



Diagnostic heterogeneity in orthopaedic oncology makes standardized recommendations regarding anticoagulation difficult

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Introduction

Patients with cancer have a high incidence of venous thromboembolism (VTE). It is estimated that fifteen percent of patients with carcinoma develop VTE (1). Sarcoma patients have a similar incidence of VTE (2). Patients undergoing major orthopedic procedures are also at increased risk for developing VTE. Asymptomatic deep venous thrombosis (DVT) rates are estimated to be between 40–60% and fatal pulmonary emboli between 0.1–7.5% in patients undergoing total hip arthroplasty, total knee arthroplasty, and fixation of a hip fracture without chemoprophylaxis (3,4). Guidelines for VTE prophylaxis after high-risk orthopaedic procedures were developed by the American Academy of Orthopaedic Surgeons and the American College of Chest Physicians for patients undergoing total hip arthroplasty, total knee arthroplasty, and hip fracture surgery, but none that specifically take into account the unique risk of patients with cancer. There is a paucity of literature evaluating VTE prophylaxis in bone and soft tissue sarcoma patients. VTE in sarcoma patients undergoing orthopaedic surgery has been studied to identify incidence and risk factors for VTE in order to balance the benefits of VTE prevention against the surgical complications from anticoagulation including bleeding, post-operative anemia, hematoma formation, and wound complications to determine an appropriate VTE prophylaxis treatment algorithm in this patient population.

General risk factors for VTE in cancer patients

As described by Virchow's triad, there are three conditions

that contribute to the formation of VTE: venous stasis, endothelial damage, and hypercoagulability. There are tumor-related, host-related, and treatment-related risk factors that contribute to higher VTE rates in cancer patients. Tumors directly activate the clotting system by secreting procoagulants such as Tissue Factor and Cancer Procoagulant to trigger coagulation and thrombus formation (5,6). Cancer patients also have increased inflammatory cytokine production such as tumor necrosis factor and different interleukins, which contribute to thrombus formation (6). The mass effect of tumors on nearby vasculature can also increase venous stasis elevating the risk of VTE (1). Patients with cancer have decreased activity levels, increased time in bed, increasing venous stasis (7). Lastly, certain chemotherapy agents directly damage endothelium, decrease natural anticoagulants, and increase platelet activation (6,8,9).

Risk factors for VTE in sarcoma patients

There are patient-related factors that contribute to the development of VTE in patients with a soft tissue or bone sarcoma. Kim *et al.* evaluated patients who underwent surgical management for lower limb malignancies before and after the introduction of VTE chemoprophylaxis and found age over 60 years, higher American Society of Anesthesiologists grade, and metastatic disease were independent risk factors for developing VTE (10). Shantakumar *et al.* performed a retrospective cohort analysis of patients older than 65 years old with and without a soft tissue sarcomas and the strongest

predictor of VTE was a recent history of VTE (11). In a study looking at patients with a primary bone sarcoma, Kaiser *et al.* found an increased pre-operative white blood cell count and the development of post-operative wound complications were independent risk factors for VTE. It is likely that an increased white blood cell count is an indicator of hemoconcentration and a hypercoagulable state. Wound complications may increase the patient's inflammatory state as well as time in bed or immobility, contributing to VTE formation (12).

Tumor-specific factors also increase the risk of VTE. When looking at tumor location, studies of lower extremity sarcomas concluded that tumors located in the hip, thigh, and pelvis are risk factors for VTE (13,14). However, other studies did not find tumor location to significantly increase VTE risk (12,15). Tumor size is a significant risk factor when reviewing patients who have undergone surgery for primary bone or soft tissue sarcomas (16). Tumor type may also play a role as the diagnosis of sarcoma not otherwise specified (NOS) had the highest rates of VTE with leiomyosarcoma and liposarcoma diagnoses having the highest association of having a recent history of VTE (11). The variability in correlation of tumor-related factors with VTE in the literature is likely related to the heterogeneity of patient diagnoses and VTE prophylaxis protocols used as well as many of these studies being underpowered to appropriately evaluate tumor-specific risk factors.

In some studies, chemotherapy is identified as a significant risk factor for VTE, whereas other studies did not find a significant difference. When Damron *et al.* reviewed primary bone and soft tissue sarcoma patients undergoing surgical intervention, 8.5% of patients who underwent chemotherapy developed symptomatic VTE, while only 1% of patients that did not receive chemotherapy developed VTE. Of the seven patients with VTE, 6 (86%) were patients also treated with chemotherapy (13). In another study, 46% of patients who developed VTE also underwent chemotherapy (9). However, when evaluating DVT rates in patients who underwent resection of benign and malignant tumors of the lower extremity, there were less patients that developed DVT who were treated with chemotherapy (15). Of 32 possible risk factors for VTE evaluated in primary bone sarcoma patients, Kaiser *et al.* did not find adjuvant chemotherapy to be a relevant risk factor (12).

Comparing VTE Prophylaxis

Studies comparing mechanical prophylaxis alone to mechanical and chemoprophylaxis in sarcoma patients

show increased rates of VTE. In a prospective review of patients who underwent tumor resection with or without reconstruction, 22% of their patients treated with intermittent sequential compression devices and compression stockings developed VTE (15). Damron *et al.* found higher rates of symptomatic VTE at 9% in bone and soft tissue patients who did not receive any chemoprophylaxis, while patients receiving different pharmacologic anticoagulants had a symptomatic VTE rate of 3% (13). However, these results only trended towards significance, illustrating the issue with power that plague many of these comparisons. Kim *et al.* similarly found slightly lower rates of VTE without statistical significance between patients with lower limb malignancies who received mechanical and chemoprophylaxis versus those who received mechanical prophylaxis alone, 12% *vs.* 13%, respectively (10).

