Frequency and Associated Factors of Venous Thromboembolism in Cervical Spine Surgery

Masashi Uehara, Shota Ikegami, Hiroki Oba, Yoshinari Miyaoka, Terue Hatakenaka, Daisuke Kurogochi, Shinji Sasao, Tetsuhiko Mimura and Jun Takahashi

Int J Spine Surg published online 6 August 2024
https://www.ijssurgery.com/content/early/2024/08/02/8624

The International Journal of Spine Surgery
2397 Waterbury Circle, Suite 1,
Aurora, IL 60504, Phone: +1-630-375-1432

International Journal of Spine Surgery Publish Ahead of Print, published on August 6, 2024 as doi:10.14444/8624

International Journal of Spine Surgery, Vol. 00, No. 0, 2024, pp. 1–5
https://doi.org/10.14444/8624

Frequency and Associated Factors of Venous Thromboembolism in Cervical Spine Surgery

MASASHI UEHARA, MD, PhD[1]; SHOTA IKEGAMI, MD, PhD[1]; HIROKI OBA, MD, PhD[1]; YOSHINARI MIYAOKA, MD[1]; TERUE HATAKENAKA, MD, PhD[1]; DAISUKE KUROGOCHI, MD[1]; SHINJI SASAO, MD[1]; TETSUHIKO MIMURA, MD, PhD[1]; AND JUN TAKAHASHI, MD, PhD[1]

[1]*Department of Orthopedic Surgery, Shinshu University School of Medicine, Matsumoto, Nagano, Japan*

ABSTRACT

Background: Venous thromboembolism (VTE) is a well-known complication after spine surgery. As many cases of cervical spine disease result in severe gait disturbance due to myelopathy, it may harbor a higher risk of VTE than other spinal disorders. However, few studies have focused primarily on cervical spine surgery to date. This investigation sought to determine the prevalence of VTE after cervical spine surgery and identify patient-based risk factors.

Methods: The medical data of 341 consecutive patients (240 men and 101 women; mean age, 68.1 years) who underwent cervical spine surgery were retrospectively examined. Logistic regression models were employed to examine the prevalence, characteristics, and risk factors of postoperative VTE.

Results: In this study, 2.6% of cervical spine surgery patients experienced postoperative VTE. In comparisons of VTE and non-VTE groups, significant differences were found for age (79.6 years vs 67.7 years, $P < 0.01$), 1-week postoperative D-dimer level (10.6 µg/mL vs 2.7 µg/mL, $P < 0.01$), and cardiovascular disease (44.4% vs 11.1%, $P = 0.011$). Multivariate analysis identified elevated postoperative D-dimer level and cardiovascular disease as significantly associated with postsurgical VTE with respective odds ratios of 1.54 and 9.52.

Conclusion: Postoperative VTE in cervical spine surgery was seen in 2.6% of cases. Patients with elevated postoperative D-dimer level and cardiovascular disease may be at increased risk of VTE and may require additional observation.

Clinical Relevance: Spine surgeons should take into account that patients with elevated postoperative D-dimer levels and cardiovascular disease may be at increased risk for VTE.

Level of Evidence: 4.

Cervical Spine

Keywords: venous thromboembolism, cervical spine, surgery, cardiovascular disease, D-dimer

INTRODUCTION

Venous thromboembolism (VTE) is a life-threatening adverse event in spine surgery that may present difficult decisions for the surgeon and patient.[1] Despite the known benefits of prophylaxis for VTE, some surgeons decline this option over concerns of increased bleeding complications and possible neurological injury. Mechanical prophylaxis remains important; however, low molecular weight heparin has been demonstrated as superior to other pharmacological therapies in decreasing major events.[2] Routine pharmacological VTE prophylaxis has not been recommended in spinal surgery due to concerns about postoperative spinal epidural hematoma and its devastating sequelae.[3] Nonetheless, deep vein thrombosis (DVT) and pulmonary embolism (PE) occur at a high incidence and pose a considerable risk to patient health as proven prophylactic measures are generally underused.[4]

The risk of VTE in spine surgery is not well characterized and varies by procedure and the degree of neurological compromise. A standardized approach to VTE prophylaxis in spine surgery is desired but must consider risk factors, choice of prophylactic agents, and timing.[5] The incidence of VTE in spine surgery varies among reports. A meta-analysis of multiple studies revealed a total incidence of VTE after spinal surgery of 0.35%.[6] As many cases of cervical spine disease result in severe gait disturbance due to myelopathy, it may carry a higher risk of VTE than other spinal disorders. However, few studies have focused primarily on cervical spine surgery to date. The present investigation sought to determine the prevalence of postoperative VTE in cervical spine surgery and identify patient-based risk factors.

