Is blood transfusion associated with an increased risk of infection among spine surgery patients?

A meta-analysis

Yu-Kun He, MM, Hui-Zi Li, MD, Hua-Ding Lu, MD, PhD

Abstract

Background: Blood transfusions are associated with many adverse outcomes among spine surgery patients, but it remains unclear whether perioperative blood transfusion during spine surgery and postoperative infection are related. Recently, many related cohort studies have been published on this topic.

Methods: This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The PubMed, Embase, and Cochrane Library databases were searched for eligible published studies. The Newcastle–Ottawa Scale (NOS) was used to assess the methodological quality of the studies, and a random-effects model was used to calculate the odds ratios (ORs) with 95% CIs. Sensitivity analyses were conducted to explore the source of heterogeneity.

Results: The final analysis included 8 cohort studies with a total of 34,185 spine surgery patients. These studies were considered to be of high or moderate quality based on their NOS scores, which ranged from 5 to 9. Pooled estimates indicated that blood transfusion increased the infection rate (OR, 2.99; 95% CI, 1.95 to 4.59; I² = 86%), which was consistent with the sensitivity analyses.

Conclusions: Our results suggest that perioperative blood transfusion is a risk factor for postoperative infection among spine surgery patients. Further study is necessary to identify other influencing factors and to establish the mechanism underlying this relationship. Additional measures may be needed to reduce unnecessary blood transfusions during spine surgery.

Abbreviations: EBL = estimated blood loss, Hb = hemoglobin, HR = hazard ratio, MD = mean difference, NOS = Newcastle–Ottawa Scale, NSQIP = National Surgical Quality Improvement Program, OR = odds ratio, PRBCs = packed red blood cells, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Keywords: blood transfusion, infection, meta-analysis, spine surgery

1. Introduction

Blood loss is one of the major concerns in spine surgery. Many measures such as stripping skeletal muscles and exposing cancellous bone can cause direct or indirect blood loss and are often accompanied by coagulopathy. As a common method used to solve the problem, blood transfusion involves the intravenous infusion of various blood components to patients, improving the oxygen transport capacity of blood and tissue oxygenation. According to the results of 1 study, 8% to 36% of spine surgery patients required perioperative blood transfusions; these transfusions were generally performed 7 days before to 30 days after surgery. Studies have shown that the factors that influence the need for transfusion are complicated, including the patient’s age, preoperative hemoglobin (Hb) level, comorbidities, treatment methods, and duration of surgery.

Blood transfusion is essential and beneficial in many cases, but it is still compromised by a series of possible complications. Recently, allogeneic blood transfusion was speculated to be an independent risk factor for bacterial infections in orthopedic surgery, which may result in higher morbidity and worse prognoses, particularly in elderly patients. This hypothesis was supported by several animal models. However, the same result was not observed when syngeneic blood was given. Most scholars believe that these observations were due to the immunosuppressive effects of allogeneic transfusions. Other research suggested that fracture patients who received less than 3 units of packed red blood cells (PRBCs) had no significant differences in morbidity complications compared to nontransfused patients. It is difficult to confirm the association between blood transfusion and infection. A meta-analysis conducted by Kim provided some useful information showing that allogeneic blood transfusion increased the risk of infection during joint replacement. However, the postoperative infection rate of spine surgery is particularly worthy of attention among orthopedic surgeries because of the long operation time and because swelling and congestion of soft tissue more readily occur. Moreover, the surgery is often accompanied by the placement of internal
transfusion policies during spine surgery. However, the relationship between perioperative blood transfusion and postoperative infection in patients who undergo spinal surgery has not been well described.\[10\]

With advances in technology, blood transfusion practices in spine surgery have undergone significant changes. The use of allogeneic transfusion has substantially decreased, whereas that of autologous and intraoperative autotransfusion has increased.\[11\] The association between blood transfusion and infection must be systematically evaluated in spine surgery. This meta-analysis was designed to determine whether perioperative blood transfusion increases the infection rate among spine surgery patients, which may help establish more appropriate transfusion policies during spine surgery.

