Risk Factors Associated with Symptomatic Deep Vein Thrombosis Following Elective Spine Surgery: A Case-Control Study

Thomas M. Zervos

Michael Bazydlo

Kelly M. Tundo

Mohamed Macki

Jack Rock

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■ BACKGROUND: **Few studies provide insight into risk factors (RFs) associated with postoperative deep vein thrombosis (DVT) following elective spinal surgery. DVTs are detrimental in this population because of the risk of pulmonary embolization or surgical site hemorrhage with treatment.**

■ OBJECTIVE: **Elective spine surgery patients have a low incidence of DVT, thus a case–control study was selected to investigate RFs associated with postoperative, symptomatic DVT.**

■ METHODS: **Cases were matched to controls in a 1:2 ratio based on surgery type. Risk of having a prior DVT and choice of subcutaneous heparin dosing following surgery was analyzed in a multivariate regression model with other potentially confounding variables.**

■ RESULTS: **A total of 195 patients were included in this study. Independent of patient age, history of DVT was associated with postoperative symptomatic DVT (odds ratio [OR], 4.09; 95% confidence interval [CI], 1.22–13.78). Two versus 3 times daily postoperative heparin dosing (OR, 1.56; 95% CI, 0.32–7.56), surgery length (OR, 1.32; 95% CI, 0.98–1.79), and patient age (OR, 1.04; 95% CI, 1.0–1.08) were not statistically significant, independent RFs. Older age and longer length of surgery trended toward association with DVT without reaching significance. Length of stay was increased from 3–5 days ($P < 0.001$) in DVT patients compared with controls.**

■ CONCLUSIONS: **These results suggest that patients with a history of DVT undergoing elective spinal surgery are at higher risk of developing symptomatic DVT postoperatively resulting in significantly increased length of stay. Further studies on additional preoperative screening and medical optimization in elective spine surgery patients may help reduce the rate of symptomatic, postoperative DVT.**

INTRODUCTION

Background/Rationale

Treatment of deep vein thrombosis (DVT) following spinal surgery can be particularly challenging because of the added risk of therapeutic anticoagulation following neurosurgical procedures. Retrospective studies in the neurosurgical literature report a 0.85%–32% risk of postoperative DVT and a rate of <1% epidural hemorrhage postoperatively in spine surgery patients.[1-4] A contemporary estimate of DVTs in patients receiving chemotherapeutic prophylaxis is 0.2%–7%, with higher rates likely occurring in more invasive procedures, such as deformity surgery.[5-7] Overall, there is a 6.4% risk of 30-day mortality in patients with venous thromboembolism.[8] Prophylactic measures, such as chemoprophylaxis and use of pneumatic compression devices, can vary between surgeons and institutions as there are no high-quality studies that investigate the benefits of these interventions in the context of spine surgery. Further characterization of the risk factors (RFs) associated with DVT formation after spinal surgery might allow specific interventions that target these high-risk subgroups.

Both the Neurocritical Care Society and the CHEST physician guidelines recommend initiation of chemoprophylaxis after spine surgery once the surgeon judges the benefit to outweigh the

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Key words
- Case–control study
- Deep vein thrombosis
- Spine surgery

Abbreviations and Acronyms
CI: Confidence interval
DVT: Deep vein thrombosis
LOS: Length of stay
MSSIC: Michigan Spine Surgery Improvement Collaborative
OR: Odds ratio
RF: Risk factor
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

potential harm.[9,10] Based on large cohort studies, a practice of starting 5000 U of subcutaneous heparin on postoperative day 1 likely has a favorable risk–benefit ratio.[2,5-7] However, variation in DVT prevention practices is dependent on patient-specific concerns and provider preferences.

Objective

There is currently no risk stratification algorithm available to help guide timing and dosing of chemoprophylaxis after neurosurgical procedures. The purpose of this case–control study is to identify RFs associated with development of symptomatic DVTs requiring treatment. This could help identify patients at the greatest risk of DVT and guide practice patterns. The selection of RFs was based on review of variables found to be associated with DVT in other patient populations.[11] In particular, asymptomatic DVT leading to subsequent symptomatic DVT is a well-established occurrence in hospitalized patients.[12] This has not specifically been tested in the elective spine surgery population.

