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Comparison of thrombodynamic tests with determination of anti-Xa activity in evaluation of the efficacy of anticoagulant therapy in patients suffering deep vein thrombosis of the lower extremities

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ABSTRACT

Deep vein thrombosis of the lower extremities remains an important medical and social problem in practical medicine. Currently, a weight-dependent low-molecular-weight heparin dosing approach is used to treat deep vein thrombosis of the lower extremities in wounded patients without regard to the state of the hemostasis system. This observational study included 30 patients with deep vein thrombosis of the lower extremities who were hospitalized for examination and treatment at the Kirov Military Medical Academy. During treatment with enoxaparin sodium at therapeutic doses, depending on body weight, the parameters of the thrombodynamics test were assessed in all patients, and antiXa activity was determined at the peak of the drug (after 3–4 h) and at the end (before the next injection) of its action. A strong inverse correlation was established between the growth rate indicator of the thrombodynamics test clot and antiXa activity at the peak (–0.777; $p < 0.05$) and at the end (–0.715; $p < 0.05$) of the action of sodium enoxaparin. The standard dose of anticoagulant drug, depending on body weight, revealed that 30% of patients were in the hypercoagulation zone, not reaching the target values of the thrombodynamic clot growth rate and anti-Xa activity. The thrombodynamics test results identified the growth rate of the test clot with antiXa activity, which allows both methods to be considered comparable for laboratory monitoring low-molecular-weight heparin therapy in wounded individuals. The insufficient anticoagulant effect in one-third of the injured individuals that received the standard and therapeutic doses of low-molecular-weight heparins requires the development of a personalized approach to titration of low-molecular-weight heparins, which may be based not on the concentration of the drug per body weight but on the achieved anticoagulant effect that optimizes the treatment outcomes and patient prognosis. Accordingly, further research is required.

Keywords: deep vein thrombosis; low molecular weight heparins; anti-Xa activity; thrombodynamics; clot growth rate; monitoring of anticoagulant therapy; wounded; a personalized approach.

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Сравнение теста «тромбодинамика» с определением анти-Ха активности в оценке эффективности антикоагулянтной терапии у раненых, страдающих тромбозами глубоких вен нижних конечностей

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АННОТАЦИЯ

Тромбоз глубоких вен нижних конечностей до сих пор является важной медико-социальной проблемой практической медицины. В настоящее время для лечения тромбоза глубоких вен нижних конечностей у раненых используется подход назначения доз низкомолекулярных гепаринов в зависимости от массы тела без учета состояния системы гемостаза. Проведено наблюдательное исследование, в которое было включены 30 раненых с установленным тромбозом глубоких вен нижних конечностей, госпитализированных для обследования и лечения в Военно-медицинскую академию им. С.М. Кирова. На фоне лечения эноксапарином натрия в лечебных дозах в зависимости от массы тела у всех пациентов оценивались параметры теста «Тромбодинамика», а также проводилось определение анти-Ха активности на пике действия препарата (через 3–4 ч), и на исходе (перед очередной инъекцией) его действия. Установлена сильная обратная корреляционная связь между показателем скорости роста сгустка теста «Тромбодинамика» и анти-Ха активности на пике (–0,777; $p < 0,05$) и на исходе (–0,715; $p < 0,05$) действия эноксапарина натрия. При стандартном назначении дозы антикоагулянтного препарата в зависимости от массы тела выявлено, что 30 % пациентов находились в зоне гиперкоагуляции, не достигнув целевых значений скорости роста сгустка теста «Тромбодинамика» и анти-Ха активности. По данным исследования отмечена тождественность результатов теста «Тромбодинамика» по скорости роста сгустка теста с анти-Ха активностью, что позволяет обе методики считать сопоставимыми инструментами лабораторного мониторинга терапии низкомолекулярных гепаринов у раненых. Недостаточный антикоагулянтный эффект у трети раненых при стандартном применении низкомолекулярных гепаринов в лечебных дозах требует разработки персонализированного подхода к титрации низкомолекулярных гепаринов, который может основываться не на концентрации препарата на массу тела, а на достигаемом антикоагулянтном эффекте, оптимизирующем результат терапии и прогноз пациентов, что требует дальнейших исследований.

Ключевые слова: тромбоз глубоких вен; низкомолекулярные гепарины; анти-Ха активность; тромбодинамика; скорость роста сгустка; мониторинг антикоагулянтной терапии; раненые; персонализированный подход.

