Factors predicting venous thromboembolism after spine surgery

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Abstract

Background: A meta-analysis was performed to explore predicted factors of venous thromboembolism (VTE) after surgery in the treatment for spine degeneration diseases.

Summary of background data: Many scholars have focused on VTE after spine surgery, but as for the risk factors of VTE have not reached a consensus.

Methods: An extensive search of literature, “spine or spinal,” “degeneration,” “after surgery or postoperation,” and “venous thromboembolism” as key words, was performed in PubMed/MEDLINE, Embase, the Cochrane library, CNKI, and WANFANG databases. The following variables were extracted: wearing elastic stocking, hypertension (HT), heart disease, diabetes, drinking, anticoagulant therapy, walking disability preoperation, smoking, sex, age, surgical duration, fusion versus nonfusion (lumbar fusion vs lumbar discectomy), surgical site (cervical vs lumbar), blood loss, and body mass index. Data analysis was conducted with RevMan 5.3 and STATA 12.0.

Results: A total of 12 studies were identified, including 34,597 patients of whom 624 patients had VTE, and the incidence of VTE was 2% in all patients who underwent spine surgery. The incidence of VTE for Asian patients was 7.5%, compared with 1% VTE for Occidental patients; the difference was significant (P < 0.0001). The pooled analysis showed that there were significant differences regarding wearing elastic stocking (odds ratio [OR] = 11.71, 95% confidence interval [CI] [1.46, 94.00], P = 0.02), walking disability preoperation (OR = 4.80, 95% CI [2.53, 9.12], P < 0.00001), surgical site (lumbar surgery) (OR = 0.23, 95% CI [0.20, 0.27], P < 0.00001), HT (OR = 1.59, 95% CI [1.21, 2.10], P = 0.001), and diabetes (OR = 2.12, 95% CI [1.09, 4.10], P = 0.03). However, there were no significant differences in blood loss, heart disease, smoking, sex, surgical duration, body mass index, surgical duration, anticoagulant therapy, wearing elastic stocking, fusion versus nonfusion, drinking, and age (all P > 0.05).

Conclusions: Based on our meta-analysis, Asian patients, patients with walking disability preoperation, patients wearing elastic stocking, patients having undergone lumbar surgery, patients with a history of HT, and patients experiencing diabetes have a higher incidence of VTE after spine surgery.

Abbreviations: BMI = body mass index, CI = confidence interval, DVT = deep vein thrombosis, HD = heart disease, HT = hypertension, OR = odds ratio, PE = pulmonary embolism, SMD = standardized mean difference, VTE = venous thromboembolism.

Keywords: meta-analysis, predicted factor, spine surgery, venous thromboembolism.

1. Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a common and potentially fatal disease. It may lead to severe morbidity with poor quality of life and even sudden death, bringing about serious burden to the patients and families. About half of all untreated DVT cases are complicated by PE, and, on the contrary, 50% to 80% of all untreated PE cases are related to DVT.[2,3] Attention must be paid on VTE for surgeons, and increasing studies reported on risk factors of VTE.

Orthopedic surgery on the lower extremities, spinal cord injury, major trauma, and hip or leg fracture had a relatively high risk for VTE.[4–6] Many studies reported on VTE after hip or knee arthroplasty.[7–13] However, several studies focused on the risk factors of VTE in patients undergoing spine surgery[3,8,15–20] and the incidence varied among these studies. Risk factors including long-time bed rest postoperatively and lack of lower limb activity are related to VTE after spine surgery. In surgical handling, venous intimal injury might occur.[21–26] VTE is a common complication for patients after degenerative spine. A previous article reported that the rate of VTE was 15% for patients who underwent posterior spinal surgery without any prevention.[27]

Although VTE is commonly seen in patients undergoing spine surgery, to our knowledge, its incidence and related risk factors remain unclear. Hence, our study is aimed to explore the incidence of VTE and the risk factors associated with VTE for the patients who underwent spine surgery by a meta-analysis.
Besides, we evaluate efficacy of using low-molecular-weight heparin after spine surgery and observe difference in incidence of VTE between Asians and the Occidentals.

2. Materials and methods

2.1. Ethics statement
It is not necessary to seek informed consent of patients, because our meta-analysis was based on published data and there is no potential harm to patients; this is approved by Ethics Committee of The Third Hospital of Hebei Medical University.

