Endolymphatic therapy for chronic lymphovenous insufficiency complicated by trophic ulcers

Tratamiento endolinfático para la insuficiencia linfática crónica complicada por úlceras tróficas

Mukhuma M. Magomedov[1], Adurahman A. Magomedov[2]*
[1]Dagestan Stat Medical University, Makhachkala, Russia
[2]Dagestan Stat Medical University, Makhachkala, Russia
**Corresponding author: Mukhuma M. Magomedov, Dagestan Stat Medical University, Makhachkala, Russia*
Email: magomedovmyxyma@gmail.com

Abstract

This article puts forward a method of endolymphatic administration of immunostimulants, which directly affect the immunocompetent cells in lymph nodes so that their effect is much more pronounced. From this perspective, selenase is especially promising, as it not only shows a pronounced antioxidant effect, but also an immunomodulating effect, which means that it normalizes the status of different parts of the immune system, as well as the immunological tolerance. This enables endolymphatic administration of drug. This article evaluates the treatment of trophic ulcers of the lower extremities in 58 patients. The main group consisted of 30 patients at mean age 68.2 (14 or 46.7%, were men; 16, or 53.3%, were women). The reference group consisted of 28 patients at mean age 67.9 (12 or 43%, were men; 16 or 57%, were women). Trials proved that endolymphatic therapy is a selective targeting on the site of pathology and the main routes of lymphatic drainage. Endolymphatic therapy improves the short-terms and long-term outcomes of patients with trophic ulcers that appeared on the background of lymphovenous problems. Clinical trial has shown that trophic ulcers were healing better in the main group. The best outcomes were displayed by 19 (63.3%) patients from the main group and 13 (46.4%) patients from the reference group. This article reports on originally designed program of complex treatment for patients with trophic ulcers that appeared on the background of lymphovenous insufficiency of the lower extremities, which implies the infusion of meronem, selenase and sulodexide as endolymphatic therapy. Designed program was proved to be effective.

Keywords: venous trophic ulcers, endolymphatic therapy, non-invasive diagnostics, sulodexide, selenase

Resumen

Este artículo presenta un método de administración endolinfática de inmunoestimulantes, que afecta directamente a las células inmunocompetentes en los ganglios linfáticos para que su efecto sea mucho más pronunciado. Desde esta perspectiva, la selenasa es especialmente prometedora, ya que no solo muestra un pronunciado efecto antioxidante, sino también un efecto inmunomodulador, lo que significa que normaliza el estado de diferentes partes del sistema inmunológico, así como la tolerancia inmunológica. Esto permite la administración endolinfática de fármaco. Este artículo evalúa el tratamiento de las úlceras tróficas de las extremidades inferiores en 58 pacientes. El grupo principal estaba formado por 30 pacientes con una edad media de 68,2 (14, o el 46,7%, eran hombres; 16, o el 53,3%, eran mujeres). El grupo de referencia consistió en 28 pacientes con una edad media de 67,9 (12, o el 43%, eran hombres; 16, o el 57%, eran mujeres). Los ensayos demostraron que la terapia endolinfática es una orientación selectiva en el sitio de la patología y las principales vías de drenaje linfático. La terapia endolinfática mejora los resultados a corto y largo plazo de los pacientes con úlceras tróficas que aparecieron en el fondo de problemas de tejido linfático. Los ensayos clínicos han demostrado que las úlceras tróficas se curaban mejor en el grupo principal. Los mejores resultados fueron mostrados por 19 (63,3%) pacientes del grupo principal y 13 (46,4%) pacientes del grupo de referencia. Este artículo informa sobre un programa de tratamiento complejo diseñado originalmente para pacientes con úlceras tróficas que aparecieron en un fondo de insuficiencia de tejido linfático de las extremidades inferiores, ~~lo~~ que implica la infusión de meronem, selenasa y sulodexida como terapia endolinfática. Se demuestra que el programa resulta efectivo.

Palabras clave: úlceras tróficas venosas, terapia endolinfática, diagnóstico no invasivo, sulodexida, selenasa.

