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Venous Thromboembolism Prophylaxis in Gynecological Oncology: The review of Guidelines

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Venous thromboembolism (VTE) is one of the leading causes of death in cancer patients. VTE prophylaxis and/or treatment in the treatment and follow-up of cancer patients will reduce mortality and morbidity rates. Although the incidence of VTE in cancer patients is high, there is not yet a standardized protocol for the prevention of VTE in the subgroup of gynecological cancer patients. VTE prophylaxis and treatment vary according to the cancer type of the patients and the treatment approaches to be applied. In this review, it is aimed to explain the pathogenesis, risk factors and treatment approaches in VTE prophylaxis in gynecological oncology patients, taking into account international consensus reports. All reviewed guidelines recommended VTE prophylaxis for all hospitalized patients with active cancer. All guidelines agree that low molecular weight heparin (LMWH) gives good results in VTE prophylaxis in patients diagnosed with gynecological cancer. Risk scoring has been recommended for outpatients after discharge, and current guidelines recommend direct oral anticoagulants (DOAC) for the prevention of VTE in high-risk patients. Due to the high risk of bleeding in the gynecological cancer patient population, the side effects of pharmacological agents should be well considered and more attention should be paid to mechanical prophylactic methods.

INTRODUCTION

Virchow first identified predisposing factors for venous thrombosis in 1856, based on a series of events. These are known as Virchow's triad and are defined as venous stasis, vascular damage and hypercoagulability [1]. The relationship between cancer and venous thromboembolism (VTE) has been known since 1865 [2]. This common complication was first demonstrated by Trosseu. Later, many studies have shown the negative effect of VTE on life expectancy. Clinically significant VTE is detected in 11% of patients with cancer [3]. The incidence of cancer-related thrombosis is increasing worldwide and has become the second leading cause of death in cancer patients [4]. Existing oncological disease often complicates the clinical course and delays treatment planning. The pathogenesis of thrombosis in cancer patients is still unclear. There are many factors that predispose to thrombosis in these patients. Tumor cells can stimulate the coagulation cascade by a direct

mechanism by releasing procoagulant substances, or they can trigger it indirectly through the stimulation of circulating inflammatory cytokines. The most well-known of these procoagulant substances is tissue factor [5, 6]. When specific cancer complications such as vascular compression or invasion of the tumor, immobilization, presence of an inflammatory event, and surgery are added to these stimuli, the probability of thrombosis increases. Finally, the prothrombotic effect may result from chemotherapy and devices used to infuse drugs such as central venous catheters (CVCs)[7, 8]. Venous thromboembolism increases in cancer patients in the presence of distant metastases. The risk is found to be even higher in the presence of hereditary thrombophilic abnormalities [9]. In their study, Levitan et al. reported that the cancers with the highest incidence in terms of VTE were ovary, brain, pancreas, lymphoma and stomach, respectively, and the probability of detecting VTE in bladder and breast cancer was low [4].

In other studies, it was thought that VTE was most frequently associated with gynecological, pancreatic and stomach cancers in cancer patients [10-12]. While the perioperative risk of DVT varies between 19.6% and 38% in patients with gynecological cancer, it has been reported between 10-15% in benign gynecology. In addition to this increased risk, gynecological oncology patients are also at high risk of developing deep vein thrombosis (DVT) as they experience hypercoagulation, immobility and vascular injuries during their treatment [13]. In a study by Karaman et al. in which they reviewed 1543 gynecological oncology patients who were operated on, they found increasing age, presence of obesity, and having undergone high-risk surgery as important risk factors for the development of PTE [14]. In a prospective study evaluating the clinical DVT risk factors of 411 gynecological surgery patients; Previous history of VTE, increasing age, diagnosis of gynecological cancer, presence of ankle edema and varicose veins, long surgical time and radiotherapy history were determined as independent risk factors. In the same study as high-risk surgical procedures; pelvic exenteration, radical vulvectomy, and inguinal-femoral lymphadenectomy have been shown [15]. Due to the specific characteristics of different types of gynecological cancer, the incidence of VTE development is unequal. The chance of experiencing VTE in the ovarian cancer population is higher than other gynecological tumor types [16]. In cervical cancer, a direct correlation was found between the size of the tumor and the risk of VTE. There are studies showing that the frequency of VTE increases nine times in individuals with tumors larger than 5 cm [12]. In endometrial cancers, the incidence of VTE varies depending on the tumor histology. The 6-month incidence of VTE is increased in endometrioid type grade 3 histology tumors compared to low grade tumors [15].