2. Methods
This study was based entirely on published data; thus, no ethical approval or patient consent were required.

2.1. Study search and selection
The PubMed, Embase, and Cochrane Library databases were searched for relevant articles published from inception to July 2017. The key words were as follows: ‘spine’ or ‘vertebra’ or ‘sacrum’ or ‘coccyx’ AND ‘blood transfusion’ AND ‘infection’ or ‘toxicemia’ or ‘sepsis’ (refer to Appendix Table 1 for details, http://links.lww.com/MD/D80). The search language was limited to English.

Two reviewers independently assessed the titles and abstracts of papers and resolved discrepancies through discussion. If an agreement could not be reached, a final decision was made by a third reviewer. The inclusion criteria were as follows:
1. observational, cohort studies;
2. studies that examined the impact of blood transfusion on the infection rate among spine surgery patients;
3. sufficient data presented to allow further analysis; and
4. data not duplicated in another manuscript (refer to Table 1 for details).

2.2. Data extraction and quality assessment
We used Microsoft Excel (Microsoft Corporation, USA) to extract the following data: first author, study period, country, demographic parameters, estimated blood loss (EBL), operative time, comorbidities, treatment methods, transfusion, study design, covariates, and outcomes of interest. The primary outcome was infection. The other outcomes included length of hospital stay and morbid complications. The quality of the included observational studies was assessed by the Newcastle–Ottawa Scale (NOS) score.\[12\] The studies were classified as low, moderate, and high quality according to NOS scores of 0 to 3, 4 to 6, and 7 to 9, respectively.

2.3. Statistical analysis
After summarizing the data from each study, we divided the patients into 2 groups: “Transfusion group” and “Non-transfusion group”, according to whether they received perioperative blood transfusion during spine surgery. The effects were assessed by adjusted odds ratios (ORs) or the mean difference (MD). ORs were used instead of hazard ratios (HRs) because of the high incidence of events. We pooled individual study data using the Mantel–Haenszel method. Because of the anticipated heterogeneity, we used a random-effects model. Heterogeneity was evaluated by the I², Chi², and Tau² statistics. A value of I² > 50% was regarded as significant heterogeneity. A two-sided P-value<.05 was considered statistically significant. To explore possible sources of heterogeneity, we performed sensitivity analyses by omitting each study individually to assess the effect of the individual study. All statistical analyses were conducted with Review Manager 5.3.\[13\]

3. Results

3.1. Study selection
A total of 1648 related studies were identified in 3 databases. Forty one studies remained after removing duplicates and irrelevant records after further assessment. Five studies were meta-analyses or reviews, 3 studies were not cohort studies, and the remaining studies did not report primary outcomes from which the required data could be extracted. No other eligible studies were identified in the references of the included studies or important reviews. Finally, 8 studies were included in our meta-analysis. The study selection process was performed as described in the flow diagram.

3.2. Study characteristics
The basic information of the 8 studies is shown in Table 2. All studies were retrospective cohort studies except for one ambispective cohort study. The sample size of the included studies ranged from 56 to 13,695. Treatment methods mainly involved various types of spine surgery. Demographic characteristics, comorbidities, preoperative Hb levels, EBL, and operative times showed wide variability across the included studies. The NOS scores of the studies are shown in Appendix Table 2., http://links.lww.com/MD/D80 4 studies were of moderate quality, and 4 were of high quality.