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“血栓动力学”试验与抗XA活性测定在下肢深静脉血栓形成伤者抗凝治疗疗效评价中的比较

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摘要

下肢深静脉血栓仍是实用医学的一个重要医学和社会问题。目前，对伤员下肢深静脉血栓形成的治疗采用的是根据体重给予低分子肝素剂量的方法，而不考虑止血系统的状态。S.M.基洛夫军事医学院对 30 名下肢深静脉血栓形成的伤员进行了检查和治疗。在根据体重使用治疗剂量的依诺肝素钠治疗的背景下，对所有患者的“血栓动力学”测试参数进行了评估，并测定了药物作用高峰期（3-4 小时后）和作用末期（下次注射前）的抗Xa活性。在依诺肝素钠作用的高峰期（-0.777；$p < 0.05$）和末期（-0.715；$p < 0.05$），血栓动力学试验的血块生长速度指数与抗Xa活性之间存在很强的反相关性。根据体重确定抗凝药物剂量的标准处方显示，30% 的患者处于高凝状态，无法达到“血栓动力学”测试的凝块增长率和抗 Xa 活性的目标值。研究数据显示，“血栓动力学”测试结果与抗 Xa 活性测试的凝块增长率结果 一致，因此这使得这两种技术都可以被认为是实验室监测低分子肝素治疗的可比工具。三分之 一的伤员在标准使用治疗剂量的低分子量肝素时抗凝血效果不足，这就需要开发一种个性化的低分子量肝素滴定方法，这种方法可能不是基于单位体重的药物浓度，而是基于所达到的抗凝血效果，从而优化治疗效果和患者的预后，这需要进一步的研究。

关键词： 深静脉血栓；低分子肝素；抗 Xa 活性；血栓动力学；血块生长速度；抗凝疗法监测；伤员；个性化方法。

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INTRODUCTION

Venous thromboembolic complications (VTEC) are a significant clinical issue in trauma surgery. The incidence of acute venous thrombosis in patients with polytrauma can reach 35%–55% [1]. Additional risk factors for VTEC development in wounded individuals include high levels of psychoemotional stress, massive hemotransfusions, and prolonged immobilization after combat trauma [2].

Low-molecular-weight heparins (LMWHs) are commonly used for the prevention and treatment of VTEC. The anticoagulant effect of LMWHs is mainly caused by Xa inhibition. Therefore, plasma anti-Xa activity (AXA) is the preferred method for monitoring the efficacy and safety of therapy [3]. The technique is based on the laboratory assessment of the ability of the patient's plasma to inactivate the factor Xa without additional antithrombin. However, this test is not commonly used in clinical practice and is generally of limited use in specialized medical institutions [4]. In addition, this test only assesses the inhibition of factor Xa and does not reflect the overall state of plasma hemostasis under the anticoagulant effects of LMWHs. To obtain a comprehensive evaluation of the hemostasis system, integral tests such as thrombodynamics (TD), thromboelastography (TEG), and thrombin generation test (TGT) should be considered. These tests show great promise. J. Sebaaly and K. Covert [5] found a significant correlation among AXA, TEG, and TGT. The TD test is a global integral test that evaluates both qualitative and quantitative characteristics of the coagulation profile of the blood plasma to identify the risks of bleeding and thrombosis [6]. The clot growth rate, which is the average growth rate of the clot calculated between 15 and 25 min after the beginning of growth, is one of the primary parameters of the TD test [7]. Currently, information in the available literature regarding the relationship between TD and AXA tests and the possibility of comparing the effectiveness of the methods is insufficient.

Thus, this study aimed to compare the results of the TD test with the determination of AXA activity in assessing the effectiveness of anticoagulant therapy in wounded patients with distal deep vein thrombosis (DVT) of the lower extremities.

MATERIALS AND METHODS

A single-center prospective observational study was conducted as part of the Optimization of Approaches to Anticoagulant Therapy for the Prevention and Treatment of Venous Thromboembolic Complications in the Wounded (cipher: OPRAVA) project, which was funded by the Priority 2030 program. The study included 30 male participants with combat trauma. The inclusion criteria were as follows: men aged 18 and 59 years who have experienced combat gunshot trauma and have undergone surgical intervention without evidence of ongoing external or intracavitary bleeding and who have been diagnosed with distal DVT of the lower extremities. The exclusion criteria were as follows: refusal to participate in the study, thrombocytopenia, and presence of concomitant pathologies, such as connective tissue diseases, hematologic diseases, malignant neoplasms, severe liver failure (Child – Pugh classes B and C), acute kidney injury, and chronic kidney disease (stages IV–V).