Introduction

The problem of treating patients with chronic lymphovenous insufficiency (CLVI) complicated by trophic ulcers of the lower extremities remains relevant. Developed countries currently have about 2% of the adult population with CLVI complicated by trophic ulcers (1). From (Dibirov & Magdiev, 2016; Zavaruev et al., 2016) it follows that incidence rates increase by 0.35%, while in people at age over 60 incidence rates are 2.5-3 times higher (Katorkin, 2015; Zavaruev et al., 2016; Ryzhkin et al., 2017). This is why designing an effective system against CLVI complicated by trophic ulcers is an important medical and social problem.

When the CLVI strikes, it induces a number of pathological events (Bogachev et al., 2014; Katorkin, 2015; Zavaruev et al., 2016; Ryzhkin et al., 2017) like an increase in hydrostatic pressure (Savelyeva & Sychev, 2018), endothelial activation (Selivestrov et al., 2016; Ryzhkin et al., 2017), production of cell-adhesion molecules, leukocyte activation and growth factor release (Khorev et al., 2017). Activated and migrated leukocytes trigger an inflammatory reaction in the tissues, which manifests in the production of cytokines, leukotrienes, prostaglandins, proteolytic enzymes, and in the release of free oxygen radicals (Shevela et al., 2017). Fibrinogen accumulates in the vessel space, and polymerizes into insoluble fibrin cuffs around the capillary (Shevela et al., 2017). At the microcirculatory level, arterioles in the hypodermis layer are affected by sclerosis and thrombosis (Ryzhkin et al., 2017), and arteriovenous shunts appear (Shevela et al., 2017). Such a combination of pathological reactions causes tissue ischemia (Yakovlev et al. 2016; Shimanko et al. 2017). Tissues accumulate denatured proteins and products of metabolism with antigenic properties, sensitizing the body (Bogachev et l. 2013). The antigen-antibody reaction occurs, forming antigen-antibody complexes (Dibirov & Magdiev, 2016), T and B lymphocyte development is blocked (Zavaruev et al., 2016), and the complement activity is reduced. Over the period of more than 3-5 years, trophic ulcer causes phagocytic activity of leukocytes to decrease (Savelyeva & Sychev, 2018). Long-term effect without proper treatment results in an endless circle of pathology progression, which is chronic inflammation – autoimmune processes – tissue ischemia (Bogachev et al., 2013; Yakovlev et al., 2016).

Despite the progress in medicine and constant improvement of treatment methods, rehabilitation for patients with CLVI complicated by trophic ulcers of the lower extremities is a serious problem, no matter what type of doctor is responsible. Surgical treatment is the only radical method in this case. However, surgery can be done only if the status of trophic ulcer allows it, or after it heals.

Considering the above-stated, new methods and multitarget drugs are needed. These requirements are met by our endolymphatic therapy, which implies the infusion of meronem, selenase and sulodexide. It activates antimicrobial, anti-inflammatory and stimulating mechanisms of reparative regeneration and protects the endothelium from damage.

The purpose of this research is to evaluate endolymphatic therapy for long-standing trophic ulcers that appeared on the background of chronic lymphovenous insufficiency.

Materials and methods

The trial was performed in the Surgery Department at the Republican Versatile Hospital. The trial involved 58 patients with trophic ulcers of lower extremities (grade C6 in CEAP classification), which have been lasting for 1.5 to 20 years.

Inclusion Criteria

— men/women at age between 20 and 80;

— trophic ulcers of lower extremities on the background of CLVI;

— written informed consent.

Exclusion Criteria

— ancle- brachial index ≤ 0.7;

— low compliance rates;

— diabetes;

— decompensated heart failure;

— systemic connective tissue diseases;

— hormonal therapy;

— pregnancy.

Randomization was performed using a random number generator. The main group consisted of 30 patients at mean age 68.2, of whom 14 (46.7%) were men and 16 (53.3%) were women. Advance (III and IV) lymphedema was diagnosed in 21 (70%) patients, and a post-thrombotic syndrome in 9 (30%) patients. Ulcers ranged in size from 2.6 to 16 cm^2.

