Review Article
Prevalence and risk factors for venous thromboembolism after elective spinal surgery: a meta-analysis

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Received December 14, 2016; Accepted January 19, 2017; Epub February 15, 2017; Published February 28, 2017

Abstract: The potential risk factors for venous thromboembolism (VTE) after spinal surgery remain controversial. The objective of the current meta-analysis was to calculate the prevalence of VTE and identify possible risk factors for it. A systematic literature search was performed from PubMed, Embase, and Cochrane Library databases. Random or fixed-effects models were used to pool odds ratios (ORs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs). Newcastle-Ottawa Scale was used to assess the methodological quality of included studies, and Stata 11.0 was used to analyze data. The cumulated prevalence of VTE, deep venous thrombosis (DVT) and pulmonary embolism (PE) after spinal surgery were 0.83%, 1.22%, and 0.45%, respectively. The pooled results revealed that major factors associated with VTE were advanced age (SMD, 0.677; 95% CI, 0.570-0.785), body mass index (SMD, 0.175; 95% CI, 0.070-0.280), and elevated preoperative D-dimer (OR, 4.313; 95% CI, 1.175-15.828). There was no sufficient evidence to demonstrate that gender, smoking, hypertension, heart disease, diabetes mellitus, operating time or intraoperative blood loss was associated with postoperative VTE. The present analysis showed that advanced age, high body mass index and elevated preoperative D-dimer value are significant risk factors for postoperative VTE after spinal surgery. Patients with these factors should be informed of the potentially increased risk of VTE.

Keywords: Venous thromboembolism, deep venous thrombosis, spinal surgery, meta-analysis, risk factor

Introduction
Venous thromboembolism (VTE), including both deep venous thrombosis (DVT) and pulmonary embolism (PE), is deemed a serious and potentially life-threatening complication, and orthopaedic patients are at significant risk for it especially after surgical procedures in the clinical practice. Except for total joint arthroplasty, VTE is also commonly seen in patients after spinal surgery [1]. Some studies have reported that the prophylactic use of pharmacologic anticoagulants, such as low-molecular-weight heparin (LMWH) or low-dose heparin, can effectively reduce the occurrence of VTE in orthopaedic patients [2-4]. However, concerns about wound hemorrhage, bleeding complications and compressive spinal epidural hematoma arise at the same time [5, 6]. Besides, despite rigid adherence to evidence based guidelines set forth by the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) regarding the use of VTE prophylaxis, DVT and PE events still occur from time to time [7]. Therefore, it is necessary for us to identify patient- or surgery-related variables that may increase the risk of VTE so that strategies can be performed to decrease the risk to a low level.

Various risk factors could affect the likelihood of individual patients having a VTE, for example, diabetes [8], dyslipidemia [9], cigarette smoking [10, 11], obesity [12], and history of DVT or PE [13]. However, there is still much ambiguity regarding how to consider these parameters when it comes to clinical decision making, and statistical support for spine-specific risk factors is currently lacking. The aim of this meta-analysis was to quantify the magnitude of the VTE
risk in patients after spinal surgery, and to identify potential risk factors for it.

Materials and methods

Literature search and inclusion criteria

The current meta-analysis was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [14]. Pubmed, Embase, and Cochrane library databases were searched to retrieve relevant studies before November 2016. We used the following search terms and boolean operators: (“thromboembolism” or “venous thrombosis” or “pulmonary embolism” or “vein thrombosis”) and (“spine” or “spinal” or “cervical” or “thoracolumbar” or “lumbar”). Reference lists of all the included articles were hand-searched to identify other potentially eligible studies, and this process was performed iteratively until no other additional articles were identified.

The titles and abstracts of the identified literatures were evaluated independently by two reviewers. The search was restricted to English language and human subjects. This analysis using the following inclusion criteria: (1) the study design was case-control study; (2) adult patients underwent elective spinal surgeries; (3) VTE events were investigated; (4) possible risk factors for VTE were explored; (5) sufficient data was present to estimate odds ratios (ORs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs). Studies were excluded if they were consisted of patients with tumor, spinal cord injury or did not report outcomes of interest.

Data extraction and outcome measures

The following variables were extracted from included studies: name of first author, publication year, country, surgical procedure, type of VTE events and number of patients with VTE events. For studies presenting data separately in two or more subgroups, we combined them into a single group first. If several included articles reported on the same population or subpopulation, only the most informative article was used in order to avoid duplication of information. All data were extracted by two authors independently, and any disagreements concerning paper eligibility were resolved by discussion and consensus. In this study, the following risk factors were investigated: gender, age, body mass index (BMI), smoking, hypertension, heart disease, diabetes mellitus, preoperative D-dimer, operating time and intraoperative blood loss.

