

Venotonics and Anticoagulants-undisclosed Potential of Drug Treatment of Chronic Venous Insufficiency

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Abstract

This work aims to conduct a comparative analysis of anticoagulant and venotonic therapy for different groups of patients with a diagnosis of acute venous thrombosis of the lower extremities. The tasks included the development of anticoagulants and venotonics combinations and dosages for treatment of a) alleviate an existing disease in a patient; b) disease prevention. Rivaroxaban showed the results of a higher recanalization level of the lower extremities veins in patients compared with warfarin. The maximum recanalization indicators of lower extremities veins, the blood flow velocity in them, and the severity of clinical symptoms were obtained for a group of patients taking a combination of rivaroxaban and diosmin.

Keywords: *Acute venous insufficiency; Venotonics; Anticoagulants; Vein recanalization; Warfarin; Rivaroxaban; Diosmin.*

Introduction

Chronic venous insufficiency can lead to the most serious consequences, for example, the trophic ulcers [1]. As you know, the effectiveness of trophic ulcers treatment is very low [2]. Other severe manifestations of chronic venous insufficiency include post-thrombotic disease. This disease has the most serious consequences, as a rule, due to insufficient indicators of deep veins recanalization. This is especially pronounced in the case of veins of the lower extremities, for example, the iliac and femoral. Veins recanalization occurs during the period of six months to a year after venous thrombosis. In the future, this process does not lead to profound structural changes having an effect for recovery or cure [3, 4].

According to statistics, on average there is 1 case of acute venous thrombosis per 1000 people in the world [5]. In some cases, mortality can reach up to one third, as, for example, with pulmonary embolism resulting from inferior vena cava thrombosis [6]. In the case of a less acute course of the disease, patients may develop venous insufficiency, which ultimately leads to disability. Among modern methods of treating post-

thrombotic disease, conservative therapy has been of the greatest use [7, 8]. This method is used, despite the presence of sections of vein occlusions of different lengths. According to several researchers, surgical intervention is ineffective in terms of treating the disease [9, 11].

This is due to the possibility of complications in the presence of chronic venous insufficiency. Another group of methods, endovascular therapy has not yet been sufficiently integrated into modern medical services, associated with a small number of observations and certain technical difficulties. From the foregoing, the urgency of the problem posed the need for quick and safe treatment of venous thrombosis, with the possibility of vein recanalization, especially of the lower extremities [12, 13].

At the same time, there are methods not fully presented and underestimated among the many methods of treatment of venous thrombosis. These include joint therapy with anticoagulants and venotonics [14]. In relation to each of the patients, a strictly individual approach is necessary, depending

on a number of factors, such as the causes of this disease. The choice of surgical methods requires greater attention. Anticoagulants and venotonics as a treatment strategy for acute venous thrombosis are primarily associated with three groups of factors. These include: a) low blood flow velocity; b) structural endothelium changes of the veins associated with the individual cell degradation and damage and the tissue as a whole.

This leads to changes in the physical characteristics of the veins as a whole - in particular, the elastic properties [15, 16]. These two groups of factors during therapy determine the choice of venotonics, which are able to bring the indicators of blood flow velocity and vein elasticity to at least a state closer to normal rates.

Finally, the third groups of factors include changes in the chemical composition of blood, in particular in the systems responsible for its coagulation and the opposite process of anticoagulation. This group of factors determines the choice of anticoagulants in therapy, designed to normalize blood chemical composition. Thus, the combined use of venotonics and anticoagulants can significantly improve the patient's condition with acute venous venous thrombosis [17].

This work aims to conduct a comparative analysis of anticoagulant and venotonic therapy for different groups of patients with a diagnosis of acute venous venous thrombosis of the lower extremities. The tasks included the development of combinations and dosages of anticoagulants and venotonics to a) alleviation of an existing disease; b) disease prevention.

Material and Methods

The studies were conducted throughout 2018 at the clinical base of the Federal State

Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University). The sample size was 210 patients with a diagnosis of iliofemoral phlebothrombosis.

In 100% of patients, clot proximal level was located above the inguinal ligament, in the external or common iliac veins. Localization of clot proximal level was carried out using the method of ultrasound (US) duplex scanning. The same method was used to determine the period of vein recanalization manifestation and its degree at different levels of veins, as well as changes in the blood flow dynamics in the deep veins of the lower extremities.