The reference group consisted of 28 patients at mean age 67.9, of whom 12 (43%) men and 16 (57%) were women. Advance (III and IV) lymphedema was diagnosed in 20 (71%) patients, and a post-thrombotic syndrome in 8 (29%) patients. Ulcers ranged in size from 2.1 to 15.8 cm^2.

Patients from both groups were comparable in age, sex, and diagnosed pathology.

Patient evaluation included the medical history, physical examination, wound status check, lab testing, and computer-based planimetry of ulcers. Changes in would size and coverage area were assessed using a computer program.

All patients underwent venous ultrasound. The underlying blood flow estimation and the qualitative assessment of blood vessels were performed using color-flow Doppler and power Doppler ultrasound.

Wounds were subjected to clinical, bacteriological and cytological assessments. Clinical assessment included the observation of healing outcomes: granulation and epithelialization. Bacteriological assessment included the microflora analysis and evaluation of infection severity (scored by bacterial load per 1 g of tissue). Cytological assessment was performed on smears, examined for granulocytes, fibroblasts, macrophages, dead neutrophils, and active phagocytosis. Cytological smear technique was performed according to Pokrovskaya and Makarov: dead tissue removal from the wound bed followed by 2-3 smears taken. In the case of uneven wound beds, smears were taken from different parts of the wound. Cellular subset composition (range from 100 to 200 cells) was expressed in percentages to get a more accurate presentation. Wound assessment also involved the diagnosis of leg swelling and pain syndrome, and their severity estimation.

Injection drugs in the regimen were sulodexide (active substance: heparinoid consisting of 80% fast moving heparin and 20% dermatan sulfate), selenase (active substance: sodium selenite), meronem (active substance: meropenem).

Patients from the main group had a catheter inserted into the lymphatic channel in their foot, and received endolymphatic infusions with 8-10-day regimen (sulodexide 2 ml, selenase 100 mg, meronem 0.5 g, once daily). Patients also took a red-vine-leaf extract in tablets (2-week regimen: one tablet twice a day). Elastic compression stockings from natural materials were a must-wear, so were the pneumatic compression devices.

Patients from the reference group were admitted for a causal therapy with red-vine-leaf extract in tables (3-week regimen: one tablet twice a day), troxevasin ointment, peroral selenase (200 mg daily), antibiotics (levofloxacin, 0.5 g twice daily), actovegin, disaggregants, elastic compression (knee-highs and stockings), pneumatic compression.

Statistical data analysis was carried out using the Statistica 6.0 program. Outcomes were compared between groups using nonparametric methods.

Results and Discussion

After 3 days of endolymphatic therapy, 49% of patients from the main group reported a reduction in pain. At the end of the course, 95% of patients cured from the pain syndrome. For the reference group, therapy helped only 46% of patients to reduce the pain, and that took 14 days.

In patients from the main group, isolation rates of microflora from tissue biopsy specimens decreased.

Ulcer specimens were put to microbiological analysis to define the bacterial load of the wound. Patient outcomes showed before and after the therapy in the main and reference groups are presented in Tables 1 and 2.

Table 1. Prior Bacterial Load of Trophic Ulcers

Bacterial Count, CFU/g	Main Group (n = 30)	Reference Group (n = 28)	p
$10^6 – 10^7$	6 (20)	5 (17.9)	0.84
$10^4 – 10^5$	21 (70)	21 (75)	0.67
$10^2 – 10^3$	3 (10)	2 (7.1)	0.69
No Bacteria Found	0	0	

Note: "n" stands for the number of patients, while the figure within the brackets is equivalent to percent.

