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Symptoms and prophylaxis of venous thromboembolism in the population of cancer and hospice patients - what is known?

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Abstract

In a group of palliative patients, venous thromboembolism (VTE) is a significant cause of death and reduction in quality of life. Current guidelines and scientific research on thromboprophylaxis most often refer to the population of oncology patients, who differ in many aspects from patients receiving palliative care. Thus, doctors working with patients undergoing palliative treatment have to face many problems related to safety and effectiveness of antithrombotic therapy in this type of care.

In the case of chronically ill patients, diagnostic process may be somewhat difficult because the symptoms resulting from the underlying diseases can mask VTE symptoms. The aim of this article is to review the literature on symptoms and thromboprophylaxis in this group of patients.

According to the latest guidelines of the American Society of Clinical Oncology (ASCO), it is not recommended to use VTE prophylaxis in outpatient oncology patients routinely, but it should be considered in high-risk patients who received a Khorana score of at least 2 before starting a new chemotherapy cycle.

In patients diagnosed with VTE, in long-term prophylaxis lasting at least 6 months, due to greater effectiveness, it is recommended to use low-molecular-weight heparins, edoxaban, rivaroxaban or apixaban instead of vitamin K antagonists, which can be used if the previously mentioned drugs are unavailable. There are some studies which show that thromboprophylaxis may be beneficial for patients in palliative care. On the other hand, another studies' results suggest that patients won't gain any benefit from prevention.

As our article shows it is very crucial to conduct scientific research on palliative patients and create clear guidelines for prophylaxis for this group of people.

Keywords: Venous Thrombosis; Pulmonary Embolism; Venosus Thromboembolism; Sign and Symptoms; Prevention and Control.

Introduction

Venous thromboembolism (VTE/VTE) is a disease entity that includes in its definition [1], deep vein thrombosis (DVT) and pulmonary embolism (PE). Although VTE is an important cause of premature death and reduced quality of life among oncological patients,[2] this group is not routinely subjected to antithrombotic prophylaxis due to the increased risk of bleeding and the lack of clear guidelines for antithrombotic prophylaxis in this group of patients.[3]

Therefore, it is so important to know the available diagnostic measures and the symptoms that patients with VTE may present, especially since palliatively treated patients and oncological patients are particularly vulnerable to VTE [4], due to immobilization and chronic inflammatory reactions.

The choice of prophylactic method to be used in a patient undergoing palliative care is influenced by many factors, such as the risk of VTE or the possibility of monitoring the anticoagulant effect, which makes it difficult to make therapeutic decisions in palliative care conditions.

Work objective

The aim of this article is to review the literature on symptoms and thromboprophylaxis to which we paid particular attention due to lack of clear guidelines for antithrombotic prophylaxis in palliative patients. Current guidelines and scientific research on thromboprophylaxis most often refer to the population of oncology patients, who differ in many aspects from patients receiving palliative care. Thus, doctors working with patients undergoing palliative treatment have to face many problems related to safety and effectiveness of antithrombotic therapy in this type of care. The crucial aspect of this article is an attempt at systematization of knowledge about prevention of deep venous thrombosis.

Symptoms

To start diagnosing deep vein thrombosis, you need to know what symptoms the patient may present with. In the case of chronically ill patients, this may be somewhat difficult because the symptoms resulting from the underlying disease mask symptoms of VTE. Additionally, severe pain, especially common in the palliative patient population, may further complicate the correct diagnosis, resulting in a delay in treatment. Moreover, in cancer cases there is a greater risk of bleeding, which means that the symptoms resulting from thrombosis may initially be masked.

The most common symptoms include: leg swelling (the presence of leg swelling is an independent predictor of deep vein thrombosis)[5], protruding veins, tenderness along the deep veins; swelling of the calf (circumference at least 3 cm larger than the other calf) or fever. The problem may be deep vein thrombosis, which does not cause any symptoms. Bleeding may also occur and may be classified as major or clinically relevant non-major.[6]

In a study of lymphoma patients, it was found that only half of the patients had VTE-related symptoms at diagnosis, while the other half had none and were only discovered incidentally during imaging for staging or tumor evaluation.[7]

Pulmonary embolism can often be hidden by other symptoms or have no symptoms at all. We can distinguish unexpected pulmonary embolism which definition is “pulmonary embolism with no clinical suspicion at the time of CT examination”.[8,9]

In the study by C. O'Connell et all, it was noted that the most common symptom among cases and controls was fatigue (44% vs. 21%, respectively). Moreover, among patients who developed signs or symptoms, shortness of breath, cough, and fatigue were significantly more common in unexpected pulmonary embolism cases than in controls. The researchers did not observe any statistically significant difference between the study group and the control group in terms of symptoms of pulmonary embolism such as tachycardia or chest pain. In turn, recent surgery and previous VTE were most closely associated with unexpected pulmonary embolism.[10]