2.2. Search strategy
An extensive search of literature was performed, “deep venous thromboembolism,” “spine surgery,” and “spinal surgery” as key words, in PubMed, Embase, the Cochrane library, CNKI, and WANFANG databases. It was not restricted to year of publication up to April 2016 and language was restricted to Chinese or English.

2.3. Inclusion criteria
Studies were included if they met the following criteria: randomized or nonrandomized controlled study, age ≥18 years, posterior spinal surgery, articles on VTE after spine surgery, and patients with spine degeneration diseases.

2.4. Exclusion criteria
Studies were excluded if they met the following criteria: the factors that we could not extract from article for abnormal distribution or no specific number; patients with spinal trauma, spinal deformities, or tumors; abstracts, letters, reviews, or case reports; repeated data; and studies not reporting outcomes of interest.

2.5. Selection of studies
Two reviewers independently reviewed all subjects, abstracts, and the full text of articles. Then the eligible trials were selected according to the inclusion criteria. When consensus could not be reached, a third reviewer was consulted to resolve the disagreement.

2.6. Data extraction and management
Two reviewers extracted data independently. The data were extracted including the following categories: study ID, study design, study location, number of patients with VTE, total patients, demographic messages (age, sex, body mass index [BMI], history of drinking, smoking, hypertension [HT], heart disease [HD], and diabetes), and clinical outcomes (wearing elastic stockings, anticoagulant therapy, walking disability, surgical site [cervical vs lumbar], fusion vs nonfusion [lumbar fusion vs lumbar discectomy], surgical duration, and blood loss).

2.7. Statistical analysis
We used RevMan 5.3 (Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 (Stata Corporation, College Station, TX) to analyze data and applied odds ratio (OR) and standardized mean difference (SMD), as summary statistics, to analyze dichotomous variables and continuous variables, respectively. Both were reported with 95% confidence intervals (CIs), and we regarded \( P < 0.05 \) as the level of statistical significance. Heterogeneity was tested using \( I^2 \). If \( I^2 > 50\% \), it implied heterogeneity, and random-effects model was used; if \( I^2 < 50\% \), we chose fixed-effects model.

2.8. Test for risk of publication bias
We used funnel plot to assess publication bias. If there is publication bias, the funnel plot should be asymmetric, and if there is no publication bias, the funnel plot should be symmetric. Egger and Begg tests were used to measure the funnel plot asymmetry using a significance level of \( P < 0.05 \).

2.9. Sensitivity analysis overall
Because of the low heterogeneity of every factor, sensitivity analysis was not employed.

3. Results

3.1. Search results
Twenty-seven English studies in MEDLINE and Embase and 6 Chinese studies in WANFANG and CNKI were searched. Of these, 6 English articles and 2 Chinese articles were excluded due to unrelated studies, either review articles or case reports, after our review of the abstract and titles. Another 12 English articles and 1 Chinese article were excluded due to data deficiency after our intensive reading of the full text. As a result, a total of 12 studies were identified for this meta-analysis. The literature search procedure is shown in Fig. 1.

Figure 1. Flow diagram of study selection.
3.2. Baseline characteristics and quality assessment

A total of 12 studies with 34,597 patients were identified, including 624 patients with VTE after spine surgery, and the incidence of VTE was 2% (0.4–14.4%). Baseline characteristics of the 2 groups are shown in Table 1.

As all included studies were retrospective studies, Newcastle Ottawa Quality Assessment Scale, maximum of 9 points, was used to assess the quality of each study. Nonrandomized case-controlled studies and cohort studies were performed by Newcastle Ottawa Quality Assessment Scale in terms of selection, comparability, and exposure for study participants. The quality for each of our included studies was relatively high, because 8 scored 8 points and 4 scored 7 points (Table 2).

3.3. Characteristics of patients

Two studies\(^{[4,28]}\) reported relation between age at surgical time and incidence of VTE. The result showed that age at surgical time did not affect incidence of VTE (P = 0.13, SMD = 4.89 [−1.48, 11.26]; heterogeneity: P = 0.05, I\(^2\) = 73%, random-effects model; Fig. 2).

Eight studies\(^{[9,28–34]}\) reported relation between sex and incidence of VTE. The result showed that sex did not affect incidence of VTE (P = 0.49, OR = 0.85, 95% CI [0.54, 1.35]; heterogeneity: P = 0.0002, I\(^2\) = 75%, random-effects model; Fig. 3).