The following methodology was used to determine the recanalization degree: weak; medium and strong severity of compression of the vein lumen when compressed by US sensor. In this case, compression was considered as weak for no more than a third of the vein lumen, medium - to half, and for strong - more than two-thirds of the lumen crosscut. An analysis of external symptoms was also performed with the help of visual analogue scale. The frequency of clinical and hardware examinations was once in 10 days, in January, March, June and December 2018.

Exclusion criteria: diagnosis of pulmonary embolism followed by surgery.

Patients were selected in 3 groups, homogeneous in age and gender composition. Significant differences by gender and age were not noted. No differences in the localization of venous lesions were observed. The first group consisted of 80 patients, the second - 70, the third group included the remaining 60 people (Table 1).

Table 1: Recanalization level of the iliac vein in patients of 3 groups at different therapy periods

Therapy period, month	Recanalization level	Patients group 1, number	Patients group 2, number	Patients group 3, number
January 2018	1	19	20	13
	2	53	39	38
	3	8	11	9
	4	-	-	-
March 2018	1	15	-	-
	2	42	27	10
	3	13	29	22
	4	10	14	18
June 2018	1	15	-	-
	2	14	-	-

December 2018	3	25	28	11
	4	26	42	49
	1	14	-	-
	2	14	-	-
	3	19	22	7
	4	33	48	53

Note. Recanalization levels: 1 - occlusion, 2 - weak, 3 - medium, 4 - strong

The first group was treated with low molecular weight heparin (enoxaparin). In this group, the treatment strategy was changed towards administration of indirect anticoagulants (warfarin drug) together with high-purity diosmin (venotonic). The dose of diosmin was 300 mg 2 times a day. For patients from group 2, the treatment strategy was to take rivaroxaban. The rivaroxaban dosage in the first three weeks was 30 mg, then, in the next 2 weeks, 20 mg each, once a day. The third group received a combination of rivaroxaban therapy and venotonics (diosmin, 300 mg 2 times a day). Administration of venotonics and anticoagulants continued throughout the year of therapy.

In addition to taking medication, patients wore compression stockings during the treatment period, of the second compression class [18]. Statistica (Stat. soft Inc., v. 6.0) was used for the statistical processing of the obtained data. The data distribution did not correspond to normal, and therefore non-parametric statistics methods were used: the Mann-Whitney U-test (for independent groups), as well as the Wilcoxon test in case of related groups when studying possible changes in therapy. The differences are significant $p \leq 0.05$.

Results

Throughout the therapy course, regardless of the strategy chosen, no patients associated with hemorrhagic complications were observed. On the contrary, we observed symptoms of the recanalization onset within a short period after therapy. On day 9 we recorded it in the lower leg veins, in some cases in a different location (popliteal vein). There were no significant differences between all three groups at the initial stage. In the next period after 30 days, recanalization of veins of different severity was already observed in the groups. This was expressed in different recanalization degrees between the more or less proximal veins sections.

General hemodynamics and its parameters (blood flow velocity) are determined by the iliac vein segment. In the treatment of acute venous insufficiency, in particular of iliofemoral phlebothrombosis, recanalization takes place last compared to the other segments of the veins. Therefore, the hemodynamic parameters of the ileal segment are presented as the most indicative in determining the effectiveness of different treatment strategies. During the first 30 days after the therapy start (January 2018); all patients still lacked signs of a high degree of recanalization of the iliac segment veins (Table 1).

Recanalization was absent in every fourth patient in all groups, without significant differences. No differences were noted between the number of patients with moderate and weak degrees of recanalization for each group. A difference in the effectiveness of the chosen therapy strategy was observed 90 days later (March 2018). In particular, occlusion was present in a number of patients from group 1, while iliac occlusion was no longer detected in patients from the other two groups ($p \leq 0.05$).

Moreover, the number of patients from group 1 with occlusion remained at the same level as at the beginning of treatment. For patients from groups 2 and 3, the first signs was observed corresponding to the process of iliac vein segment restoration. These differences intensified six months and a year after the start of therapy. So, a high degree of recanalization has already been noted for 26 patients from group 1 and twice as many ($p \leq 0.05$) the number of patients from two other groups.

At the end of the therapy course, a high recanalization level was noted in almost all patients from group 3 (53 out of 60) and for the majority of patients from group 2 (48 out of 70). For patients from group 1, the final recanalization indicators are half as low (33 out of 80, $p \leq 0.05$).

