

Efficacy And Safety Of Trombles[®] Neo And Detralex[®] In The Treatment Of Chronic Venous Diseases Are The Results Of An Open-Label, Comparative, Multicenter Randomized Prospective Study

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ABSTRACT

Chronic venous diseases (CVD) of the lower limbs are an acute medical and social problem due to their widespread distribution among a significant part of the population, and patients rarely seek medical help in the early stages of the disease. Medication based on micronized purified flavo-noid fraction (PMFF) play a leading role in the elimination of CVD symptoms of lo-wer limbs. The article presents the results of a multi-center open randomized clinical study conducted in Russia on the efficacy and safety (phase III) of the generic drug Trombles[®] Neo (diosmin+hesperidin) in comparison with the reference product Detralex[®] with the participation of 130 patients with symptomatic CVD of lower limbs C2-C3 class of the CEAP classification. The results of the study indicate no less efficacy and comparable safety of Trombles[®] Neo in relation to changes (decrease) in the severity of CVD symptoms after a 60-day course of therapy.

Keywords: Purified micronized flavono-id fraction (PMFF), diosmin, hesperidin, chronic venous diseases (CVD)

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INTRODUCTION

Lower limb CVD is one of the most common vascular pathologies. Two-thirds of patients in Russia complain of such symptoms as bloated legs, heavy legs, and pain in the legs, puffiness, and night cramps [1]. Risk factors for CVD are age, overweight, family history, deep vein thrombosis, and smoking. Specific risk factors for women were menopause, an increase in the number of births, and low physical activity. Due to their mass occurrence, CVD have a huge impact both on the state of individuals and on the health of society as a whole [2,3].

Conservative medication plays an important role in the complex treatment and prevention of complications of CVD [4]. There is a wide selection of phlebotropic medicinal products obtained from plant raw materials or by chemical synthesis. G-benzopyrons, pycnogenols, saponins, synthetic substances and combined drugs have the ability to affect venous tone, thereby reducing the manifestation of venospecific symptoms [1].

From the standpoint of modern evidence-based medicine, PMFF, which belongs to the group of g-benzopyrons, has the greatest effectiveness in relieving symptoms of CVD. The most well-known drug of this group with a high level of evidence is Detralex, which contains diosmin and flavonoids in terms of hesperidin in a ratio of 9:1 [5].

The most important therapeutic effects of PMFF are inhibition of leukocyte-endothelial adhesion and venous valve protection. Numerous clinical studies have shown that the mechanism of action of Detralex[®] is implemented by increasing the tone of the wall of veins and lymphatic vessels, strengthening the venous wall, suppressing inflammation of an aseptic nature, proteolysis and elimination of proteins from tissues. In addition, there is an increase in the number of functioning lymphatic capillaries, which in turn leads to a decrease in the severity of edema and a decrease in symptoms in patients [6].

Therapeutic Trombles[®] Neo (film-coated tablets manufactured by ZAO "Obninsk chemical and pharmaceutical company", Russia) is equivalent in concentration of active substance and dosage form to Detralex[®]. A comparative clinical study was conducted to confirm the equivalence of the therapeutic effect and safety profile of both drugs.

Materials and methods

The clinical study was approved by the Ministry of Health of the Russian Federation, clinical trial protocol №: TLN-02-2019, trial registration № 328, date of registration – 24.06.2019. The study was conducted in accordance with the principles of the Helsinki Declaration and GCP (Good Clinical Practice). Its Protocol and patient information consent were reviewed and approved by the ethics committee.

The objective of the study was to evaluate the effectiveness and safety of Trombles[®] Neo (film-coated tablets 1000 mg) in comparison with Detralex[®] (film-coated tablets 1000 mg) in patients with symptomatic lower limbs C2-C3 class CVD according to the CEAP classification.

Study design

A prospective, randomized, multicenter, open-label comparative study of efficacy and safety. The study included a screening period of up to 7 days, a therapy period of 60 days, and a follow – up period of up to 15 days, total duration of participation for the patient was no more than 82 days. The study conducted 5 visits – a screening visit (Visit 0), a randomization/initiation visit (Visit 1), an interval visit (Visit 2), a final study visit (Visit 3), and a study closeout visit (Visit 4).

