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Original Article

Postoperative Venous Thromboembolism in Extramedullary Spinal Tumors

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Abstract

Context: Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is the fatal complication following spine surgery and the appropriate perioperative prophylaxis is still debated. **Aims:** The aim of this study is to evaluate the incidence of along with risk factors for postoperative VTE in surgically treated extramedullary spinal tumor patients. **Setting and Designs:** The study design involves single institute and retrospective cohort study. **Subjects and Methods:** The cohort database was reviewed between the periods of January 2014 and June 2019. Patients undergoing surgery for spine tumor, extradural tumor, and intradural extramedullary were consecutively collected. **Statistical Analysis Used:** The incidence of VTE and clinical factors reported to be associated with VTE were identified, and then analyzed with an appropriate Cox regression model. **Results:** The study identified 103 extramedullary spinal tumor patients. Three patients (2.9%) were diagnosed with a proximal leg DVT, while symptomatic PE did not identify. Risk factors associated with DVT occurrence were as follows: operative time ≥8 h (Hazard ratio [HR] 13.98, $P = 0.03$) and plasma transfusion (HR 16.38, $P = 0.02$), whereas plasma transfusion was the only significant factor, after multivariate analysis (HR 11.77, $P = 0.05$). **Conclusions:** Patients who underwent surgery for extramedullary spinal tumors showed a 2.9% incidence of DVT. The highest rate of DVT was found in patients who received plasma transfusion. More attention should be paid on perioperative associated factors for intensive prevention coupled with early screening in this group.

Keywords: *Extramedullary tumor, plasma transfusion, spinal tumor, spine tumor, venous thromboembolism*

Introduction

Spinal tumors are oncologic disorders that involve the spinal column, spinal meninges, and spinal cord. It can originate primarily in the spine or spinal cord, or metastasize from cancer has spread from another organ. From the tumor origin, they were classified into the tumor within spinal cord, called intramedullary tumor, and outside, called extramedullary spinal tumor.[1,2] However, these two groups are quite difference in many aspects, such as its natural history of intramedullary tumor is more severe with functional dependent and treatment outcome is poorer than extramedullary lesions.[3,4]

In extramedullary tumor, surgery plays a primary role. The procedures including laminectomy for spinal tumor removal, and/or spinal decompression, with or without instrumentations.[5-7]

Gross tumor removal and functional recovery were better achieved, but postoperative complication rates are still high.[8,9] Venous thromboembolism (VTE) is the leading, fatal complication following this type of surgery, and the role of perioperative prophylaxis is still debated.[10,11]

Existing data report the incidence rate of VTE after spine operations, ranges from 0.4% to 14.4%.[12-15] Although the incidence varies up to 25% in asymptomatic patients.[16,17] Some studies indicated the patients with walking disability, hypertension, and diabetes were associated with VTE development.[13]

The standard guidelines for in-hospital VTE prophylaxis place spinal surgical patients in a high-risk group.[18,19] However, their recommendation was established based on the data from other spinal diseases, especially spinal trauma and degenerative diseases. Despite these remarks, considerable knowledge gaps continue to exist. The specific incidence and risk factors

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of perioperative VTE in extramedullary spinal tumor is not clearly understood. Hence, this study aimed to evaluate the incidence of VTE and to define perioperative factors associated with VTE occurrences, following extramedullary spinal tumor surgery at our institute.

Subjects and Methods

Study designs and population

This is a retrospective review, obtained from the cohort database. We extracted data from Songklanagarind hospital, a university, and a principal referral center in Southern Thailand. All spine and spinal cord tumor patients who underwent surgical treatment, between January 2014 and June 2019, were evaluated. The tumors were reevaluated from the exact pathology adjoined with the official pathological reports, which included both primary and metastasis tumors. We excluded the intramedullary spinal cord tumors for better homogeneity clinical severity and treatment outcome. Furthermore, intramedullary tumors rarely found in our institution. Other exclusion criteria were the patients with a history of any thrombosis, preoperative VTE, and coagulopathy.

