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Ginkgo biloba, troxerutin and heptaminol chlorhydrate combined treatment for the management of venous insufficiency and hemorrhoidal crises

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Abstract. – OBJECTIVE: Ginkor Fort® (Tonipharm, Recordati Group; GB-T-H combined treatment) comprises ginkgo biloba extract, troxerutin and heptaminol chlorhydrate. It is a venotonic and vasculoprotective agent that strengthens veins, increases vessel resistance, and reduces permeability. Thanks to these synergistic actions, it is indicated for the treatment of signs and symptoms of venous insufficiency (VI) and signs related to the hemorrhoidal crisis. This review recapitulates the rationale for using venotonics to manage VI and discusses available evidence on the use of GB-T-H combined treatment to manage VI and hemorrhoidal crisis.

MATERIALS AND METHODS: Papers were retrieved by a PubMed search using different keywords. No language or publication date restrictions were used. Documents from the Authors' literature collection were also considered. Papers were selected for inclusion according to their relevance to the topic.

RESULTS: Preclinical and clinical studies showed that the GB-T-H combined treatment acts on both the acute phase symptoms and the pathogenetic mechanisms of the VI, through the prevention of the hypoxia-induced activation of endothelial cells, the reduction of the capillary tone and the hemostatic activity. This leads to the long-term slowing of the disease progression, suggesting that the GB-T-H combined treatment can manage the acute clinical manifestations and as a prevention measure with prolonged use in both VI and hemorrhoidal crises. In the available study, the GB-T-H combined treatment showed excellent tolerability.

CONCLUSIONS: Available literature evidence and extensive clinical experience support the use of the GB-T-H combined treatment as an effective and safe option for treating and preventing the clinical manifestation of VI and hemorrhoidal crisis.

Key Words:
Venous insufficiency, Hemorrhoidal crises, Ginkgo biloba, Troxerutin, Heptaminol chlorhydrate, Ginkor fort®.

Introduction

Venous insufficiency (VI) defines a state of alteration of the venous wall, with an increase in lateral pressure and permeability and a reduction in flow. VI may result from different pathogenic mechanisms, including incompetent valves, venous obstruction, muscle pump dysfunction or a combination of them[1]. This leads to evident clinical manifestations in some districts above all, such as the lower limbs, anus and male genitals. Symptoms vary according to the involved district. The clinical signs of the VI of lower limbs are categorized into seven classes (C0-C6)[2]. Frequently reported symptoms are telangiectasia or reticular veins and varicose veins, edema, leg pain and heaviness. More advanced symptoms comprise trophic disorders (pigmentation or eczema), skin fibrosis and venous ulceration, which can become a chronic wound in the advanced forms of the disease[3-5]. When chronic (i.e., C3-C6), VI becomes a self-propelling inflammatory process leading to tissue damage and the production of many algogenic substances[6,7].

An abnormal venous flow of the lower extremities is observed in up to 50% of individuals. Up to 17% of men and 40% of women may experience a chronic form of VI in their lifetime, significantly impacting their quality of life[5,7,8]. Advancing age, family history, prolonged standing, obesity, smoking, sedentary lifestyle, lower extremity trauma, prior venous thrombosis, the presence of an arteriovenous shunt and high estrogen states are all considered risk factors for lower limbs VI[9].

Clinical manifestations related to VI of the anus and hemorrhoidal veins are mainly pain, bleeding, itching, irritation and tenesmus[10,11]. These symptoms represent the hemorrhoidal crisis, which causes considerable discomfort and worsens the

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patient's quality of life[12,13]. Even if it is difficult to establish its real impact since only a minority of the patients consult a doctor, hemorrhoid disease prevalence was estimated as 36% among the general population, with a higher incidence in middle-aged people[14-16]. It was estimated that about 50% of the general population experience symptomatic hemorrhoids in their life[17]. Lifestyle habits (diet, frequency of physical activity, consumption of tobacco or alcohol) are contributing factors to the hemorrhoidal disease, family history, and excess weight[18-20]. Of note, up to 85% of pregnant women experience hemorrhoids in the third trimester[14].

Considering the clinical consequences, VI is a condition that should be treated from its early stages (from the first symptoms) to avoid complications, chronic disease, and invasive treatments.