METHODS

Study Design

A case–control study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) criteria.[13] The study was approved by our institutional review board (IRB#10557). Institutional review board approval for waiver of patient consent was met in accordance with the Health Insurance Portability and Accountability Act, Privacy Rule, Section 164.512.

Setting

Cases and controls were identified using the Michigan Spine Surgery Improvement Collaborative (MSSIC), a collaborative quality initiative. Specific details regarding MSSIC data collection protocols and definitions are provided by Chang et al.[14] This is an adult population of lumbar and cervical spinal surgery for stenosis, disc herniation, and degenerative disease. Data were collected from 2014–2017.

Participants

A total of 65 DVT cases were identified in this time period. Surgery for tumors, traumatic fractures, deformity, scoliosis, and acute spinal cord injury are currently not within the scope of MSSIC. No cases within the MSSIC dataset occurring in this time period were excluded.

Controls were patients without an identified DVT in the post-operative period. Lower extremity ultrasounds were not obtained on asymptomatic controls. A total of 130 controls were matched in a 1:2 ratio based on procedure type (arthrodesis and/or laminectomy), cervical versus lumbar location, exact number of levels, and date of surgery (+/− 1 month). If more than 2 controls matched a case, 2 were randomly selected to be included in this study. Matching criteria were determined a priori. Cases and controls were drawn from a total study population of 4431 patients.

Variables

Cases were identified as having a new blood clot on venous duplex ultrasound, venogram, or computed tomography scan within 90 days postoperatively. Venous ultrasound was performed at the discretion of the treating physician. History of DVT is defined as documented by primary care physician or anywhere in the history. Information regarding outcome, exposure, confounders, and effect modifiers for variables are provided in prior publications.[14]

Data Sources

Retrospective chart review was performed to obtain information regarding heparin dose and timing, intraoperative platelet administration, perioperative (within 24 hours before or after surgery) glucocorticoid administration, and peripherally inserted central catheter/central line use. Retrospective chart review was performed by one author and verified by a second author. Data sources for the remaining variables are provided in prior publications.[14] Cases and controls were taken from the same population.
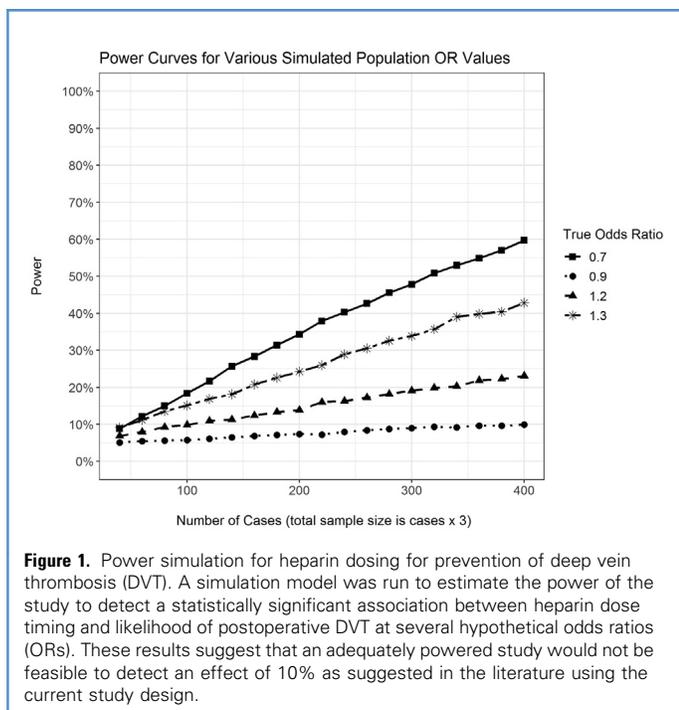
Bias

The retrospective nature of this study introduces information bias. Patients were contacted 3 times postoperatively as part of the MSSIC initiative, however, they were not specifically asked about DVT after discharge. For example, it is possible that a patient was treated at an outside hospital for a DVT and was misclassified. Also, lower extremity ultrasounds were only obtained on patients who exhibited clinical symptoms consistent with DVT. It is possible that patients with asymptomatic DVT in the control group were not identified. Also, the number of patients with asymptomatic DVT preoperatively could not be ascertained.