MATERIALS AND METHODS

The protocol of this study was approved by Shinshu University Hospital Institutional Review Board (no.

5931). Informed written consent was obtained from all patients prior to the study.

A total of 450 patients underwent cervical spine surgery between January 2016 and April 2022 at our hospital. Of these, 105 cases of trauma and 4 cases missing preoperative D-dimer level data were excluded. The remaining 341 consecutive patients (240 men and 101 women; mean ± SD age, 68.1 ± 13.5 years) were retrospectively enrolled, including 177 with cervical spondylotic myelopathy, 49 with ossification of the posterior longitudinal ligament, 33 with cervical spondylotic amyotrophy, 15 with herniated disc, 17 with tumors, 17 with atlantoaxial subluxation, 10 with retro-odontoid pseudotumor, 8 with cervical lesion due to rheumatoid arthritis (RA), and 15 with other disorders. The preoperative Japanese Orthopedic Association (JOA) score was 10.6 ± 3.6 points. Regarding cardiovascular disease comorbidities, 9 patients had atrial fibrillation, 18 had coronary artery disease, 7 had heart failure, 8 had valvular disease, 3 had aortic aneurysm, and 6 had other disorders. Preoperatively, VTE was seen in 3 patients (0.9%). Among them, 2 patients had preoperative DVT, although neither exhibited new DVT postoperatively. None of the patients with DVT had the known hypercoagulable conditions of hemophilia B Leyden, factor V, anti-SSA/SSB antibodies, or lupus anticoagulant. Anticoagulants were given to 19 patients (5.6%). All patients received mechanical compression as postoperative DVT prophylaxis in this cohort. One patient with preoperative DVT was administered heparin postoperatively. The surgical techniques used were posterior decompression in 204 patients, posterior instrumented fusion with or without decompression in 96 patients, and anterior decompression and fusion in 41 patients. We administered tranexamic acid (TXA) immediately before surgery in 286 patients (83.9%). Postoperative VTE occurred in 6 patients (2.1%) who received TXA and in 3 patients (5.5%) who did not, with no significant difference in frequency between TXA and no TXA patients (P = 0.16). The cohort was separated into groups based on the presence (VTE group) or absence (non-VTE group) of postoperative VTE within 2 weeks after surgery, and related variables were examined using multivariate analysis to assess the risk factors of VTE. D-dimer level was routinely measured within 1 month preoperatively and within 1 week postoperatively. We performed lower limb echocardiography and contrast-enhanced computed tomography in all cases with suspected VTE symptoms and D-dimer level ≥10 μg/mL.[7] VTE was frequently asymptomatic and diagnosed by contrast-enhanced computed tomography when the D-dimer level was elevated.

Welch's t test was used for continuous comparisons, while Fisher's exact test was adopted for proportional comparisons. Logistic regression models were employed to identify factors associated with VTE, with the presence of VTE as a response variable and patient-related factors, including age, sex, surgical procedure (posterior decompression, posterior instrumented fusion, or anterior decompression and fusion), number of fused intervertebral levels, surgical time, blood loss volume, preoperative and 1 week postoperative D-dimer level, and comorbidity history (diabetes mellitus [DM], RA, dialysis, cancer, and cardiovascular disease such as coronary artery disease, arrhythmias, and aortic aneurysm) as explanatory variables. Factors achieving $P < 0.1$ in univariate analysis were considered for subsequent multivariate analysis. The selection of factors included in the multivariate analysis was performed by stepwise model testing based on Akaike's information criterion. Cut-off values of postoperative D-dimer level for VTE occurrence were determined by receiver operating characteristic (ROC) curve analysis. All statistical testing was conducted using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics. The level of significance was set at $P < 0.05$.