Venotonics are a heterogeneous class of drugs comprising plant extracts (i.e., flavonoids) and synthetic compounds (i.e., calcium dobesilate). Venotonics can act on the vein walls, increasing their tonus, and thus, reducing pain can stabilize capillary permeability and increase lymphatic drainage[21-23]. This activity provides a hemodynamic effect (which improves venous return) and an anti-inflammatory venous impact[24,25]. Based on these properties, orally administered venotonics are widely used to manage various conditions, including chronic venous insufficiency, lymphoedema, and hemorrhoids.

Ginkor Fort® (Tonipharm, Recordati Group; hereafter termed GB-T-H combined treatment) is a plant-derived venotonic composed of ginkgo biloba extract (24% of Ginkgo heterosides and 6% of Ginkgolides Bilobalides), troxerutin and heptaminol chlorhydrate. Thanks to the synergistic action of its components, the GB-T-H combined treatment is indicated for the treatment of signs and symptoms of the VI and the functional signs related to the hemorrhoidal crisis [SmPC; unpublished data].

The present review aims to briefly recapitulate the biological and clinical rationale for using venotonic drugs to manage VI and discuss available literature evidence on the use of the GB-T-H combined treatment to treat symptoms related to VI and hemorrhoidal crisis.

Materials and Methods

The literature revision was conducted by a PubMed search, using different combinations of pertinent keywords (Ginkor Fort AND venous insufficiency; Ginkor Fort AND hemorrhoids; venoactive drugs AND venous insufficiency; venoactive drugs AND hemorrhoids; ginkgo biloba OR troxerutin OR heptaminol chlorhydrate AND venous insufficiency; ginkgo biloba OR troxerutin OR heptaminol chlorhydrate AND hemorrhoids), without any limitations in terms of publication date and language. Documents from the Authors' personal collection of literature were also considered. Papers were selected for inclusion according to their relevance for the topic, as judged by the Authors.

Venoactive Drugs for the Treatment of Signs and Symptoms of the Venous Insufficiency

A healthy lifestyle and diet represent prevention measures to stimulate correct blood flow. The initial management of leg VI involves conservative measures (compressive stockings are the mainstay of conservative management) to reduce symptoms and prevent the development of secondary complications and progression of the disease[26,27]. Dietary and lifestyle changes are usually considered the first step for any conservative strategy in a hemorrhoidal crisis.

Further pharmacological therapies should be considered if conservative measures fail or provide an unsatisfactory response, and venotonic treatments represent the first-line choice.

Different groups of venoactive drugs have been evaluated in the treatment of VI, including α-benzopyrenes (coumarins), flavonoids (diosmin, micronized purified flavonoid fraction, rutin and rutosides, troxerutin), saponins (escin from horse chestnut extracts, ruscus extract) and other plant extracts, such as anthocyans, proanthocyanidins, heptaminol and extracts from ginkgo biloba[1,2,22,28]. The principle for using this group of drugs in the treatment of VI is to improve venous tone, capillary permeability and lymphatic drainage, reduce inflammation, and manage hemorheological disorders[2,22].

For example, coumarin alone or combined with rutin improves lymph flow and reduces high-protein edema by stimulating proteolysis[29,30]. Flavonoids act on leukocytes and endothelium to modulate the inflammatory response and reduce edema[7,31]. A micronized purified flavonoid fraction (MPFF) has been shown to reduce edema-related symptoms as either primary treatment or in conjunction with surgical therapy[32].

Regarding the hemorheological disorders, venotonic treatments can limit the erythrocyte aggregation (ginkgo biloba), decrease blood viscosity (MPFF and calcium dobesilate) and increase erythrocyte velocity (MPFF)[2].

The review by Lichota et al[22] reports a detailed description of the different venoactive compounds, along with an exhaustive overview of their effects in inflammation and chronic VI.

Venotonic and Vasculoprotective Activities of the ginkgo biloba, Troxerutin and Heptaminol Chlorhydrate Combined Treatment

The synergistic action of the GB-T-H combined treatment is based on the therapeutic activity of each component. ginkgo biloba, thanks to its flavonoids and terpene lactones components, has anti-ischemic properties and a role against cellular hypoxia, along with venotonic, vasodilatory and neuroprotective properties[22,33]. Troxerutin, formerly called "vitamin P" is a flavonoid hemi-synthetically derived from *Sophora japonica*. It allows the increase of capillary resistance and the decrease of capillary permeability, reducing edemas locally. Troxerutin is generally used to treat the pre-varicose and varicose syndrome as supplementary management in varicose ulcers and control symptoms of thrombophlebitis[7,22,34,35]. Heptaminol chlorhydrate, the third component of the GB-T-H combined treatment, has been shown to reduce venous stasis, having an *in vitro* venoconstrictor activity through partial agonist effects on α-adrenergic receptors[36] and promoting venous return by peripheral action on veins and lymphatic networks [SmPC]. The venotonic activity appears to be confirmed by *in vivo* and clinical pharmacological studies[36]. These actions are accompanied by local inhibitory properties against specific algogenic mediators (histamine, bradykinin, serotonin), lysosomal enzymes and free radicals that cause inflammation and degradation of collagen fibers.

