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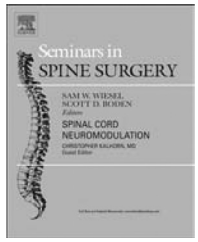

Venous thromboembolism in spine surgery: Review of the current literature and future directions

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A B S T R A C T

Venous thromboembolism (VTE) is a serious adverse event that can profoundly affect the neurologic recovery and rehabilitation of spine patients. While routine pharmacologic VTE prophylaxis has been implemented in other orthopaedic surgical subspecialties its use has not been recommended in spinal surgery. Concern regarding post-operative spinal epidural hematoma and its devastating sequelae are a major focus of the discussion surrounding routine VTE prophylaxis in spine surgery. While pharmacologic prophylaxis may be beneficial in high risk patients, further large scale, prospective analyses are necessary to elucidate the role and risks of routine VTE screening and pharmacologic prophylaxis in spine surgery patients.

1. Introduction

Venous thromboembolism (VTE) encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE events can have serious consequences for patients and can develop after trauma, during hospitalization, with prolonged immobilization (e.g. bedrest/sitting), from other medical conditions, and in the post-operative period.

The incidence of DVT in the United States has been reported to be 2 million per year.[1] The vast majority are distal lower extremity DVT, which are located below the knee and typically are non-fatal. However, distal DVT has the potential to migrate to the proximal vasculature with increased morbidity and risk for PE.[2] Deaths from PE occur in 100 000 individuals annually.[1] The morbidity, mortality, and cost associated with VTE has led to the creation of VTE prevention guidelines. In orthopedic joint arthroplasty patients, Medicare considers VTE to be a "never event," added to the list of such egregious medical errors as wrong-site surgery and patient death from incorrect medication.[3] As such, VTE represents a serious, but potentially preventable, condition.

In considering the etiology of, and risk factors for, the development of VTE, patients undergoing spine surgery are very similar to patients undergoing joint arthroplasty. The American College of Chest Physicians strongly recommends 10–14 days of pharmacologic VTE prophylaxis following joint arthroplasty.[4] With the application of these strict regulations for joint arthroplasty patients, VTE rates that had been quoted as high as 40%,[5] have now been reduced to 2%–4%.[1] VTE is a serious health problem that can adversely affect the neurologic recovery and rehabilitation of spine patients. Despite the similar VTE risk profile of spine surgery and joint arthroplasty patients, routine use of pharmacologic VTE prophylaxis is not endorsed for patients undergoing spine surgery.[4] There are a multitude of reasons for the apparent discrepancy in VTE prophylaxis recommendations. This article will attempt to shed light on this subject by exploring the following questions:

- What are the specific risk factors for VTE in spine patients?
- What are the rates of VTE in spine patients?
- What methods can reliably detect VTE in spine patients?

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- What prophylactic methods, particularly pharmacologic VTE prophylaxis, can safely reduce VTE in spine patients?
- Are there any consensus recommendations for preventing VTE in spine patients?

2. What are the specific risk factors for VTE in spine patients?

VTE are thought to arise from a complex interplay of multiple factors. Virchow's Triad, which includes venous stasis, vascular injury, and hypercoagulable state, has served to describe the pathophysiology of VTE.[6] In specific regards to spine surgery patients, there are significant risk factors for VTE, particularly as the patient's age and case complexity increases.[7] Patients can be at considerable risk for VTE even before surgery, and as such, it is helpful to consider VTE risk factors as they pertain to the following patient care periods: Pre-Operative, Intra-Operative, and Post-Operative.

The Pre-Operative period encompasses many patient-specific VTE risk factors. Prior VTE has always been considered a risk for future VTE as it suggests a hypercoagulable state – one of the tenets of Virchow's Triad.[6] Other hypercoagulable states include the presence of neoplasm and metastatic disease, pulmonary circulatory disorder, spinal cord injury, and multi-system trauma.[8] In an analysis of the Nationwide Inpatient Sample database, Oglesby et al. found the highest odds ratio for the development of VTE was the presence of a pulmonary circulatory disorder (OR 3.8 for DVT, OR 370 for PE).[5] Concomitant lower extremity fractures also increase VTE risk, likely from intimal injury as a result of the fracture, subsequent immobility, and increased need for multiple operations.[9] Spinal cord injury can lead to patient immobility and therefore increased VTE risk, with more proximal levels of spinal cord injury and worse ASIA Impairment Scale further increasing VTE risk.[10] Iversen et al. found impaired circadian variations in hemostatic and fibrinolytic factors, suggesting another possible mechanism for increased VTE in spinal cord injury patients.[11]