RESULTS

Table 1 summarizes the characteristics of the VTE and non-VTE groups. Nine (2.6%) of the 341 patients who underwent cervical spine surgery experienced postoperative VTE. DVT occurred in 8 cases (2.3%), and PE occurred in 3 cases (0.88%), although no cases were fatal. Among the 3 cases of PE, 1 was an isolated occurrence, and 2 were coexistent with DVT. In 6 of the 9 cases (66.7%) of VTE, anticoagulants or antiplatelet drugs were prescribed for VTE by the cardiologist. We observed no significant differences in gender, disease, preoperative JOA score, surgical procedure, surgical time, blood loss volume, preoperative D-dimer level, or rate of DM, hypertension, RA, cancer, or dialysis between the VTE and

Table 1. Patient characteristics and operative details by group.

Characteristics	VTE group ($N = 9$)	Non-VTE group ($N = 324$)	P
Gender, men:women	6:3	227:97	>0.99
Age, y, mean ± SD	79.6 ± 9.7	67.7 ± 13.5	<0.01
Disease			0.54
Cervical spondylotic myelopathy	7	166	
Herniated disc	0	15	
Tumor	1	16	
Atlantoaxial subluxation	0	16	
Pseudotumor	0	10	
Cervical spondylotic amyotrophy	0	32	
Ossification of the posterior longitudinal ligament	0	49	
Other	1	20	
Preoperative Japanese Orthopedic Association score	7.0 ± 6.9	10.6 ± 3.5	0.46
Surgical procedure			
Fusion, *n* (%)	4 (44.4%)	131 (40.4%)	>0.99
Fused vertebral levels, mean ± SD	3.7 ± 4.5	1.8 ± 2.6	0.24
Surgical time, min, mean ± SD	228 ± 101	167 ± 85	0.10
Blood loss volume, mL, mean ± SD	259 ± 306	119 ± 147	0.20
Preoperative D-dimer, µg/mL, mean ± SD	7.9 ± 12.4	1.1 ± 1.2	0.14
Postoperative D-dimer, µg/mL, mean ± SD	10.6 ± 4.4	2.7 ± 2.1	<0.01
Diabetes mellitus, *n* (%)	3 (33.3%)	63 (19.4%)	0.38
Hypertension, *n* (%)	3 (33.3%)	106 (32.7%)	>0.99
Rheumatoid arthritis, *n* (%)	1 (11.1%)	11 (3.3%)	0.28
Cardiovascular disease, *n* (%)	4 (44.4%)	36 (11.1%)	0.011
Atrial fibrillation, *n* (%)	1 (11.1%)	8 (2.4%)	0.21
Coronal artery disease, *n* (%)	2 (22.2%)	16 (4.8%)	0.076
Heart failure, *n* (%)	0 (0%)	5 (1.5%)	>0.99
Cancer, *n* (%)	1 (11.1%)	27 (8.3%)	0.55
Dialysis, *n* (%)	1 (11.1%)	7 (2.1%)	0.19

Abbreviation: VTE, venous thromboembolism.
Notes: Values represent the mean ± SD.

non-VTE groups. The VTE group was significantly older (79.6 years vs 67.7 years, $P < 0.01$), had a higher postoperative D-dimer level (10.6 µg/mL vs 2.7 µg/mL, $P < 0.01$), and had higher rates of cardiovascular disease (44.4% vs 11.1%, $P = 0.011$) compared with the non-VTE group. The univariate analysis detected $P < 0.1$ for the factors of age, preoperative JOA score, fused vertebral levels, surgical time, blood loss volume, preoperative D-dimer level, postoperative D-dimer level, and cardiovascular disease as candidates for inclusion in the multivariate analysis. As a result of the stepwise method, a model including age, fused vertebral levels, pre- and postoperative D-dimer level, and cardiovascular disease was ultimately found to be optimal. Multivariate analysis revealed significant associations with VTE for postoperative D-dimer level (OR: 1.54, 95% CI: 1.23–1.94, $P < 0.01$) and cardiovascular disease (OR: 9.52, 95% CI: 1.08–84.0, $P = 0.042$; Table 2).