Assessment of methodological quality

We applied the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of observational studies [15]. There were three main items to be based on in this scale, which
includes the selection of the study groups (0-4 points), the comparability of the groups (0-2 points) and the determination of either the exposure or the outcome of interest (0-3 points). Nine was the perfect score of this scale, and only studies awarded six or more scores were regarded as high-quality studies.

**Statistical analysis**

From each eligible study, we extracted the adjusted ORs with 95% CIs for dichotomous outcomes and SMDs with 95% CIs for continuous outcomes. When the adjusted OR was not available, we calculated and used a crude OR. The associations between each variable and the risk of VTE were analyzed with \( P < 0.05 \) indicating a significant difference. Heterogeneity among the studies was qualitatively tested by Q-test statistics with the significance set at \( P < 0.10 \) [16], and was quantitatively tested by \( I^2 \) statistics with \( I^2 > 50\% \) indicating large inconsistency. A random-effects model was used to calculate pooled ORs or SMDs if there was significant heterogeneity (\( P < 0.10 \) or \( I^2 > 50\% \)), otherwise, a fixed-effects model was used. The pooled results were summarized graphically using forest plots.

We also performed sensitivity analysis to test the reliability of the results by excluding studies with poor quality, and re-analyzed the association between each potential variables and risk of VTE events. Publication bias was calculated by Begg test if the number of analyzed studies is more than 10 [17], and \( P < 0.10 \) was judged as statistically significant. All analyses were performed using the software Stata 11.0 (Stata Corporation, College Station, TX).

**Results**

**Literature search results**

Using the search strategy described above, a total of 857 citations were initially retrieved. Of these citations, 315 were duplicates and were excluded. After reviewing the titles and abstracts, 496 articles were deemed to be irrelevant and 46 were considered of interest. The full texts of the 46 articles were retrieved for detailed evaluation. Thirty-two of these articles were further excluded, and only 14 articles were left and ultimately included in the meta-analysis [18-31] (Figure 1).

**Characteristics of included studies**

Of the included studies, 6 were carried out in USA, 5 in Japan, and 3 in China. The outcome of quality assessment of included studies was summarized as follows: 5 studies scored 8, 6 studies scored 7, 2 studies scored 6, and 1 study scored 5. Other basic characteristics of included studies are summarized in **Table 1**.

**Prevalence of VTE**

These 14 datasets included a total of 824,422 patients. Seven studies reported the preva-
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### A. Study ID

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oda (2000)</td>
<td>0.52 (−0.00, 1.04)</td>
<td>4.27</td>
</tr>
<tr>
<td>Yoshiwa (2011)</td>
<td>0.67 (−0.24, 1.58)</td>
<td>1.41</td>
</tr>
<tr>
<td>Yoshioka (2013)</td>
<td>0.40 (0.09, 0.71)</td>
<td>11.92</td>
</tr>
<tr>
<td>Yoshioka (2015)</td>
<td>0.55 (0.21, 0.88)</td>
<td>10.42</td>
</tr>
<tr>
<td>Wei (2016)</td>
<td>0.75 (0.62, 0.88)</td>
<td>71.98</td>
</tr>
<tr>
<td>Overall (I² = 24.0%, p = 0.261)</td>
<td>0.68 (0.57, 0.79)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

### B. Study ID

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oda (2000)</td>
<td>−0.14 (−0.66, 0.38)</td>
<td>4.09</td>
</tr>
<tr>
<td>Yoshiwa (2011)</td>
<td>0.18 (−0.72, 1.08)</td>
<td>1.34</td>
</tr>
<tr>
<td>Yoshioka (2013)</td>
<td>0.10 (−0.21, 0.41)</td>
<td>11.34</td>
</tr>
<tr>
<td>Yang (Sci Rep) (2015)</td>
<td>−0.03 (−0.56, 0.50)</td>
<td>3.92</td>
</tr>
<tr>
<td>Yoshioka (2015)</td>
<td>0.05 (−0.28, 0.38)</td>
<td>9.94</td>
</tr>
<tr>
<td>Wei (2016)</td>
<td>0.24 (0.11, 0.36)</td>
<td>69.36</td>
</tr>
<tr>
<td>Overall (I² = 0.0%, p = 0.594)</td>
<td>0.17 (0.07, 0.28)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