Study Size

A simulation was run to estimate the power of the study to detect a statistically significant association between heparin dose timing and the likelihood of postoperative DVT at several hypothetical odds ratios (ORs) (**Figure 1**). The process was performed by simulating data for the covariates used in the logistic regression model for a population of 25,000 patients. The associations between these covariates and DVT were set to levels similar to those obtained by the model run on the real data in our sample, and an intercept was chosen to control the rate of DVT in the simulated population. A total of 500 random samples of 65 cases and 130 controls were then drawn from the population. The proportion of statistically significant ORs for heparin dose timing from the logistic models represented the estimated power. This process was repeated 50 times and the power estimates of each run were averaged to smooth uncertainty from the samples.

Quantitative Variables

Summary measures of patient and surgical characteristics were compared between patients who experienced a DVT postoperatively and those that did not. The χ^2 tests were used for categorical variables, t-tests were used for normally distributed variables, and the Wilcoxon rank-sum tests were used for variables with skewed distributions. For categorical variables with cell counts too small for the χ^2 tests, the Fisher's exact test was used.

Figure 1. Power simulation for heparin dosing for prevention of deep vein thrombosis (DVT). A simulation model was run to estimate the power of the study to detect a statistically significant association between heparin dose timing and likelihood of postoperative DVT at several hypothetical odds ratios (ORs). These results suggest that an adequately powered study would not be feasible to detect an effect of 10% as suggested in the literature using the current study design.

Statistical Methods

A multivariable Firth-logistic regression model was also constructed to evaluate the association between heparin dose timing and postoperative DVT, adjusting for age, history of DVT, length of surgery, spine location (cervical vs. lumbar), number of levels, and procedure type (fusion vs. decompression alone). This type of model is interpreted in the same way as a regular logistic model but it helps handle issues that can arise when sets of predictor variables almost completely separate cases from controls. Multivariable analysis was performed on complete cases.

RESULTS

Participants

Of the 195 patients, there was 100% participation and 3-year follow-up data for age, sex, body mass index, American Society of Anesthesiologists grade, history of DVT, EuroQuol-5D surveys, spine location, blood loss, drain use, surgery length, and length of stay (LOS). Information on heparin dose and timing, glucocorticoid use, peripherally inserted central catheter or central line, and platelet transfusion was available for 117 patients.

Descriptive/Outcome Data

Baseline characteristics for the patients in our study are provided in **Table 1**. Baseline age (P = 0.002), history of DVT (P < 0.001), and LOS (P < 0.001) were found to be different between the 2 groups. Lovenox was used as a postoperative chemoprophylaxis in 1 patient. There was a trend toward significance of developing a DVT in the patients who received a perioperative platelet transfusion (P = 0.097, 7% vs.14%). Other potential RFs were not found to be statistically significantly different (**Table 1**).

Main Results

Based on prior studies, known RFs for DVT were tested in a multivariate analysis to test for confounder-adjusted estimates. In multivariate analysis, history of DVT was the only RF to reach statistical significance (**Table 2**). Independent of patient age, history of prior DVT was associated with symptomatic postoperative DVT (OR, 4.09; 95% confidence interval [CI], 1.22–13.78). Two versus 3 times daily postoperative heparin dosing (OR, 1.56; 95% CI, 0.32–7.56), surgery length (OR, 1.32; 95% CI, 0.98–1.79), and patient age (OR, 1.04; 95% CI, 1.0–1.08) were not statistically significant. Older age and longer length of surgery had a trend toward association with DVT formation.

There was 1 case of postoperative spinal hematoma requiring reoperation. This occurred in a patient who was started on aspirin 81 mg and heparin 5000 U every 8 hours on postoperative day 1 due to cardiovascular RFs. After a prolonged recovery, he/she returned to his/her preoperative baseline.