Table 2. Effects of patient-related factors on venous thromboembolism.

Factor	Univariate OR (95% CI)	Univariate P	Multivariate OR (95% CI)	Multivariate P
Age (+1 y)	2.91 (1.27–6.70)	0.011	1.85 (0.73–4.66)	0.18
Women	1.17 (0.28–4.77)	0.82		
Preoperative Japanese Orthopedic Association score	0.76 (0.55–1.55)	0.096		
Fusion	1.18 (0.31–4.47)	0.80		
Fused vertebral levels	1.21 (1.00–1.46)	0.047	1.25 (0.97–1.60)	0.080
Surgical time	1.01 (1.00–1.01)	0.043		
Blood loss volume	1.00 (1.00–1.01)	0.015		
Preoperative D-dimer	1.61 (1.25–2.07)	<0.01	1.20 (0.94–1.52)	0.14
Postoperative D-dimer	1.60 (1.33–1.92)	<0.01	1.54 (1.23–1.94)	<0.01
Diabetes mellitus	2.07 (0.50–8.51)	0.31		
Hypertension	1.03 (0.25–4.19)	0.96		
Rheumatoid arthritis	3.56 (0.40–31.0)	0.25		
Cardiovascular disease	6.40 (1.64–24.9)	<0.01	9.52 (1.08–84.0)	0.042
Cancer	1.37 (0.16–11.4)	0.76		
Dialysis	5.66 (0.62–51.6)	0.12		

Abbreviation: CI, confidence interval.

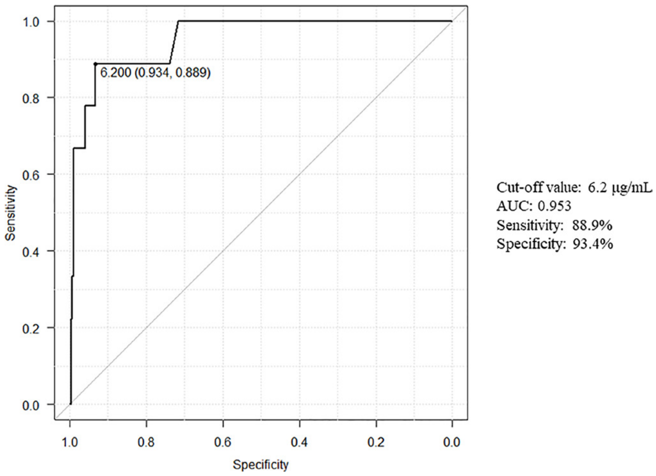

Figure. A cut-off value for 1-wk postoperative D-dimer level of 6.2 μg/mL provided a sensitivity of 88.9% and specificity of 93.4% for identifying venous thromboembolism occurrence. *Abbreviation:* AUC, area under the receiver operating characteristic curve.

When the cut-off value of 1-week postoperative D-dimer level was investigated by ROC curve analysis, a value of 6.2 μg/mL provided a sensitivity of 88.9% and specificity of 93.4% for identifying VTE occurrence (area under the ROC curve: 0.953; Figure).

When comparing patients undergoing anterior and posterior surgery, we found a trend toward younger age, longer operative time, less blood loss, and lower preoperative D-dimer level for anterior surgery. VTE occurred in 0 patients who underwent anterior surgery and 9 patients (3.0%) who underwent posterior surgery, with no significant difference between the groups (Table 3).

DISCUSSION

This study investigated the prevalence and patient-based risk factors of VTE in cervical spine surgery. We observed that 2.6% of 341 consecutively treated patients experienced postoperative VTE. With high respective OR values of 1.54 and 9.52, multivariate analysis showed postoperative D-dimer level and cardiovascular disease to be strongly linked with VTE onset. Additionally, a 1-week postoperative D-dimer cut-off value of 6.2 μg/mL was identified to discriminate VTE occurrence.

Table 3. Comparisons between anterior and posterior surgery cases.