Overview of the Literature Evidence on the Activity of the GB-T-H Combined Treatment

Preclinical Evidence

One possible mechanism behind varicose veins, a clinical sign of VI, is the activation of endothelial cells by hypoxic conditions occurring in the leg veins during blood stasis[22,37]. *In vitro* studies[38-40] showed that the combined drug treatment provided protection of endothelial cells against hyperoxia and hypoxia-reoxygenation and prevented endothelial cells' activation by hypoxic conditions both in cell culture and in a completely perfused saphenous vein. In addition, the increased adherence and subsequent activation of neutrophils to the endothelium of the human saphenous vein exposed to hypoxic conditions was also significantly reduced by the treatment[39]. Another *in vitro* study[41] demonstrates the better and longer preservation of the structural and functional qualities of the venous wall after the treatment with the GB-T-H combined treatment.

Clinical Studies

Four pivotal trials[42-45] defined the therapeutic activity of the combined drug to manage the functional symptoms of VI. The main features of these studies are summarized in Table I. The studies by Zuccarelli et al[42] and Natali et al[43] were two double-blind, randomized controlled clinical trials designed to evaluate the improvement of the clinical signs of VI and the reduction of the associated symptoms (premenstrual syndrome, hemorrhoids) during the treatment with the GB-T-H combined treatment[42,43]. Each functional and physical sign was quantified based on intensity according to a rating system and composite index. The treatment tolerability was also assessed. Approximately, 40 women with VI of the lower limbs, on an outpatient basis, were involved in each arm of the two studies (treatment *vs.* placebo). In both studies, the GB-T-H combined treatment was effective in reducing VI symptoms compared to the placebo (pain, cramps, edema, leg heaviness) during the entire study period (baseline *vs.* day 20: $p<0.01$; day 20 *vs.* day 40: $p<0.05$; Figure 1). A good tolerability profile was reported at the end of both studies[42,43].

The studies by Glikmanas et al[44] and Sarles et al[45] were two double-blind, randomized, controlled clinical trials involving parallel groups (treatment *vs.* placebo) of 25 and 34 patients, respectively, with recent, not treated congestive hemorrhoidal crisis[44,45]. Patients were treated with three capsules of the GB-T-H combined treatment for the first 3 days and then two capsules for the other 3 days. A maintenance phase was also included in both studies. Functional signs (pain, oozing, bleeding, pruritus, tenesmus) and physical signs (hemorrhoidal stage, scratching lesions, conges-

Table I. Main features of the GB-T-H combined treatment registration studies.

Study	Patients	Treatment	End Point	Main results
A. Venous insufficiency treatment				
Zuccarelli et al[42]	Two groups of 36 women with VI of the lower limbs, on an outpatient basis	2 capsules/day for 40 days vs placebo Washout period: 20 days before the start of the treatment	Improvement of the clinical signs of VI; reduction of the associated symptoms (premenstrual syndrome, hemorrhoids); tolerance	The combined venotonic treatment was effective in reducing VI symptoms compared with placebo (pain, cramps, edema, leg heaviness) from the first check at day 20 (p<0.01) and between days 20 and 40 (p<0.05) in both studies A good tolerability profile was reported at the end of both studies
Natali et al[44]	Two groups of 40 women with VI of the lower limbs, on an outpatient basis	2 vials/day × 40 days vs placebo (two vials have the same composition as two capsules). Washout period: 20 days before the start of the treatment	Improvement of the clinical signs of VI; reduction of the associated symptoms (premenstrual syndrome, hemorrhoids); tolerance	
A. Venous insufficiency treatment				
Glikmanas et al[44]	Two groups of 25 patients with recent congestive hemorrhoidal crisis not treated	Initial stage: 3 capsules/day for 3 days, then 2 capsules/day for 3 days Maintenance stage: 1 capsule/day for 20 days/month, for 3 months	Improvement of functional signs (pain, oozing, bleeding, pruritus, tenesmus); improvement of physical signs (hemorrhoidal stage, scratching lesions, congestion); overall physician's assessment; tolerance	Consistent results between the two studies On day 7, fast and clear improvement in functional signs, especially pain and bleeding (p<0.02), corroborated by improvement in physical symptoms (p<0.05) in patients treated with the GB-T-H combination Improvement confirmed at day 30. A good tolerability profile was reported at the end of both studies
Sarles et al[44]	Two groups of 34 patients with recent congestive hemorrhoidal crisis not treated	Initial stage: 3 capsule/day for 3 days, then 2 capsules/day for 3 days Maintenance stage: 2 capsules/day for 21 days	Improvement of functional signs (pain, oozing, bleeding, pruritus, tenesmus); improvement of physical signs (hemorrhoidal stage, scratching lesions, congestion); overall physician's assessment; tolerance	