Table 2. Microbiological Results of Trophic Ulcer Specimens

Isolate	Prior to Treatment		p	After Treatment		p
	Main Group (n = 30)	Reference Group (n = 28)		Main Group (n = 30)	Reference Group (n = 28)	
St. aureus	19 (63.3)	17 (61)	0.86	1 (3.3)	3 (10.7)	0.27
Ps. aeruginosa	7 (23.3)	6 (21)	0.83	0	4 (14.2)	0.057
Association	3 (10)	4 (14)	0.64	1 (3.3)	4 (14.2)	0.15
No Bacteria Found	1 (3.3)	1 (4)	0.89	28 (93.4)	17 (60.7)	0.004

Note: "n" stands for the number of patients, while the figure within the brackets is equivalent to percent.

Table 1 shows that bacterial load of 10^4–10^5 CFU/g was found in wounds of 21 (70%) patients from the main ground and in wounds of 21 (75%) patients from the reference group, so data are evidently comparable. Microbiological profiles displayed by patients from the main group are illustrative of rapid bacterial count decrease on the ulcer surface, down to zero, in 28 (93%) patients. In the reference group, only 17 (61%) patients had no bacterial populations in their wounds. These differences are statistically significant (Table 2).

Cytological results for both groups are presented in Table 3. Smears taken from trophic ulcers in the main group revealed fundamental differences in the cellular subset composition between the prior and post evaluations. Wound assessment revealed an increase in the number and activ-

ity of neutrophils. All patients from this group had their ulcers healing from the inside out, and the wound edges began to epithelize. Swelling and heavy feeling in legs subjectively reduced after 2-3 days of treatment.

Morphological changes in the tissue of trophic ulcers, treated with endolymphatic drug administration, indicated high clinical benefit of sulodexide, selenase, and meronem used in combination (Tables 4-6). The observations revealed enhanced leukocyte and macrophage reactions, accelerated resolution of inflammation and dead tissue detachment. Granulation process enhanced because of the growth of blood vessels and mobilization of adventitial fibroblastic cells. Aside from boosted DNA synthesis and fibroblast differentiation, we detected fibrillogenesis (Table 6). With drugs injected in combination, granulation process accelerated together with epithelization. Treatment efficiency measure is the closure rate of trophic ulcers (Table 5). In the main group, 19 (63.3%) patients had their wounds closed at the end of treatment. In the reference group, trophic ulcers closed in 13 (46.5%) patients, (p = 0.204). Surgical intervention in the venous system was to eliminate the reflux. Six patients from the main group and four from the reference group underwent split-thickness skin grafting. Ulcers have fully healed in 26 (83.3%) patients from the main group and in 18 (64.3%) patients from the reference group. The remaining patients were dismissed with significant improvements and eliminated pain syndrome. Notable therapy-induced epithelization occurred in 10 (33%) patients from the main group and in 2 (7.1%) from the reference group, (p=0.018).

At 6 months of rehabilitation, complete ulcer healing was achieved in 18 (64.3%) patients from the reference group and in 26 (86.6%) patients from the main group, (p=0.0624).

Table 3. Cytological Findings in Smears from Wounds

Smear Result	Prior to Treatment		ρ	After Treatment		ρ
	Main Group (n = 30)	Reference Group (n = 28)		Main Group (n = 30)	Reference Group (n = 28)	
Degeneration with Inflammation	2 (6.7)	5 (18)	0.21	0	2 (71)	0,15
Inflammation	24 (80)	21(75)	0.65	10 (33.3)	16 (57.1)	0.074
Inflammation with Regeneration	4 (13.3)	2 (7)	0.45	20 (66.7)	10 (35.7)	0.022

Note: "n" stands for the number of patients, while the figure within the brackets is equivalent to percent.

Table 4. Granulation Progress

Stages of Wound Coverage	Main Group (n = 30)		ρ	Reference Group (n = 28)		ρ
	Prior to Treatment	After Treatment		Prior to Treatment	After Treatment	
No Granulation Tissue Found	20 (67)	1 (3.3)	< 0.0001	20 (71.4)	6 (21.4)	0.004
Partial Coverage	6 (20)	8 (26.6)	1.0	6 (21.4)	10 (35.7)*	0.092
Full Coverage	3 (10)	20 (66.7)	< 0.0001	2 (7.2)	10 (35.7)*	0.042
Over Granulation	1 (3.3)	1 (3.3)	0.05	0	2 (7.1)	0.16

Note: "*" indicates significant difference in values between groups.