Characteristics	Anterior Group (*N* = 41)	Posterior Group (*N* = 300)	*P*
Gender, men:women	30:11	210:90	0.85
Age, y, mean ± SD	57.8 ± 11.2	69.4 ± 13.3	<0.01
Surgical time, min	193 ± 67	164 ± 87	0.016
Blood loss volume, mL	68 ± 93	130 ± 158	<0.01
Preoperative D-dimer, μg/mL	0.6 ± 0.3	1.5 ± 2.7	<0.01
Postoperative D-dimer, μg/mL	3.0 ± 2.1	2.9 ± 2.6	0.89
VTE, *n* (%)	0 (0%)	9 (3.0%)	0.60

Abbreviation: VTE, venous thromboembolism.
Note: Values represent the mean ± SD unless otherwise indicated.

Postoperative VTE is a common but potentially life-threatening complication after spine surgery.[1] In fact, VTE is the third most common cardiovascular disease and can lead to chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome.[8] Fawi et al reported the incidence of VTE in spine surgery to be 0.59% without low molecular weight heparin.[9] Cox et al described that implementing an aggressive VTE prophylaxis protocol with compressive devices and subcutaneous heparin after spine surgery significantly reduced DVT incidence without increasing complications. This approach effectively decreased VTE occurrence without added morbidity.[10] In their study, 941 patients in the preprotocol group met the inclusion criteria: 25 had DVT (2.7%) and 6 had PE (0.6%). In the postprotocol group, 992 patients met the inclusion criteria: only 10 had DVT (1.0%) and 5 had PE (0.5%).[10] In a systematic review, the incidence of DVT in postoperative spinal patients ranged from 0.3% to 31%, with an overall rate of 2.1%.[11] Kepler et al reported an 0.35% overall incidence of VTE in their meta-analysis.[5] The incidences of VTE and PE after cervical spine surgery were 2.6% and 0.88%, respectively, and higher than those in previous studies of all spine surgery, including the thoracolumbar spine. This difference may have been influenced by a higher proportion of cervical spine disease with reduced activities of daily living due to gait disturbance and other problems.

VTE is a complex disease with multiple risk factors, such as major surgery, multiple trauma, hip fracture, lower extremity paralysis, previous VTE, higher age, cardiac or respiratory failure, prolonged immobility, presence of central venous lines, estrogens, and various hematological conditions.[12] A meta-analysis of whole-spine surgery revealed that older age, woman, diabetes, chronic kidney disease, nonambulatory preoperative activity status, elevated D-dimer level, long surgical time, spine fusion, and blood transfusion were associated with a higher incidence of VTE as well.[12] However, body mass index, obesity, hypertension, coronary heart disease, spondylolisthesis, intraoperative blood loss, surgical procedure, and surgical site did not show significant associations.[5] We witnessed no significant differences in gender, disease, surgical procedure, surgical time, blood loss volume, preoperative D-dimer level, or rate of DM, hypertension, RA, cancer, or dialysis between the VTE and non-VTE groups. However, multivariate analysis revealed postoperative D-dimer level and cardiovascular disease to be significantly associated with VTE.

D-dimer cut-off values have been proposed in spinal surgery. Yoshiiwa et al reported the cut-off value of D-dimer level for DVT after spine surgery to be ≥10 μg/mL.[7] Ikeda et al noted that preoperative D-dimer level differed significantly between DVT and non-DVT groups, with a cut-off value of 1.4 μg/mL.[13] Hamidi and Riazi determined the cut-off value of D-dimer for VTE after spine surgery as >2.1 μg/mL on the third postoperative day.[14] In our study, multivariate analysis supported that postoperative D-dimer level was significantly associated with VTE, with a calculated 1-week postoperative cut-off value of 6.2 μg/mL.

The present study had several limitations, including its small sample size, relatively short follow-up period, and retrospective design. We may have also underestimated asymptomatic VTE cases as we conducted routine VTE testing only when symptoms were suspected or when D-dimer level was ≥10 μg/mL, which was higher than the ROC-determined threshold. Nevertheless, our analysis of outcomes in 341 patients receiving cervical spine surgery uncovered a 2.6% incidence of postoperative VTE and significant associations of postoperative D-dimer level and cardiovascular disease.