Moreover, patients from the groups 1 and 2 showed no occlusion signs, as well as a weak recanalization level. Medium cases in patients from these groups are also not numerous, with a tendency to decrease from indicators for six months to the final, a year after the start of therapy. For patients from group 1, the presence of occlusion did not change in the future, while in the case of the onset of recanalization, there was further progress.

In case if the recanalization begins in the first 30 days of therapy, further processes will take place with more pronounced signs of restoration of normal blood flow in the veins. In addition, our data show that the strategy effectiveness for patients from groups 2 and 3 is significantly greater compared to that for patients from group 1.

The most effective treatment strategy of patients was the one for group 3. At the end of therapy, recovery was observed in the majority of them. Another conclusion is the effectiveness of prescribing anticoagulants at the very initiation of therapy. This statement applies primarily to patients with a diagnosis of iliofemoral phlebothrombosis. The

enhancement of the effect up to the cure can be observed with the combined appointment of venotonic, also from the beginning of the treatment period. The analysis of blood flow velocity indicators at the beginning of therapy is not accurate. The first recanalization signs were observed in some patients on the 9th day of therapy and beyond, but we continued to determine the blood flow velocity a month after the start of therapy. This is due to the fact that at this time, all patients already have recanalization of at least the popliteal vein, which makes it more accurate to measure blood flow velocity. This article compares blood flow velocity indices after 30 days from the start of therapy in dynamics with other treatment periods.

The choice of the popliteal vein is also not accidental, since there is a faster recanalization in comparison with other veins. In addition, in the popliteal vein, blood flow rates are more constant in magnitude and reliable compared to the veins of the lower leg. According to our data, significant differences between all groups were recorded throughout the entire treatment period (Table 2).

Table 2: Comparative indicators of an increase in blood flow velocity (% , popliteal vein) in patients of different groups on day 9 of therapy and in its later periods

Therapy period	Group 1	Group 2	Group 3
March 2018	18.3±2.9	33.7±0.6	37.7±0.7
June 2018	22.4±2.5	50.5±4.5	59.3±4.0
December 2018	34.1±3.6	68.9±4.3	86.8±5.6

By 3 months (March 2018), the recorded indicators of an increase in blood flow velocity for patients from groups 2 and 3 were 1.4x and 1.8x higher than those in patients from group 1 ($p \leq 0.05$). Statistical differences also persisted between patients from groups 2 and 3 - in group 3, the blood flow velocity was on average 1.1x higher than in group 2 ($p \leq 0.05$).

In general, this pattern tended to persist for patients both within the same group (on average 1.5 times between different periods of therapy, $p \leq 0.05$), and between different groups. Moreover, the gap between group 1 and the rest of the groups increased as the observation period moved away from the start of therapy, on average 2.0x, $p \leq 0.05$. The reason for this lies in the ongoing recanalization of the popliteal vein, and,

further, of the remaining veins entering the venous system of the lower limb. The difference between the blood flow velocity at the beginning of observations and the end of therapy for patients of group 1 was 1.8x, for group 2 - 2.0x, and, finally, for group 3 - 2.3x ($p \leq 0.05$).

The difference in the change in blood flow velocity between different groups is also significant and at the end of the treatment period was 2.0x between group 1 and 2, 2.5x between group 1 and 3 and 1.2x between group 2 and 3 ($p \leq 0.05$). A similar pattern was observed in the weakening of clinical symptoms in patients. In general, the symptoms eased, but there was a variation depending on the degree of recanalization of the deep veins and their blood flow velocity (Fig. 1).

