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Incidence, Diagnosis, and Risk Factors of Venous Thromboembolism after Surgery for Malignant Bone and Soft Tissue Tumor of Lower Extremity

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Abstract

Objective: This study aimed to prospectively evaluate the incidence, characteristics, and risk factors of venous thromboembolism (VTE) development, and the diagnostic value of blood coagulation markers in patients receiving surgery for malignant bone and soft tissue tumor of lower extremity.

Methods: A prospective study of 20 patients who were examined using ultrasonography. Serum soluble fibrin monomer complex (SFMC) and D-dimer were measured in the perioperative period. VTE incidence, VTE development time, change in blood coagulation markers, and effect of each risk factor were evaluated.

Results:VTE was found in 8 of 20 patients. Four of these 8 patients had the finding of pulmonary embolism (PE) without symptom. Onset time of VTE was from day 1 to 7 after surgery. The cutoff value of SFMC was <3 μg/mL at any measurement point and D-dimer was approximately 2 μg/mL in receiver operating characteristic analysis. Body mass index was the only significant risk factor.

Conclusion: VTE showed high incidence and often occurred in the early period in only physical prophylaxis after surgery. SFMC or D-dimer was not always useful to detect VTE development. With regard to rehabilitation intervention, risk management is required until 1 week after surgery.

Keywords: Venous thromboembolism; Sarcoma; Lower extremity; Rehabilitation

Introduction

The occurrence of venous thromboembolism (VTE) after total hip or knee arthroplasty is an important problem as complications during post-operative rehabilitation, but the risk was minimized by recent induction of the anticoagulant therapy that was safe and effective. On the other hand, for malignant bone and soft tissue tumor surgery, it is expected that the incidence of postoperative VTE will be high because of invasiveness with musculoskeletal resection and the added risk factor of malignant disease [1,2]. However, established guidelines about diagnostic procedures and prophylaxis for VTE in the perioperative period are not available. This is because there are few studies that examined the association with incidence, risk factors according to the site of blood coagulation markers, method of image techniques, and timing with respect to screening for diagnosing postoperative VTE development in malignant bone and soft tissue tumors. In rehabilitation after surgery of malignant bone and soft tissue tumor in the lower extremity, it is important that the incidence of VTE, time of onset, and screening method in risk management to perform rehabilitation safely are known. The purpose of this study was to evaluate the incidence and characteristics of VTE development, risk factors of VTE onset, and diagnostic value of blood coagulation markers in patients who received surgery and postoperative physical prophylaxis for malignant bone and soft tissue tumor of the lower extremity at our institution.

Materials and Methods

Patient population

This was a prospective study that was performed in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of our institute, and all patients provided written informed consent before being enrolled in this study.

We reviewed 20 patients who had received wide resection of malignant bone and soft tissue tumor arising from the lower leg at our institution between January 2010 and February 2013. There were 14 men and 6 women, with a mean age at time of surgery of 69 years (range, 31 to 85 years). The tumors were located in the thigh (n=15) and calf (n=5). Metastatic bone tumor was found in 1 case and primary soft tissue sarcomas were found in 19 cases, and the localizations of soft tissue sarcoma were subcutaneous (n=2), intermuscular (n=8), and intramuscular (n=9). All tumors localized in subcutaneous tissue were resected with muscles and reconstructed with muscular flap and skin graft. The histologic diagnosis of the resected tumor was liposarcoma in 7 patients, undifferentiated pleomorphic sarcoma in 5 patients, myxofibrosarcoma in 2 patients,

synovial sarcoma in 2 patients, metastatic bone tumor in 1 patient, and other soft tissue sarcoma in 3 patients.