3.3. Infection rate
The pooled analysis suggested that blood transfusion increased the infection rate among spine surgery patients (8 studies; OR, 2.99; 95% CI, 1.95–4.59; Fig. 1), with high heterogeneity (I² = 86%). The sensitivity analyses showed that the ORs ranged from 2.65 (95% CI, 1.76–3.99) to 3.27 (95% CI, 1.93–5.54), and the I² statistic ranged from 78% to 88%. Two studies

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### Table 1

<table>
<thead>
<tr>
<th>Inclusion and exclusion criteria of the current meta-analysis.</th>
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<tbody>
<tr>
<td><strong>Detailed inclusion and exclusion criteria based on PICOS framework</strong></td>
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<tr>
<td><strong>Populations</strong></td>
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<td><strong>Intervention/Exposure</strong></td>
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<td><strong>Control</strong></td>
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<td><strong>Study design</strong></td>
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<td><strong>Exclusion criteria</strong></td>
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Table 2
Baseline characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Number of patients (Exposure/Control)</th>
<th>Age (mean) (Exposure/Control)</th>
<th>Comorbidity</th>
<th>Treatment methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Covariates in Multivariable model</strong></td>
<td><strong>Number of patients</strong></td>
<td><strong>Sex</strong></td>
<td><strong>Comorbidity</strong></td>
</tr>
<tr>
<td><strong>Author/year</strong></td>
<td><strong>Study design</strong></td>
<td><strong>(Exposure/Control)</strong></td>
<td><strong>Male</strong></td>
<td><strong>(Exposure/Control)</strong></td>
</tr>
<tr>
<td>Aladine et al, 2017</td>
<td>Ambispective cohort study</td>
<td>60/100</td>
<td>57.78/56.28</td>
<td>Diabetes, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), hyperlipidemia, peripheral vascular disease (PVD), hypertension (HTN), and atrial fibrillation, DVT, PE, hematoma, cardio-pulmonary arrest, and CVA</td>
</tr>
<tr>
<td>Christian et al, 2017</td>
<td>Sweden Retrospective cohort study</td>
<td>36/20</td>
<td>64.3/67.3</td>
<td>–</td>
</tr>
<tr>
<td>Daniel et al, 2017</td>
<td>America Retrospective cohort study</td>
<td>603/360</td>
<td>59.52/215.194</td>
<td>Transient ischemic attack (TIA), cerebrovascular attack (CVA), myocardial infarction (MI), kidney injury, deep venous thrombosis (DVT), pulmonary embolism (PE), and disseminated intravascular coagulation (DIC).</td>
</tr>
<tr>
<td>Purvis et al, 2017</td>
<td>America Retrospective cohort study</td>
<td>2374/4557</td>
<td>63.7/58.8</td>
<td>Thrombotic event, kidney injury, respiratory event, ischemic event</td>
</tr>
<tr>
<td>Ahmed et al, 2016</td>
<td>America Retrospective cohort study</td>
<td>2407/11288</td>
<td>63.75/8.9</td>
<td>DVT, PE, MI</td>
</tr>
<tr>
<td>Janssen et al, 2016</td>
<td>America Retrospective cohort study</td>
<td>293/3428</td>
<td>64/113/1865</td>
<td>Congestive heart failure, Dementia, Chronic pulmonary disease, Rheumatologic disease, Liver disease, Diabetes, Hemiplegia or paraplegia, Renal disease, tumor, AIDS/HIV</td>
</tr>
<tr>
<td>Kato et al, 2016</td>
<td>Japan Retrospective cohort study</td>
<td>4275/4275</td>
<td>72.7/26.9/27.14</td>
<td>Diabetes, Cardiovascular diseases, cerebrovascular diseases, and hemodialysis</td>
</tr>
<tr>
<td>Triulzi et al, 1992</td>
<td>America Retrospective cohort study</td>
<td>248/5</td>
<td>30.3/32.8/34.1</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: EBL = Estimated Blood Loss, ASA = American Society of Anesthesiologists, TIA = Transient Ischemic Attack, CVA = Cerebrovascular Attack, MI = Myocardial Infarction, DVT = Deep Vein Thrombosis, PE = Pulmonary Embolism, CVA = Cerebrovascular Accident, DIC = Disseminated Intravascular Coagulation.
(Purvis et al, 2017 and Janssen et al, 2016) were identified as the source of statistical heterogeneity (refer to Table 2 for details). We found that removing either 1 of the studies did not significantly reduce heterogeneity: $I^2 = 82\%$ when we removed the study by Purvis et al 2017, and $I^2=78\%$ when we removed the study by Janssen et al 2016 (Appendix Fig. 1 and Appendix Fig. 2, http://links.lww.com/MD/D80). However, when both studies were removed, no heterogeneity was observed among the 6 remaining studies, but the result was not substantially changed ($I^2 = 0\%;$ OR, 1.93; 95% CI, 1.65–2.26; Fig. 2). Since only 8 studies were included, a funnel plot was not appropriate for this study.