VI: Venous insufficiency.

tion) were evaluated according to an intensity rating system and a composite index. The treatment tolerability was also assessed. Consistent results between the two studies were reported. A fast and evident improvement in functional signs in the acute phase, especially pain and bleeding (p<0.02 compared to baseline), was supported by the improvement in physical symptoms (p<0.05 and p<0.01, respectively, compared to baseline; Figure 2). Improvements were observed until the end of the maintenance phase[44,45].

Subsequent to the market authorization, other studies increased the evidence of using the combined drug for the treatment of VI and related functional symptoms (Table II). They were often local studies published in languages other than English. Thus, to favor a better understanding of the study contents and their results, a summary of the key aspects of each is reported in the following paragraphs.

Liadov et al[46]

This work presents an experience with conservative treatment in 117 patients with VI and edematous syndrome. A complex of rehabilitation measures was used in addition to the GB-T-H combined treatment. Assessments on the microcirculatory changes, malleolar volume, subcutaneous fat thickness, subjective sensations, and quality of life were performed. Results demonstrated the association's effectiveness with GB-T-H combined treatment and rehabilitation treatment in this group of patients[46].

Pokrovskiĭ et al[47]

In the prospective study by Pokrovskiĭ et al[47], 60 patients with variceal disease and chronic VI were enrolled, and the GB-T-H combined treatment was used. The main assessments regard lower limb pain, heaviness and discomfort, night palsies and paresthesia, and edema. Measures also included the digital photo-plethysmography assessment, which can be used with the venous return time and muscular-venous pump capacity analyses combined with ultrasonic examination for the quantitative assessment of venous outflow disturbances. The treatment with the GB-T-H combination resulted in the regression of the clinical complaints according to the 6-score analog scale. Photo-plethysmography showed a