The results of the study by M Sahut D'Izarn et all among the 66 patients with unexpected pulmonary embolism, showed that 27 (41%) had one or more symptoms suggesting pulmonary embolism before computed tomography, 23% had dyspnea, 9% had chest pain, 1% had hemoptysis, and 8% had leg pain. Moreover, researchers observed that Patients with unexpected pulmonary embolism were significantly older and were more likely to have advanced disease and adenocarcinoma than patients without pulmonary embolism.[11]

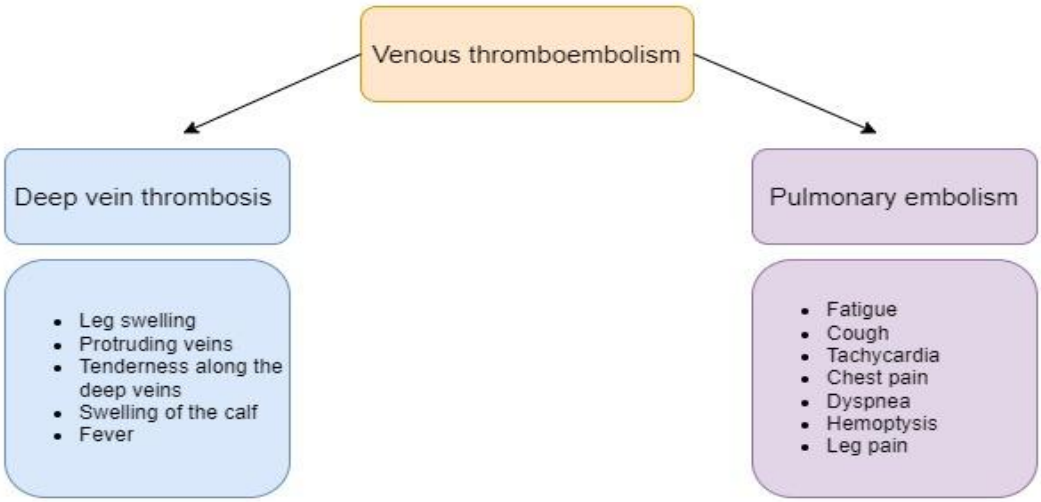

Figure 1. Sign and symptoms in Venous thromboembolism. [5,6,10,11]

Prevention of venous thromboembolism in palliative care.

The World Health Organization (WHO) indicates that the aim of palliative care is to improve the quality of life of patients and their families facing problems related to a life-threatening disease, by preventing and alleviating suffering, thanks to early detection, correct assessment and treatment pain and other physical, psychosocial and spiritual problems.[12]

Relatively often, VTE occurs in these patients, with few symptoms and is detected accidentally, which may cause significant discomfort and even mortality. Therefore, it is so important to develop appropriate guidelines for the prevention of venous thromboembolism in palliative patients. The choice of the preventive method to be used in a patient undergoing palliative treatment is influenced by the patient's characteristics, which include, among others: the risk of VTE and the risk of bleeding, as well as the availability, costs and possibility of monitoring the anticoagulant effect.[13]

The results of an observational study conducted by Tardy et al on 1,199 people admitted for the first time to a palliative care unit suggest that when deciding to introduce VTE prophylaxis in palliative patients, the high risk of bleeding should be taken into account. The most common reason for admission, in as many as 90.7% of patients, was cancer. A high incidence of clinically significant bleeding (9.8%) was observed, which was related to antithrombotic therapy (most often a prophylactic dose of low molecular weight heparin), with a simultaneous low incidence of VTE (0.5%).[14,15]

Primary prophylaxis

Primary prevention used in the general population includes: early mobilization, mechanical methods (elastic stockings with gradual compression and an intermittent pneumatic compression device) and anticoagulants (heparins, selective factor Xa inhibitors, vitamin K antagonists and direct oral thrombin inhibitor).[13]

Patients who are hospitalized in palliative care units differ in many aspects from patients belonging to the general population. Current guidelines and scientific research most often refer to the oncology patient population. There are no VTE prevention guidelines for patients admitted to hospice care, therefore further research is necessary on the safety and effectiveness of antithrombotic therapy in this type of care.