DISCUSSION

Key Results

Established RFs for developing DVT in the neurosurgical patient population include the presence of either benign or malignant tumors, spinal cord injury, head trauma, hemorrhagic or ischemic stroke, duration of surgery, and decreased mobility or limb movement.[15] After elective spinal procedures, retrospective cohort studies have identified the following associations with postoperative DVT: previous DVT, postoperative urinary tract infection, creatinine >2.0 mg/dL, presence of an inferior vena cava filter, longer hospital stay, surgery type, and presence of a spinal fracture.[6,16] These factors all directly or indirectly impact blood flow stasis, endothelial injury, and/or hypercoagulability. Postoperative DVT specifically following elective spinal surgery is less well studied, partly because of the lower incidence of DVT in this population. Based on the Neurocritical Care Society and the CHEST Physician guidelines, the lack of rigorously developed and extensively validated models of DVT risk in well-defined surgical populations limits the authors' ability to make evidence-based recommendations.[9,10]

During the time period of this study, heparin was the chemoprophylactic agent of choice for patients undergoing elective spine surgery at our institution. This practice is supported by literature suggesting that there is no significant difference in the rate of DVT or postoperative hematoma in patients treated with low-molecular-weight heparin versus unfractionated heparin after similar procedures.[17] Furthermore, in a survey of chemoprophylaxis techniques among North American surgeons, there was equivalent use of low-molecular-weight heparin and unfractionated heparin after degenerative/deformity surgery.[18] Prospective, randomized controlled trials are warranted to further compare these practice patterns in the context of elective spine surgery.

The dosing and timing of subcutaneous heparin following spine surgery is controversial. Because of the risk of spinal epidural hematoma, some advocate for no chemoprophylaxis and when it is used, the dose can vary between providers.[6] In one retrospective study, in which heparin dosing was variable between providers,

Table 1. Pre- and Postoperative Baseline Characteristics

Characteristic	Summary Measure	No DVT (N = 135)	DVT (N = 65)	P Value
Age	Mean +/− SD	61.1 +/− 12.3	65.5 +/− 12.1	0.002
Male	Count (%)	66 (49%)	37 (57%)	0.287
BMI	Mean +/− SD	30.6 +/− 5.7	31.6 +/− 7.1	0.293
Aspirin within 7 days of surgery	Count (%)	14 (20%)	10 (32%)	0.195
ASA grade >2	Count (%)	93 (69%)	48 (74%)	0.472
History of DVT	Count (%)	7 (6%)	15 (29%)	<0.001
EQ-5D anxiety/depression				
Not anxious/depressed	Count (%)	27 (34%)	14 (39%)	0.156
Moderately anxious/depressed	Count (%)	46 (57%)	15 (42%)	
Extremely anxious/depressed	Count (%)	7 (9%)	7 (19%)	
EQ-5D pain				
No pain	Count (%)	3 (4%)	4 (11%)	0.261
Moderate pain	Count (%)	37 (45%)	18 (49%)	
Extreme pain	Count (%)	42 (51%)	15 (41%)	
EQ-5D mobility				
Some problems walking	Count (%)	11 (14%)	5 (14%)	>0.999
No problems walking	Count (%)	69 (85%)	31 (86%)	
Confined to bed	Count (%)	1 (1%)	0 (0%)	
Chemoprophylaxis	Count (%)	108 (80%)	57 (88%)	0.234
Heparin dose timing				
Subcutaneous 5000 U Q8 hours	Count (%)	21 (20%)	14 (26%)	0.393
Subcutaneous 5000 U Q12 hours	Count (%)	82 (80%)	39 (74%)	
Heparin per 24 hours per kg	Mean +/− SD	157.4 +/− 39.1	149.0 +/− 44.3	0.433
Glucocorticoid use	Count (%)	91 (68%)	47 (72%)	0.528
VTE prophylaxis	Count (%)	134 (99%)	65 (100%)	>0.999
PICC or central line	Count (%)	0 (0%)	7 (22%)	>0.999
Platelet transfusion	Count (%)	9 (7%)	9 (14%)	0.097
Spine location				
Lumbar	Count (%)	87 (64%)	42 (65%)	0.981
Cervical	Count (%)	48 (36%)	23 (35%)	
Fusion	Count (%)	87 (64%)	43 (66%)	0.812
Multiple levels	Count (%)	96 (72%)	47 (72%)	0.985
Blood loss (50 cc)	Median (IQR)	2.5 (1.0, 5.8)	3.5 (1.5, 7.0)	0.152
Drain left in place postoperatively	Count (%)	88 (65%)	41 (63%)	0.770
Length of surgery (hours)	Median (IQR)	2.2 (1.5, 3.2)	2.5 (1.8, 3.6)	0.142
Length of stay (days)	Median (IQR)	3.0 (2.0, 4.0)	5.0 (3.0, 8.8)	<0.001

DVT, deep vein thrombosis; SD, standard deviation; BMI, body mass index; ASA grade, American Society of Anesthesiologists grade; EQ-5D, EuroQuol-5D; VTE, venous thromboembolism; PICC, peripherally inserted central catheter; IQR, interquartile range.