Screening methods

We planned frequent examination for 7 days after surgery as we predicted that VTE was more likely to occur at the early period in reference to previous reports of joint replacement and spine surgery [3-6]. All patients were examined with duplex ultrasonography assessments of both lower extremities before the operation, and 1, 3, 7, and 14 days after surgery. The soluble fibrin monomer complex (SFMC) (Nanopia SF, Sekisui Medical Co. , LTD.) was measured before the surgery, and at 1, 3, 7, and 14 days after the surgery and D-dimer (Nanopia D-dimer, Sekisui Medical Co., LTD.) was measured before the surgery, and at 1, 3, 7, 14 and 21 days after the surgery. All patients received mechanical prophylaxis, including compression stocking of the unaffected side, compression bandage of the affected side, and intermittent pneumatic compression devices after surgery. Rehabilitation was initiated 2 days after surgery in all patients. If VTE was detected with echography, patients were examined with additional contrasted computed tomography to confirm the diagnosis of VTE, and patients diagnosed with VTE were treated with heparin sodium and/or warfarin potassium.

Statistical analysis

The Cox proportional-hazards model was used to examine the association between VTE and possible risk factors such as age, gender, histological grade, stage, body mass index (BMI), operation time, intraoperative blood loss, suction drain insertion period, ambulation time, and diseased limb load. Significance was defined as $p<0.05$. We evaluated the utility of SFMC and the D-dimer in the VTE diagnosis using the Cox proportional-hazards model that assumed the VTE onset was a response variable. At first, we examined whether the peak value of SFMC and D-dimer of each case to each testing point was associated with VTE onset. Next, we analysed the association of each measurement time and VTE development after defining the cut-off value of SFMC as 7 g/mL and that of D-dimer as 10 μg/mL. The cutoff value of SFMC and D-dimer varies in several reports because of the differences in the surgery and measurement test kit [3-6]. In this study, we set the cut-off value of SFMC to 7 μg/mL for a value greater than the upper limit of the normal level (6.9 μg/mL) at our institution. We set it to 10 μg/mL above the cutoff value of D-dimer and attempted the analysis using this value because the mean D-dimer value in patients with or without VTE was approximately 10 μg/mL in the past reports. After that, we calculated the cutoff values of SFMC and D-dimer for VTE diagnosis using receiver operating characteristic (ROC) analysis. All statistical analyses were performed using the statistical package R, version 3.2.0 (available at http://www.r-project.org).

Results

VTE was found in no patient preoperatively. Upon the ultrasonographical evaluation after surgery, VTE was found in 8 of 20 patients (40%). Four of 8 patients with VTE had the finding of pulmonary embolism (PE) in enhanced computed tomography (CT), but all patients had no symptom. Onset time of VTE was 1 day in 4 patients, 3 days in 3 patients, and 7 days in 1 patient after surgery. VTE developed in 5 patients in the diseased side and in 3 patients in the bilateral side (Table 1).

No.	Age	Sex	Localization of VTE	Onset(days)	PE
1	78	M	lower leg (affected side)	1	+
2	69	M	lower leg (both sides)	1	-
3	51	F	lower leg (both sides)	1	+
4	84	M	lower leg (affected side)	7	-
5	64	M	lower leg (affected side)	3	-
6	85	F	lower leg (affected side)	3	+
7	83	M	lower leg (both sides)	1	-
8	58	F	lower leg (both sides)	3	+

VTE: Venous Thromboembolism; **PE:** Pulmonary Embolism

Table 1: Characteristics of the patients with VTE.

All patients suspected of VTE in ultrasonography were found to have VTE upon enhanced CT from the chest to the lower extremities. The clinical data of histological grade (high grade), stage (2 and 3), BMI, operation time, intraoperative blood loss, suction drain insertion period, ambulation time, and diseased limb load in the 20 patients are summarized in Table 2.

No.	Grade	Stage	BMI	Operative time (min)	Bleeding (ml)	Drain withdrawal (day)	Ambulation time (day)	Diseased limb load (day)	VTE
1	high	IIA	21.9	74	30	1	1	3	+
2	high	IV	30.4	325	380	8	1	14	+
3	low	IB	18.5	54	10	1	1	1	-
4	high	III	25.4	380	280	13	1	1	+
5	high	IIA	23.2	205	50	2	2	14	-
6	low	IB	21.6	295	180	7	7	7	+
7	high	III	24.6	406	650	14	1	1	-
8	low	IB	22.7	163	250	14	1	1	-

9	high	III	23.7	343	1000	3	3	3	-
10	high	III	27.4	270	600	12	2	10	+
11	high	III	23.7	166	150	6	1	1	-
12	low	IB	25.3	187	30	6	1	3	-
13	low	IB	22.8	108	50	6	1	3	-
14	high	III	22.1	242	270	5	1	4	-
15	high	III	21.7	149	100	6	1	2	-
16	high	III	22	142	60	3	1	7	+
17	high	III	28.8	226	5010	1	7	7	+
18	high	III	28.6	144	120	14	1	2	+
19	high	III	18	371	700	7	2	14	-
20	high	III	25	227	250	13	1	3	-
VTE: Venous Thromboembolism									

Table 2: Clinical data of the patients.

