Original Article

Prevalence of Symptomatic Venous Thromboembolism in Patients with Malignant Bone and Soft Tissue Tumors Undergo Surgery without Chemoprophylaxis

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Background: The prevalence and risk factors of venous thromboembolism (VTE) in malignant bone and soft tissue tumor patients that undergo surgery is reported in many studies. However, there is lack of studies on the patients without chemoprophylaxis.

Objective: To evaluate the prevalence and risk factors for VTE after surgery in malignant bone and soft tissue tumor patients without chemoprophylaxis

Materials and Methods: A retrospective medical chart review identified 260 cases of malignant bone and soft tissue tumor operated between 2008 and 2017. Official diagnostic reports were reviewed from the Picture Archiving and Communication System (PACs). The incidence of VTE and its risk factors were assessed using Chi-square test, t-test, and binary logistic regression.

Results: The overall prevalence of symptomatic VTE was 0.8% (2/260 patients), all of which had PE. No fatal VTE was detected. Asymptomatic pulmonary embolism (PE) was identified in two patients (0.8%) Mean follow up interval of the available data was 9.5 (3 to 36) months. No significant risk factor was found.

Conclusion: The authors found that patients with malignant bone and soft tissue tumors that underwent surgery without chemoprophylaxis in the authors' center had lower prevalence of VTE when compared to most previous studies whose patient received chemoprophylaxis.

Keywords: Venous thromboembolism, Sarcoma, Cancer, Deep vein thrombosis, Pulmonary embolism, Thromboprophylaxis, Chemoprophylaxis

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Venous thromboembolism (VTE), composing of deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common serious complication of cancer patients[1] and the fatality rate is 2.2-fold when compared with those in the tumor-free population[2]. Bone and soft tissue cancer patients that underwent major orthopedic surgery are reported to have particular risk for VTE because of the malignancy itself and the major orthopedic surgery are known as a strong risk factor for develop VTE[3].

However, there is still diversity of the prevalence of VTE, and identifiable risk factors were reported in the patients that underwent surgery for orthopedic malignancy. Most of the reports did not provide baseline data about the prevalence and risk factors in these patients if chemoprophylaxis was not used[4-10].

There is one report from the American Society of Anesthesiologists (ASA) that compare between groups with and without chemoprophylaxis for patients with orthopedic oncology that underwent surgery, but the number of patients in the group without chemoprophylaxis is limited, and there is no statistically significant difference between the groups[11].

For patient with malignancy that underwent surgery, chemoprophylaxis was strongly recommended by the American Society of Oncology (ASCO) Clinical Practice Guideline Update[12], but their evidence was based on abdominal and pelvis surgery, which is not specific to orthopedic oncology patients.

To the best of the authors knowledge, there is still no report about the prevalence in these patients and standard guidance using chemoprophylaxis for this group of patients in Thailand. In the present study, the authors 'institute also used just mechanical prophylaxis to prevent VTE in these patients due

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to concern about the potential complication of chemoprophylaxis. However, baseline data about prevalence of VTE is needed to guide in treatment of this group of patients.

The present study aimed to identify the prevalence and the risk factors of symptomatic VTE in malignant musculoskeletal patients that underwent surgery without chemoprophylaxis in the authors' institute.

Objective

To evaluate the prevalence and risk factors for VTE after surgery in malignant bone and soft tissue tumor patients without chemoprophylaxis.

Materials and Methods

A retrospective study based on medical records and images was designed. Two hundred sixty consecutive patients treated surgically in the orthopedic oncology unit in the authors' institution between January 2008 and December 2017 were included. Patients were excluded if the presence of any of the following was identified, preexisting VTE, recent anticoagulant therapy, recent major surgery, and follow up less than three months post operation.

To prevent VTE, only early range of motion exercise and mobilization were used. No pharmacological prophylaxis was applied in any cases.

Symptomatic VTE was defined as clinically suspected patient for DVT or PE from medical records confirmed by official reports by diagnostic radiologists on Picture Archiving and Communication System (PACs) using doppler ultrasound for DVT and computerized tomographic angiography (CTA) or v/q scan or autopsy for PE. Unfortunately, the authors had no autopsy report on any death patients, thereby, underestimating the true rate of fatal VTE. Asymptomatic VTE was incidentally detected after pulmonary CTA scheduled before surgery to work up for pulmonary metastasis from the underlying malignancy in each patient. The authors defined postoperative VTE if it occurred within six months after surgery to include the effect of adjuvant chemotherapy, which is the potential risk factor. There is a report that VTE can occur at nearly one year after orthopedic surgery[13].

Univariate analysis was performed for risk factors of VTE. The chi-square test in the case of proportions and by the t-test in the case of continuous variables was used. A p-value of less than 0.05 was considered statistically significant. The present study was approved by the Institutional Review Board at the authors' institution (Reference No. HE601357).