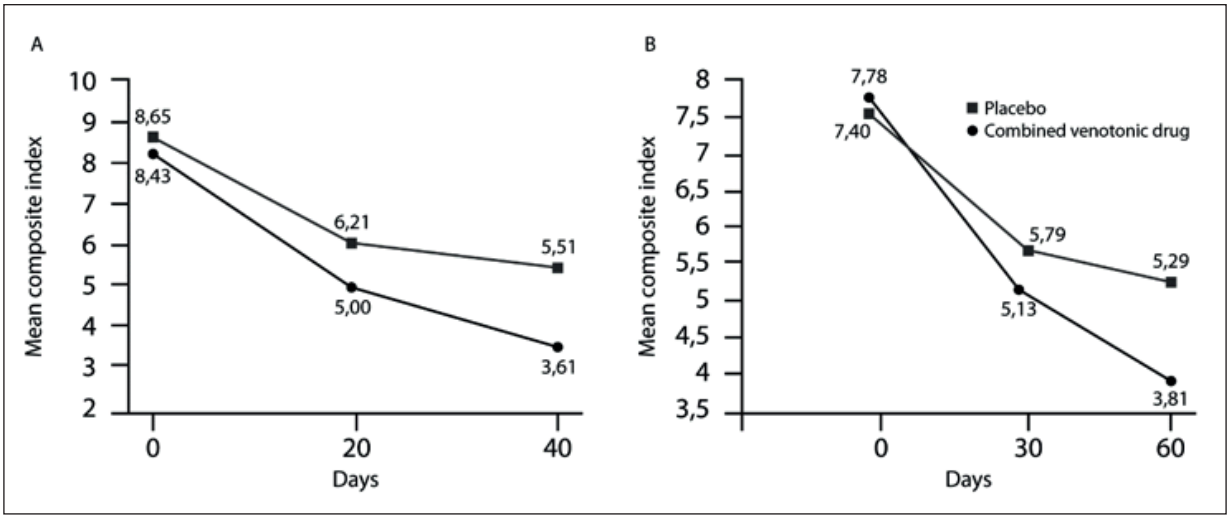

Figure 1. Improvement of the mean composite index values in patients with VI of the lower limbs treated with the GB-T-H combined treatment. **(A)** Results from the Zuccarelli study and **(B)** the Natali study [Adapted from[42,43]].

statistically significant rise of the muscular-venous pump capacity, demonstrating the grown functional capacities of leg pumps and supporting the feasibility of the GB-T-H combined treatment as adjunctive therapy in complex treatment of patients with lower limb VI symptoms[47].

Cluzan et al[48]

This study aimed at determining if the GB-T-H combined treatment has a beneficial effect on lymphatic function and lymphedema symptoms. A three-arm, double-blind, placebo-controlled trial was conducted on 48 patients with upper extremity lymphedema secondary to breast cancer treatment. Improvements in symptoms, signs, and lymphoscintigraphic kinetic parameters (radiocolloid half-life and lymphatic migration speed) were assessed in response to treatment. A statistically significant effect on limb heaviness was reported[48].

Zhukov and Kukol'Nikova[49]

In this study, 30 patients with compensated VI free of trophic ulcers of the legs received the GB-T-H combined treatment twice a day for 1 month. The drug effectiveness was assessed by subjective appraisal of the patients, physical examination,

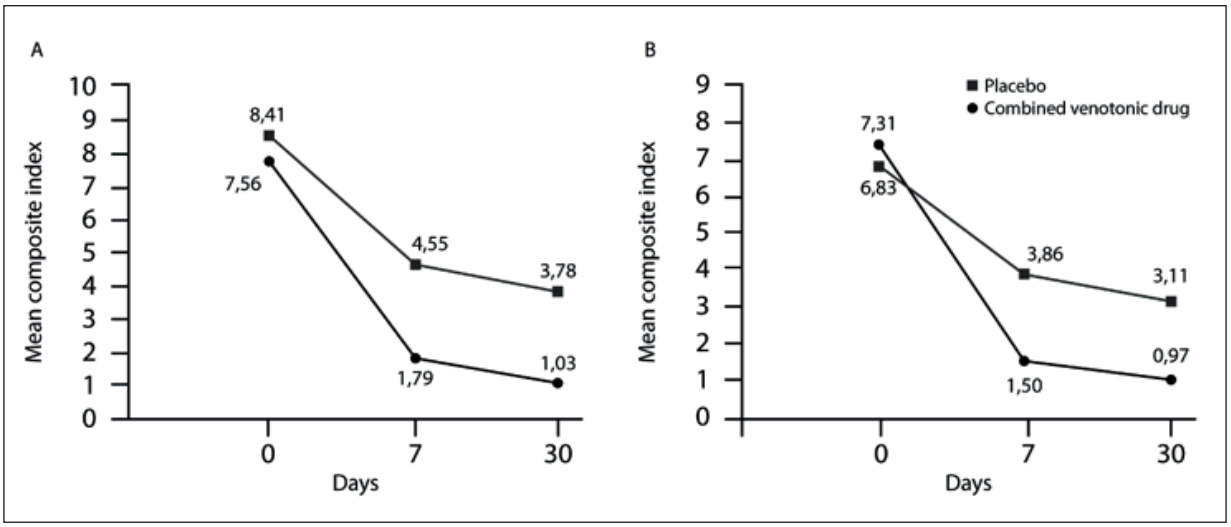

Figure 2. Improvement of the mean composite index values related to functional signs **(A)** and physical symptoms **(B)** in patients with congestive hemorrhoidal crisis treated with the GB-T-H combined treatment [Adapted from[45]].

Table II. Main features of the GB-T-H combined treatment post marketing trials.