Table 1

| First author          | Year | Country | No. of participants | Venous thrombosis | Total | Study type         |
|-----------------------|------|---------|---------------------|-------------------|-------|-------------------|
| Hiroshi Takahashi     | 2012 | Japan   | 11                  | 1,975             |       | Retrospective study|
| Si-Dong Yang          | 2015 | China   | 147                 | 861               |       | Retrospective study|
| Timothy Y Wang        | 2015 | USA     | 15                  | 1,346             |       | Retrospective study|
| Malcolm Nicol         | 2009 | UK      | 3                   | 1,111             |       | Retrospective study|
| Hiroki Tomimaga       | 2014 | Japan   | 20                  | 80                |       | Retrospective study|
| Katsuhiro Yoshikawa   | 2015 | Japan   | 36                  | 459               |       | Retrospective study|
| Bret A Ferree         | 1993 | USA     | 3                   | 57                |       | Retrospective study|
| Bret A                | 1994 | USA     | 283                 | 27,684            |       | Retrospective study|
| Jian-Ping Chen        | 2012 | China   | 4                   | 185               |       | Retrospective study|
| Jian-Gang Li          | 2015 | China   | 39                  | 556               |       | Retrospective study|
| Zhi-Feng Yue          | 2013 | China   | 32                  | 202               |       | Retrospective study|
| Total                 |      |         | 624                 | 34,597            |       |                   |

Table 2

The quality assessment according to the Newcastle Ottawa Quality Assessment Scale (NOQAS) of each study.

| Study                  | Selection | Comparability | Exposure | Total score |
|------------------------|-----------|---------------|----------|-------------|
| Hiroshi Takahashi, 2012| 3         | 2             | 3        | 8           |
| Si-Dong Yang, 2015     | 3         | 2             | 3        | 8           |
| Timothy Y Wang, 2015   | 3         | 2             | 3        | 8           |
| Malcolm Nicol, 2009    | 2         | 2             | 3        | 7           |
| Hiroki Tomimaga, 2014  | 2         | 2             | 3        | 7           |
| Katsuhiro Yoshikawa, 2015| 2       | 2             | 3        | 7           |
| Bret A, 1993           | 3         | 2             | 3        | 8           |
| Hwan Mo Lee, 2013      | 3         | 2             | 3        | 8           |
| Bret A, 1994           | 3         | 2             | 3        | 8           |
| Jian-Ping Chen, 2012   | 2         | 2             | 3        | 7           |
| Jian-Gang Li, 2015     | 3         | 2             | 3        | 8           |
| Zhi-Feng Yue, 2013     | 3         | 2             | 3        | 8           |

Two studies\(^{[4,28]}\) reported that BMI of patients at the surgical time was negatively related to incidence of VTE. The result showed that BMI did not affect incidence of VTE (P = 0.44, SMD = -0.77 [−2.73, 1.19]; heterogeneity: P = 0.06, I\(^2\) = 72%, random-effects model; Fig. 4).

Two studies\(^{[33,35]}\) reported relation between history of drinking and incidence of VTE. The result showed that a history of drinking did not affect incidence of VTE (P = 0.57, OR = 0.83, 95% CI [0.43, 1.59]; heterogeneity: P = 0.85, I\(^2\) = 0%, fixed-effects model; Fig. 5).

Four studies\(^{[31,33–35]}\) reported relation between history of smoking and incidence of VTE. The result showed that a history of smoking did not affect incidence of VTE (P = 0.13, OR = 1.20, 95% CI [0.95, 1.51]; heterogeneity: P = 0.36, I\(^2\) = 6%, fixed-effects model; Fig. 6).

Five studies\(^{[30–33,35]}\) reported relation between history of HT and incidence of VTE. The result showed that a history of HT significantly increased the incidence of VTE (P = 0.001, OR = 1.59, 95% CI [1.21, 2.10]; heterogeneity: P = 0.10, I\(^2\) = 49%, fixed-effects model; Fig. 7).

Four studies\(^{[30–33,35]}\) reported relation between history of HD and incidence of VTE. The result showed that a history of HD did not affect incidence of VTE (P = 0.16, OR = 0.86, 95% CI [0.69, 1.06]; heterogeneity: P = 0.81, I\(^2\) = 0%, fixed-effects model; Fig. 8).