Table 1. Diagnosis

Diagnosis	n (%)
Osteosarcoma	72 (27.7)
Metastatic adenocarcinoma	33 (12.7)
Liposarcoma	23 (8.8)
Pleomorphic sarcoma	19 (7.3)
Synovial sarcoma	19 (7.3)
Multiple myeloma	12 (4.6)
Lymphoma	9 (3.5)
Leiomyosarcoma	9 (3.5)
Chordoma	8 (3.1)
Chondrosarcoma	8 (3.1)
MPNST	6 (2.3)
Ewing sarcoma	6 (2.3)
Fibrosarcoma	5 (1.9)
Rhabdomyosarcoma	5 (1.9)
Spindle cell sarcoma	5 (1.9)
Unspecific grade sarcoma	3 (1.2)
High grade sarcoma	2 (0.8)
Malignant melanoma	2 (0.8)
Metastatic thyroid cancer	2 (0.8)
Adamantinoma	2 (0.8)
Squamous cell carcinoma	2 (0.8)
Desmoplastic small round cell tumor	1 (0.4)
Low grade sarcoma	1 (0.4)
Intermediate grade sarcoma	1 (0.4)
Clear cell sarcoma	1 (0.4)
Epithelioid cell sarcoma	1 (0.4)
Metastatic leiomyosarcoma	1 (0.4)
Metastatic clear cell carcinoma	1 (0.4)
Metastatic melanoma	1 (0.4)

MPNST=malignant peripheral nerve sheath tumor

Results

Two hundred sixty patients underwent surgery and included 120 females (46.2%) and 140 males (53.8%). Patients had a mean age of 40.6 (range 2 to 84) years at the time of operation. Osteosarcoma, metastatic adenocarcinoma, and liposarcoma were the most common. Other diagnostic cell types are shown in Table 1. Mean follow up interval of the available data was 9.5 (3 to 36) months.

The overall prevalence of symptomatic VTE was 0.8% (2/260 patients), which all cases had PE. No fatal VTE was detected. Asymptomatic PE was identified in two patients (0.8%), which were diagnosed incidentally by pulmonary CTA as mentioned above. The characteristics of these patients

Table 2. Profile of the patients with VTE

Case	Diagnosis	Site	Sex, age (year)	Type of surgery	Event	Time of VTE	Symptom
Symptomatic VTE							
1	Metastatic clear cell carcinoma	Axial	M, 60	Total vertebrectomy and posterior instrumentation	PE	3 days	Dyspnea
2	Multiple myeloma	Axial	F, 63	Incisional biopsy	PE	8 weeks	Dyspnea
Asymptomatic VTE							
3	Undifferentiated spindle cell sarcoma	Axial	M, 60	Decompressive laminectomy and posterior instrumentation	PE	17 weeks	
4	Liposarcoma	LE	M, 31	Wide excision	PE	2 days	

VTE=venous thromboembolism; LE=lower extremities; Axial=spines and pelvis; M=male; F=female; PE=pulmonary embolism

Table 3. Risk factors for VTE

Variables	VTE (–); n (%)	VTE (+); n (%)	Univariate analysis; p-value
Sex			
Male	137 (52.7)	3 (1.2)	0.392
Female	119 (45.8)	1 (0.4)	
Age (year); mean±SD	40.5±20.9	46.5±17.37	0.073
Location			
Upper extremity	51 (19.6)	0 (0.0)	0.181
Lower extremity	162 (62.3)	2 (0.8)	
Axial skeleton	43 (1.7)	2 (0.8)	
Metastatic bone cancer			
Yes	41 (15.8)	1 (0.4)	0.628
No	215 (82.7)	3 (0.8)	
Pathological fracture			
Yes	26 (10.0)	0 (0.0)	0.502
No	230 (88.5)	4 (1.5)	
Size (mm); mean±SD	115±119	N/A	N/A
Postoperative chemotherapy			
Yes	102 (39.2)	0 (0.0)	0.105
No	154 (59.2)	4 (1.5)	
Plastic surgery			
Yes	44 (16.9)	0 (0.0)	0.363
No	212 (81.5)	4 (1.5)	
Intramedullary nailing			
Yes	18 (6.9)	0 (0.0)	0.583
No	238 (91.5)	4 (1.5)	

VTE=venous thromboembolism; N/A=not available, missing data of size of tumor in VTE group; SD=standard deviation

are listed in Table 2.

All symptomatic PE occurred in admission period and most of the VTE (3/4, 75%) were identified before three months postoperative period.

