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Обоснование выбора метода профилактики тромботических осложнений у пациентов хирургического профиля высокого риска (обзор литературы)

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АННОТАЦИЯ

Введение. Венозные тромбоэмболические осложнения (ВТЭО), в том числе тромбоз глубоких и подкожных вен, тромбоэмболию легочных артерий, выносят в разряд важнейших клинических проблем, касающихся профессиональной сферы многих медицинских специальностей. К факторам высокого риска тромбообразования относят хирургические вмешательства, приводящие к активизации системы гемостаза. Несмотря на существующие международные и российские клинические рекомендации по лечению и профилактике ВТЭО, в которых подробно описываются методы и алгоритмы профилактики у пациентов с различными нозологиями, в том числе с выраженным полиморбидным фоном, процент ВТЭО остается высоким. В научном сообществе продолжаются дискуссии в отношении эффективности многообразных подходов к профилактике ВТЭО в разных клинических группах пациентов. Существуют алгоритмы, предусматривающие использование антикоагулянтных препаратов в стандартных дозировках и комбинациях. Однако у пациентов с коморбидным фоном изолированной консервативной антикоагулянтной терапии бывает недостаточно для эффективной профилактики ВТЭО.

Заключение. В настоящее время имеется необходимость усовершенствования алгоритмов профилактики ВТЭО у пациентов с коморбидной патологией, разработки четких показаний к методам как медикаментозной, так и механической профилактики и их комбинации.

Ключевые слова: *тромбоз глубоких вен; тромбоэмболия легочных артерий; антикоагулянтная терапия; профилактика тромботических осложнений*

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Justification of Choice of Thromboprophylaxis Method in Patients with High-Risk Surgical Profile: A Literature Review

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ABSTRACT

INTRODUCTION: Venous thromboembolic complications (VTEC) such as deep and subcutaneous vein thrombosis and pulmonary embolism are the most important clinical problems in many specialties. High-risk factors for thrombus formation include surgical interventions leading to the activation of the hemostatic system. Despite the existing international and Russian clinical recommendations on the treatment and prophylaxis of VTEC containing a detailed description of the methods and algorithms of prophylaxis in patients with different nosologies including patients with polymorbidities, the incidence of VTEC remains high. In the scientific community, there is a continuing discussion of the effectiveness of various approaches to VTEC prophylaxis in different clinical groups of patients. Algorithms available prescribe anticoagulants at standard doses and combinations. However, in patients with comorbidities, isolated conservative anticoagulant therapy may be insufficient for effective VTEC prophylaxis.

CONCLUSION: Currently, there is a need to improve the algorithms of VTEC prophylaxis in patients with comorbid pathologies to elaborate clear indications for the use of both pharmacological and mechanical prevention methods and their combinations.

Keywords: *deep vein thrombosis; pulmonary embolism; anticoagulant therapy; thromboprophylaxis*

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ECO•VECTOR

LIST OF ABBREVIATIONS

VTEC — venous thromboembolic complications
IU — international units
LMWH — low molecular weight heparin
UFH — unfractionated heparin
DVT — deep vein thrombosis
PE — pulmonary embolism

INTRODUCTION

Venous thromboembolic complications (VTEC), such as deep vein thrombosis (DVT), thrombophlebitis of great saphenous vein and pulmonary embolism (PE), are among the leading healthcare problems involving many medical specialties. As it follows from the analysis of the modern literature sources, 50–70 new cases of VTEC per 100 thousand population are annually recorded. With this, the annual incidence of VTEC in elderly patients increases to 200 cases per 100 thousand population. The annual record of PE is 35–40 cases per 100 thousand population [1, 2].

VTEC are among the most common causes of death among oncologic patients. V. V. Ptushkin wrote in his review (2017) that many forms of cancer manifest in the form of migrating thrombotic complications. With this, in patients with primary forms of thrombosis, that is, without evident causes, the frequency of the subsequent identification of oncopathology reaches 10% [3].

This study aimed to comparative analysis of the currently existing methods of thromboprophylaxis in surgical patients on the basis of the literature data.

Epidemiology of Thrombotic Complications in Surgical Patients

The incidence of DVT in the general population starts from 160 cases per 100 thousand population annually, of lethal PE — 60 cases per 100 thousand population. Thus, PE is the third most common cardiovascular complication [4, 5].

