on a prospective analysis of the results of examination and complex treatment of 106 CVI patients with CVU who underwent surgical treatment in the period from 2012 to 2017. The study was carried out in compliance with Ethical Principles for Medical Research Involving Human Subjects, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 59th WMA General Assembly, Seoul, Republic of Korea, October 2008. Written informed consent was obtained from all patients before inclusion in the study.

The main group (MG) consisted of 52 patients (mean age of 62.80±1.52 years), who were additionally prescribed the enterosorbent DHS and magnesium orotate [13,14] in the complex of the baseline therapy (diosmin drugs, antiplatelet agents, decongestant therapy, and compression stockings). The *prescribed dosage* of magnesium orotate was 1000 mg three times a day for seven days, then 500 mg two to three times a day. The duration of the course was at least 4-6 weeks. The possibility of a repeated course of treatment was determined based on the patient's status. As DHS, the enterosorbent "Benta" (Krymfarmed) was prescribed: 3 grams three times a day, 30 minutes before meals. The contents of the "Benta" package were dissolved in 100ml of warm drinking water, mixed thoroughly and taken orally. The course of administration was 7 days.

The comparison group (CG) consisted of 54 patients (mean age of 61.59±1.68 years) who received the above-mentioned baseline therapy.

For both groups of patients, the common clinical sign was the presence of CVU in the exudation phase (CEAP class C6S). All patients had both single and multiple CVU. The CVU duration ranged from 6 months to 5 years. CVU of the lower third of the leg was diagnosed in 97(91.5%) patients. Most often, CVUs were formed on the left leg, where they were diagnosed in 56(52.8%) patients. On the medial surface of the leg, CVUs were diagnosed in 57(53.8%) patients, on the lateral surface – in 9(8.5%) patients, on the posterior surface – in 10(9.4%) patients, and on the anterior surface – in 21(19.8%) patients. CVUs on various surfaces of the middle third of the leg were detected in 9(8.5%) patients. The CVU area ranged from 3.0 cm² to more than 20.0 cm². At the same time, in 28(26.4%) patients, the CVU area was up to 5 cm², in 74(69.8%) patients – from 6 cm² to 20 cm², in 4(3.8%) patients – exceeded 20 cm².

Demographic indicators in MG and CG did not show statistical differences. In both groups, women prevailed (58.5% versus 41.5% for men). In addition, the studied groups of patients were comparable in terms of the presence of concomitant diseases. None of the identified comorbidities at the time of treatment and at the stages of complex treatment had a pronounced manifestation and did not significantly affect the results of the presented study. The local treatment of CVUs was performed after their surgical treatment, regardless of their origin.

We used conventional slab phlebectomy to implement pathogenetically substantiated surgical correction of existing hemodynamic disorders, in order to eliminate pathological veno-venous refluxes and to exclude irreversibly transformed areas of the saphenous veins of the lower extremities from the bloodstream in 60.87% (in both groups) of patients with varicose veins,. In patients with CVUs with post-thrombotic syndrome, surgical treatment was performed on 16.2% of patients.

The clinical parameters used to assess the effectiveness of complex treatment were the timing of wound cleansing, the appearance of granulations, changes in the intensity of pain syndrome, the timing of the onset of epithelialization, the presence or absence of side effects of treatment, and the average bed-day. These parameters were also recorded.

The area of the purulent wound and CVU was assessed in both groups using the method of digital photography and

further computer calculation of the area of the defect. For this purpose, we used the LesionMeter program, which is an application for the iPhone. The LesionMeter program allows us to measure the area of neoplasms, skin lesions, or CVU of any shape without additional tools. Measurement of the CVU area began with photographing it against the background of a standard size plastic bank card. With the CVU contours outlined with a finger, the application subsequently calculated CVU area itself. A dynamic study of the wound area and CVU was performed upon admission, on Day 7 and Day 14 of treatment. The rate of CVU healing was calculated using the formula: Vs = (S-Sn) / t, according to the method of L.N. Popova (1942), where S is the CVU area before treatment, Sn is the CVU area for further measurements, t is the number of days between the measurements.[15]

The statistical analysis was performed using the statistical software Microsoft Excel 2010. The mean (M) and standard error of the mean (SEM) were calculated. Student's unpaired and paired t-tests were used to compare average values for data with normal distribution. A probability value of $P \leq 0.05$ was considered statistically significant.