### C. Study ID

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang (Sci Rep) (2015)</td>
<td>4.09 (2.12, 7.88)</td>
<td>32.54</td>
</tr>
<tr>
<td>Yang (Medicine) (2015)</td>
<td>1.51 (0.80, 2.87)</td>
<td>32.67</td>
</tr>
<tr>
<td>Wei (2016)</td>
<td>12.14 (8.95, 16.47)</td>
<td>34.80</td>
</tr>
<tr>
<td>Overall (I² = 94.6%, p = 0.000)</td>
<td>4.31 (1.18, 15.83)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis.
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Twelve studies described the prevalence of DVT, and the pooled result was 1.22% (4,801/394,261). The cumulated rate of PE after spinal surgery was 0.45% (1,743/387,940), which was based on the raw data of 5 studies.

Potential risk factors

A meta-analysis of combinable data was conducted to analyze the risk factors for VTE following spinal surgery. Significant heterogeneity was observed among studies when evaluating gender, hypertension, heart disease and preoperative D-dimer. On the basis of the combined ORs or SMDs, the following significant risk factors were identified: advanced age (SMD, 0.677; 95% CI, 0.570-0.785), high BMI (SMD, 0.175; 95% CI, 0.070-0.280), and preoperative elevated D-dimer value (OR, 4.313; 95% CI, 1.175-15.828). The outcomes of analyses for the significant risk factors were presented by forest plots in Figure 2. Gender, smoking, hypertension, heart disease, diabetes mellitus, operating time or intraoperative blood loss were not identified as the significant risk factors for VTE after spinal surgery (Table 2).

Sensitivity analysis and publication bias

The exclusion of one study with low quality [18] did not affect the statistical significance of any risk factors, which means that the results were robust. Funnel plot and Begg test showed that no significant publication bias was found among studies concerning the risk of gender difference (Figure 3).

Discussion

This meta-analysis systematically reviewed available literatures and found that: (a) The accumulated prevalence of VTE, DVT, and PE after spinal surgery were 0.83%, 1.22%, and 0.45%, respectively; (b) Multiple risk factors were identified to be associated with VTE, including advanced age, high BMI, and preoperative elevated D-dimer value; (c) Gender, smoking, hypertension, heart disease, diabetes mellitus, operating time or intraoperative blood loss were not identified as the significant risk factors for VTE after spinal surgery. This information may help surgeons optimize the patient’s preoperative condition, and further decrease the incidence of postoperative VTE events.

Although there has been increasing studies about VTE after orthopaedic surgery, the exact incidence of PE and DVT after spinal surgery has not been clarified. In the literature, there is a wide range of VTE incidence after spinal surgery, from as low as 0.29% up to 23.4% [25, 32, 33]. This meta-analysis reported a DVT rate of 1.22% and a PE rate of 0.45%. However, we should notice that the results are greatly affi-

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**Table 2.** Detailed data on 10 potential risk factors for venous thromboembolism after spinal surgery and the outcome of meta-analysis

<table>
<thead>
<tr>
<th>Potential risk</th>
<th>No. of studies</th>
<th>Pooled OR or SMD</th>
<th>LL 95% CI</th>
<th>UL 95% CI</th>
<th>P value</th>
<th>Q-test (P) I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>12</td>
<td>0.923ᵇ</td>
<td>0.753</td>
<td>1.133</td>
<td>0.444</td>
<td>0.009</td>
</tr>
<tr>
<td>Age (year)</td>
<td>5</td>
<td>0.677ᵇ</td>
<td>0.570</td>
<td>0.785</td>
<td>0.000</td>
<td>0.261</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>6</td>
<td>0.175ᵇ</td>
<td>0.070</td>
<td>0.280</td>
<td>0.001</td>
<td>0.594</td>
</tr>
<tr>
<td>Smoking</td>
<td>2</td>
<td>0.860ᵇ</td>
<td>0.374</td>
<td>1.977</td>
<td>0.722</td>
<td>0.700</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>1.270ᵇ</td>
<td>0.779</td>
<td>2.072</td>
<td>0.338</td>
<td>0.006</td>
</tr>
<tr>
<td>Heart disease</td>
<td>6</td>
<td>1.371ᵇ</td>
<td>0.825</td>
<td>2.279</td>
<td>0.224</td>
<td>0.052</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6</td>
<td>1.300ᵇ</td>
<td></td>
<td>1.106</td>
<td>1.527</td>
<td>0.075</td>
</tr>
<tr>
<td>Preoperative elevated D-dimer</td>
<td>3</td>
<td>4.313ᵃ</td>
<td>1.175</td>
<td>15.828</td>
<td>0.028</td>
<td>0.000</td>
</tr>
<tr>
<td>Operating time (min)</td>
<td>4</td>
<td>0.119ᵇ</td>
<td>-0.084</td>
<td>0.321</td>
<td>0.251</td>
<td>0.599</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml)</td>
<td>4</td>
<td>0.106ᵇ</td>
<td>-0.097</td>
<td>0.308</td>
<td>0.306</td>
<td>0.400</td>
</tr>
</tbody>
</table>