Study	Patients	Treatment	Measures	Main results
A. Venous insufficiency treatment				
Liadov et al[46]	117 patients with VI and edematous syndrome	Rehabilitation measures in addition to the GB-T-H combined treatment	Microcirculatory changes, malleolar volume, thickness of subcutaneous fat, subjective sensations, quality of life	The association of rehabilitation measures with the GB-T-H combined treatment showed a high effectiveness
Pokrovskiĭ et al[47]	60 patients with variceal disease and VI	GB-T-H combined treatment	Lower limb pain, heaviness and discomfort feelings, night palsies and paresthesia. Measures also included the digital photo-plethysmography assessment	This study supports the feasibility of the GB-T-H combined treatment as an adjunctive therapy in complex treatment of patients with lower limb VI symptoms
Cluzan et al[48]	48 patients with upper extremity lymphedema secondary to breast cancer treatment	GB-T-H combined treatment *vs* placebo	Effect on lymphatic function or lymphedema symptoms; lymphoscintigraphic kinetic parameters (radiocolloid half-life and lymphatic migration speed)	A statistically significant effect on limb heaviness was observed in the treatment group
Zhukov, Kukol'nikova[49]	30 patients with compensated VI without leg trophic ulcers	GB-T-H combined treatment (1 capsule twice a day for 1 month)	Subjective appraisal of the patients, physical examination, repeated measurements of the leg at the malleolus level	A considerable improvement was observed in 90% patients. Improvement of the condition occurred in 10% of patients. Side effects were absent
Janssens et al[41]	48 patients with VI	GB-T-H combined treatment *vs* placebo	Count of circulating endothelial cells in peripheral blood	In the treatment group, the mean values of the of circulating endothelial cell count decreased by 14% after a 4-week treatment, whereas in the placebo group, the decrease was less (8%). The decrease was significantly higher in the treatment group than in the placebo group
Palade et al[50]	32 patients with varicose veins pathology	Hygienic–dietetic measures, contention, surgery and the GB-T-H combined treatment	Subjective and objective evaluation of symptomatology	Amelioration of symptomatology in 71% of patients
B. Hemorrhoidal crises treatment				
Hep et al[51]	45 patients	GB-T-H combined treatment		A benefit in the use of the GB-T-H combined treatment was documented
Soullard, Contou[52]	37 ambulatory patients with proctological conditions	GB-T-H combined treatment	Evaluation of the treatment hemostatic activity	Improvement of functional syndrome, pruritus ani and rectorrhagia were reported in the most of patients

VI: Venous insufficiency.

and repeated leg circumference measurements at the malleolus level. The treatment produced a considerable improvement in 90% of patients. Side effects were absent, and the treatment was well tolerated[49].

Janssens et al[41]

In the study by Janssens et al[41], the number of circulating endothelial cells detached from the vascular wall was used to assess endothelium injury in patients with primary chronic VI. A randomized, double-blind, placebo-controlled clinical trial evaluated the effectiveness of the GB-T-H combined treatment in 48 patients with chronic VI. In the active treatment group, the mean values of the circulating endothelial cell count were significantly decreased by 14% after a 4-week treatment (p=0.039), compared to the placebo group (Figure 3)[41].

Palade et al[50]

This work reports a clinical experience concerning using the GB-T-H combined treatment to treat varicose veins pathology. A group of 32 patients was treated by the standard of care (hygienic-dietetic, contention, surgery) and the GB-T-H combined treatment. Study results showed a consistent amelioration of subjective and objective symptomatology in 71% of patients[50].

Hep et al[51]

Venotonic drugs are used to manage the hemorrhoidal crises because of their ability to influence the vessel wall tone, decrease the capillary permeability, improve circulation, decrease the edema, and counteract the inflammatory mediators. Within this study, in 45 patients, the GB-T-H combined treatment was used (two capsules twice a day in the first week and then two capsules daily in the second week of the treatment), and a benefit was documented[51].

Soullard and Contou[52]

A total of 37 ambulatory patients with proctological conditions were treated with the GB-T-H combined treatment used as preparatory therapy before instrumental treatment (sclerosants or elastic ligatures). The hemostatic activity was mainly evaluated. After treatment, the functional syndrome (heaviness, tenesmus) in 29 patients was absent in nine cases, reduced in 13, and unchanged in seven. Pruritus ani, which was present in 14 patients, was absent in four cases, reduced in five, unchanged in four, and impossible to evaluate in one case. Rectorrhagia disappeared in 12 out of 20 cases and was reduced in four cases. Overall, there were 12 very satisfactory results, 13 incomplete results, three moderate results, and nine cases where no effect was noted[52].