This study examined and treated wounded patients at the Kirov Military Medical Academy. For anticoagulant therapy, patients received therapeutic doses of enoxaparin sodium (enoxaparin) based on their body weight. The local ethical committee of the Kirov Military Medical Academy approved the study (Protocol No. 278, dated May 30, 2023), and all patients provided voluntary informed consent to participate.

A blood sample was taken by puncturing the ulnar vein, and blood was collected in a vacuum tube containing sodium citrate at 3.2% concentration. The first portion of the blood collected was discarded. The plasma obtained after centrifugation at 1600 g for 15 min was used to determine AXA activity the chromogenic method using an AST TOR 500 automatic coagulometer (Instrumentation Laboratory Company, Italy). The results were expressed in IU/mL.

In the TD test, the prepared plasma was processed according to the manufacturer's instructions. The clot growth rate (V) was estimated using the original reagents and the diagnostic laboratory system "Thrombodynamics Registrator T-2" from Hemacor Limited Liability Company (Russia). Laboratory studies were conducted at the Central Clinical and Diagnostic Laboratory of the Kirov Military Medical Academy and the Nikiforov All-Russian Center for Emergency and Radiation Medicine at two time points: at the peak (after 3–4 h) and end of the drug's effect (day 7) of anticoagulant therapy before the next injection.

Data were statistically processed using Statistica 10.0. Quantitative characteristics are represented by the median (*Me*) and quartiles [*Q*25–*Q*75]. Independent groups were compared, differences were identified using the nonparametric Mann – Whitney test, and the Spearman correlation analysis method was used to investigate the relationship between quantitative characteristics. A threshold value of statistical significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

The mean and interquartile range of *V* at the peak of drug action were 8.9 [7.4; 11.0] μm/min in patients receiving therapeutic doses of LMWHs for distal DVT. However, 23 (77%) patients had results within the recommended range of 7–14 μm/min [6]. The results in 5 (17%) patients were below these values, and 2 (6%) patients had values above the recommended therapeutic window, which could pose risks of hemorrhagic complications or thrombosis, respectively.

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In the TD test, the recommended range of the index at the peak of enoxaparin action, which is between 0.5 and 1.1 IU/mL [8], was reached in only 22 (73%) patients. In 6 (20%) patients, AXA values did not reach the lower limit of the range, indicating possible insufficient efficacy of the drug. In addition, the values in 2 (7%) patients exceeded the therapeutic AXA range. An analysis was conducted to determine the minimum daily anticoagulant activity of enoxaparin and assess the risk of complications during the minimal effect of the drug immediately before the next injection [5]. At the end of the drug's action, *V* was below the recommended range in 1 (3%) patient, within the recommended range in 20 (67%), and in the hypercoagulation zone in 9 (30%) patients.

Currently, no standardized criteria have been established for determining the target AXA range at the end of enoxaparin action. However, O.N. Startsev et al. [8] suggested that the minimum value (before the next injection) for different patient populations during therapy should be 0.3–0.6 IU/mL. According to the OPRAVA study, AXA levels were within the reference range in 11 (36.7%) patients at the end of enoxaparin treatment. In addition, 14 (46.7%) patients had AXA levels < 0.3 IU/mL, and 5 (16.7%) had levels > 0.6 IU/mL.

The comparative analysis of the results showed statistically significant differences between the data obtained at the peak and end of enoxaparin action (Table 1).

Correlation analysis showed a strong inverse correlation between *V* in the TD and AXA tests both at the peak ($r = -0.777$; $p = < 0.05$) and end ($r = -0.715$; $p < 0.05$) of enoxaparin action, as shown in Figure 1.

In the next stage, the distribution of *V* in the TD and AXA tests among patients with distal DVT of the lower extremities who were treated with LMWHs was evaluated. At the peak of anticoagulant therapy, the *V* and AXA parameters of 16 patients were within the recommended range, whereas the ranges for *V* and AXA were not reached in 5 and 7 patients, respectively. In addition, two patients had values exceeding the range for both *V* and AXA parameters (Fig 1.). In addition, 30% of the patients who received standard therapeutic doses of anticoagulant therapy based on their body weight were in the hypercoagulation zone according to *V* and did not achieve the target values of AXA at the end of enoxaparin action. A patient was in the hypocoagulation zone according to the parameters of clot growth rate and AXA, and four patients had AXA values exceeding the recommended range. No clinically significant bleeding episodes were observed during anticoagulant therapy.