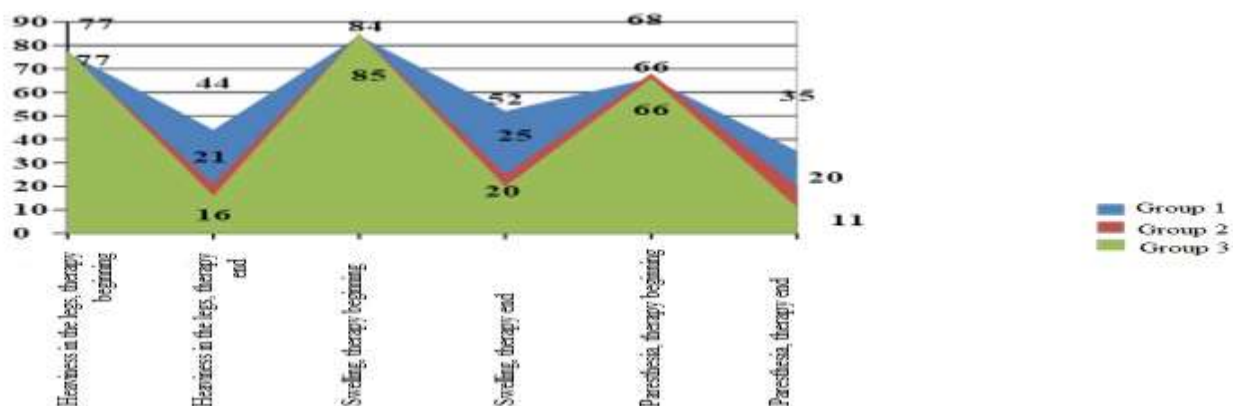


Figure 1: Changes in symptoms at different periods of therapy (in %)
Note. The assessment was carried out on a visual-analogue scale of 100 points

Severe leg pain at the end of therapy was indicated by 1.7x fewer patients in group 1, 3.6x less in group 2 and 4.8 times less in group 3. For the swelling index, in group 1 there was a decrease by 1.6 times, in the 2nd group - by 3.3 times and by 3 - by 4.2 times. Finally, for the paresthesia index in group 1, a 1.9-fold decrease was recorded, in 2 - by 3.3 times, and for 3 groups of patients - by 6 times.

Discussion

Cases of lower extremities vein thrombosis are quite common among the population. According to statistics, on average, from 100 to 150 cases are observed for every 100 thousand people [19]. There is also a direct age dependence in the form of an exponent - the larger the age, the more cases there are [20, 21]. Almost every third person suffers from varicose veins. These rates may vary significantly in developing countries [22].

At the same time; varicose veins are characterized by concomitant chronic venous insufficiency [23, 24]. In chronic venous insufficiency, changes occur in the morphological and physiological parameters of the veins and their blood flow velocity; degradation changes cause a high probability of blood clots and premature sudden death [25, 27].

The therapy using venotonics and anticoagulants, usually acting as an adjuvant, remains underestimated [28]. At the same time, these groups of drugs have a direct effect on improving blood flow and vein elasticity. Recanalization processes are taking place, followed by restoration of the functional characteristics of the veins [29]. The use of a well-constructed drug therapy strategy has several advantages.

Firstly, the quality of medical care is improved and the number of possible complications is reduced [10, 11].

Secondly, financial costs for the purchase of previously ineffective or ineffective drugs are reduced [30, 31]. In the diagnosis of post-thrombophlebitis disease, in particular in iliofemoral phlebothrombosis, the most significant factor for recovery or improvement of the existing condition is the level of recanalization [32, 33]. A well-designed pharmacotherapy strategy of using rivaroxaban from the very beginning showed better results in comparison with patients who were prescribed warfarin.

Indicators of blood flow velocity increased, the processes of recanalization of veins of the lower extremities began to occur faster. Significant differences were also present in the occlusion rates, which were absent in all patients when taking anticoagulants. In most of the patients from the group taking rivaroxaban, we estimated the level of vein recanalization as medium or high, while some patients from the 1st group (taking warfarin) had occlusion and recanalization indicators corresponding to medium and high levels were observed only in half.

The combination of venotonics and anticoagulants did not lead to possible hemorrhagic complications in any of the patients treated. This combination therapy, on the contrary, made it possible to improve the condition of patients without risk to their health, to obtain statistically significant results in terms of deep vein recanalization and in the speed of blood flow in them. In addition, there have been changes for the better and in the severity of clinical symptoms.

Thus, the combination of rivaroxaban and diosmin with respect to warfarin and diosmin proved to be a more effective method of therapy. When undergoing therapy, the deadline is critical. As our data showed, it is 3 months. At this time, there are active basic processes of destruction of the thrombus.

In the case of preservation of an occlusion at any site in the future, successful recanalization is extremely unlikely. When using rivaroxaban from the very beginning of therapy, hypocoagulation occurs, this leads to increased recanalization of veins. Nevertheless, maximum results were obtained when venotonics (diosmin) were added to therapy, which significantly increased blood flow velocity. Not the least role in recovery is played by wearing

compression stockings, as well as physical activity (exercise, being in clean air).

Conclusions

Rivaroxaban showed the results of a higher level of recanalization of the lower extremities veins in patients compared with warfarin. The maximum indicators of recanalization of the veins of the lower extremities, the blood flow velocity in them, and the severity of clinical symptoms were obtained for a group of patients taking a combination of rivaroxaban and diosmin.

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