OR, odds ratio; SMD, standardized mean differences; LL, lower limit; UL, upper limit; BMI, body mass index. *OR value; *SMD value; †Fixed-effects model was performed; ‡Random-effects model was performed.
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Figure 3. Begg’s funnel plot to assess publication bias (with pseudo 95% confidence limits) of the case-control studies that investigated gender (male) as a risk factor for VTE events ($P = 0.244$).

Nowadays, though an emphasis has been placed on the prevention of venous thromboembolic disease in hospitalized patients, and many orthopaedic subspecialties have already defined standards for prophylaxis against venous thromboembolic disease [2-4], there is still a scarcity of existing data in the field of spinal surgery regarding specific risk factors for postoperative VTE events.

This study confirmed the anticipated advanced age as a risk factor for postoperative DVT after spinal surgery, as reported in other studies as well [34]. For example, Oda et al [19] reported that increased age was a risk factor for DVT after posterior spinal surgery in the year of 2000. Similarly, in the study conducted by Wei et al [31], the mean age in VTE positive patients were significantly higher than that in VTE negative patients. As many elderly people undergo spine operations nowadays, it is extremely important to know that these patients are at high risk for developing VTE.

High BMI value has become increasingly common among patients who have undergone spinal surgery. Usually, we used a BMI value of 30 kg/m² as the threshold for obesity. This study showed that BMI of patients with VTE was significantly higher than that without VTE, which means that high BMI may be a risk factor for postoperative VTE, and this result is consistent with several previous studies [10, 11, 35].

Preoperative D-dimer is usually used to test the existence of blood clots or thrombosis, which is associated with the VTE events. A standard cutoff of 0.50 μg/ml was used in routine clinical practice, with values above that level considered positive. It can be regarded as a predictor for VTE which was helpful for diagnostic aid in suspected VTE. Although an elevated D-dimer concentration is indicative of the presence of thromboembolic disease, it is not deemed a specific indicator of this disease [36]. However, whether an elevated level of D-dimer before spinal surgery was associated with the occurrence of postoperative VTE has not been definitely established. In this meta-analysis, the results showed that the preoperative plasma D-dimer level was a significant preoperative risk factor for VTE after spinal surgery.

There are some factors that were not demonstrated as significant risk factors, including gender, smoking, hypertension, heart disease, diabetes mellitus, operating time and intraoperative blood loss. In previous studies, the effects of these factors are controversial [8, 11]. We considered that these factors may also have an effect on the postoperative VTE. However, definite conclusions could not be drawn based on current data, because the effect might be too minor to be detected or the number of studies were not enough to conclude a statistically significant result. Therefore, these variables should not be ignored in the further research.

The extensive literature search and strict inclusion criteria are the strengths of the present study. The absence of important publication bias supports the robustness of the main find-
ings. However, there are still some limitations to be noticed. First, the surgical sites, types of VTE, and duration of follow-up were varied amongst these studies, which would result in considerable heterogeneity and may have an effect on final results. Second, though both DVT and PE were investigated, we did not make further subgroup analyses because of the relatively small numbers of studies in each subgroup. Third, because of the limited numbers of studies, it was impossible to estimate the effects of every potential risk factor. Further studies should also pay attention to other factors. Finally, most of the observational studies were retrospective, and this can result in considerable bias and had potential impacts on the final results. Consequently, these quantitative results should be interpreted with caution.

Despite of the limitations mentioned above, this study is clinically valuable to some extent. In summary, the present analysis demonstrates that advanced age, high BMI and preoperative elevated D-dimer value are significant risk factors for postoperative VTE after spinal surgery. Awareness of these risk factors may help surgeons optimize patient’s preoperative condition, and help decrease the incidence of postoperative VTE.

Disclosure of conflict of interest

None.

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