Results

All patients were examined according to the same program. In both groups, the clinical picture was characterized by a significant severity of all clinical signs. Ultrasound findings indicated a pronounced venous and functional insufficiency of the lower extremities. At the same time, in the MG patients, as a result of the application of the proposed complex treatment of CVU, the indicators of clinical effectiveness have significantly improved (Table 1).

Table 1.

Therapeutic efficacy of complex treatment of CVU in CVI

Group	n	Timing of wound clearing (day)	Timing of the onset of granulations (day)	Timing of the onset of epithelialization (day)	Average bed-day (day)
MG	52	6.17±0.24	9.52±0.33	13.06±0.37	16.89±0.42
CG	54	8.92±0.25	14.09±0.31	17.11±0.27	21.85±0.33
P-value		<0.05	<0.05	<0.05	<0.05

We found that in MG the relief from inflammatory phenomena, reduction of edema and pain, occurred much faster. Patients subjectively noted an improvement in their well-being. The onset of the granulation phase of the wound process and wound cleansing also occurred faster in MG than in CG ($P<0.05$). In particular, in MG, the wound clearing was observed in 6.17±0.24 days versus 8.92±0.25 days in CG ($P<0.05$). The average timing of the onset of granulations in MG was 9.52±0.33 days versus 14.09±0.31 days in CG ($P<0.05$), and the average terms of the onset of epithelialization were 13.06±0.37 days and 17.11±0.27 days ($P<0.05$), respectively. All taken together, these improvements determined the possibility of reducing the average bed-day in the patients of MG to 16.89±0.42 days versus 21.85±0.33 days in CG ($P<0.05$).

The data obtained during the assessment of the repair processes correlate with the indicators of the CVU healing rate (Table 2). Thus, the average rate of CVU healing in MG during the first 14 days after the start of complex treatment using the proposed pharmacotherapy was significantly higher than in CG ($P<0.05$). In MG, the healing rate increased by more than 24.55% in comparison with CG.

Table 2.

CVU healing rate during the first 14 days after the start of complex treatment

Group	Average rate of epithelialization (cm^2) in day	*P*-value
MG	0.088±0.0062	<0.05
CG	0.062±0.0043	

All of the above are illustrated by the following clinical case. A 64-year-old man presented to the Simferopol Central Regional Clinical Hospital for outpatient treatment with a diagnosis of "Varicose veins of the right lower extremity. CVI stage 3. Trophic ulcer of the right leg" (Fig.1). At the time of inspection, the area of the lower leg CVU was 4.10 cm^2. After 8 days of the treatment, the CVI area decreased to 3.59 cm^2. By Day 15 of treatment, a further decrease in the CVI area was noted to 2.87 cm^2. On Days 23, 30 and 35, the CVI area was 1.16 cm^2, 0.93 cm^2, and 0.79 cm^2, respectively (Fig.2).

Fig. 1. *A 64-year-old man. Varicose veins of the right lower extremity. CVI stage 3. Trophic ulcer of the right leg. Day 1 of complex treatment.*

Since the compared groups of patients at the start of the study did not differ in clinical-anthropometric or biochemical parameters, or in the size of the wound surface, and since surgical treatment of CVI was a standard procedure and was

performed every other day by two surgeons, in accordance with the protocol, the differences in the rate of CVU healing can be attributed only to the effect of the proposed pharmacological correction in complex treatment.

Fig. 2. *A 64-year-old man. Varicose veins of the right lower extremity. CVI stage 3. Trophic ulcer of the right leg. Day 14 of complex treatment.*

Given the diversity of the modern pharmacological market, the selection of effective combinations of drugs, as well as their use regimens for the treatment of CVU, remains relevant. Moreover, these approaches must have a high degree of safety for the patients and relative financial availability, and must also affect the maximum number of links in pathogenesis. Taking into account that under conditions of disturbed trophism in the wound the synthesis of tissue elements is extremely slowed down, it seems advisable to use medications that stimulate regeneration processes along with various methods aimed at improving trophism. From these positions, the proposed methods and methods of pharmacotherapy are optimal, effective, and safe treatment regimens in the complex treatment of complicated CVD forms.