The days required for ambulation were for all patients less than 3 days except one, which required 7 days (an average of 1.55 days). However, seven patients (35%) required more than 7 days for the diseased limb load time and VTE occurred in five of them. Analysis of the association between each risk factor and VTE development in a Cox proportional-hazards model showed that BMI was the only significant risk factor of VTE development (Table 3).

Candidates	Hazard Ratio (95%CI)	p-value
Age (+1 year)	1.02 (0.96-1.08)	0.562
Gender (man)	0.68 (0.16-2.84)	0.593
Grade (high)	3.16 (0.39-25.8)	0.283
Stage (Stage II)	4.05 (0.25-65.2)	0.324
Stage (Stage III)	2.65 (0.31-22.8)	0.375
BMI (+1)	1.41 (1.08-1.84)	0.012
Operative time (+1 hr)	1.07 (0.71-1.62)	0.752
Bleeding (+100 ml)	0.91 (0.68-1.22)	0.545
Drain withdrawal (+1 day after)	1.06 (0.91-1.24)	0.455
Ambulation (+1 day after)	1.09 (0.73-1.61)	0.686
Diseased limb load (+1 day after)	1.12 (0.97-1.30)	0.11
VTE: Venous Thromboembolism; CI: Confidence Interval		

Table 3: Impact of each risk factor on VTE onset.

The change of blood coagulation markers is presented in Figure 1. Only two patients contained SFMC levels at onset that was beyond the normal upper limit (6.9 μg/mL) in VTE development. On the contrary, SFMC levels exceeded the normal upper limit in four cases in the VTE non-development cases.

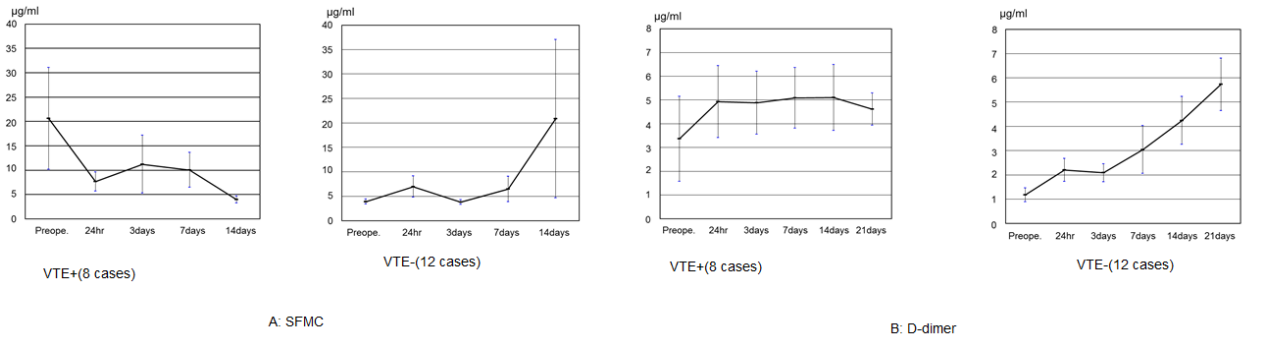


Figure 1: Preoperative and postoperative SFMC, D-dimer levels in cases with or without VTE (SFMC level was high in patients with VTE and beyond the normal upper limit, but was almost maintained within the normal range in patients without VTE until 7 days after surgery (A). D-dimer level was maintained at a high level after surgery in patients with VTE. In contrast, D-dimer level was low preoperatively and showed an upward trend after 7 days in patients without VTE (B). Error bars represent standard error. (A. SFMC, B. D-dimer)).