Patients who met all the selection criteria were randomized into 2 groups in a ratio of 1:1. as the study therapy, the drug Trombles[®] Neo was prescribed at a dose of 1000 mg, and as a comparison therapy, the drug

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Detralex® was prescribed at a similar dose. The compared drugs were administered peroral, once a day for 60 days. The study involved 130 patients, all of them completed all the procedures. All patients were informed of the purpose and nature of the study and signed an informed consent to participate in the study.

Primary inclusion criteria

1. The existence of a signed Informed Consent to participate in the study from the patient.
2. Patients of both sexes aged 18 to 65 years with CVD of lower limbs C2-C3 CEAP class.
3. The presence of at least 3 symptoms of CVD listed in the screening: heavy legs, pain, cramps, "fatigue" of the legs.
4. The total score for the Chronic Venous Disease quality of life Questionnaire (CIVIQ-20) is ≥ 35 points.
5. The level of pain in the lower limbs is ≥ 3 cm on the Visual analog scale (VAS).

Primary exclusion criteria

1. Use of venotonizing, venoprotective and other phlebotropic medication for 2 months before inclusion in the study.
2. Patients who underwent phlebectomy or sclerotherapy within 3 months before being included in the study.
3. CVD of lower limbs C0-C1 and C4-C6 class according to the international classification of CEAP.
4. Thrombosis, phlebitis, deep vein thrombophlebitis of the lower limbs in the previous 12 months.
5. Hemodynamically significant diseases of the peripheral arteries.
6. Concomitant decompensated diseases or acute conditions, the presence of which may significantly affect the results of the study.
7. The need, according to the research doctor, for surgical intervention: phlebectomy or sclerotherapy.
8. Lower limb injuries for 6 months prior to inclusion in the study.
9. Chronic heart failure III-IV FC according to the NYHA classification.
10. Disorders in the coagulation system and fibrinolysis, determined by the results of a coagulogram.
11. Pregnancy and breastfeeding.

Efficacy evaluation criterion

The primary criterion for evaluating the effectiveness of therapy was the proportion of the patients who had a therapeutic response at Visit 3 (final study) compared to the baseline level (Visit 0, screening).

The therapeutic response in this study was based on at least two of three conditions being met simultaneously:

- the decrease in total score of the quality of life questionnaire CIVIQ-20 at least 5 points by the end of the treatment compared to baseline assessment.
 - reducing the intensity of pain syndrome by at least 1 point by VAS end of the course of treatment compared to the initial assessment.
 - reduction of the malleolar volume by at least 0.2 cm by the end of the course of treatment.
- Secondary efficacy evaluation criteria were:
- The average change in the degree of discomfort in the legs compared to VAS on Visits 2 and 3 compared to the baseline level.

- The average change in the Venous Clinical Severity Score (VCSS) on Visits 2 and 3 compared to the baseline.
- The average change in the severity of leg pain in VAS on Visits 2 and 3 compared to the baseline level.
- Average change in the overall quality of life score CIVIQ-20 on Visits 2 and 3 compared to the original level.
- The average change in the malleolar volume at Visits 2 and 3 compared to the baseline level.

Safety evaluation criteria

The evaluation of treatment safety was based on the collection of data on registration of adverse events (AEs) and serious adverse events (SAEs), as well as physical examination data, determination of the main vital indicators (blood pressure, heart rate, body temperature), results of clinical, biochemical blood tests, clinical urine analysis and 12-lead ECG.

Statistical methods

To analyze differences, we used analysis of variance for independent groups with repeated measurements (ANOVA mixed model). Secondary efficacy parameters were analyzed using parametric statistics (Student t-test, ANOVA) and/or nonparametric statistics (Fisher's exact test, Pearson's chi-squared test, Mann-Whitney test, Wilcoxon test).

RESULTS

During the entire study, none of the patients were eliminated, and no significant deviations from the protocol were registered, therefore, the population of intent-to-treat (ITT) and per protocol (PP) coincided, the effectiveness analysis was performed in ITT taking into account data obtained from 130.