Chemoprophylaxis decreases the rate of VTE in sarcoma patients and patients with metastatic bone disease, but the optimal regimen remains elusive. Multiple chemoprophylactic agents are currently used in major orthopedic surgeries and total joint arthroplasty procedures, including aspirin, low molecular weight heparin, warfarin, and factor Xa inhibitors (14). These agents are under investigation in orthopaedic oncology patients as well. The use of low molecular weight heparin decreased the rate of VTE from 18% to 4% in patients who underwent total hip arthroplasty for reconstruction after tumor resection or pathologic fracture (17). There was no significant increase in wound complications; however, the study was underpowered to assess specific complications. The use of low molecular weight heparin after resection and reconstruction of lower extremity tumors has also decreased the rate of symptomatic VTE to 1.1% (9).

Out of concern for bleeding and wound-related complications, aspirin has been studied to determine if it has similar efficacy against VTE with a lower complication profile. Patel *et al.* performed a retrospective review to compare symptomatic VTE rates in patients who underwent surgery for pelvis and lower extremity sarcomas and placed either on aspirin or low molecular weight heparin. This appropriately powered study found no statistically significant difference in VTE rates between aspirin (8%) and low molecular weight heparin (9%). However, the aspirin group had a slightly higher complication rate (7%) when compared to low molecular weight heparin (4%). There was selection bias as patients who received low molecular weight heparin were more likely to be older, have hip/pelvis sarcomas, or undergo arthroplasty, all of which are risk factors for VTE (18).

Mendez *et al.* retrospectively reviewed 130 patients for symptomatic VTE after being placed on either on aspirin or non-aspirin VTE prophylaxis (i.e., sequential compression device alone, unfractionated heparin, low molecular weight heparin, warfarin) and treated surgically for primary soft tissue sarcomas, bone sarcomas, or metastatic carcinomas. The aspirin group was found to have a lower VTE rate (3%) when compared to the non-aspirin group (10%). However, these results were not found to be statistically significant. Both groups had similar VTE events, but there were more patients in the aspirin group (3/103) than the non-aspirin group (4/39), which can skew results. Aspirin was used in more patients who had soft tissue sarcomas, sarcomas located in the thigh, and in patients likely more mobile than the non-aspirin group, which could explain why the aspirin group had a lower VTE rate. There was also selection bias as patients in the non-aspirin group included those who had a history of VTE when history of VTE was found to be a significant risk factor for VTE in this study. The non-aspirin group also included patients in whom there was concern for early return to the operating room, requiring a prophylactic agent more easily reversible. However, this study found a statistically significant increased risk for VTE with increasing estimated blood loss (7), and patients undergoing multiple surgeries likely have higher cumulative blood loss. It may be unfair to include patients who had mechanical prophylaxis alone in the non-aspirin group as previous studies concluded mechanical prophylaxis to be inferior to mechanical and chemoprophylaxis (10,13). Patients took aspirin 325 mg twice daily following surgery, but length of prophylaxis was not reported for either group. Similarly, not all studies disclosed the dosing and/or length of VTE prophylaxis, making it difficult to compare results (14).

Although the aspirin group had a lower VTE rate, this group had higher complication rates which included need for blood transfusion (15% *vs.* 8%), total units of packed red blood cells transfused (2.5 *vs.* 2.3 units), major wound complications requiring surgery (8 *vs.* 1 patient), and post-operative infection (7% *vs.* 2%) (14). Again, the complication rates were not statistically significant but the study was not powered to detect these differences. The results of Menedz *et al.* are consistent with Patel *et al.*, and Menedz *et al.* has similar issues with selection bias in each treatment group (18).

Conclusions

Based on the current literature, it is difficult to make a

conclusion on the optimal VTE prophylaxis regimen given the heterogeneity of patients studied as well as the prophylactic regimens that patients were placed on. Some studies looked specifically at primary bone or soft tissue sarcomas while others included carcinoma and hematologic metastatic disease. Majority of studies are retrospective in nature, allowing for significant selection bias for different VTE prophylaxis regimens. The issue of reviewing smaller patient populations is reflected well in the Mendez *et al.* article and other articles presented. Although there were differences in rates of VTE, complications, and risk factors with various VTE prophylaxis regimens, often times significance was not reached due to lack of patients and heterogeneity of patients studied. All of these factors make it difficult to find the appropriate VTE prophylaxis regimen for each patient.

When discussing anticoagulation with patients, it is also important to evaluate complications such as hematoma formation, post-operative anemia, excessive bleeding, and wound complications as large sarcoma resections and radiation therapy can place these patients at increased risk. However, not all studies evaluate these complications and majority are also underpowered to determine the significance of these complications. There are also no specific and systematic definitions for relevant complications. In order to fully gain better insight into VTE prophylaxis in soft tissue and bone sarcoma patients, a multicenter, prospective, registry needs to be established to evaluate treatment efficacy and complication profile in this unique patient population.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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