Other patient-specific VTE risk factors include measures indicative of overall health and medical comorbidities. In an analysis of the National Surgical Quality Improvement Program database, Schoenfeld et al. found BMI > 40, Age > 80, and ASA Classification > 3 to be significant risks for DVT; whereas BMI > 40 and male gender were the only patient factors linked to PE.[1] Yoshida et al. came to similar conclusions in developing a sliding scale to predict perioperative complications in spine surgery.[7]

Intra-Operative risk factors primarily revolve around the complexity, invasiveness, and length of surgery. Elective, degenerative spine surgery cases have less incidence of VTE when compared to complex deformity and trauma cases.[12] Complex deformity and trauma cases are more likely to involve longer operative times, longer fusion constructs, increased blood loss, as well as the potential for multi-stage/multi-approach surgery. All of these intra-operative factors have been shown to significantly increase the risk for VTE.[1,5,13–15]

Risk factors during the Post-Operative period relate to the lack of use of prophylactic measures to reduce VTE. Such measures include early patient mobilization, sequential compression devices, inferior vena cava (IVC) filters, and pharmacologic VTE prophylaxis.[4,8] Most will agree that patient mobilization is necessary in the post-operative period. However, the other prophylactic VTE measures, particularly pharmacologic, are under considerable debate as to their efficacy and safety in spine patients.[16] While pharmacologic VTE prophylaxis may reduce the risk of VTE, it comes at risk of spinal epidural hematoma, resultant neurologic deficit, and wound drainage.[17] As such, post-operative VTE risk factor modification will be a focus in the latter part of this article.

3. What are the rates of VTE in spine patients?

Quoted rates of VTE in spine patients range from 0.3%–31%.[18] This wide variation in quoted rates reflects the difficulty in studying VTE in spine patients as well as the heterogeneity of the current literature on the subject. Studies vary in regards to the patient populations, spine surgery techniques, methods for detecting VTE, VTE prophylaxis, and follow-up periods. Almost all studies employ sequential compression devices at the minimum, and as such, it is difficult to ascertain the true incidence of VTE in spine patients without any prophylaxis.[8] Further confounding these issues is that VTE is likely a relatively rare event, and thus requires a large patient population for adequate study.[18] The current literature is likely also not capturing all VTE events as almost 50% of VTE occur after hospital discharge and these VTE events may be diagnosed at another medical facility.[15]

In a meta-analysis published in 2018, Mosenthal et al. found a 1% incidence of DVT and 0.81% incidence of PE in spine surgery patients who did not receive any pharmacologic VTE prophylaxis.[18] Upon taking a deeper look into the literature, the rates of VTE increase based on comorbid conditions, type of surgery, and case complexity/invasiveness.

Comorbid conditions such as cancer, spinal cord injury, and cardiopulmonary issues can significantly increase the incidence of VTE with quoted rates from 11%–31%.[10,15,19] In stratifying based on the type of surgery and pathology being treated, trauma and deformity cases have higher incidence of VTE (DVT 5.3%–6%, PE 2%–2.7%) when compared to elective degenerative cases (DVT 2.3%, PE 0.4%).[12] The addition of an instrumented fusion significantly increases the incidence of VTE when compared to a decompression procedure alone. There is no significant difference in overall VTE rates in comparing lumbar to cervical procedures (see Table 1).[5,13]

The diagnosis of VTE leads to a profound impact on overall cost, length of stay, and mortality. VTE can lead to a delay in mobilization and hospital discharge, which can subsequently

Table 1 – VTE event/1000 in Lumbar and Cervical Surgery (Adapted from References 5,13).

	Lumbar decompression	Lumbar fusion	Anterior cervical	Posterior cervical decompression	Posterior cervical fusion
DVT	2.4	4.3	2.7	4.2	13.4
PE	1.0	2.6	1.0	1.4	6.3
Overall	4.9		5.0		

lead to comorbid conditions that require additional treatment and adversely affect recovery.[12] The aggregate cost of spine surgery and hospitalization without VTE ranges from $7000–$28 000. This cost increases to $25 000–$60 000 with the diagnosis and subsequent treatment of VTE.[5,13] Length of stay substantially increases from 0.8–1.4 days without VTE to 14–21 days with VTE. The presence of DVT results in 15-fold increase in mortality rate, and the presence of PE produces a staggering 40- to 150-fold increase in mortality rate.[5,13] Approximately 20% of patients with PE will die within the first day, and up to 11% may die within the first 3 months, even with treatment.[20] These sobering statistics are the impetus for improving the detection and prevention of VTE in spine patients.