With the demonstration of the negative effects of VTE on mortality in cancer patients, the importance of VTE prophylaxis in these patients has increased. One of the important points is that patients with gynecological malignancy have a high risk of bleeding, which may complicate the management of VTE prophylaxis due to the nature of the tumor, especially in advanced stages. A previous systematic review and meta-analysis of gynecological surgery patients showed that pharmacological prophylaxis reduced the risk of VTE by approximately 50%, while leading to a similarly increased risk of major postoperative bleeding [17]. Overall VTE rates were found to be significantly lower in patients who underwent minimally invasive surgery [18]. Therefore, the selection of the patient for whom prophylaxis will be initiated becomes important. Although a certain standard has been established in VTE prophylaxis in these patients with the guidelines published in recent years, there is still a need for new studies on treatment durations, treatment regimens and complications. In this review, we searched the guidelines in PubMed, SCOPUS, Web of Science, EMBASE, and CINHAL regarding VTE prevention in gynecological cancer patients which was conducted according to PRISMA criteria. We evaluated the recommendations reported by oncological and hematological societies regarding VTE prevention in gynecological cancer patients published from January 2000 through March 2023. We searched for the following keywords: “venous thromboembolism prevention”, “cancer”, and “guidelines”.

In this review, we aimed to emphasize the current literature regarding Venous Thromboembolism Prophylaxis in Gynecological Oncology and re-visit the prophylactic measures for prevention of VTE in these operations.

VTE prophylaxis in cancer patients should be

evaluated under three main groups: hospitalized patients, patients undergoing surgery, and outpatients.

Prevention of VTE in the Hospitalized Medical Patient with Cancer

VTE is the most common preventable cause of morbidity and mortality in hospitalized patients. Hospitalized gynecological cancer patients are at twice the risk of VTE as the general population [18]. National comprehensive cancer network (NCCN)[19], American society of clinical oncology (ASCO)[20], Associazione Italiana di Oncologia Medica (AIOM)[21], Sociedad Española de Oncología Médica (SEOM)[22], British society of hematology (BCSH)[23], Society for Haemostasis and Thrombosis (SISETS)[24] guidelines and 2015 Canadian consensus recommendations [25], American society of hematology (ASH)[26] published recommendations for patients hospitalized for any reason. They strongly recommended the use of VTE medical prophylaxis for all patients with cancer and stated that Direct acting oral anticoagulants (DOACs) should be continued for 3-6 months after discharge in patients at risk for VTE by performing Khorana scoring before each patient's discharge. The ESMO guideline accepted immobilization as a major risk factor and recommended prophylaxis only in immobilized cancer patients who were hospitalized for an acute reason [27]. Interestingly, ITAC/ISTH guidelines did not recommend VTE prophylaxis in hospitalized cancer patients, not specifying the reason for not recommending it [28].