The collected demographic data examples by the age, gender, body mass index, comorbid diseases, duration of symptoms, and ambulatory ability were collected. The ambulatory ability, either preoperative or postoperative, were classified into a dependent ambulation group as the patients cannot ambulate by themselves or use assisted devices, and independent ambulation groups. Perioperative risk factors were reviews such as tumor pathology, history of radiation/chemotherapy, and steroids used. Intraoperative factors included: operative time, spinal instrumentation, estimated blood loss (EBL), and blood transfusion. Prolong operative time is defined when the period was more than the 75th percentile.[20] Finally, postoperative neurological status was reported.

Management of venous thromboembolism

We routinely evaluated the risk of hospitalized patients with Caprini scores.[21] All of our patients were categorized into a moderate level of risk (≥2 points) or higher. According to the standard guidelines,[19] we aimed to evaluate leg ultrasonography (USG) in every patient. The USG, compression ultrasound with or without doppler techniques, was performed by experienced radiologists. This investigation was weekly scheduled in both preoperative and postoperative until discharge. However, we could not achieve this aim, USG screening, in all asymptomatic deep-vein thrombosis (DVT) cases because of resource limitations.

The VTE prophylaxis protocol in our institute included with early ambulation, rehabilitation, using intermittent pneumatic compression (IPC), and additional chemical prophylaxis (low-molecular weight heparin [LMWH]) if the patients have a low risk of bleeding. The diagnosis of DVT was obtained with the same method of screening, and those of PE was made only in patients with associated symptoms, such as acute dyspnea, deoxygenation, or unexplained shock, using computed tomography angiography.

Statistical analysis

We used the R version 3.4.0 software (R Foundation, Vienna, Austria) for the statistical analysis. The sample size was calculated for estimating the infinite population proportion by alpha 0.05 and delta 0.06. Descriptive statistics were used for the patient's characteristics. The Kaplan–Meier (KM) method was used for performed survival curve in VTE-free possibilities, while the Cox proportional-hazard regression analysis was used for defining the univariable and multivariable associated factors of VTE. Multivariable analysis was performed by the backward stepwise method. Statistical significance was determined when the $P < 0.05$. The ethical committee of the institute approved this research: REC.61-252-10-1.

Results

Clinical characteristics

The patient's characteristics are presented in Table 1. The study included 103 extramedullary spinal tumor patients who received surgical treatment within our institute. The majority of cases were female (61.2%), and the mean age was 49.9 ± 17.0 years. The major underlying diseases were: obesity, hypertension, dyslipidemia, and diabetes mellitus. The mean duration of symptoms, estimated from the patient's history to operative day, was 75.3 days (0–365 days). Of all the tumor cases, 50.5% were preoperative ambulatory dependent, with profound neurological deficits. Pathological of tumors were found in a variety of types, and a majority of cases were schwannoma (35.0%), meningioma (26.2%), and spine metastasis (20.3%) [Table 2]. The majority of extramedullary spinal tumors were located in thoracic (56, 51.6%), followed by cervical (35, 36.0%) and lumbosacral region (12, 12.4%).

In all cases, laminectomy and tumor removal was performed, and a quarter of patients received instrumentation with pedicular screws fixation (2.4 ± 1.8 levels). The mean operative time was 331.4 min (range 155-680 min). The mean EBL was 422.4 ml (range 20–3500 ml). About three in four patients (77.3%) did not require any transfusions. However, 13.6% of all patients received fresh frozen plasma (FFP). The median time for the length of hospital stay was 14 days (range 6–184 days), and the median follow-up times was 224 days (range 13–1773 days).