Baseline characteristics

The average values of age, body weight, and height were comparable in both groups and in all populations of the analysis. No statistically significant differences between the study groups were found in any of the populations ($p < 0.05$). The diagnosis of CVD was determined in patients in accordance with clinical symptoms and the results of objective and/or instrumental examination at least 6 months before the screening Visit. According to the results of the quality of life assessment of patients with chronic venous insufficiency (CIVIQ-20) at the screening visit, all patients included in the study had a total score of ≥ 35 and was in the range of 35 to 64 points in patients in the Trombless® Neo group, in the Detralex® group, total score was in the range of 35 to 68 points. There was no statistically significant difference between the groups for this indicator ($p = 0.675$).

All randomized patients met the inclusion/exclusion criteria and were comparable in both groups for the analyzed initial parameters of the disease. Differences in the average values for these indicators between the groups are not statistically significant ($p > 0.05$).

The groups in both populations were also mainly balanced in terms of the main vital indicators, results of laboratory tests (clinical blood analysis, biochemical blood analysis, clinical urine analysis).

Efficiency evaluation

According to the research protocol, the primary criterion for evaluating effectiveness is the proportion of patients

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who had a therapeutic response to treatment (Visit 3) compared to the baseline level. An efficiency analysis was performed for the primary endpoint in the ITT population. Based on the results of the total assessment of the

presence of TEC at Visit 3, it was found that the therapeutic response was not achieved only in one patient in group T and one patient in group R (table 1).

Table 1. Summary of therapeutic response at Visit 3 in the ITT population

Treatment group	Reduction of the malleolar volume by at least 0.2 cm			Reduction the intensity of pain syndrome by 1 point at least, according to VAS.			Reduction of the total score of the patient's quality of life according to the CIVIQ-20 questionnaire by at least 5			Therapeutic response		
	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total
T	60	5	65	62	3	65	63	2	65	64	1	65
R	59	6	65	61	4	65	63	2	65	64	1	65
Total	119	11	130	123	7	130	126	4	130	128	2	130
p-value	1.000 ²			1.000 ²			1.000 ²			1.000 ²		

¹Pearson's Chi-Square Yates' Cont. Correction
²Fisher's Exact

The calculated lower limit of 95% CI for the difference in the proportion of patients who achieved a therapeutic response was -0.0423 (p=0.000), this value does not cross the established limit of no less effectiveness -0.2 (-20%), which indicates no less effectiveness of the study drug Trombless® Neo compared to Detralex®.

Secondary outcome measure

As a result of the inter-group comparison, no statistically significant differences were found between the groups of patients who took the drug T and R in any of the populations (ITT and PP) for all secondary criteria for evaluating effectiveness.

Thus, based on the results of the analysis, it can be concluded that the studied medication Trombless® Neo is

Table 2. The incidence of AEs

Medication	Patients with AE		Total	p ¹ value
	Yes	No		
T	41	24	130	1.000
R	41	24		

1-Pearson's Chi - Square criterion

When evaluating the number of patients who had registered AEs, no statistically significant differences were found in the comparison groups T and R (p = 1,000). During the study, no cases of SAEs development had been recorded.

The most common AEs were deviations of laboratory parameters (clinical and biochemical blood tests, clinical urine analysis). According to the researchers, these deviations have no connection or have a dubious connection with the use of the studied medications. There were no statistically significant differences in the nature of AEs between the groups of patients taking the drug T and R (p value 0.05).

The results of the physical examination did not reveal any differences between the groups at any of the analyzed visits. There were no statistically significant differences between the studied medications in terms of their effect on vital indicators - heart rate, blood pressure, and body temperature (p > 0.05).

no less effective than Detralex® in relation to the primary and secondary criteria for evaluating effectiveness.

Safety evaluation

The safety population included all patients who were initiated with the study medication or a comparative medication - 65 patients in each group (n=130).

During this clinical study, a total of 176 AEs were registered (91 AEs in the group of patients taking the study drug Trombless® Neo, and 85 AEs in the group of patients taking the drug Detralex®. In total, AEs were identified in 82 patients - 41 patients in the T group and 41 patients in the drug group (Table 2).