The most important problem is effective prophylaxis of postoperative VTEC, from the economic point of view as well. In case of VTEC, the expenses are mostly associated with hospitalization, they are comparable with the expenses on the treatment of myocardial infarction and stroke and in the USA they amount to US$ 9 thousand for DVT and US$ 12 thousand for PE [6, 7].

Epidemiological investigations of cancer patients showed that venous thrombosis of different locations is identified in 10%–15% of patients. However, in the study of S. I. Felder, et al. (2019) it is noted that with use of high-tech diagnostic methods, the incidence of DVT of distal veins in cancer patients reaches 41%, while in the general group of surgical patients it does not exceed 26% [8]. According to A. A. Fokin and K. V. Bagaev (2019), the leading risk factor for the total thromboembolism is a combination of the oncologic process and surgical intervention [9]. It is necessary to emphasize the relationship between VTEC and form/location of tumor process. For example, the incidence of VTEC is highest in patients with mucin-producing adenocarcinomas in the gastrointestinal tract (stomach, large intestine, pancreas), lungs (non small-cell lung cancer, small-cell cancer), small pelvic organs in females. Less often, these disorders are noted in malignant neoplasms of breast, prostate or kidneys. A combination of oncologic diseases with venous insufficiency increases the incidence of VTEC [10].

Influence of Surgical Intervention on Hemostasis

On average, 25% of PE and DVT of the lower limbs are directly related to surgeries [11, 12]. In orthopedic interventions, thrombotic complications occur in about 50% of cases, in abdominal, gynecological, urological surgical interventions — in 30% [13, 14].

According to D. Ferreira, et al. (2017), VTEC in the postoperative period in patients with malignant neoplasms occur 3–5 times more often than in patients without oncologic process [15]. On the contrary, in 40%–80% of patients with oncologic diseases the operation is associated with subsequent development of thrombotic complications of the distal veins, in 10%–20% of patients — with thrombosis of lower limb veins in the proximal part, 1%–5% of patients die from PE in the postoperative period [16].

Morphological examinations confirm the influence of tumor cells on the endothelium leading to release of the vascular permeability factors and to activation of the coagulation system [17].

Risk of PE at the age under 40 is 0.03%, from 40 to 60 years — 0.09%, from 60 to 80 — 0.26%. The risk of PE in 85-year old patients is 200 that of 30-year old ones which is predetermined by age-related shifts in the coagulation and anti-coagulation systems of blood [18, 19]. Another risk factor of VTEC is overweight: obesity 3 times increases the risk of VTEC [20]. Intake of oral contraceptives/substitution hormonal therapy also increases the risk of thrombotic complications several times [18–19].

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Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism in Surgical Patients

The prophylaxis of disorders in hemostasis and of related thrombotic complications in surgical patients includes two groups of measures: *mechanical* (aimed at acceleration of venous blood flow) and *pharmacological.*

The medical drugs most commonly used for the prophylaxis of venous thromboembolism in cancer patients are heparins. Heparin has relatively weak anticoagulant properties which significantly enhance when it binds with antithrombin III [21–23]. In recent years, low molecular weight heparins (LMWH) with molecular weight less than 5,400 Da (within 4000–6500 Da) and with almost complete absence of large-molecular weight components have become widespread (molecular weight of heparin is 15,000 Da) [24, 25]. Low molecular weight heparins possess more powerful anti-Xa activity, but lower antithrombin (anti-IIa) activity. Heparins with large molecular weight (> 20,000 Da) possess opposite properties [21–25].

In contrast to unfractionated heparins (UFH), LMWH minimally bind with blood cells, plasma proteins, vascular endothelium, which leads to longer retention of free preparation in circulation and to increase in its half-life (T1/2). Thus, T1/2 of UFH is about 90 min., T1/2 of LMWH — from 108 to 252 min [26, 27]. This permits to be limited to several injections at the required dose per day. It was shown that the influence of LMWH on Xa factor is linearly dependent on the prescribed dose. These pharmacological characteristics show that *LMWH level in plasma is predictable and does not need constant monitoring* [28].

The studies evaluated safety of LMWH when used for the prophylaxis of VTEC in oncological patients undergoing surgical operations. Thus, there was considered a possibility of using dalteparin at the doses 2500 international units (IU) and 5000 IU once a day in the preoperative and postoperative period. The incidence of VTEC was 14.9% in patients receiving 2500 IU, and 8.5% — in those receiving 5000 IU. This study first showed that increase in the dose of *LMWH can increase the effectiveness of thromboprophylaxis in patients with malignant neoplasms without increase in frequency of hemorrhagic complications* [29, 30].