Table 1: Baseline characteristics

Characteristic	*n* (%)
Total number of patients	103
Gender	
Male	40 (38.8)
Female	63 (61.2)
Age	
Mean of age (years)	49.9±17.0
<50	47 (45.6)
≥ 50	56 (54.4)
Comorbidities	
ASA classification	
2	36 (35.0)
3	67 (65.0)
BMI (kg/m^2)	
<18.5	10 (9.7)
18.5-<22.9	39 (37.9)
≥23.0	54 (52.4)
Hypertension	34 (33.0)
Dyslipidemia	20 (19.4)
Diabetes mellitus	14 (13.6)
Tobacco used	11 (10.7)
Aspirin used	5 (4.9)
Steroid used	41 (39.8)
History of radiotherapy	11 (10.7)
History of chemotherapy	7 (6.8)
Operation data	
Type of surgery	
Laminectomy and tumor removal	77 (74.8)
+ Instrumentation	26 (25.2)
Mean of operation time (mins)	331.4±123.5
Mean of EBL (ml)	422.4±484.4
Transfusion	
PRC transfusion	26 (25.2)
FFP transfusion	14 (13.6)
Platelet transfusion	7 (6.8)
Ambulatory status	
Preoperative	
Independent	51 (49.5)
Dependent	52 (50.5)
At discharge	
Independent	58 (56.3)
Dependent	41 (39.8)
Death	4 (3.9)
VTE	
Screening DVT	68 (66.0)
Prophylaxis VTE	
IPC alone	40 (38.8)
LMWH alone	4 (3.9)
IPC and LMWH	16 (15.5)
VTE diagnosis	
DVT	3 (2.9)
PE	0

ASA – American Society of Anesthesiologists; BMI – Body mass index; EBL – Estimated blood loss; FFP – Fresh frozen plasma; PRC – Pack red cell; VTE – Venous thromboembolism; DVT – Deep-vein thrombosis; LMWH – Low molecular weight heparin; IPC – Intermittent pneumatic compression; PE – Pulmonary embolism

Table 2: Type of pathology (*n*=103)

Tumor pathology	*n* (%)
Spine tumor	
Metastasis	21 (20.3)
Chordoma	4 (3.8)
Lymphoma	4 (3.8)
Cavernous hemangioma	1 (1.0)
Sarcoma	1 (1.0)
Intradural extramedullary tumor	
Schwannoma	36 (35.0)
Meningioma	27 (26.3)
Myxopapillary ependymoma	2 (1.9)
Neurofibroma	2 (1.9)
Germ cell tumor	1 (1.0)
Ganglioneuroma	1 (1.0)
Hemangiopericytoma	1 (1.0)
MPNST	1 (1.0)
Paraganglioma	1 (1.0)

MPNST – Malignant peripheral nerve sheath tumor

Venous thromboembolism prophylaxis and incidence

The adherence to screening protocol was achieved in 68 patients (66%) by underwent leg USG. The prophylaxis method was applied in the postoperative period, 40 patients with IPC alone, 16 patients with a combination of LMWH and IPC, and four patients with LMWH alone. The rest of the patients, around 40%, did not receive DVT screening and prophylaxis (IPC and/or LMW H) due to our resource limitation. Three cases were diagnosed with leg DVT in the femoral vein. Only one patient has symptomatic DVT, ipsilateral leg edema, before the diagnosis. DVT was detected in the postoperative day 8th, 75th, and 177th during admission for postoperative care and rehabilitation. Two of them had been using intermittent pneumatic calf compression prophylaxis before DVT was diagnosed. We did not found symptomatic pulmonary embolism (PE) in this study. The DVT patients' characteristics and their possible risk factors are shown in Table 3.

Risk factors for venous thromboembolism occurrence

The KM curve of the incidence of VTE is shown in terms of VTE-free probabilities [Figure 1a] Owing to the incidence of VTE being infrequent, the median of VTE-free time could not be determined. VTE-associated factors were prolonged operative time and FFP transfusion. These two factors were presented in KM curves and log-rank tests, as shown in Figures 1b and c.