Six studies\(^{[30–33,35]}\) reported relation between history of diabetes and incidence of VTE. The result showed that a history of diabetes significantly increased the incidence of VTE (P = 0.03, OR = 2.12, 95% CI [1.09, 4.10]; heterogeneity: P < 0.0001, I\(^2\) = 81%, random-effects model; Fig. 9).

3.4. Clinical outcomes

Two studies reported relation between wearing elastic stocking and incidence of VTE. The result showed that wearing elastic stocking significantly increased the incidence of VTE (P = 0.02, OR = 11.71, 95% CI [1.46, 94.00]; heterogeneity: P = 0.85, I\(^2\) = 0%, fixed-effects model; Fig. 10).

Three studies\(^{[28,31,32]}\) reported relation between walking disability preoperation and incidence of VTE. The result showed that walking disability preoperation significantly increased the incidence of VTE (P < 0.00001, OR = 4.80, 95% CI [2.53, 9.12]; heterogeneity: P = 0.64, I\(^2\) = 0%, fixed-effects model; Fig. 11).

Two studies\(^{[4,28]}\) reported relation between surgical duration and incidence of VTE. The result showed that surgical duration
did not affect incidence of VTE ($P = 0.29$, SMD $= 19.71 [-17.01, 56.42]$; heterogeneity: $P = 0.47$, $I^2 = 0\%$, fixed-effects model; Fig. 12).

Two studies\[4,28\] reported relation between blood loss and incidence of VTE. The result showed that blood loss did not affect incidence of VTE ($P = 0.40$, SMD $= 42.51 [-56.26, 141.27]$; heterogeneity: $P = 0.42$, $I^2 = 0\%$, fixed-effects model; Fig. 13).

Six studies\[30–33,35,36\] reported relation between anticoagulation therapy and incidence of VTE. The result showed that anticoagulation therapy did not affect incidence of VTE ($P = 0.31$, OR $= 0.64$, 95% CI $[0.27, 1.51]$; heterogeneity: $P = 0.002$, $I^2 = 74\%$, random-effects model; Fig. 14).

Five studies\[28,34–37\] reported relation between lumbar fusion and incidence of VTE. The result showed that lumbar fusion did not affect incidence of VTE ($P = 0.15$, OR $= 0.65$, 95% CI $[0.36, 1.17]$; heterogeneity: $P = 0.07$, $I^2 = 54\%$, random-effects model; Fig. 15).

Two studies\[28,34\] reported relation between surgery site (cervical vs lumbar) and incidence of VTE. The result showed that lumbar surgery significantly increased the incidence of VTE ($P < 0.00001$, OR $= 0.23$, 95% CI $[0.20, 0.27]$; heterogeneity: $P = 0.95$, $I^2 = 0\%$, fixed-effects model; Fig. 16).

### 3.5. Publication bias

After a detection of publication bias by STATA 12.0, no publication bias was found for all included studies (all $P > 0.05$). The funnel plot did not indicate any publication bias in sex (Begg, $P = 0.621$; Egger, $P = 0.173$), drinking (Begg, $P = 0.317$), smoking (Begg, $P = 1.000$; Egger, $P = 0.631$), HT (Begg, $P = 0.142$; Egger, $P = 0.177$), HD (Begg, $P = 0.497$; Egger, $P = 0.910$), diabetes (Begg, $P = 0.573$; Egger, $P = 0.448$), wearing elastic stockings (Begg, $P = 0.317$), anticoagulant therapy (Begg, $P = 0.851$; Egger, $P = 0.711$), walking disability postoperation (Begg, $P = 0.602$; Egger, $P = 0.806$), and fusion (Begg, $P = 0.327$; Egger, $P = 0.171$).
the risk factors for this prevalence. As we know, this is the first meta-analysis to summarize and analyze the risk factors of VTE after spine surgery. And we also evaluate efficacy of low-molecular-weight heparin after spine surgery and observe difference in incidence of VTE between Asians and the Occidentals. The results showed that Asian ethnicity, walking disability preoperation, wearing elastic stocking, lumbar surgery, history of HT, and diabetes were risk factors for VTE after spine surgery.

A total of 34,597 patients from 12 articles were included in our study, including 624 patients with VTE after spine surgery; the incidence of VTE was 2%. Moreover, we surprisingly found that in 316 of 4214 Asian patients with VTE, the incidence of VTE was 7.5%; however, compared with 308 of 30,383 Occidental patients with VTE, the incidence of VTE was 1%. The difference was significant ($P < 0.0001$), which implied that the Asian patients were more likely to suffer from VTE after spine surgery, but the reason was still unclear.