Table 5. Epithelization Progress

Epithelization	Main Group (n = 30)		ρ	Reference Group (n = 28)		ρ
	Prior to Treatment	After Treatment		Prior to Treatment	After Treatment	
No Epithelium Found	20 (66.7)	0	< 0.0001	18 (64.3)	0	< 0.0001
Partial Epithelization	7 (23.3)	1 (3.3)	0.028	8 (28.6)	6 (21.4)	0.49
Edge Epithelization	3 (10)	10 (33.3)	0.033	2 (7.1)	9 (32)	0.022
Full Epithelization	0	19 (63.3)	< 0.0001	0	13 (46.5)	0.0001

Table 6. Morphometric Parameters of Cell in the Wound Space in Response to Treatment, %, (M ± δ)

Parameter	Main Group (n = 30)		ρ	Reference Group (n = 28)		ρ
	5th Day	7th Day		5th Day	7th Day	
Shrinkage of the Nuclei of Endotheliocytes	9.7±1,6	9.8±1.4	0.8	9.1±1.6*	9.2±1.2	0.08
Endothelial Cell DNA Synthesis	0.19±0.06	0.23±0.05	0.007	0.06±0.02*	0.10±0.01*	< 0.0001
Fibroblast DNA Synthesis	0.13±0.01	0.18±0.04	< 0.0001	0.04±0.01*	0.16±0.04	< 0.0001
Adventitial Cell DNA Synthesis, %	0.16±0.01	0.20±0.09	0.02	–	0.08±0.04	–

Note: "*" indicates significant difference in values between groups.

No drug-induces negative side effects were reported.

All patients felt pains in the trophic ulcer space at admission, which usually is the main cause of performance degradation. Our treatment resulted in positive outcomes, more specifically in reduction or complete disappearance of pain.

Trophic ulcers that are present for a long time have a rough rigid bottom covered with fibrin deposits, and almost do not bleed. Our treatment not only reduced the swelling in legs, but also the sclerosis of underlying tissues. The ulcer became cleaner, but mechanical cleaning made the bleeding more intense. Granulation and edge epithelialization processes started soon after that. Therapy-induced ulcer healing progressed with less cicatricial deformities and the surrounding skin color turned more natural, compared to closed ulcers in patients from the reference group. Treatment for trophic ulcers was combined with compression therapy in both groups (class II).

The major healing inhibitors were tissue ischemia and swelling caused by abnormal macro- and microcirculation in deep tissue, inflammation and autoimmune system activation. The use of selenase, which is an active immunomodulator and a powerful antioxidant, reduces lipid peroxidation, improves the immune status and eliminates toxic metabolic products in the body. Bacteriological, cytological and morphometric results collected during the research indicative positive healing dynamics that were significantly better in patients, who went through endolymphatic therapy. At the same time, no statistically significant difference in wound closure rate was detected between two groups, due to insufficient number of patients included in the trial. Endolymphatic administration of sulodexide, selenase and antibiotics stimulates reparative tissue regeneration. This allows shortening the period of time needed to prepare patients for surgery and improving the quality of life if radical intervention is impossible. Endolymphatic therapy can be successful when preparing trophic ulcers for autografting. The revealed tendency of healing rates to rise after endomylphatic therapy calls for further trials with more patients involved.