For determining the factors that were associated with a VTE-free period, the Cox proportional-hazard regression model was used and shown the results of the univariate analysis in Table 4. After applying the Cox regression analysis, by backward stepwise method, to establish significant factors in univariable analysis, three significant factors were revealed these being: operative

Table 3: Deep-vein thrombosis patients' characteristics (*n*=3)

Case number	Patients factors and preoperative factors							Intraoperative factors			
	Age, sex	Pathology	Spine level	Postoperator ambulatory	ASA class	BMI (kg/m^2)	Smoking	Steroid use	Spinal instrument insertion	Operative time (mins)	EBL (ml)	FFP transfusion
1	21, female	Ganglioneuroma	C	Dependent	2	23.2	No	Yes	Yes	230	150	No
2	57, female	Spinal metastasis	LS	Independent	2	23.4	No	No	Yes	595	2000	Yes
3	66, male	Spinal metastasis	T	Dependent	3	22	Yes	Yes	Yes	490	2000	Yes

Case number	Postoperative factors			DVT diagnosis and management			
	Postoperative ambulatory	Postoperative infection	Postoperative DVT prophylaxis	DVT signs or symptoms	Leg DVT location	Time to diagnosed DVT (postoperator)	Management
1	Independent	No	IPC	Asymptomatic	Proximal	8 days	Anticoagulant
2	Dependent	No	No	Leg edema	Proximal	177 days	Anticoagulant
3	Dependent	Yes (UTI)	IPC	Asymptomatic	Proximal	75 days	Anticoagulant

C – Cervical; EBL – Estimated blood loss; IPC – Intermittent pneumatic compression; LS – Lumbrosacral; T – Thoracic; UTI – Urinary tract infection; DVT – Deep-vein thrombosis; FFP – Fresh frozen plasma; BMI – Body mass index

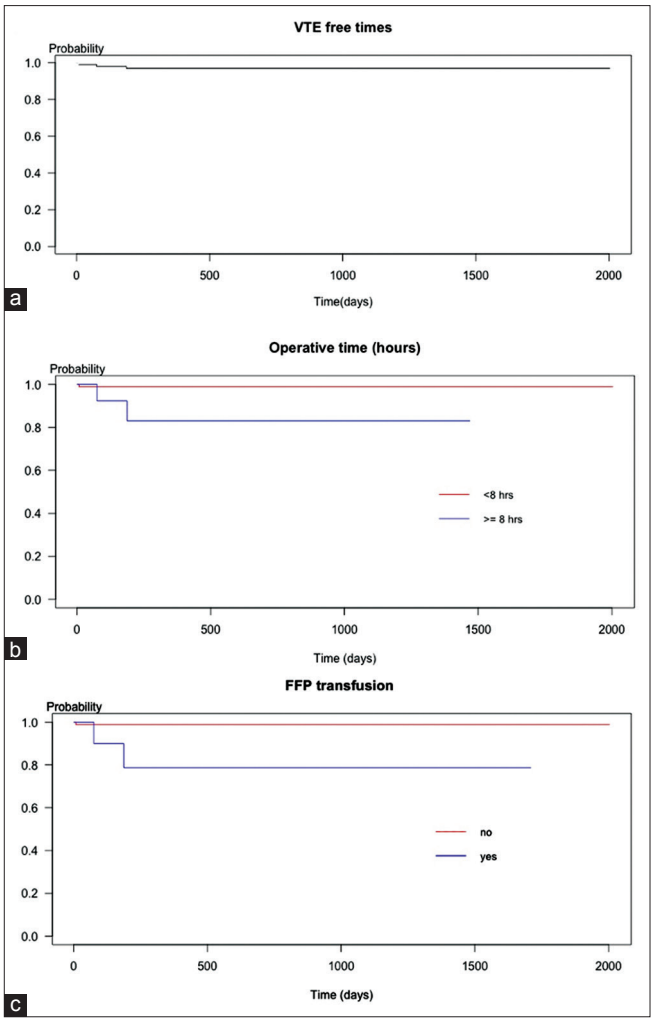

Figure 1: The Kaplan–Meier curve for venous thromboembolism -free probabilities. (a) Kaplan–Meier curve for overall median venous thromboembolism-free time that has not yet been reached. (b) Kaplan–Meier curves shows venous thromboembolism-free probability was significantly lower in patients with operative times of 8 h, or more (blue line) (log-rank test, *P* = 0.005). (c) Kaplan–Meier curves shows venous thromboembolism-free probability was significantly lower in patients with fresh frozen plasma transfusion (blue line) (log-rank test, *P* = 0.002)

