Original Article

Postoperative Venous Thromboembolism in Extramedullary Spinal Tumors

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. 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%) \[^{[2]}\] [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).
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 LMWH) 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
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 specifically associated with symptomatic PE, and a combination of both EBL and BMI. The VTE occurrence 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 specifically associated with symptomatic PE, and a combination of both EBL and BMI. The VTE occurrence was significantly related to VTE occurrence in multivariable analysis (HR 11.77, *P* = 0.05).
VTE is one of the common complications, which leads to higher morbidity and mortality in spine surgery.\textsuperscript{[16,22]} This group of patients included surgically treated degenerative diseases, trauma, scoliosis, and 

| 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
However, this issue is beyond the objective.

A possible explanation could be owing to cytokine-related inflammation and immunomodulation, as well as increased coagulation. 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. 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.

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. 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. 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 dependent 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.

References
1. Ciftdemir M, Kaya M, Selcuk E, Yalniz E. Tumors of the spine. World J Orthop 2016;7:109-16.
2. Mechtler LL, Nandigam K. Spinal cord tumors: New views and future directions. Neurourol Urodyn 2013;31:241-68.
3. Ng Z, Ng S, Nga V, Teo K, Lwin S, Ning C, Yeo TT, et al. Intradural spinal tumors-review of postoperative outcomes comparing intramedullary and extramedullary tumors from a single institution’s experience. World Neurosurg 2018;109:e229-32.
4. Bhat AR, Kirmani AR, Wani MA, Bhat MH. Incidence, histopathology, and surgical outcome of tumors of spinal cord, nerve roots, meninges, and vertebral column – Data based on single institutional (Sher-I-Kashmir Institute of Medical Sciences) experience. J Neurosci Rural Pract 2016;7:381-91.
5. Brooks FM, Ghatahora A, Brooks MC, Warren H, Price L, Brahmabhatt P, et al. Management of metastatic spinal cord compression: Awareness of NICE guidance. Eur J Orthop Surg Traumatol 2014;24 Suppl 1:S255-9.
6. Samartzis D, Gillis CC, Shih P, O’Toole JE, Fessler RG. Intramedullary spinal cord tumors: Part II management options and outcomes. Global Spine J 2016;6:176-85.
7. Fridley J, Gokaslan ZL. The evolution of surgical management for vertebral column tumors. J Neurosurg Spine 2019;30:417-23.
8. Guzik G. Surgical treatment in patients with spinal tumors – Differences in surgical strategies and malignancy-associated problems. An analysis of 474 patients. Ortop Traumatol Rehabil 2015;17:229-40.
9. Hussain AK, Vig KS, Cheung ZB, Phan K, Lima MC, Kim JS, et al. The impact of metastatic spinal tumor location on 30-day perioperative mortality and morbidity after surgical decompression. Spine (Phila Pa 1976) 2016;43:E648-55.
10. McLynn RP, Diaz-Collado PJ, Ottesen TD, Ondeck NT, Cui JJ, Bovonratwet P, et al. Risk factors and pharmacologic prophylaxis for venous thromboembolism in elective spine surgery. Spine J 2018;18:970-8.
11. Kahn SR, Morrison DR, Cohen JM, Emed J, Tagalakis V, Roussin A, et al. Interventions for implementation of thromboprophylaxis in hospitalized medical and surgical patients at risk for venous thromboembolism. Cochrane Database Syst Rev 2013;4:CD008201.
12. Piper K, Algattas H, DeAndra-Lazarus IA, Kimmell KT, Li YM, Walter KA, et al. Risk factors associated with venous thromboembolism in patients undergoing spine surgery. J Neurosurg Spine 2017;26:90-6.