Only one case with VTE development showed >10 μg/mL of D dimer, and similarly, there was only one VTE non-development case with >10 μg/mL of D dimer. An analysis of the association between the peak value of SFMC, D-dimer, and VTE onset at each measurement point revealed that SFMC levels had significant associations with VTE onset at the following time points: preoperative, 24 h, days 3 and 7 after surgery (Table 4-1A).

A. SFMC		
Candidates	**Hazard Ratio (95% CI)**	**P-value**
Before surgery (+1 μg/mL)	1.03 (1.004-1.06)	0.022
The maximum until 24 h after surgery (+1 μg/mL)	1.03 (1.003-1.06)	0.032
The maximum until 3 days after surgery (+1 μg/mL)	1.03 (1.003-1.06)	0.029
The maximum until 7 days after surgery (+1 μg/mL)	1.03 (1.000-1.06)	0.047
The maximum until 14 days after surgery (+1 μg/mL)	1.00 (0.99-1.02)	0.729
B. D-dimer		
Candidates	**Hazard Ratio (95% CI)**	**P-value**
Before surgery (+1 μg/mL)	0.93 (0.81-1.07)	0.331
The maximum until 24 h after surgery (+1 μg/mL)	1.14 (1.00-1.30)	0.057
The maximum until 3 days after surgery (+1 μg/mL)	1.19 (1.05-1.34)	0.008
The maximum until 7 days after surgery (+1 μg/mL)	1.16 (1.02-1.31)	0.022
The maximum until 14 days after surgery (+1 μg/mL)	1.18 (1.03-1.35)	0.019
The maximum until 21 days after surgery (+1 μg/mL)	1.18 (1.01-1.36)	0.034
VTE: Venous Thromboembolism; CI: Confidence Interval		

Table 4-1: Impact of the maximum value of SFMC and D-dimer measured at each point on VTE onset.

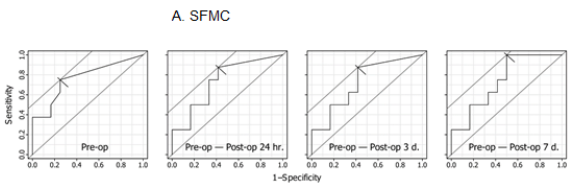
D-dimer levels also had significant associations with VTE onset on day 3, 7, 14, and 21 after surgery (Table 4-1B). When we defined the cut-off value of SFMC as 7 μg/mL, there was no significant association between SFMC level and VTE onset at any measurement point (the Cox proportional-hazards model, Table 4-2A).

A. SFMC (The cut-off value was set to 7 μg/mL)

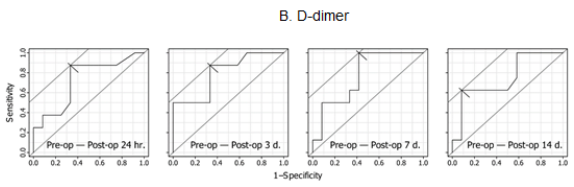
Candidates	Hazard Ratio (95% CI)	P-value
By 24 h after surgery more than 7 μg/mL	1.95 (0.48-7.81)	0.348
By 3 days after surgery more than 7 μg/mL	2.39 (0.59-9.64)	0.219
By 7 days after surgery more than 7 μg/mL	1.95 (0.48-7.81)	0.348
By 14 days after surgery more than 7 μg/mL	1.67 (0.37-7.48)	0.505
B. D-dimer (The cut-off value was set to 10 μg/mL)		
Candidates	**Hazard Ratio (95% CI)**	**P-value**
By 24 h after surgery more than 10 μg/mL	5.64 (1.06-30.0)	0.042
By 3 days after surgery more than 10 μg/mL	8.23 (1.72-3.94)	0.008
By 7 days after surgery more than 10 μg/mL	3.85 (0.90-16.4)	0.069
By 14 days after surgery more than 10 μg/mL	4.39 (1.06-18.1)	0.041
By 21 days after surgery more than 10 μg/mL	4.04 (0.98-16.6)	0.054
VTE: Venous Thromboembolism; CI: Confidence Interval		

Table 4-2: Impact of the value of SFMC and D-dimer measured at each point on VTE onset compared with the cut-off value.