RESULTS AND DISCUSSION

The high level of prevalence, progressive and not infrequently complicated course determine the importance of timely diagnosis of CVD and effective treatment that can stop the progression of the disease and prevent possible complications. Pharmacotherapy in the coming years will remain the main way to help patients with CVD. It can be an independent method of therapy or complement surgical interventions in the preparation of the patient for a surgery, as well as serve as prevention of relapse of the disease in the postoperative period. Treatment of CVD is based on the use of drugs that normalize the structure and function of the venous wall, improve lymphatic drainage and microcirculation. They are the basis of drug therapy of CVD regardless of its origin (varicose disease, congenital abnormalities, phlebopathy, consequences of deep vein thrombosis, etc.).

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The reproduced drug Trombless® Neo demonstrated good results in the study. When compared with the reference drug Detralex®, it was shown that the analyzed treatment groups were comparable in both the main and additional parameters of effectiveness. For the primary outcome measure, it was shown that the lower limit of 95% CI for the difference in the proportion of patients who achieved a therapeutic response at the end of the therapy period was -0.0423 (p=0.000), this value does not cross the border of no less effective -0.2.

For secondary outcome measure, the absence of differences between the compared groups was also shown. According to the results of the analysis can also be concluded that the drug Trombless® Neo is safe because it has no pronounced negative effect on the results of the study of laboratory and instrumental methods in dynamics (before and after a course of the drug), and does not cause negative changes in the organs and organ systems by physical examination. The study medication does not have a significant effect on vital signs and is not inferior in safety to the comparative medication Detralex®.

Thus, according to the results of the conducted clinical study, it can be concluded that the non-inferiority of the medication Trombless® Neo in comparison with the medication Detralex® in relation to the change (decrease) in the severity of symptoms of CVD in patients after 60 days of therapy with the studied medications.

CONCLUSION

Before the pharmacotherapy of CVD there are many tasks, the main medication in the treatment of any forms of this disease should be a medication that has a complex effect on all pathogenetic links. This is exactly the medication, the main components of which are hesperidin and diosmin. It has a complex mechanism of action: it improves venous tone, stimulates lymphatic outflow and reduces the severity of inflammation, as well as improves microcirculation [7,8].

Trombless® Neo is a complete analog of Detralex® widely used throughout the world. The results of this study indicate that It is therapeutic equivalent to the original, the drug has successfully passed registration procedures and received permission from the Ministry of Health of Russia for clinical use.

REFERENCES

1. Raffetto JD. Pathophysiology of chronic venous disease and venous ulcers. *Surgical Clinics of North America*, 2018, 98(2): 337–347.
2. Nebylitsin YS, Sushkov SA, Solodkov AP, Doroshenko AS. Endothelial dysfunction in acute and chronic venous insufficiency. *News of Surgery. Novosti Khirurgii*, 2008, 4: 141–153.
3. Coleridge Smith O. Chronic venous insufficiency; update. *Phlebology*, 2001, 32:10–13.
4. Allaert FA. Meta-analysis of the impact of the principal venoactive drugs agents on malleolar venous edema. *Int Angiol*, 2012, 31: 310-315.
5. Jantet, G. Chronic venous insufficiency: worldwide results of the RELIEF study. Reflux assessment and quality of life improvement with micronized Flavonoids. *Angiology*, 2002, 53(3): 245–256.
6. Manthey JA. Biological properties of flavonoids pertaining to inflammation. *Microcirculation*, 2000, 7(6 Pt 2): 29–34.
7. Gracas C, de Souza M, Cyrino FZ, de Carvalho JJ, Blanc-Guillemaud V, Bouskela E. Protective effects of micronized purified flavonoid fraction (MPFF) on a novel experimental model of chronic venous hypertension. *European Journal of Vascular and Endovascular Surgery*, 2018, 55(5): 694–702.
8. Wang L, Tu YC, Lian TW, Hung JT, Yen JH, Wu MJ. Distinctive antioxidant and antiinflammatory effects of flavonols. *Journal of Agricultural and Food Chemistry*, 2006, 54(26): 9798–9804