4. What methods can reliably detect VTE in spine patients?

Physical exam and clinical suspicion for VTE will always be paramount in detecting VTE and preventing the negative sequelae associated with VTE. DVT can present with lower extremity pain, swelling, and redness, but not all DVTs are clinically apparent, particularly those involving the distal vasculature.[2,20] Clinical suspicion for PE should be high in a patient with dyspnea and pleuritic chest pain, but PE involving only segmental pulmonary arteries may be clinically silent.[20] Even in spinal cord injury patients who are at high risk for VTE, asymptomatic VTE has been quoted to occur in 16.9% of these patients.[10] As such, there is high likelihood that VTE may occur more frequently than what is quoted in the literature, and the diagnosis of and screening for VTE should not be solely guided by clinical symptoms.

There are several validated scoring systems to help guide clinical suspicion for VTE (e.g. Wells Score, Geneva Score). These scoring systems consist not only of clinical signs and symptoms, but also include notable risk factors that increase pre-test probability for VTE.[20] In specific regards to spine patients, spinal cord injury, poly-trauma, tumor diagnosis, multi-stage surgery, elevated BMI, advanced age, and comorbid conditions should raise the clinical suspicion for potential VTE.[1,5,7,9,10,13–15]

When there is high clinical suspicion and risk factors for VTE, appropriate screening tools should be accessible, reproducible, and associated with reasonable specificity and sensitivity. VTE screening tests include the following:

- D-dimer – blood test that measures the degradation product of cross-linked fibrin blood clot. D-dimer levels will be elevated in VTE but can be elevated in trauma, the post-operative state, and in cancer. As such, specificity is low (55%) but the high sensitivity (90%) makes it an effective test to rule out VTE.[10]
- Compression ultrasonography – diagnostic imaging test that is commonly used for DVT. While it has a low sensitivity for proximal (62%) and distal (48%) DVT, its high specificity (90%) makes it an effective imaging test to rule-in DVT.[10,20]
- Computerized tomographic pulmonary angiography (CTPA) – diagnostic imaging of choice for PE due to its high sensitivity, high specificity, and widespread availability. Sensitivity and specificity vary between 83%–100% and 89%–96% respectively.[21]

These diagnostic tests are often not used in isolation, but rather are used as part of a diagnostic algorithm to improve diagnostic accuracy and VTE detection.[20] The particular difficulty with spine patients is that there is no consensus statement that recommends an appropriate length of time that spine patients need to be screened for VTE or for the frequency at which these diagnostic tests should be performed.[4,8] The lack of a consensus recommendation is a reflection of the heterogeneity of the current literature, although multiple studies have attempted to investigate different VTE screening protocols in selected high risk spine patient groups.

Akeda et al. utilized compression ultrasonography in the pre- and post-operative period in a prospective study of 209 high risk spine patients. 4.3% of patients had VTE already present in the pre-operative period, and an additional 6.7% developed VTE post-operatively with a median date of detection 4.75 days post-op.[2] Schairer et al. found that the median time for VTE after discharge was at a median of 9 days post-operatively.[15] Such data suggests not only that some high risk spine patients should be sent for VTE screening pre-operatively, but also that those same high risk spine patients may benefit from VTE screening 1–2 weeks post-operatively.

Furlan et al. performed a systematic review highlighting the role of VTE screening in acute spinal cord injury patients. While spinal cord injury patients have perhaps the highest risk for VTE amongst spine patients, the systematic review was unable to support or refute a recommendation for routine VTE screening. The authors did hypothesize that routine screening up to 3 months after injury would help detect asymptomatic VTE, and as such, could help reduce the first-year mortality following spinal cord injury (quoted as high as 9.7%).[10]

While there is a definite need for additional research in order to develop pre- and post-operative VTE screening protocols for spine patients, the aforementioned risk factors and pre-test probability should guide clinical suspicion. For high risk patients, some degree of pre- and post-operative VTE screening (e.g. lower extremity ultrasound, D-Dimer) will be beneficial in reducing VTE events and subsequent morbidity and mortality. While the recommended timing and frequency of testing is unknown, high clinical suspicion should also influence the prophylactic measures employed to further reduce VTE events.