time ≥8 h (Hazard ratio [HR] 13.98, $P = 0.03$) and FFP transfusion (HR 16.38, $P = 0.02$). Only FFP transfusion was significantly related to VTE occurrence in multivariable analysis (HR 11.77, $P = 0.05$).

Discussion

The present study shows the incidence rate of VTE, specifically was DVT, among postoperative extramedullary spinal tumors patients at 2.9%. Leg DVT alone was more common than symptomatic PE, or a combination of both. The VTE occurrence was associated with prolonged operation times and FFP transfusion. Wherein, FFP transfusion was associated with the EBL, as shown in the violin plot [Figure 2]. All of these significant factors correspond to the intraoperative period.

Table 4: Cox regression analysis of venous thromboembolism occurrence

Factor	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender				
Male	Ref			
Female	1.27 (0.12-14)	0.85		
Age (years)				
<50	Ref			
≥ 50	1.69 (0.15-18.65)	0.67		
ASA classification				
2	Ref			
3	0.27 (0.03-3.01)	0.29		
BMI				
< 23.0	Ref			
≥ 23.0	1.90 (0.17-20.59)	0.61		
Tobacco use				
No	Ref			
Yes	4.30 (0.39-47.52)	0.23		
Aspirin use				
No	Ref			
Yes	0.46 (0-60.35)	0.80		
Steroid				
No	Ref			
Yes	3.21 (0.29-35.40)	0.34		
Postoperative radiotherapy				
No	Ref			
Yes	4.46 (0.40-49.22)	0.22		
Type of surgery				
No instrumentation	Ref			
Instrumentation	579.88 (0-1963472609.91)	0.41		
Operative time (h)				
<8 h	Ref			
≥ 8 h	13.98 (1.27-154.40)	0.03	9.95 (0.86-115.30)	0.066
EBL (mL)				
<400	Ref			
≥400	3.35 (0.30-36.95)	0.32		
FFP transfusion				
No	Ref			
Yes	16.38 (1.47-182.23)	0.023	11.77 (1.01-138.1)	0.049
Ambulation status				
Preoperative				
Independent	Ref			
Dependent	2.16 (0.20-23.83)	0.53		
Postoperative*				
Independent	Ref			
Dependent	0.74 (0.07-8.16)	0.81		
DVT prophylaxis				
No	Ref			
Yes	1.50 (0.14-16.45)	0.74		
Schwannoma				
No	Ref			
Yes	0.03 (0-497.14)	0.47		

*Death cases were excluded. HR – Hazard ratio; CI – Confidence interval; DVT – Deep-vein thrombosis; EBL – Estimated blood loss; BMI – Body mass index; Ref - Reference

VTE is one of the common complications, which leads to higher morbidity and mortality in spine surgery.[16,22] This group of patients included surgically treated degenerative diseases, trauma, scoliosis, and

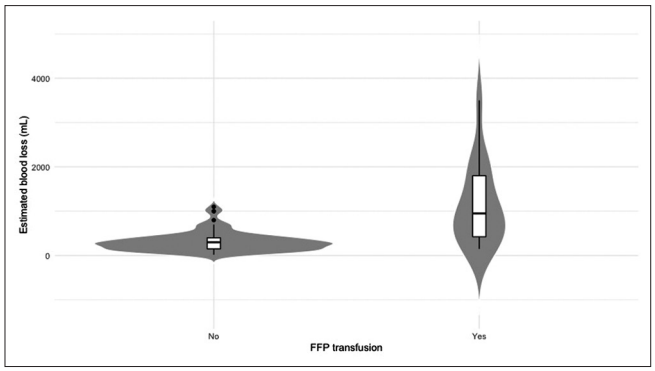

Figure 2: Violin plots demonstrate the non-parametric data of estimated blood loss in fresh frozen plasma transfusion and non-transfusion group. The median of estimated blood loss in fresh frozen plasma transfusion group was higher (950 mL vs. 300 mL). Wilcoxon Rank sums test found significantly different (*P* < 0.001)