When we defined the cut-off value of D-dimer as 10 μg/mL, there was significant association between D-dimer level and VTE onset on days 1, 3, and 14 after surgery (Table 4-2B). The cut-off value of SFMC was less than 3 μg/mL at any measurement point; the cut-off value of D-dimer was 1.5 μg/mL at 24 h, 1.7 μg/mL at 3 days, and 2.1 μg/mL at 7 days after surgery in our ROC analysis (Figure 2).



	Threshold	Sensitivity	Specificity	AUC
Before surgery	LT 3(μg/ml)	75	75	0.766
Until 24 hours after surgery	LT 3	87.5	58.3	0.734
Until 3 days after surgery	LT 3	87.5	58.3	0.724
Until 7 days after surgery	LT 3	100	50	0.74
LT: Less than				



	Threshold	Sensitivity	Specificity	AUC
Until 24 hours after surgery	1.5(μg/ml)	87.5	66.7	0.724
Until 3 hours after surgery	1.7	87.5	66.7	0.797
Until 7 hours after surgery	2.1	100	58.3	0.771
Until 14 hours after surgery	5.7	62.5	91.7	0.745
Until 21 hours after surgery	9.8	62.5	91.7	0.719
AUC: Area under the curve				

Figure 2: Optimal cutoff value in each measurement time calculated using a receiver operating characteristic (ROC) curve. The cutoff value of SFMC with regard to VTE development was less than 3 μg/mL at each time (A). The cutoff value of D-dimer was low until 7 days after surgery, and was less than 10 μg/mL even at 14 or 21 days after surgery (B). (A. SFMC, B. D-dimer).

Discussion

In orthopaedic surgery, it is important that postoperative VTE development is prevented for safe rehabilitation. When we think about VTE prophylaxis, it is important to know which time point after surgery VTE is easy to occur at, or how we can diagnose VTE. It was reported that the onset of distal deep venous thromboembolism (DVT) was between 1 to 5 days [3] or 9.7 days [7] after surgery in total knee arthroplasty (TKA), 21.5 days [7] after surgery in total hip arthroplasty (THA), and 15.3 (median: 9.5) days after surgery in long spinal fusions [8]. Thus, the development time of VTE varies depending on surgical procedure (operative method or invasion). It is believed that peripheral circulatory damage can easily occur during wide resection of malignant bone and soft tissue tumor arising from the lower extremity, and it is predicted that the risk of VTE development is equally high with TKA and THA. According to the seventh American College of Chest Physicians (ACCP) guidelines, distal VTE occurs in 20-40% of the high-risk group, and it becomes 40-80% in the most high-risk group. In this study, distal VTE occurred in 8 of 20 patients (40%) after the wide resection of malignant bone and soft tissue tumor in the lower extremity. This was equal to the VTE incidence of high-risk or most high-risk groups shown in the ACCP guidelines [9] and was equal to the incidence of hip fracture, THA, and TKA without VTE prophylaxis.

There are few reports about postoperative VTE development in malignant bone and soft tissue tumors [10-21]. As large studies occasionally include patients receiving anticoagulant therapy or localization of the upper extremity, we cannot compare the

postoperative VTE incidences and risk factors equally. The reasons why the VTE incidence was high in our study may be due to the following: the patient population was selected from cases of malignant bone and soft tissue tumors in the lower extremity resected muscles, all patients did not receive anticoagulant therapy, and patients with distal VTE were included in VTE development cases. Moreover, we think that there are not patients whom we failed to diagnose VTE because we underwent ultrasonography frequently until 14 days after surgery and confirmed the VTE suspected cases by contrasted CT.

Our results indicate that VTE developed at early stages after surgery (from day 1 to day 3) in almost all patients and there was no patient in whom VTE was detected after day 8. There are no reports that mention the onset of VTE in malignant bone and soft tissue tumor in detail. We should be concerned with the development of VTE during the early postoperative period after wide resection and anticoagulant medical therapy as VTE prophylaxis in malignant bone and soft tissue tumor in the lower extremity. A further study will be necessary regarding the safety of anticoagulant therapy in malignant bone and soft tissue tumors in the future. This is because most patients who underwent limb salvage surgery did not receive anticoagulant therapy during the early postoperative period due to concerns of bleeding and wound complications [13].