After CVU healing, elective surgical interventions were performed, the purpose of which was to eliminate venous stasis and create hemodynamic prerequisites for the normalization of blood circulation in the tissues of the affected limbs. We used conventional slab phlebectomy to implement pathogenetically substantiated surgical correction of existing hemodynamic disorders, in order to eliminate pathological veno-venous refluxes and to exclude irreversibly transformed areas of the saphenous veins of the lower extremities from the bloodstream in 60.87% (in both groups) of patients with varicose veins.

For CVU patients with post-thrombotic syndrome, surgical treatment was performed on 16.2% of them. In this category of patients, a smooth course of the early postoperative period was observed. All patients noted an insignificant severity of pain in the operated limb, which made it possible to use only non-narcotic analgesics even on the first day after the operation and contributed to the early activation of patients. There were no wound complications in the postoperative period. Skin sutures were removed after 6-7 days. In all patients, the wounds healed by primary intention. Patients were discharged for outpatient treatment on days 7-10 under the supervision of a surgeon at the local polyclinic.

Of the 48 operated patients in MG, 14(29.16%) were examined in the late postoperative period (after 6 months and 1 year). No signs of CVU recurrence were found in any case. All patients noted a steady improvement in the quality of life.

Based on the results obtained, an algorithm for the complex treatment of patients with CVU was developed and proposed for use in clinical practice (Fig.3).

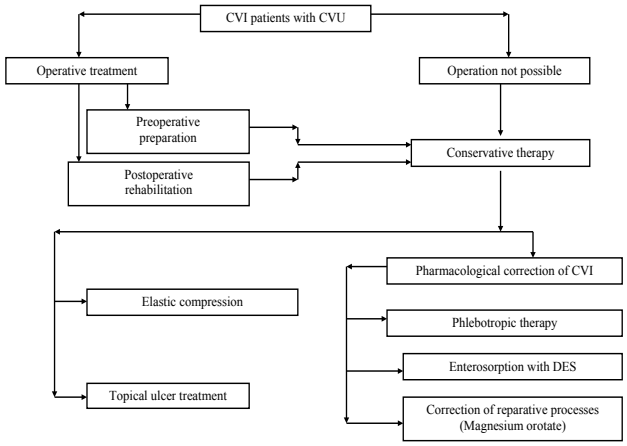

Fig. 3. *Algorithm for complex treatment of CVI patients with CVU*

All of the above-mentioned therapeutic measures used in the complex allow us to effectively treat CVU and provide adequate preoperative preparation, as well as effective postoperative and medical-social rehabilitation of patients.

Thus, the complex treatment of CVU and purulent-necrotic wounds in CVI with the inclusion of the proposed methods of pharmacological correction has a sufficient clinical justification. The application of the proposed pharmacological correction may become a promising auxiliary method of treatment in patients with necrotic ulcerative lesions of the skin of venous origin. The effect of the proposed pharmacotherapy on the regeneration processes determines the possibility of additional inclusion of DHS and magnesium orotate in the treatment protocol for patients with CVU.

In conclusion, the use of the proposed method of drug correction in the complex treatment of CVU ensures the effectiveness of treatment, a reduction in the duration of inpatient treatment, and the reliability of rehabilitation in the postoperative period.

Competing Interests

The authors declare that they have no competing interests.

References

1. Shimanko A, Dibirov M, Zubritskiy V, Zemlyanoy A, Tsuranov S, Matveyev D, Shvidko V, Majorov A, Tyurin D. [Modern approach to treatment of venous trophic ulcers in patients with chronic diseases of lower extremities' veins]. Medicinskij Mestnik MVD. 2015;4(77):10-14. [Article in Russian].
2. Katorkin SE, Melnikov MA, Kravtsov PF, Zhukov