Implications for clinical practice

GB-T-H combined treatment is a plant-derived composed of ginkgo biloba extract (24% of Ginkgo heterosides and 6% of Ginkgolides Bilobalides), troxerutin and heptaminol chlorhydrate. Its use is indicated for treating signs and symptoms of the VI and of the functional signs related to the hemorrhoidal crisis when the traditional conservative measures give unsatisfactory responses.

Literature evidence supports the effectiveness of this treatment. The results of preclinical and clinical studies indicate that the venotonic combined drug has an effect both on the acute phase symptoms (reduction of leg pain and heaviness), and on the pathogenetic mechanisms of the VI, through the prevention of the hypoxia-induced activation of endothelial cells occurring during blood stasis, the reduction of the capillary tone and permeability and thanks to its hemostatic effect. Overall, these activities lead to the long-term slowing of the disease progression, suggesting that the GB-T-H combined treatment can be used to manage the acute phases of the clinical manifestations of VI and hemorrhoids and as a prevention measure with prolonged use in both conditions.

In the available clinical studies, more than 700 patients were evaluated. The GB-T-H combined treatment showed excellent tolerability, with only negligible adverse events reported[42-45]. Moreover, the extensive clinical experience accumulated for over 30 years further supports using this drug to treat VI and related functional symptoms.

Conclusions

According to the above-mentioned literature currently available, the treatment with the GB-T-H combination produced a considerable improvement in most of the treated patients. A fast and evident improvement in functional signs in the acute phase was reported, along with the improvement in the physical symptoms related to VI and hemorrhoidal crisis, favoring a preventive action in both conditions. Side effects were absent, and the treatment was well tolerated.

A broad clinical experience supports the literature evidence. It suggests that the GB-T-H combined treatment can be considered an effective and safe venotonic and vasculoprotective agent for managing the clinical manifestation of VI and hemorrhoidal crisis.

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Conflicts of Interest

None of the Authors declared conflict of interests.

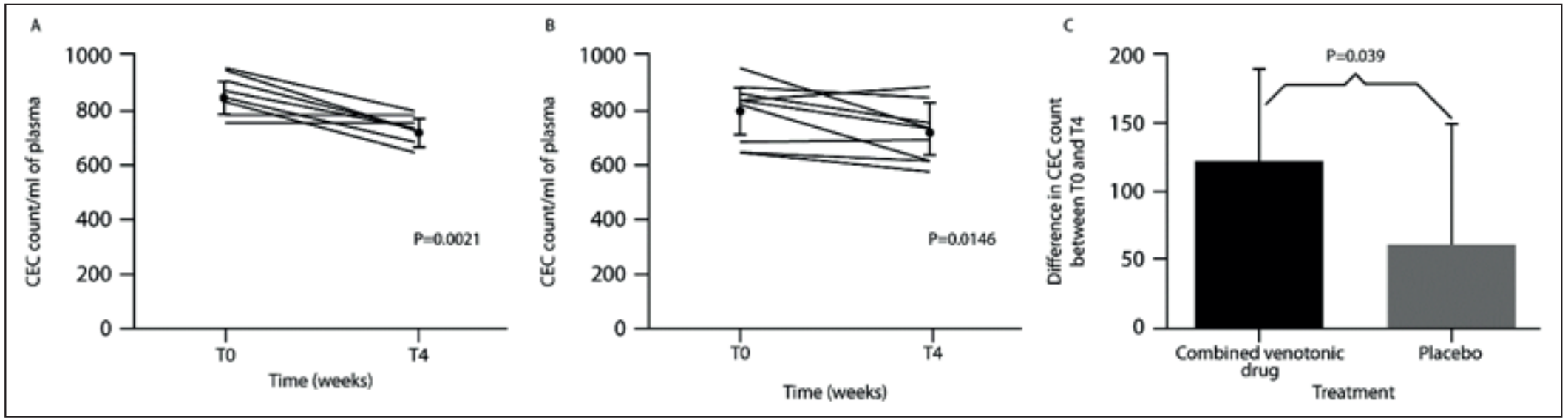

Figure 3. Circulating endothelial cell (CEC) count in the patients treated with the GB-T-H combined treatment **(A)** and in patients who received placebo **(B)**. **(C)** Mean difference in the CEC count between before (T0) and after the 4-week treatment (T4) with the GB-T-H combined treatment for the two groups of patients (mean±SD) [Source: original].

Authors' Contributions

All Authors contributed to the definition and contextualization of the paper contents, critically edited the manuscript, and approved its final version for submission.

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