CONCLUSION

In cervical spine surgery, postoperative VTE may occur in approximately 2.6% of patients, with the incidence of PE at 0.88%. Elevated postoperative D-dimer level (OR: 1.54) and cardiovascular disease (OR: 9.52) showed significant associations with postoperative VTE. Special attention may be warranted for patients exhibiting one or both risk factors to reduce postoperative complications and improve outcomes.

REFERENCES

1. Eskildsen SM, Moll S, Lim MR. An algorithmic approach to venous thromboembolism prophylaxis in spine surgery. *J Spinal Disord Tech*. 2015;28(8):275–281. doi:10.1097/BSD.0000000000000321

2. Heck CA, Brown CR, Richardson WJ. Venous thromboembolism in spine surgery. *J Am Acad Orthop Surg*. 2008;16(11):656–664. doi:10.5435/00124635-200811000-00006

3. Lee SI, Allen RT, Garfin S. Venous thromboembolism in spine surgery: review of the current literature and future directions. *Seminars in Spine Surgery*. 2019;31(4):100757. doi:10.1016/j.semss.2019.100757

4. Brambilla S, Ruosi C, La Maida GA, Caserta S. Prevention of venous thromboembolism in spinal surgery. *Eur Spine J*. 2004;13(1):1–8. doi:10.1007/s00586-003-0538-7

5. Kepler CK, McKenzie J, Kreitz T, Vaccaro A. Venous thromboembolism prophylaxis in spine surgery. *J Am Acad Orthop Surg*. 2018;26(14):489–500. doi:10.5435/JAAOS-D-17-00561

6. Zhang L, Cao H, Chen Y, Jiao G. Risk factors for venous thromboembolism following spinal surgery: a meta-analysis. *Medicine*. 2020;99(29):e20954. doi:10.1097/MD.0000000000020954

7. Yoshiiwa T, Miyazaki M, Takita C, Itonaga I, Tsumura H. Analysis of measured D-dimer levels for detection of deep venous thrombosis and pulmonary embolism after spinal surgery. *J Spinal Disord Tech*. 2011;24(4):E35–9. doi:10.1097/BSD.0b013e3181f60603

8. Krafft A. The problem of risk assessment and prophylaxis of venous thromboembolism in pregnancy. *Thromb Haemost*. 2007;98(6):1155–1156.

9. Fawi HMT, Saba K, Cunningham A, et al. Venous thromboembolism in adult elective spinal surgery: a tertiary centre review of 2181 patients. *Bone Joint J*. 2017;99-B(9):1204–1209. doi:10.1302/0301-620X.99B9.BJJ-2016-1193.R2

10. Cox JB, Weaver KJ, Neal DW, Jacob RP, Hoh DJ. Decreased incidence of venous thromboembolism after spine surgery with early multimodal prophylaxis: clinical article. *J Neurosurg Spine*. 2014;21(4):677–684. doi:10.3171/2014.6.SPINE13447

11. Glotzbecker MP, Bono CM, Wood KB, Harris MB. Thromboembolic disease in spinal surgery: a systematic review. *Spine*. 2009;34(3):291–303. doi:10.1097/BRS.0b013e318195601d

12. Anderson FA, Spencer FA. Risk factors for venous thromboembolism. *Circulation*. 2003;107(23 Suppl 1):I9–16. doi:10.1161/01.CIR.0000078469.07362.E6

13. Ikeda T, Miyamoto H, Hashimoto K, Akagi M. Predictable factors of deep venous thrombosis in patients undergoing spine surgery. *J Orthop Sci*. 2017;22(2):197–200. doi:10.1016/j.jos.2016.11.014

14. Hamidi S, Riazi M. Cutoff values of plasma D-dimer level in patients with diagnosis of the venous thromboembolism after elective spinal surgery. *Asian Spine J*. 2015;9(2):232–238. doi:10.4184/asj.2015.9.2.232

Funding: No funding was received for this study.

Disclosures: The authors report no disclosures or conflicts related to this study.

Corresponding Author: Masashi Uehara, Department of Orthopaedic Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan; masashi_u560613@yahoo.co.jp