5. What prophylactic methods, particularly pharmacologic VTE prophylaxis, can safely reduce VTE in spine patients?

There is considerable debate in regards to the recommended and optimal strategy to prevent VTE in spine patients. While there is agreement on the safety and efficacy of early post-operative mobilization and sequential compression devices for VTE prevention, most of the debate centers on the safety and potential risks associated with pharmacologic VTE prophylaxis.[4,5,8,12] Pharmacologic VTE prophylaxis includes medications such as heparin, low-molecular weight heparin, and warfarin.

There is a clear, defined role for pharmacologic VTE prophylaxis in joint arthroplasty patients, with demonstrated reduction in VTE morbidity and mortality.[13] However, the risk for catastrophic or permanent neurologic injury as a result of uncontrolled bleeding from these pharmacologic agents is exceedingly low in the joint arthroplasty patient population. In regards to spine patients, Spinal Epidural Hematoma (SEH) is a dreaded complication in the post-operative and post-injury period. The severity of its potential complications has led to a reluctance to routinely start pharmacologic VTE prophylaxis amongst the spine surgery community.[17] Glotzbecker et al. found a wide variability in the use and timing of pharmacologic VTE prophylaxis following spine surgery.[16] 63% of spine surgeons polled in the online survey based their use or avoidance of pharmacologic VTE prophylaxis on personal experience rather than published literature.[16] This is a disturbing practice trend that likely is a result of the relative rarity of SEH, a pervasive and understandable fear of the potential complications of SEH, as well as the paucity of high-quality studies on the safety and efficacy of pharmacologic VTE prophylaxis in spine patients.

Quoted rates of SEH range from 0%–1% with a recent meta-analysis calculating an overall incidence of 0.2% across all studies included in the analysis.[17] These studies included patients who received pharmacologic VTE prophylaxis as well as patients that did not. In considering only patients who received pharmacologic VTE prophylaxis, the incidence of SEH is 0.3%.[18]

The similar incidence of SEH between spine patients with and without pharmacologic VTE prophylaxis may suggest that such prophylactic medications are safe in spine patients. However, many of the available studies included in the meta-analysis have small sample sizes. This makes it difficult to accurately determine the incidence of a rare complication such as SEH and even more difficult to evaluate the safety of pharmacologic VTE prophylaxis in spine patients.[18] While there is a possible trend towards heparin causing increased rates of SEH and wound complications when compared to other agents, there is insufficient data to stratify the risk of complication by type of pharmacologic VTE prophylaxis agent used.[12] Therapeutic doses of heparin used to treat spine patients diagnosed with VTE has been linked to a statistically significant increase in the rate of reoperation for SEH when compared to control patients. Therapeutic doses of low molecular weight heparin did not lead to increased rate of reoperation for SEH.[22] Shiu et al. postulate that heparin may be more prone to supra-therapeutic levels during initial treatment titration, producing the increased rates of SEH.[22]

Despite these concerns, VTE is still a preventable condition. In particular groups that are at high risk for VTE (e.g. trauma, cancer, spinal cord injury), the risks of VTE may outweigh the risks of SEH. As such, it makes sense to consider pharmacologic VTE prophylaxis for selected patients. Jacobs et al. retrospectively examined the safety of pharmacologic VTE prophylaxis in patients undergoing spinal fusion for spinal trauma. The pharmacologic agents administered in the study were heparin, enoxaparin, fondaparinux, and dalteparin. The study found no difference in incidence of wound drainage requiring reoperation between control and pharmacologic VTE prophylaxis groups. There was no reported SEH in either group with a trend towards reduced VTE in the prophylaxis group (7% VTE in prophylaxis group versus 14.3% VTE in control ($p = 0.096$)).[19] Kim et al. retrospectively analyzed the safety of early (<48 h) versus late (>48 h) post-operative low molecular weight heparin after operative fixation of spine fractures. There were no reported SEH or post-operative bleeding events. There was a 6.2% incidence of VTE, with 12 out of the 13 VTE events occurring in the late (>48 h) treatment group, suggesting that earlier initiation of pharmacologic VTE prophylaxis is better in decreasing the incidence of VTE.[23]