### 3.4. Other outcomes

To further understand the impact of blood transfusion on spine surgery patients, we also analyzed the length of hospital stay and morbid complications. According to the results, blood transfusion was associated with a longer hospital stay (4 studies; MD, 3.55; 95% CI, 1.97–5.14; Fig. 3) and a higher rate of morbid complications (5 studies; OR, 2.65; 95% CI, 1.23–5.71; Fig. 4) among spine surgery patients. The studies showed high heterogeneity ($I^2 = 73\%$ in Fig. 3 and $I^2 = 98\%$ in Fig. 4); however, the results were consistent in the sensitivity analyses. When we separately removed the studies to investigate the sources of heterogeneity, the results were as follows: MD, 2.76; 95% CI, 1.63 to 3.90 (Fig. 5) and MD, 2.80; 95% CI, 2.35 to 3.35 (Fig. 6). Therefore, the results still fully indicated the adverse effects of blood transfusion on patient prognosis.

### 4. Discussion

This review was performed by strictly following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The results showed that perioperative
blood transfusion increased the risk of infection among spine surgery patients, which has also been supported by other studies. Many studies have observed a relationship between blood transfusion and superficial wound infections. Some small case-control studies have suggested that blood transfusion increases surgical site infection after spine surgery, but the number of such studies was too small to perform a separate analysis. To ensure the consistency of the included studies, we did not include these studies in our analysis. For other surgical procedures such as joint replacement, some evidence suggests that blood transfusion is related to increased infection rates. However, significant differences exist between arthroplasty and spine surgery. Spine surgery often involves less blood loss, and the subsequent infection is greatly affected by the surgical site, surgical route, and other confounding factors, which increases the difficulty of identifying the relationship between blood transfusion and infection.[14,15,16]

The increased infection rate caused by blood transfusion is usually attributed to transfusion-related immunosuppression.[17] However, the mechanism responsible for this relationship remains unknown. Other possible factors including transfusion errors and transfusion-transmissible infections also cause serious risks, but they seldom occur and are entirely preventable.[17]

Many potential confounding factors might have affected our results. For example, the use of a urinary catheter, which was usually in place longer than 120 minutes, might increase the infection rate among surgical patients.[2] The different infection rates between the Transfusion group and the Non-transfusion group could also be explained by the difference in blood loss.

Moreover, our results suggested a relationship between blood transfusion and other interesting outcomes including the length of hospital stay and morbid complications in spine surgery patients. Together, these factors revealed the adverse effects of blood transfusions on patient prognosis, but the relationship among these factors is still unclear. Because of the lack of standardization of transfusion protocols in the database, the results might be biased, and additional relevant studies are required.

Recently, a related systematic review suggested an association between allogeneic transfusion and infection in spine surgery patients based on several low-strength studies with a high or...
The current evidence indicates that perioperative blood transfusion increases the risk of postoperative infection among spine surgery patients. Because of the high heterogeneity among studies, the results should be interpreted cautiously, and more randomized, controlled, high-quality studies are necessary to clarify the influence of other factors, such as EBL and operative time, on infection.

Author contributions
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References