Endolymphatic administration of drugs to patients with CLVI complicated by trophic ulcers has a positive effect on inflammation so that healing process is more rapid (Kucharzewski et al., 2003; Katorkin, 2015). Infusions into lymphatic vessels improve hemolymph circulation in impaired area so that arterial inflow increases by 29-30%, lymphatic drainage by 35-40%, and microcirculation efficiency index by 28-30%. Unlike standard methods, our technique with regional lymphatic stimulation can significantly improve ulcer healing on the background of lymphovenous insufficiency (Dibirov & Magdiev, 2016; Santema et al., 2016). Ulcer healing rate was higher by 17-20% when treated with endolymphatic therapy. At 6 months of rehabilitation, complete ulcer healing was achieved in 18 (64.3%) patients from the reference group and in 26 (86.6%) patients from the main group. At this point, hemolymph circulation and lymphatic circulation are linked (Meissner, 2016; Shimanko et al., 2017). Disturbances in blood circulation spark changes in the lymphatic channel and lymph node. At first, when venous stasis happens, compensatory processes take place, and then, performance of the lymph node reduces because of damage and triggers the emergence of CLVI and trophic ulcers on legs. Thus, research results show that trophic ulcer treatment with endolymphatic administration of drugs is path to microcirculation improvement, accelerated a granulation and complete wound healing, which was achieved in 86.6% of patients.

Conclusions

1. Article identified the therapeutic benefit of endolymphatic therapy for venous trophic ulcers in patients with chronic lymphovenous insufficiency of lower limbs.
2. Article reported on a designed method of trophic ulcer treatment that allowed achieving good outcomes in 86.6% of patients in a 1.9 times shorter period and remission over 3 years in 92.1% of patients.
3. Endolymphatic therapy activated local and humoral immune systems and made their responses 2.5 times stronger, boosted endotheliocytes by making their mitotic activity 1.6 times higher, accelerated capillary formation and angiogenesis in granulation tissue by 2.8 times.

Originally designed program of complex treatment for patients with CLVI complicated by trophic ulcers succeeded in projecting positive effect on microflora and regional lymph drainage, and in stimulating re-regeneration and epithelialization of trophic ulcers.

References

1. Bogachev, V. Yu, Golovanova, O.V., Kuznetsov, A.N., Shekoyan, A.O., & Bo-gacheva, N.V. (2013). Elektromuskulare Stimulation mit Veinoplus zur Therapie «fchro-nischen ve-nosen Odems. VASOMED, 1, 52–53.
2. Bogachev, V.Yu., Vasilyev, V.E., Lobanov, V.N., Golovanova, O. V., Kuznetsov, A. N., & Ershov, P. V. (2014). The application of electric muscle stimulation for the treatment of ve-nous trophic ulcers. Journal of Venous Disorders (Flebologiya), 3, 18-22.
3. Coccheri, S., & Mannello, F. (2013). Development and use of sulodexide in vascular / diseas-es: implications for treatment. Drug Des Devel Ther.
4. Dibirov, M.D., & Magdiev, A.Kh. (2016). The Treatment of Venous Trophic Ulcers in the Elderly Patients. Journal of Venous Disorders (Flebologiya), 4, 224–226.
5. Han, S.K., Kim, H.S., & Kim, W.K. (2009). Efficacy and safety of fresh fibroblast al lografts in the treatment of diabetic foot ulcers. Dermatol Srg, 35(9), 1342–1348.
6. Katorkin, S.E. (2015). The Evaluation of the Effectiveness of the

Application of Sulodexide for the Combined Treatment of the Patients Presenting with Trophic Ulcers on the Lower Extremities of Venous Etiology. Journal of Venous Disorders (Flebologiya), 4, 35–41.

7. Khorev, N.G., Kuznetsova, V.D., & Konkova, V.O. (2017). Plethysmography as a Method for the Functional Evaluation of Venous Reflux and Obstruction Associated with Chronic Venous Disease. Journal of Venous Disorders (Flebologiya), 1, 32–36.

8. Kirsner, R.S., Marston, W.A., Snyder, R.J., Lee, T.D., Cargill, D.I., & Slade, H.B. Spray- applied cell therapy with human allogeneic fibroblasts and keratinocytes for the treatment of chronic venous leg ulcers: a phase 2, multicentre, double- blind, ran-domised, placebo-controlled trial. Lancet, 380(9846), 977-985.

9. Kucharzewski, M., Franek, A., & Koziolek, H. (2003). Treatment of venous leg ulcers with sulodexide. Phlebologie, 32(5), 115–120.

10. Meissner, M.H. (2016). What is effective care for varicose veins? Phlebology, 31, 80–87.

11. Nathoo, R., Howe, N., & Cohen, G. Skin substitutes: an overview of the key players in wound management. J Clin Aesthet Dermatol., 7(10), 44–48.