Table 2. Multivariable Logistic Regression (n = 117)

Variable	OR (95% CI)	P Value
Heparin dose timing		
Subcutaneous 5000 U Q8	Referent	-
Subcutaneous 5000 U Q12	1.56 (0.32, 7.56)	0.562
Age (years)	1.04 (1.00, 1.08)	0.054
History of DVT	4.09 (1.22, 13.78)	0.014
Surgery length (hours)	1.32 (0.98, 1.79)	0.052
Spine location		
Lumbar	Referent	-
Cervical	1.27 (0.48, 3.36)	0.618
Multiple levels	0.56 (0.21, 1.52)	0.243
Arthrodesis	0.89 (0.29, 2.73)	0.836

OR, odds ratio; CI, confidence interval; DVT, deep vein thrombosis.

standardization of heparin to 5000 U 3 times daily, resulted in a statistically significant decrease in thrombotic complications without increasing the number of patients with bleeding complications.[7] To our knowledge, this is the only other study to look at the effect of postoperative spine surgery heparin dosing.

By utilizing a case–control study design and matching based on surgical procedure, we sought to identify additional RFs. The case–control study design is a preferable method over cohort studies when an event is uncommon.[19] In spine surgery-specific studies, the risk of DVT has been shown to be associated with invasiveness of procedure, ambulatory status, and malignancy.[4,20] Matching patents by procedure type nullified the invasiveness of the procedure as a confounding RF.

At our institution, subcutaneous heparin is historically the preferred chemotherapeutic agent due to its short half-life, ability for reversal, and well-established safety profile. To specifically test the significance of postoperative heparin dosing, a power analysis was performed for this variable based on existing literature. Despite the case–control study design, we found that the estimated sample number to reach a power of 0.8 was not feasible due to an inadequate sample size and estimated effect size of 10% based on the findings in other publications (**Figure 1**).[8]

The identification of preexisting RFs for DVT formation allows surgeons to be informed when implementing preventative measures. From an administrative perspective, LOS was increased from an average of 3 to 4 days postoperatively. Six of the patients who developed a DVT required an inferior vena cava filter placement postoperatively. Fortunately, the treatment of DVT for patients in this study did not lead specifically to postoperative hematoma or mortality. The morbidity of this complication and economic burden are likely sequela, but were not specifically investigated in this study.

Limitations/Generalizability
Based on an estimated effect size of 10% increased risk of DVT in 2 versus 3 times daily heparin dosing, an adequately powered study to investigate this as an RF in the spinal population is not currently feasible using the MSSIC database, even with inclusion of all participating centers. Utilizing a 1:3 or 1:4 case to control ratio may have increased the power, possibly allowing associations, such as age and length of surgery, in the multivariable logistic regression to meet the $P < 0.05$ criteria. However, based on the power calculations for detecting a significant association for postoperative heparin dosing with DVT, the increase in the number of controls would not have changed the findings for this association. It is well established in the epidemiologic literature that there are diminishing gains with increased number of controls.[21] Greater than 3 controls are rarely justified,[22] and there is often little benefit to utilizing more than 2 controls per case.[23]

CONCLUSIONS
Identification of RFs associated with postoperative DVT may open the pathway for future targeted interventions in the elective spine surgery population. To the best of our knowledge, this is the only study on the impact of postoperative heparin dosing after spinal surgery. We found no clear association with 2 versus 3 times daily heparin dosing and postoperative DVT formation. However, failure to detect a difference may have been due to inadequate sample size. We did find that patients with a history of treated DVT were more likely to have a symptomatic DVT postoperatively, which significantly increased the LOS. Further studies investigating interventions that target this population are warranted.

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