The usefulness of SFMC and D-dimer was reported as a non-invasive, simple, and easy screening method in other diseases and surgeries. SFMC expression is found in the early stages of coagulation activation, and its elevation in concentrations reflects thrombinogenesis. D-dimer reflects the presence of thrombosis as a product when fibrin was broken down by plasmin. There are some reports that examined the utility of SFMC and D-dimer levels during postoperative VTE screening in joint replacement and spinal surgery. Watanabe et al. described that SFMC was not useful as a predictor of VTE development and D-dimer was at high levels in the VTE development cases on day 4 after surgery for total knee replacement and the cut-off value for D-dimer was 7.5 μg/mL [4]. Sudo et al. indicated that an SFMC level more than 11.9 μg/mL on day 1 after surgery and a D-dimer level of 17.7 μg/mL or more on day 4 after surgery are associated with VTE development in total hip and knee replacement [5]. Yoshioka et al. reported that the plasma concentrations of SFMC in patients with VTE were increased on day 1 after spine surgery and the cutoff value was 20.8 μg/mL; in contrast, the plasma concentrations of D-dimer in patients with VTE were increased on day 7 and the cut-off value was 6.5 μg/mL [6]. In our study, there was a relationship between the peak value of SFMC and D-dimer in each case and VTE onset at each measurement point. In addition, when we defined the cut-off value of SFMC as 7 μg/mL and D-dimer as 10 μg/mL, there was a significant association between the D-dimer level and VTE onset on days 1, 3, and 14 after surgery. Therefore, we think that it is proper that examination for VTE may be done when the plasma concentrations of coagulation markers are at high levels. However, the cut-off value of SFMC to predict VTE development was less than 3 μg/mL at any measurement point, and the cut-off value of D-dimer was from 1.5 μg/mL to 2.1 μg/mL and between 24 h and 7 days after surgery in ROC analysis. These results indicate that the prediction in the change of the SFMC or D-dimer level was difficult in diagnosis of VTE development.

Previous reports have indicated that tumor size [14], prosthesis reconstruction [14], chemotherapy [14,15], elderly population [17,18], American Society of Anaesthesiologists grade [17], metastatic disease [17,19], intraoperative oxygen saturation drop [19], higher preoperative white blood cell count [20], post-operative wound complications [20], diabetes mellitus [21], history of VTE [21] and intraoperative blood loss [21] are risk factors for VTE during postoperative management of malignant bone and soft tissue tumors. However, these do not lead to a definite conclusion because the background for the analysis varies. In this study, limited to malignant bone and soft tissue tumors arising from the lower leg, only BMI was associated with VTE incidence. Ambulation time and diseased limb load time that are thought to be an index of the rehabilitation intervention seemed to be associated with VTE development; however, there was no significant difference. These results may be affected in that the mean ambulation time was short, 1.55 days, as rehabilitation intervention from the next day after surgery was carried out in all cases. There was no significant difference, but we should note that VTE incidence tended to be high in the patients where diseased limb load time was late on pushing forward rehabilitation. A large study that synchronizes background variables such as the tumor site or the operation invasion will be necessary in the future.

In conclusion, it was found that VTE incidence was high, and VTE often occurred early (from day 1 to day 3) in only physical prophylaxis after surgery of malignant bone and soft tissue tumors arising from the lower limb even if postoperative ambulation and rehabilitation intervention were performed quickly. For the purposes of detecting VTE development early, the elevation of blood coagulation markers such as SFMC or D-dimer were not always useful in the current study. We think that the realistic and non-invasive screening method is ultrasonography around three days after surgery. It will be necessary to evaluate VTE incidence and the onset time when postoperative anticoagulant therapy was provided in the future, but the importance of screening during the early postoperative period does not change even if the VTE incidence is reduced. With respect to rehabilitation intervention, risk management that considers VTE development in detail is necessary until at least 1 week after surgery.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Conflict of Interest

All authors declare that they have no conflict of interest.

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