In another study, another LMWH, enoxaparin, was used, starting from the preoperative period at 40 mg once a day, in comparison with UFH at 5000 IU 4 times a day. The incidence of VTEC was 18.2% among patients receiving UFH, and 14.7% among patients receiving enoxaparin, *with comparable safety profile of both schemes.*

According to a European multi-center study involving 1896 patients, the incidence of VTEC with use of fraxiparine at prophylactic doses after abdominal surgeries was 2.8%, and with UFH — 4.5%. With this, fraxiparine, in contrast to heparin, did not increase the frequency of hemorrhagic complications [31].

In patients of the *general surgical profile*, the frequency of DVT is 4.85% in the group of LMWH and 5.84% in the group of UFH, the incidence of PE is 0.25 and 0.58%, respectively. Among *traumatological patients*, frequency of DVT is 16.36% (LMWH group) and 19.5% (UFH group), frequency of PE — 1.3% and 2.26%, respectively. In whole, effectiveness of reduction of the frequency of postoperative VTEC with LMWH is 21% higher than with UFH, of PE — 56% higher, which *indicates a higher efficiency of prophylaxis with LMWH* [32, 33].

Surgical tactics in phlebothromboses of the inferior vena cava system directly depends on the level and length of lesion, phase of thrombotic process, existence of complications [34].

According to the data presented in the scientific literature, nowadays, in case of thrombotic lesion of the vein of shin with the absence of complications, the *traditional tactics is conservative therapy without surgical intervention* — anticoagulant therapy, elastic compression. Some researchers recommend implantation of vena cava filter in case of PE, others adhere to the open surgical intervention tactics — l*igation of the external iliac vein* [35, 36].

Conservative therapy is conducted in full volume in the presence of thrombophlebitis of superficial veins of the lower limbs without signs of progression and the presence of PE. There is no doubt that in the *presence of ascending thrombophlebitis of the great saphenous vein or development of PE, a crossectomy operation is indicated* [37].

In the presence of thrombosis in the femoral-popliteal segment (occlusive or parietal phlebothrombosis) with no signs of PE, the generally accepted tactics is *conservative treatment.* Signs of progression of thrombosis in the course of treatment, development of PE, formation of floating thrombosis are considered *indications for open surgical treatment to the extent of ligation of the external iliac vein*. In case of floating thrombosis, the preference is given to endovasal intervention or open surgery (in the absence of technical possibilities) — thrombectomy, plication of the inferior vena cava [38].

CONCLUSION

Despite the existing international and Russian clinical recommendations on treatment and prophylaxis of VTEC with a rather detailed description of methods and algorithms of prophylaxis in patients with different nosologies including polymorbid patients, the *percent of thrombotic and hemorrhagic complications* remains high. In this context, in the scientific community, there is a continuing discussion of the effectiveness of various

approaches to prophylaxis of venous thromboembolic complications in different clinical groups of patients. Currently, there exists a necessity to improve the algorithms of prophylaxis of venous thromboembolism in patients with comorbid pathology, to develop clear indications for use of both pharmacological and mechanical prophylaxis methods and of their combinations.

Prophylactic measures were shown to reduce the risk of venous thromboembolic complications in hospitalized patients of surgical profile, *however, the conducted studies do not permit to specificate the management tactics in individual clinical subgroups*.

The active development of techniques and varieties of surgical interventions in recent years has significantly changed the degree and quality of impact on the body and its microstructures, therefore, the most difficult task is *to assess all the cumulative individual characteristics of patient management, in particular a high-risk patient.* Obviously, these changes cannot but have an impact on approaches to the prophylaxis of major complications of surgical tactics, especially such important ones as venous thromboembolic events.

Nowadays, in the era of active development of pharmacology, one should not forget about a large group of comorbid patients that have to receive multicomponent therapy which often creates an unpredictable and impassable barrier in the form of drug interactions and undesirable reactions.

The combination of the described issues and difficulties determines the urgent need for interdisciplinary multicenter studies to create evidence-based algorithms for the management of surgical patients with different initial data, for effective prophylaxis of venous thromboembolism.

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