Prevention of VTE in the Surgical Patient with Cancer

Patients undergoing cancer surgery have a higher risk of postoperative VTE development compared to patients undergoing non-cancer surgery, and postoperative VTEs in these patients are more mortal [29]. All the above-mentioned guidelines recommend prophylactic anticoagulation in surgical oncological settings. One of the important questions here is when to start prophylaxis. In a systematic review, thromboprophylaxis with low molecular weight heparin (LMWH) before and 12 hours after surgery was found to be less effective [30]. However, it has been shown that the possibility of postoperative bleeding increases with UFH, which is started two hours before the pre-operative period. Based on this information, the general recommendation was to administer thromboprophylaxis two preoperatively and 6 hours postoperatively [31]. The absolute essential for the correct management of the patient is to make the correct risk assessment. In the determination of prophylactic methods, the benefit-harm ratio, cost, effectiveness, applicability and compatibility must be taken into consideration. In addition to early mobilization, prophylactic methods in patients at risk can be examined under two main headings as mechanical methods and pharmacological methods. Mechanical methods; Compression stockings (ICC) and intermittent pneumatic compression (APC) applications aimed at reducing venous stasis and stimulating endogenous fibrinolysis.

Compression Stockings: Most thrombi form within 24 hours per/post-operative. These stockings are intended to reduce stasis in the lower extremity. In a review study about 5 randomized controlled trials; It is stated that the occurrence of DVT is reduced by 36% with Below-knee compression (BC)[32]. In a study conducted in the group of patients who underwent gynecological operation, groups using Cold compression therapy (CCT) and not receiving prophylaxis were prospectively compared and DVT was not detected in the group using CCT, while DVT was diagnosed in 4 cases in the group that did not receive prophylaxis. It has been shown that the risk of DVT is reduced with the use of CCTs [33]. Intermittent Pneumatic Compression: They are designed as a pump and separate socks for each patient. The aim is to activate the venous blood flow by pulsatile drainage of the calf veins. Intermittent pneumatic compression was investigated in two randomized controlled studies on gynecological surgery [34, 35]. IPC was started with surgery, and IPC was removed by mobilization on the first postoperative day. As a result of this study, no significant difference was found between the groups in terms of DVT. In the second study conducted by the same group, IPC was used for at least 5 days or until discharge from the hospital, and the frequency of DVT decreased from 37.6% to 12.7%. There are some studies showing that IPC is as effective as pharmacological treatment [16, 34]. Jian Ping Feng et al. reported in their systematic review and

meta-analysis that included seven randomized, controlled trials involving 1001 participants in 2017 that stated Intermittant pneumotic compression (IPC) effectively reduced the complications of VTE in gynecological surgery [35]. NCCN [19], ITA/ISTH [28], ASCO [20], AIOM [21], SEOM [22], ASH [26] guidelines adopt mechanical methods as monotherapy only if pharmacological methods are contraindicated.

Pharmacological Interventions

Pharmacological treatments aim to inhibit clot formation and different steps and pathways of coagulation. Current anticoagulant drugs are warfarin, standard unfractionated heparin (UFH), LMWH, factor Xa inhibitors and direct thrombin inhibitors [31]. Unfractionated Heparin: UFH is the most studied pharmacological treatment for thromboprophylaxis. Its molecular weight varies between 3000-30000 daltons and it acts on factor Xa and thrombin. UFH given 2 hours before the operation and at intervals of 8-12 hours postoperatively has been shown to prevent DVT [36]. The biggest concern in administering UFH two hours before surgery is the risk of bleeding. There is no evidence that it increases peroperative blood loss, but bleeding and hematoma from the postoperative wound site is a known complication. Heparin-induced thrombocytopenia may develop in approximately 6% of patients using UFH. For this reason, preoperative platelet counts of the cases should be performed and it should be known that this side effect can occur within 100 days [9]. Low molecular weight Heparin: These are molecules obtained from UFH fragments by chemical and enzymatic depolarization. Their molecular weight is 4000-6500 daltons. In many studies conducted in the field of oncologic surgery, it has been shown that LMWH has equal efficacy to UFH in perioperative prophylaxis [37-39].