12. Ryzhkin, V.V., Vorontsova, A.V., Lobastov, K.V., Schastlivtsev, I.V., Barinov, V.E., Naumov, E.K., & Laberko, L.A. (2017). Dynamics of Residual Venous Obstruction after Electrical Stimulation of Crural Muscles following the Completion of the Standard Course of Anticoagulation Therapy in Patients with Postthrombotic Syndrome: the Results of the Com-parative Non-Randomized Study. Journal of Venous Disorders (Flebologiya), 11(3), 131-141

13. Santema, T.K., Poyck, P.P., & Ubbink, D.T. (2016). Systematic review and meta-analysis /of skin substitutes in the treatment of diabetic foot ulcers: Highlights of a Cochrane Systematic review. Wound Repair Regen.

14. Savelyeva, M.I., & Sychev D.A. (2018). Potential of the Transdermal Drug Delivery Systems for the Topical Treatment of Chronic Venous Diseases. Journal of Venous Disorders (Flebologiya), 1, 40–49.

15. Selivestrov, E.I., Avakyants, I.P., Nikishkov, A.S., & Zolotukhin, I. A. (2016). Epidemiology of Chronic Venous Disease. Journal of Venous Disorders (Flebologiya), 1, 35–40.

16. Shevela, A.I., Novikov, P.B., & Seryapina, Y.V. (2017). The Experience with the Use of Compression Stockings for the Treatment of Chronic Venous Diseases: the Evaluation of Safety and Effectiveness. Journal of Venous Disorders (Flebologiya), 1, 47–52.

17. Shimanko, A.I., Dibirov, M.D., Zubritsky, V.F., et.al. (2017). The Combined Treatment of Trophic Ulcers of Venous Etiology. Journal of Venous Disorders (Flebologiya), 2.

18. Yakovlev, M.M., Panov, A.V., Kalmykova, N.V., & Moiseev, S. I. (2016). The Use of Cellu-lar Products for the Combined Treatment of a Giant Crural Trophic Ulcer. Journal of Venous Disorders (Flebologiya), 3.

19. Zavaruev, A.V., Bregadze, A.A., & Kozka, A.A. (2016). The Experience with the Surgical Treatment of Venous Trophic Ulcers. Journal of Venous Disorders (Flebologiya), 2, 103–105.

Manuel Velasco (Venezuela) **Editor en Jefe** - Felipe Alberto Espino Comercialización y Producción
Reg Registrada en los siguientes índices y bases de datos:

WEB OF SCIENCE (WOS)
SCOPUS, EMBASE, Compendex, GEOBASE, EMBiology, Elsevier BIOBASE, FLUIDEX, World Textiles,
OPEN JOURNAL SYSTEMS (OJS),
REDALYC (Red de Revistas Científicas de América Latina, el Caribe, España y Portugal),
Google Scholar
LATINDEX (Sistema Regional de Información en Línea para Revistas Científicas de América Latina, el Caribe, España y Portugal)
LIVECS (Literatura Venezolana para la Ciencias de la Salud), LILACS (Literatura Latinoamericana y del Caribe en Ciencias de la Salud)
PERIÓDICA (Índices de Revistas Latinoamericanas en Ciencias), REVENCYT (Índice y Biblioteca Electrónica de Revistas Venezolanas de Ciencias y Tecnología)
SABER UCV, DRJI (Directory of Research Journal Indexing)
CLaCaLIA (Conocimiento Latinoamericano y Caribeño de Libre Acceso), EBSCO Publishing, PROQUEST

Esta Revista se publica bajo el auspicio del
Consejo de Desarrollo Científico y Humanístico
Universidad Central de Venezuela.
CDCH-UCV

cdch-ucv.net publicaciones@cdch-ucv.net

WWW.REVHIPERTENSION.COM
WWW.REVDIABETES.COM
WWW.REVSINDROME.COM
WWW.REVISTAAVFT.COM