A study conducted on a group of 1,141 patients by Kowalewska et al showed that 6.7% of patients received antithrombotic prophylaxis upon discharge to hospice care. The most common were aspirin (57.1%), enoxaparin (26%) and warfarin (20.8%). Patients with a history of atrial fibrillation, mitral or aortic valve replacement, or treatment for VTE were much more likely to be prescribed anticoagulant therapy, while those with a history of cancer, liver disease, or cerebrovascular disease were much less likely to be prescribed. In 55% of patients previously receiving antithrombotic prophylaxis, the same drugs were continued as before, although in 54.5% of cases this had no documented justification. [16]

It has been shown that physicians are reluctant to use VTE prophylaxis based on low molecular weight heparins. This is due to fears of its negative impact on the quality of life of patients and the lack of guidelines for palliative care. [17,18]

According to the latest guidelines of the American Society of Clinical Oncology (ASCO), in hospitalized patients with active cancer, acute disease or limited mobility, who do not have bleeding or other contraindications, pharmacological VTE prophylaxis should be initiated. None of the current guidelines recommend the routine use of VTE prophylaxis in outpatient oncology patients, but it should be considered in high-risk patients who received a Khorana score of at least 2 before starting a new chemotherapy cycle. [19–22]

The aim of the study conducted by Weber et al was to determine the usefulness of prophylactic antithrombotic treatment in oncological patients referred to palliative care in a

specialized center. The study found no clear benefits or drawbacks to prophylactic nadroparin administration. One case of VTE and one major bleeding event occurred in the nadroparin group, while two minor bleeding events occurred in the control group. Moreover, only 20 people took part in the study, so it is impossible to detect a significant clinical difference and draw reliable conclusions about the usefulness of such treatment.[15,23]

However, in another study conducted by Angelli et al on 1,150 patients with metastatic or locally advanced cancer receiving chemotherapy, a thromboembolic event occurred in 15 of 769 patients (2.0%) receiving nadroparin and in 15 of 381 (3.9%) being in the placebo group. Major bleeding was observed in 0.7% of people receiving antithrombotic prophylaxis. However, it did not occur in the placebo group. The results of this study indicate that prophylaxis with this low molecular weight heparin reduces the incidence of thromboembolic events with no significant increase in bleeding compared to the placebo group. [24]

Another study by Angelli et al showed similar results using low molecular weight heparin semuloparin at a dose of 20 mg once daily in a group of oncological patients treated with chemotherapy. In the group receiving this low molecular weight heparin, VTE occurred in 20 of 1,608 (1.2%) people compared to 55 of 1,604 (3.4%) people in the placebo group. The incidence of clinically significant bleeding was 2.8% and 2.0% for semuloparine and placebo, respectively. [25]

A study conducted by Carrier et al showed that the use of apixaban at a dose of 2.5 mg twice daily in oncological patients who were starting chemotherapy and belonged to the group of medium or high risk of thromboembolism (received a score of 2 or more on the Khorana scale) significantly reduced the incidence of thromboembolism among these patients. The incidence of VTE was 4.2% in the apixaban group and 10.2% in the placebo group. At the same time, it was noted that the incidence of bleeding episodes was higher in the group of patients receiving apixaban (2.1%) than in those receiving placebo (1.1%). However, major bleeding events belonging to categories 3 and 4 of major bleeding episodes accounted for only 20% of all major bleeding episodes and their frequency was comparable in both groups. Serious bleeding occurred mainly in the gastrointestinal tract, genital tract and hematuria.[26]

In a retrospective cohort study by Polesello et al conducted on 453 patients taking anticoagulant therapy after admission to palliative care, it was observed that the probability of VTE in this group of patients was lower (4.6%) compared to the group of patients who discontinued treatment (6 .7%). At the same time, an increase in the frequency of bleeding was observed in patients treated with anticoagulants (10.8% vs. 7.6%), although these differences were not statistically significant..[27]

However, the results of a retrospective cohort study conducted by Al.-Ansari et al showed that cancer patients with a short expected survival time will not benefit from the use of prophylaxis, because it does not reduce the risk of fatal VTE in patients in the terminal phase of cancer. The study involved 719 patients, among whom 31.29% and 17.5% were taking thromboembolic prophylaxis on admission and at death, respectively. The incidence of clinically suspected fatal VTE was 6.5%, and statistically it was higher in the group of patients taking antithrombotic prophylaxis than in the group of people who were not taking it. [28]

The authors of another small prospective study on a group of 127 patients whose life expectancy was shorter than 6 months found that primary antithrombotic prophylaxis may not be included or even safely discontinued in patients previously taking it who were admitted to a palliative care unit. Of all participating patients, 41 (32.3%) were taking prophylaxis on admission. During their stay, 36 of them (87.8%) discontinued prophylaxis, which resulted in the development of VTE in one patient. However, in the group of patients who did not take prophylaxis at admission or throughout the study period, six patients developed VTE. The results obtained in the study show that the risk of symptomatic VTE in the group of patients qualified for the study is 7.6%. This risk was not considered clinically significant by the authors. [15,29]

Study, reference	Study population	Findings
Al.-Ansari et al[28]	719 patients	Cancer patients with a short expected survival time will not benefit from the use of prophylaxis, because it does not reduce the risk of fatal VTE in patients in the terminal phase of cancer.