In a retrospective cohort study conducted with gynecological oncology patients in 2012, it was shown that peroperative blood loss and transfusion need did not increase with LMWH, and the length of hospital stay and operation time did not change in patients who underwent major gynecological surgery [40]. How long the thromboprophylaxis should continue is an unanswered question. Epidemiological data reveal that VTE events mostly occur after discharge. It has been found that up to 40% of VTE in patients undergoing cancer surgery occurs after 21 days postoperatively [41]. In another study, VTE occurred after the 7th postoperative day in 76% of cases after gyneco-oncological surgery [42]. NCCN recommended prophylaxis during the hospitalization in patients who will undergo surgery without risk factors, but did not specify a specific period [19]. The American College of Chest Physicians (ACCP) and the American College of Obstetrics and Gynecology (ACOG) have classified minor surgical procedures that will take less than 30 minutes as low risk and recommended early and frequent mobilization for prophylaxis in the population undergoing gynecological surgery. However, he defined having cancer surgery over the age of 60 and having a history of VTE as high risk and recommended the use of APK or CCT together with LMWH or UFH for prophylaxis. For these patients, they found LMWH to be used for 1 month after discharge [42, 43]. ASCO, on the other hand, defined laparoscopic or laparotomic cancer operations that will take longer than 30 minutes as high risk and recommended pharmacological prophylaxis for 7-10 days postoperatively and even said that prolonged thromboprophylaxis can be applied in the presence of additional risk factors [28]. In a study evaluating the cost-effectiveness of thromboprophylaxis methods used in patients who underwent laparotomy for ovarian cancer, it was reported that prolonged use of UFH (for four weeks) was the most effective and inexpensive method [44]. All the guidelines analyzed, a recent randomized controlled trial demonstrated the safety and efficacy of the use of DOACs in postoperative gynecologic cancer patients, but clinical practice still routinely supports only the use of LMWH or fondaparinux for postoperative VTE prophylaxis in oncologic patients [45, 46].

Prevention of VTE in Ambulatory Cancer Patients Undergoing Chemotherapy

Chemotherapeutic agents increase the risk of thromboembolism by causing endothelial damage, decreased protein C and S levels, and decreased antithrombin-III level [47]. Blom et al., in their large retrospective screening of 66 thousand patients, they found a 2.2-fold increase in the frequency of thromboembolism in cancer patients who received

chemotherapy compared to cancer patients who did not receive chemotherapy [9]. Another study showed that 12.6% of patients experienced VTE 12 months after starting chemotherapy [10]. Among antineoplastic treatments, especially platinum-based agents play a role in increasing the risk of cancer-related thromboembolism [48, 49]. It has been shown that platinum group chemotherapeutics induce endothelial dysfunction by increasing proinflammatory changes and cell adhesion molecules [50-52]. Therefore, gynecological cancer patients who are more likely to receive these treatments have a higher risk of VTE complications [53]. Thromboprophylaxis is recommended for selected groups in outpatient cancer patients. Cancer patients who have undergone abdominal or pelvic surgery, and multiple myeloma patients who receive treatments with high thrombogenic effect such as thalidomide-lenalidomide are in this group. Although a decrease in the frequency of thromboembolism has been demonstrated with prophylactic LMWH treatment in patients receiving chemotherapy, the level of evidence for this issue is recommended as 2A in high-risk patients [19].

CONCLUSION

All of the above guidelines recommended medical prophylaxis in outpatients on systemic therapy only if considered at high risk based on Khorana or other VTE risk scores. The use of DOACs in a subset of patients has been shown to be safe, and all guidelines reviewed recommended the safe use of DOACs over LMWH for prophylaxis in outpatients considered at high risk of VTE. Also, the guidelines recommended the use of thromboprophylactic strategies in patients undergoing surgery and chemotehrapy. VTE prophylaxis has a significant effect on mortality in cancer patients. Despite convincing data and increased awareness by clinicians, there is still significant heterogeneity in clinical practice for prophylactic protocols of VTE in oncological patients. More randomized studies are needed on this subject.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

This is a review of the literature and doesn't need an ethical approval number.

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