13. Wang T, Yang SD, Huang WZ, Liu FY, Wang H, Ding WY. Factors predicting venous thromboembolism after spine surgery. Medicine (Baltimore) 2016;95:e5776.
14. Cloney M, Dhillon ES, Roberts H, Smith ZA, Koski TR, Dahdaleh NS. Predictors of readmissions and reoperations related to venous thromboembolic events after spine surgery: A single-institution experience with 6869 patients. World Neurosurg 2018;111:e91-7.
15. Schulte LM, O’Brien JR, Bean MC, Pierce TP, Yu WD, Meals C. Deep vein thrombosis and pulmonary embolism after spine surgery: Incidence and patient risk factors. Am J Orthop (Belle Mead NJ) 2013;42:267-70.
16. Takahashi H, Yokoyama Y, Iida Y, Terashima F, Hasegawa K, Saito T, et al. Incidence of venous thromboembolism after spine surgery. J Orthop Sci 2012;17:114-7.
17. Tominaha H, Setoguchi T, Tanabe F, Kawamura I, Tsuneyoshi Y, Kawabata N, et al. Risk factors for venous thromboembolism after spine surgery. Medicine (Baltimore) 2015;94:e466.
18. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr., et al. Prevention of venous thromboembolism. Chest 2001;119:1325S-75S.
19. Geerts WH, Heit JA, Clagett GP, Pineo GF, Anderson FA Jr., Wheeler HB, et al. Prevention of venous thromboembolism. Chest 2001;119:1325S-75S.
20. Basques BA, Fu MC, Buerba RA, Bohl DD, Golinvaux NS, Grauer JN. Using the ACS-NSQIP to identify factors affecting hospital length of stay after elective posterior lumbar fusion. Spine (Phila Pa 1976) 2014;39:497-502.
21. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. Dis Mon 2005;51:70-8.
22. Park JH, Lee KE, Yu YN, Park YH, Choi SA. Incidence and risk factors for venous thromboembolism after spine surgery in Korean patients. World Neurosurg 2019;128:e229-307.
23. Mosenthal WP, Landy DC, Boyajian HH, Idowu OA, Shi LL, Ramos E, et al. Thromboprophylaxis in spinal surgery. Spine (Phila Pa 1976) 2018;43:E474-81.
24. Zacharia BE, Kahn S, Bander ED, Cederquist GY, Cope WP, McLaurin L, et al. Incidence and risk factors for preoperative deep venous thrombosis in 314 consecutive patients undergoing surgery for spinal metastasis. J Neurosurg Spine 2017;27:189-97.
25. Bhimani AD, Denyer S, Esfahani DR, Zakrzewski J, Aguilar TM, Mehta A. Surgical complications in intradural extramedullary spinal cord tumors – An ACS-NSQIP analysis of spinal cord level and malignancy. World Neurosurg 2018;117:e290-9.
26. Fisahn C, Sanders FH, Moisi M, Page J, Oakes PC, Wingerson M, et al. Descriptive analysis of unplanned readmission and readmission rates after intradural spinal tumor resection. J Clin Neurosci 2017;39:32-6.
27. Cheng H, Clymer JW, Po-Han Chen B, Sadeghirad B, Ferko NC, Cameron CG, et al. Prolonged operative duration is associated with complications: A systematic review and meta-analysis. J Surg Res 2018;229:134-44.
28. Weber M, Benditz A, Woermer M, Weber D, Gritka J, Renkawitz T. Trainee surgeons affect operative time but not outcome in minimally invasive total hip arthroplasty. Sci Rep 2017;7:6152.
29. Douros A, Jobski K, Kollhorst B, Schink T, Garbe E. Risk of venous thromboembolism in cancer patients treated with epoetins or blood transfusions. Br J Clin Pharmacol 2016;82:839-48.
30. Zacharski LR. Hypercoagulability preceding cancer. The iron hypothesis. J Thromb Haemost 2005;3:585-8.
31. Khorana AA, Francis CW, Blumberg N, Culakova E, Refaai MA, Lyman GH. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. Arch Intern Med 2008;168:2377-81.
32. Yarranton H, Cohen H, Pavord SR, Benjamin S, Hagger D, Machin SJ. Venous thromboembolism associated with the management of acute thrombotic thromboembolic purpura. Br J Haematol 2003;121:778-85.
33. Pandey S, Vyas GN. Adverse effects of plasma transfusion. Transfusion 2012;52 Suppl 1:65S-79S.
34. Karhade AV, Vasudeva VS, Dasenbrock HH, Lu Y, Gormley WB, Groff MW, et al. Thirty-day readmission and reoperation after surgery for spinal tumors: A national surgical quality improvement program analysis. Neurosurg Focus 2016;41:E5.
35. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.