Among the patients with symptomatic PE, one had secondary bone sarcomas and one had primary bone sarcoma. The metastatic bone sarcoma was adenocarcinoma and the primary bone sarcomas was multiple myeloma. All the patients with asymptomatic VTE were soft tissue sarcoma.

Age, gender, cell type, location of tumor, pathological fracture, metastatic bone tumor, size of tumor, preoperative chemotherapy, plastic surgery, and intramedullary nailing were not significant risk factors (Table 3).

Discussion

The authors determined the rate of postoperative VTE in patients without chemoprophylaxis in the present study center. Of the 260 patients, two had PE (0.8%). The authors identified many patients with tumors located in axial skeletons among the patients with VTE (3/4 overall VTE patients). This is in contrast with those reported by Damron et al[7] that most tumor location in patients with VTE was lower extremities. Asymptomatic VTE was identified in half of overall VTE in the present study indicating that a large proportion of VTE can occur without detectable symptoms. This is similar to the study of Morii et al[5] that used D-dimer to screen musculoskeletal tumor patient during chemotherapy session or after underwent surgery and detected an overall of VTE 2.7%, of which six cases from eight cases (75%) were asymptomatic. Despite that more VTE cases can be detected by using D-dimer screening, Morii et al[5] stated that further detailed studies are needed for more comprehensive understanding of VTE before using this screening method as a routine practice.

The rate of overall VTE in patient with axial skeletal surgery was 6.6% (3/45), similar result to the retrospective study in patient with spinal metastasis that underwent surgery[10], but most of the patients in the present study had primary bone malignancy. Further study in patient with malignant spinal tumor

is needed to identified prevalence and risk factors.

The authors found two patients with asymptomatic PE (0.8%), which is not a small number. All of those were accidentally confirmed PE by pulmonary CTA scheduled before surgery to work up for pulmonary metastasis. This emphasized that physician may be underestimating the true prevalence of VTE, and the prospective study using ultrasound doppler and CTA screening after the surgery to detect any DVT or PE may answer the question more accurately. However, concern is rising about the timing for screening and the cost of the investigations

In the present study, there was no significant identifiable risk factor due to the limited number of patients. This is emphasizing the need for further study having a more cases if the primary purpose were to identify the risk factors of VTE in this group of the patients.

VTE occurred at a mean of 6.42 (0.4 to 17) week after surgery. Similar results were reported in previous studies, which most of the events occurred within three months of the operation[4,6,7,9].

The present study results about timing disagree with those of Mitchell et al[4] in showing that more than half of patients with VTE occurred before definite surgery. However, the present series showed that 75% of VTE occurred after the definite surgery, while Mitchell et al[4] reported 53% of VTE occurred before definite surgery.

The overall rate of VTE (1.5%) was relatively lower than the previous report with chemoprophylaxis[4-9] despite using only early mobilization to prevent VTE in the present study institute. Additionally, Kim et al[8] reported that there was no statistical difference between patients given chemoprophylaxis and those without chemoprophylaxis in the occurrence of DVT after lower limb surgeries in orthopedic malignancy patients. However, the lower result may be underestimated due to lack of routine screening investigation as mentioned above. However, the present study finding is enough to emphasize that using chemoprophylaxis is unlikely to have the benefit in the authors' center due to lower rate of VTE in the present study that weight more than the risk of bleeding complication of orthopedic procedures in musculoskeletal tumor patients.

The present study had limitations. First, the authors may underestimate the prevalence of VTE because of retrospective design and lack of routine screening by clinical and radiological to detect postoperative VTE. In addition, the association between risk factors and VTE show no significant factor due to the small number of patients and the very low prevalence of DVT. At the beginning, the authors planned to develop all significant risk factors from univariate analysis to analyze with multivariable logistic regression model but there was no significant risk factor from the analysis, so the authors did not proceed to analyze with multivariable logistic regression.

The authors believe that a larger prospective study with routine screening would be valuable to identify the prevalence and risk factors of VTE in this group of patients.

Conclusion

The authors retrospectively described the prevalence and profile of the patients with VTE in consecutive patients with a musculoskeletal tumor treated surgically without chemoprophylaxis in the authors' institution. The incidence in this group of patients was relatively lower than most recent studies in groups of patients without chemoprophylaxis.

What is already known on this topic?

Prevalence of VTE in malignant bone and soft tissue tumor patients that underwent surgery was reported in countries that use chemoprophylaxis in this group of the patients.

To the best of the authors' knowledge, there is no known standard guideline that recommended to use chemoprophylaxis in this group of patients in Thailand and the prevalence is still unknown.

What this study adds?

The prevalence of VTE in malignant bone and soft tissue tumor patients that underwent surgery without chemoprophylaxis in Thailand was low. There is a high prevalence of VTE in spinal oncology surgery.

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Conflicts of interest

The authors declare no conflict of interest.

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