Such studies are encouraging as they suggest a potentially safe role in preventing VTE in high risk spine patients. However, the study authors caution that larger scale, prospective studies are required to determine the safe timing and ideal application for these pharmacologic agents.[12,19,23] It should be pointed out that pharmacologic VTE prophylaxis has not been shown to have a statistically significant effect in reducing VTE events in all spine patients. In a 2018 meta-analysis of 28 studies, Mosenthal et al. found a non-significant trend towards reduced VTE events with pharmacologic VTE prophylaxis (DVT–0.56% incidence with pharmacologic VTE prophylaxis vs. 1.0% with compression devices only; PE–0.58% incidence with pharmacologic VTE prophylaxis vs. 0.81% with compression devices only), but there was no significant demonstrable reduction in VTE events with pharmacologic agents.[18] It is important to note that this meta-analysis did not stratify the VTE incidence based on VTE risk factors such as spinal cord injury, trauma, and cancer. As such, pharmacologic VTE prophylaxis may have a much more profound effect in preventing VTE in these higher risk spine patients. In considering a high-risk group like cervical spinal cord injury patients, Class II evidence suggests that pharmacologic VTE prophylaxis be initiated and continued for 2–3 months following spinal cord injury. Such recommendations are borne out of the fact that a vast majority of VTE events occur within 2–3 months of spinal cord injury.[24]

6. Are there any consensus recommendations for preventing VTE in spine patients?

The North American Spine Society (NASS) and the American College of Chest Physicians (ACCP) published similar recommendations in 2009 and 2012, respectively, in regards to the detection and prevention of VTE in spine patients. Both groups have similar recommendations, albeit Grade 2C, which represents a weaker recommendation due to uncertain risks/benefits and low-quality evidence.4, 8 These Grade 2C recommendations include the following:

- All spine surgery patients should have mechanical prophylaxis (e.g. mobilization and sequential compression devices) unless contraindicated.
- Spine patients at low risk for VTE may not require pharmacologic VTE prophylaxis.
- Spine patients at high risk for VTE (trauma, spinal cord injury, malignancy, multi-stage or prolonged surgery, hypercoagulable state, elevated BMI) may benefit from pharmacologic VTE prophylaxis and should be evaluated on a case-by-case basis as to when pharmacologic VTE prophylaxis is initiated.

Neither NASS or ACCP were able to provide recommendations in regards to the ideal VTE screening method/protocol, safe timing to initiate pharmacologic VTE prophylaxis or treatment, or ideal pharmacologic agent for VTE prophylaxis.4, 8 The lack of recommendations in these areas, as well as the fact that the available recommendations are only Grade 2C, highlights a need for high-quality, prospective, large-scale studies in the area of safely detecting and preventing VTE in spine patients.

7. Summary

VTE represents a serious, but potentially preventable, condition. The medical consequences that can occur following VTE are a considerable burden to patients and the healthcare system as a whole. Spine surgery patients are at considerable risk for VTE, and while there are some modifiable risk factors, a majority of significant VTE risk factors are non-modifiable (e.g. traumatic injury, neurologic deficit, presence of cancer, invasiveness of operation, and relative post-operative immobility). There is a wide range of quoted rates of VTE in spine patients, and this likely reflects the variability in screening methods, timing of screening tests, as well as the possibility of clinically silent and unreported VTE events. As such, the actual rate of VTE may in fact be higher than current quoted rates.

Given the negative sequelae associated with VTE, there is particular emphasis on preventing VTE. While there is agreement on the benefit, safety, and efficacy of early post-operative mobilization and sequential compression devices, the use of pharmacologic VTE prophylaxis remains a subject of debate. There is no consensus recommendation on the safe timing, duration, and type of pharmacologic VTE prophylaxis. Spine surgeons self-report wide variability in the use of pharmacologic VTE prophylaxis, largely due to the dreaded and potentially devastating complication of uncontrolled post-operative bleeding leading to spinal epidural hematoma. Spinal epidural hematoma remains a rare event, making it difficult to study, but available studies suggest a similar rate of spinal epidural hematoma with and without pharmacologic VTE prophylaxis.

Based on current knowledge, the clinical decision on which VTE prevention measure(s) to employ should be based on the patient as a whole. Patients who suffer severe trauma, spinal cord injury, or malignancy should be considered for pharmacologic VTE prophylaxis. The lack of consensus recommendations highlights a need for high-quality, prospective, large-scale studies in order to detect and prevent VTE in spine patients.

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