AA, Kushnarchuk MJ, Repin AA. [Efficiency of Layer Dermatolipectomy (Shave Therapy) in Complex Treatment of Patients with Lower Limbs Venous Trophic Ulcers]. Novosti Khirurgii. 2016;24(3):255-264. doi: 10.18484/2305-0047.2016.3.255. [Article in Russian].
3. Bogdanec LI, Smirnova ES, Vasil'ev IM. [Povyshenie effektivnosti lecheniya trofícheskih yazv venoznogo geneza]. Ambulatory Surgery: Hospital-Replacing Technologies. 2014;1-2:16-21. [Article in Russian].
4. Matveev SA, Stoyko YuM, Masayshvili KV, Karpyshev DS. [Ambulatory treatment of gerontological patients with venous trophic ulcers]. Bulletin of Pirogov National Medical & Surgical Center . 2014;9(3):16-19. [Article in Russian].
5. Alavi A, Sibbald RG, Phillips TJ, Miller OF, Margolis DJ, Marston W, Woo K, Romanelli M, Kirsner RS. What's new: Management of venous leg ulcers: Treating venous leg ulcers. J Am Acad Dermatol. 2016 Apr;74(4):643-64; quiz 665-6. doi: 10.1016/j.jaad.2015.03.059.
6. Sergeev NA, Shestakov MS, Fomina ED, Grishakov PI. [Venous trophic ulcers: diagnostics, conservative and complex treatment (literature review)]. Verhnevolzhskij medicinskij zhurnal. 2016;15(2):23-29. [Article in Russian].
7. Katorkin SE, Zhukov AA, Kushnarchuk MJ. [Combined treatment of vasotrophic ulcers in lower limbs chronic venous insufficiency]. Novosti Hirurgii. 2014;22(6):701-709. doi:10.18484/2305-0047.2014.6.701.[Article in Russian].
8. Wittens C, Davies AH, Bækgaard N, Broholm R, Cavezzi A, Chastanet S, de Wolf M, Eggen C, Giannoukas A, Gohel M, Kakkos S, Lawson J, Noppeney T, Onida S, Pittaluga P, Thomis S, Toonder I, Vuylsteke M, Esvs Guidelines Committee, Kolh P, de Borst GJ, Chakfé N, Debus S, Hinchliffe R, Koncar I, Lindholt J, de Ceniga MV, Vermassen F, Verzini F, Document Reviewers, De Maeseneer MG, Blomgren L, Hartung O, Kalodiki E, Korten E, Lugli M, Naylor R, Nicolini P, Rosales A. Editor's Choice - Management of Chronic Venous Disease: Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2015 Jun;49(6):678-737. doi: 10.1016/j.ejvs.2015.02.007.
9. Mikitin IL, Karapetyan GE, Kochetova LV, Yakimov SV, Pakhomova RA. [Modern view on treatment of trophic ulcers]. Kreativnaya Hirurgiya i Onkologiya. 2013;(4):108-112. doi:10.24060/2076-3093-2013-0-4-108-112. [Article in Russian].
10. Bilyayeva OO, Korzhyk NP, Myronov OM, Balinska MI, Yemets VV. [Role of enterosorpents in treatment of complicated varicose disease]. Klinichna Hirurgija. 2014;6:43-45. [Article in Ukrainian].
11. Ursova NI. [The role of enterosorbents in treatment of endogenous intoxication syndrome]. Voprosy Sovremennoi Pediatrii – Curent Pediatrics. 2012;11(6):26-31. doi: 10.15690/vsp.v11i6.489. [Article in Russian].
12. Kalinin RE, Suchkov IA, Pshennikov AS, Kamaev A.A, Isakov SA, Ryabkov AN. Application of Magnesium Drugs and Their Influence on the Indicators of Connective Tissue Dysplasia in Patients with Varicose Veins. Novosti Khirurgii. 2018;26(1):51-59. doi: 10.18484/2305-0047.2018.1.51
13. Hryvenko SH, Izosimov VV, inventors; Hryvenko SH, Izosimov VV, assignees. [The method of conservative treatment of varicose veins of the lower extremities]. Ukraine patent UA 89297. April 10, 2014. [In Ukrainian].
14. Dzjubanovs'kij IJa, Hryvenko SH, Izosimov VV, inventors; Dzjubanovs'kij IJa, Hryvenko SH, Izosimov VV, assignees. [The method of treating complicated varicose disease of the lower extremities]. Ukraine patent UA 112033. November 25, 2016 [In Ukrainian].
15. Popova LN. How the boundaries of the formed epidermis change during wound healing. Abstract of PhD Thesis. Voronezh, 1942. [In Russian].