Anticoagulant therapy is a recognized and highly effective treatment option for venous thrombosis of the lower extremities. Therefore, physicians of various specialties must understand laboratory basics and monitor anticoagulants, their safety, and risk factors for hemorrhagic complications during their use [9]. A laboratory technique that enables monitoring of anticoagulant therapy in real clinical practice must be selected [10]. According to V.I. Petrov [11], the optimal "therapeutic" range of coagulation, which ensures maximum efficacy and safety of anticoagulant therapy, may not be achieved when treating venous thrombosis of the lower extremities if hypocoagulation is not actively monitored and corrected (titration of the drug dose) based on the obtained results.

Currently, many studies have demonstrated the benefits of monitoring anticoagulant therapy using integrated hemostasis assessment tests. According to Y.L. Ketsko and O.V. Tereshina [12], evaluating thromboelastometry parameters over time aids in predicting the development of pulmonary thrombosis, reducing complications, and lowering the risk of mortality in patients with COVID-19. Lobanova et al. (13) found that thromboelastography may be crucial in identifying patients with COVID-19 who require active anticoagulant therapy because of increased thrombosis risk. Conversely, patients at low risk of thrombosis may not require anticoagulant therapy. In the comparative monitoring of TGT and AXA, P. Vermeiren et al. [14] concluded that TGT has low sensitivity under low-dose LMWH therapy and can only be considered an additional parameter of laboratory monitoring.

AXA determination is considered the "gold standard" for monitoring LMWHs. In patients diagnosed with VTEC, LMWH dose adjustment under AXA control may be necessary for pregnant women, individuals with very low (< 40 kg) or very high (> 144 kg) body weight, and those with severe renal dysfunction [15]. Meanwhile, a meta-analysis conducted by the American Society of Hematology during the development of relevant recommendations did not reveal any additional benefits of the individualized selection of the LWMH dose under AXA control in patients with obesity and severe renal impairment [16]. In addition, A. Taylor et al. [17] demonstrated that AXA monitoring was not beneficial for VTEC prophylaxis in trauma cases. In the study of

Table. Results of determining the rate of clot growth and anti-Xa activity in wounded patients treated with enoxaparin
Таблица. Результаты определения скорости роста сгустка и анти-Xa активности у раненых на фоне лечения эноксапарином

Indicators	*V*, μm/min		AXA, IU/mL	
	At the peak	At the end	At the peak	At the end
Number of patients	8.9 [7.4; 11.0]	19.7 [14.2; 24.7]*	0.7 [0.5; 0.9]	0.25 [0.1; 0.43]*
Recommended range	7–14	13–23	0.5–1.1	0.3–0.6

Note: * — $p < 0.05$.
Примечание: * — $p < 0,05$.