Nicol et al.\(^{[36]}\) and Ferree and Wright\(^{[37]}\) explored whether wearing elastic stocking increased the incidence of VTE after spine surgery or not. Our result implied that patients who wore elastic stocking after operation were more likely to suffer from VTE, compared with those who did not wear them ($P=0.02$). Our result was opposite to prevention guideline for VTE, but the reason was still unclear. We need prospective randomized controlled trials (RCTs), multicenter studies, and a big sample to demonstrate whether wearing elastic stocking increases the incidence of VTE after spine surgery or not.

Five studies\(^{[30–33,35]}\) reported the relation between history of HT and incidence of VTE. Yang et al.\(^{[30]}\) proved that a history of HT significantly increased the incidence for VTE, but Tominaga et al.\(^{[31]}\) had an idea that was opposite of that of Yang et al. In our analysis, the result showed that a history of HT significantly increased the incidence for VTE ($P=0.001$). We had a hypothesis that the vascular elasticity was usually not well for the patients with HT, which may affect hemodynamics and blood coagula-
tion mechanism, and this may be related to higher incidence of VTE postoperation.

Six studies\cite{30-35} reported relation between history of diabetes and incidence of VTE. Yang et al\cite{30} and Tominaga et al\cite{31} believed that a history of diabetes was not an important key for VTE, but Herzog and coworkers\cite{34} had an opposite idea. In our analysis, the result showed that a history of diabetes significantly increased the incidence for VTE ($P = 0.03$). The fact that diabetes, as an independent factor, significantly increased the incidence of VTE has never been highlighted in previous studies. But our
results indicated that we must control blood glucose of patients preoperation and postoperation, especially postoperation. Higher blood glucose and endocrine metabolic disturbances for patients may cause hormone imbalance for the whole body, which may lead to patients with diabetes to suffer from VTE easily.

Three studies\cite{3,19,23} reported relation between walking disability preoperation and incidence of VTE. In our analysis, the result showed that walking disability preoperation significantly increased the incidence for VTE ($P<0.00001$). Having walking disability preoperation means that lower limbs have a poor disability of muscle contraction function, leading to slow blood flow in lower extremities, due to which VTE occurs easily.

In clinic, attention must be paid to patients with walking disability postoperation and measures must be taken to prevent incidence of VTE.

Two studies\cite{28,34} reported relation between surgery site (cervical vs lumbar) and incidence of VTE. The result showed

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure12}
\caption{The standardized mean difference (SMD) estimate relationship between surgical duration and incidence of vein thrombosis after spine surgery. CI = confidence interval, df = degrees of freedom, SD = standard deviation.}
\end{figure}
that lumbar surgery significantly increased the incidence of VTE (P < 0.00001). Patients who underwent cervical surgery left bed earlier postoperatively, compared with patients who underwent lumbar surgery. The results showed that leaving the bed to do postoperative functional exercise early was beneficial to prevent incidence of VTE.

Six studies[30–33,35,36] explored the relation between anticoagulant therapy and VTE. Some authors believed that anticoagulant therapy could lower incidence of DVT. Shepherd and Mills[14] reported that the use of pharmacological prophylaxis significantly reduced the prevalence of DVT compared with mechanical prophylaxis or no prophylaxis. But Yang et al[30] and Tominaga et al[31] disagreed with it. Our result showed that anticoagulation signiﬁcantly increased the incidence of VTE after spine surgery. To provide objective data on the clinical results of both procedures, a well-designed, prospective RCT should be performed in the future.

4.1. Study limitations

This study has several limitations. First, we could not perform subgroup analysis or single spine degeneration disease analysis due to few included articles. Some factors that we considered initially, such as D-dimer and surgical time >2 versus <2 hours, could not be extracted. Second, we mainly explored the prevalence and risk factors of VTE in lumbar and cervical degeneration diseases regardless of other spine diseases. Finally, none of the studies included in the meta-analysis was a RCT. Although our study has limitations, to our knowledge, this is the first meta-analysis to explore risk factors of VTE after spine surgery.

In summary, we found that Asian patients, patients with walking disability preoperation, patients wearing elastic stockings, patients with a history of HT, patients having undergone lumbar surgery, and patients experiencing diabetes significantly increased the incidence of VTE after spine surgery. To provide objective data on the clinical results of both procedures, a well-designed, prospective RCT should be performed in the future.

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