Angelli et al[24]	1,150 patients with metastatic or locally advanced cancer receiving chemotherapy	Prophylaxis with this low molecular weight heparin reduces the incidence of thromboembolic events with no significant increase in bleeding compared to the placebo group.
Angelli et al[25]	3,212 patients	Prophylaxis with semuloparin reduces the incidence of thromboembolic events with no significant increase in bleeding compared to the placebo group.
Carrier et al[26]	563 patients	Prophylaxis with apixaban reduces the incidence of thromboembolic events with increase in bleeding compared to the placebo group.
Legault et al[29]	127 patients whose life expectancy was shorter than 6 months	Primary antithrombotic prophylaxis may not be included or even safely discontinued in patients previously taking it who were admitted to a palliative care unit.
Polesello et al[27]	453 patients taking anticoagulant therapy after admission to palliative care	Probability of VTE in this group of patients was lower (4.6%) compared to the group of patients who discontinued treatment (6 .7%). There was no significant increase in bleeding compared to this placebo group.
Weber et al[23]	20 patients referred to palliative care in a specialized center	The study found no clear benefits or drawbacks to prophylactic nadroparin administration.

Table 1. Research summary on primary prophylaxis in patients in palliative care.

Mechanical methods

The role of mechanical methods, such as graduated compression stockings and intermittent pneumatic compression, as VTE prevention remains unclear. They can be used in hospitalized

patients who have contraindications to the use of anticoagulants. However, the skin condition should be monitored for signs of skin damage or ulceration, especially in people receiving antiangiogenic drugs or corticosteroids or having other risk factors that impede wound healing. The use of mechanical methods was associated with a higher risk of skin damage and ulceration compared to the control group. [30–32]

Secondary prevention

According to the latest ASCO guidelines, in patients diagnosed with VTE, initial prophylaxis may be performed using low molecular weight heparins, unfractionated heparin, fondaparinux, rivaroxaban or apixaban. In patients with newly diagnosed VTE and without renal dysfunction who start treatment with a parenteral anticoagulant, it is still recommended to use low-molecular-weight heparin prophylaxis for the first 5-10 days, although no differences in effectiveness were found compared to the use of low doses of unfractionated heparin. and the risk of bleeding. Low molecular weight heparins are widely preferred due to their once-daily administration and reduced risk of heparin-induced thrombocytopenia (HIT). [3,17,19,21,22,32–34]

In long-term prophylaxis lasting at least 6 months, due to greater effectiveness, it is recommended to use low-molecular-weight heparins, edoxaban, rivaroxaban or apixaban instead of vitamin K antagonists, which can be used if the previously mentioned drugs are unavailable.[22]

Secondary prevention using filters placed in the inferior vena cava is recommended only when there are absolute contraindications to anticoagulant treatment. After implantation of the filters, adverse events occurred, such as displacement or rupture of the device, perforation of the inferior vena cava, and embolization of the element.

The use of filters in combination with anticoagulant therapy has not been observed to provide greater benefits compared to anticoagulant therapy alone, therefore the device should be removed when the clinical indications have passed and the patient can switch to pharmacological treatment.[21,32,35,36]

Summary

Symptoms are often non-specific and may go unnoticed in patients at the end of life especially when the symptoms resulting from the underlying diseases can mask VTE symptoms. Severe pain, which is quite common in the palliative patient population, may further complicate the correct diagnosis, resulting in a delay in treatment.

Existing guidelines and scientific research on antithrombotic prevention most often refer to the population of oncological patients, who differ in many aspects from patients receiving palliative care, therefore further research on the safety and effectiveness of antithrombotic therapy in this type of care is necessary. Especially in case of divergent results of up to now studies, it is crucial to conduct more research on bigger group of people to gain more certain and homogenous results.

In our work, we tried to show what kind of obstacles, doctors working with patients undergoing palliative treatment, have to face. We hope that this will increase awareness of this problem, which will result in scientific research and the development of appropriate diagnostic and therapeutic standards.

Disclosure

Author's contribution:

Analysis and Preliminary Research: Piotr Daniel, Justyna Składanek

Planning and Designing: Karina Otręba

Writing and Editing: Justyna Składanek

Data Analysis: Karolina Czupryńska

Scientific Verification: Joanna Cieszkowska

Summary and Conclusions: : Michał Leśkiewicz

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