oncologic patients. The recent meta-analysis determined the epidemiology of VTE in spine surgery, which found that: the incidence rate of VTE was 1.7% in non-DVT prophylaxis patients. However, this study analyzed the data primarily from degenerative diseases more than any other group.[23]

The rate of VTE in spinal tumors has been varied in its reports. In the most extensive study, metastasis spine tumors patients, the authors collected 314 patients, which 34 (10.8%) were diagnosed with a DVT, and 4 (1.3%) were diagnosed with a PE during the 30-day perioperative period.[24] This high incidence is more common than the report from patients requiring surgery for intradural extramedullary tumors.[25,26] Our study found that the incidence rate of VTE was no difference between metastasis patients and intradural extramedullary tumors group. Hence, the difference in pathology does not show any statistical significance in regression analysis.

This report specifies the useful information on the risk factors within this population, primarily recognizing the critical risk factor was an operative duration. Shortening the operative time will reduce the risk of VTE. The period, which is found to be at risk for VTE, varies from 2 to 6 h in previous studies.[27] The operative time from our result seems to be longer than other studies. It might be because of two reasons. First, we count the duration from the patients enter into the operating room, including from the process of preparing and preinduction of anesthesia to the patient is observed in the recovery room after the surgery finished. Some studies may count the time only the duration of anesthesia.[27] Second, our institute is an academic hospital in which all patient preparation processes and operations will couple with resident training. The learning curve of trainees might require longer operative time as shown in previous hip surgery.[28] However, this issue is beyond the objective of this study.

Blood transfusion is related to a higher VTE incidence in oncologic patients.[29] A possible explanation could be owing to cytokine-related inflammation and immunomodulation, as well as increased coagulation.[30] However, the majority of evidence found a strong association in red blood cell transfusion, and some evidence shows an association in the platelet transfusion group.[31] In our study, the multivariable analysis found statistical significant between FFP transfusion and a higher risk of VTE occurrence. This finding is located in a few of the other existing evidence, especially the use of large volumes of FFP in plasma exchange therapy.[32,33]

For spine oncologic surgery, all of the patients could be classified into a VTE high-risk group. This is a result of numerous factors that can conduct them hypercoagulable and predisposed to clot development. Furthermore, neurological deficit and dependent ambulation increased the risk for perioperative DVT.[12,17,34] Although ambulation status was not found statistically significant.

Some strengths of this study are the mention of spinal oncologic patients, these being a rare entirety in clinical practices. To our knowledge, this is the first reported data from Southeast Asia, which conducts a high number of ultrasound screening patients in this population. The data suggested that factors associated with VTE development are dependent on intraoperative factors. The systematic perioperative VTE prophylaxis should be more emphasized.

The major limitation of this study is retrospective bias, which was confounded by the variety of pathology, which has differences in its natural history and disease severity. Especially in metastasis patients, primary cancer, as well as cancer stage, can affect VTE risks that have not been mentioned. Second, the number of patients is too small to associate with the low incidence of spinal tumors in our country.[35] Third, the incidence of VTE occurrence is minimal even in the same lower limit of many previous studies. The factors associated with the incident should be emphasized to re-evaluate in other institutes. Therefore, multicenter research could offer more clarification of the magnitude of these problems and clarified the association of our findings.

Conclusions

The incidence of postoperative VTE also found in extramedullary tumor, about 3%. The VTE occurrence was depended on the intraoperative periods in case of prolonged operative times and FFP transfusion.

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Conflicts of interest

There are no conflicts of interest.

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