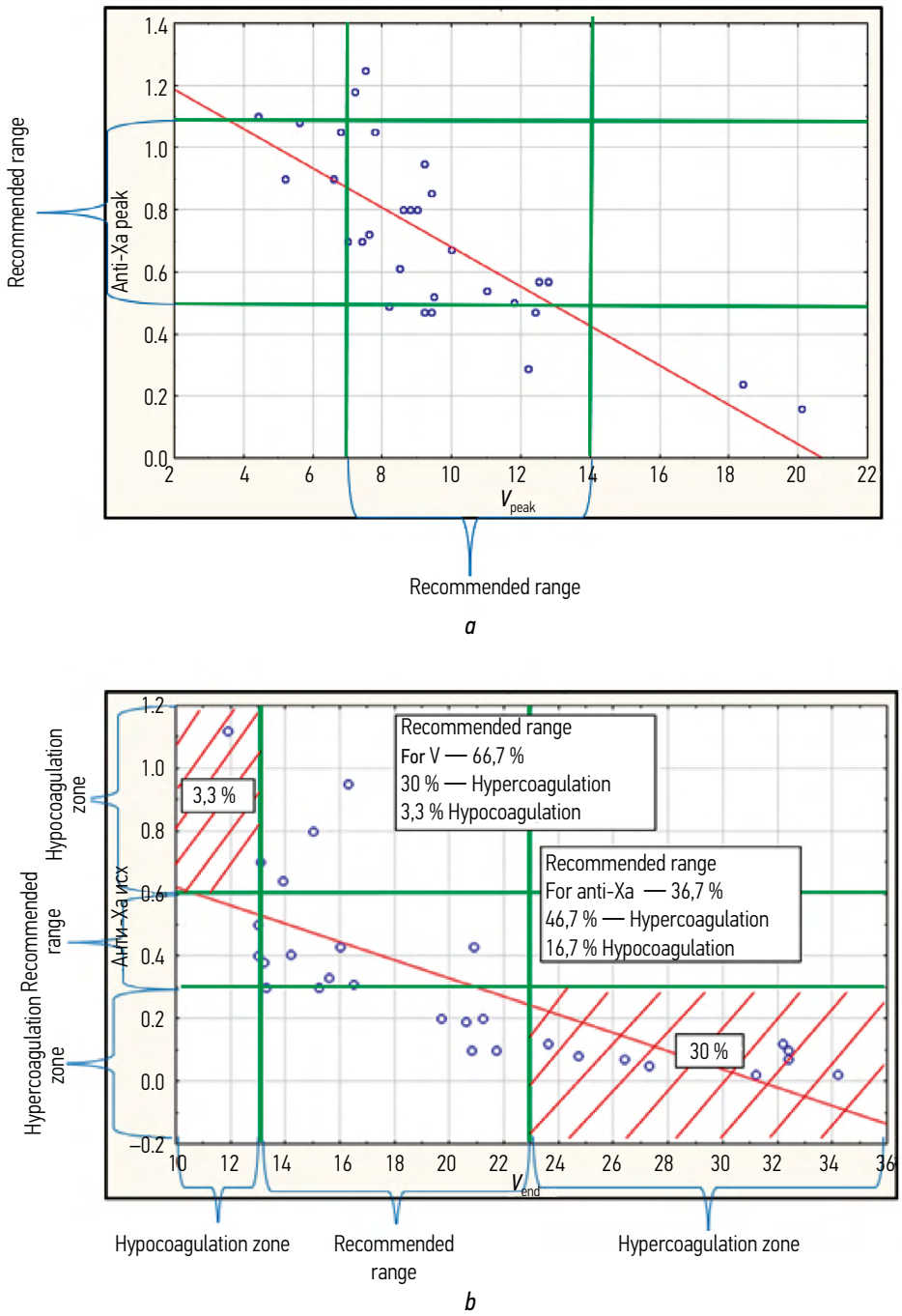

Fig. Comparison of the rate of clot growth and antiXa activity: *a* — at the peak; *b* — at the end of the action of low-molecular-weight heparin

Рис. Сопоставление скорости роста сгустка и анти-Ха активности: *a* — на пике; *b* — на исходе действия низкомолекулярного гепарина

VTEC prophylaxis strategies, W. Tingting, X. Xiaotong, and Ch. Wenjun et al. [3] found that changing the LWMH dose under AXA control resulted in a 56% reduction in the relative risk of VTEC development. The minimum LWMH content at the end of the drug's action was more informative than that at the peak of its action. M. Trunfio et al. [18] demonstrated the advantage of AXA monitoring when prescribing LWMHs to patients with COVID-19. In this study, laboratory monitoring values at the end of anticoagulant action were more effective in assessing the efficacy of the therapeutic doses prescribed with LWMHs than at peak levels. In addition, we previously [19] demonstrated that studying *V* in the TD test at the end of drug action allowed for a comparative evaluation of prophylactic anticoagulant therapy regimens.

More studies are warranted to resolve the contradictory data regarding the monitoring of anticoagulant therapy, particularly in special cohorts such as those with wounds. The OPRAVA study used an integrated methodology to evaluate the effectiveness of LWMHs, including the TD test and AXA determination, performed at the peak of anticoagulant

action and at its residual content [20]. The study found that the standard prescription of anticoagulant therapy only led to achieving the target ranges of selected monitoring methods in 70% of cases.

The study's limitations include a small sample size and short follow-up period and the absence of a control group of patients who underwent elective surgery. These factors may affect the accuracy of the results and conclusions.

CONCLUSIONS

The results of the TD tests and AXA determination correlate with each other, allowing for an equally effective evaluation of anticoagulant therapy with LWMHs. The TD test expands the possibilities of laboratory diagnostics and improves the monitoring of anticoagulant therapy, which may enhance its effectiveness. This technique can be an alternative tool for monitoring anticoagulant therapy with LWMHs in wounded patients because *V* yields results comparable with those of the AXA test. Because one-third of the wounded patients had V and AXA values not within the recommended range after the administration of the standard dose of enoxaparin based on body weight, the prescription of anticoagulant therapy must be personalized. The personalization of therapeutic techniques in wounded patients suffering from distal DVT of the lower extremities can be considered a promising approach to optimize the results of therapy and patient prognosis. This approach is based on achieving the anticoagulant effect rather than the drug concentration per body weight. Further research is required to support this claim.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

The contribution of each author. V.V. Salukhov — development of a general concept, research design, writing an article; E.V. Kryukov — development of a general concept, research design, writing an article; N.A. Varavin — collection, systematization and analysis of data, statistical processing of material; O.N. Startseva — data collection and processing, statistical processing of material.

Competing interests. The authors declare that they have no competing interests.

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