The efficacy and safety of topical administration of tranexamic acid in spine surgery: a meta-analysis

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Résumé

Background: Nous avons mené une analyse de méta-analyse de trials contrôlés randomisés (RCTs) et non-RCTs pour évaluer l'efficacité et la sécurité de l'acide tranexamic (TXA) en chirurgie de la colonne vertébrale.

Méthodes: Les articles académiques pertinents ont été identifiés dans les bases de données Cochrane Library, MEDLINE (1966–2017.11), PubMed (1966–2017.11), Embase (1980–2017.11), et ScienceDirect (1985–2017.11). Les sources secondaires ont été identifiées à partir des références des publications incluses. Les données ont été analysées avec RevMan 5.1.

Résultats: Trois RCTs et un non-RCT ont rencontré les critères d'inclusion. Il y avait des différences significatives dans la perte totale de sang (MD = −267.53, 95% CI −373.04 to −106.02, P < 0.00001), le volume de drainage (MD = −413.00, 95% CI −481.17 to −122.84, P < 0.00001), le niveau de hémoglobine postopératoire (MD = 0.95, 95% CI 0.44 to 1.47, P = 0.0003), et la durée d'hospitalisation (MD = −143.42, 95% CI −202.19 to −240.67, P < 0.00001). Aucune différence significative n'a été trouvée pour la nécessité de transfusion, le thrombophlébite profonde (DVT), l'embolie pulmonaire (PE), la hémorragie d'abcès de la plaie, et le risque de complications associées.

Conclusions: La présente analyse de méta-analyse indique que l'application topique de TXA en chirurgie de la colonne vertébrale réduit la perte totale de sang et le volume de drainage et préserve un niveau plus élevé de hémoglobine postopératoire sans augmenter le risque de DVT, d'hémorragie, de DVT, et de PE.

Mots clés: Acide tranexamic, Colonne vertébrale, Perte de sang, Transfusion, Méta-analyse

Introduction

La chirurgie de la colonne vertébrale est associée à une perte sanguine importante péri-opératoire qui peut mener à une anémie aiguë et à des complications graves [1]. Les transfusions sanguines sont souvent nécessaires pour corriger une anémie aiguë et elles portent leurs propres risques, tels que l'hémolyse, les réactions anaphylactiques, et une transmission de maladies infectieuses [2, 3]. De plus, les transfusions sanguines augmentent le fardeau économique. Plusieurs interventions conservatrices ont été utilisées pour minimiser la perte sanguine, par exemple la hémodilution, le sauvetage du sang, l’anesthésie hypotensive, l’électrocoagulation binaire, et les agents hémostatiques. Cependant, de nombreux patients continuent de nécessiter des transfusions sanguines.

Le TXA, un médicament antifibrinolytique compétitif qui bloque le site de liaison à la lysine du plasmine, a été utilisé pour diminuer la perte sanguine en chirurgie de la colonne vertébrale depuis de nombreuses années [5]. Différents essais ont rapporté que l’administration intraveineuse de TXA réduisait la perte sanguine et les transfusions sanguines allogéniques en chirurgie de la colonne vertébrale sans augmenter les complications associées [6–8]. En théorie, il reste un problème non résolu concernant la potentielle thrombogénicité de l’administration intraveineuse de TXA [9]. L’administration topique de TXA réduirait la thrombogénicité du TXA intraveineux [9]. Les études récentes [10–12] ont rapporté que l’administration topique de TXA réduirait la perte sanguine et les transfusions sanguines en chirurgie de la colonne vertébrale sans augmenter les complications associées. Cependant, il existe des limites aux résultats de ces études antérieures telles que le petit nombre de patients et les résultats inconclusifs. Par conséquent, nous avons mené une analyse de méta-analyse de grande échelle pour évaluer l’efficacité et la sécurité de l’administration topique de TXA en chirurgie de la colonne vertébrale.
topical application of TXA in spinal surgery from randomized controlled trials (RCTs) and non-RCTs.

**Methods**

**Search strategy**

Electronic databases were searched, including Cochrane Library, MEDLINE (1966–2017.11), PubMed (1966–2017.11), Embase (1980–2017.11), and ScienceDirect (1985–2017.11). In addition, the same search terms were manually searched for the reference lists of all included studies, relevant books, review articles, and meeting proceedings to identify trials that might have been missed in the electronic search. The search process was conducted as follows in Fig. 1. The key words “tranexamic acid,” “topical,” “spine,” and “surgery” were used in combination with the Boolean operators AND or OR.

**Inclusion criteria**

Studies were considered eligible for inclusion if they met the following criteria: (1) patients treated with spine surgery; (2) the intervention used TXA and studies contained a control group; (3) the outcomes included blood loss, blood transfusion, post-operative Hb level, length of hospital stay, peri-operative outcomes, and complications; and (4) the study was a published or unpublished comparative trial (RCTs or non-RCTs).

**Exclusive criteria**

We excluded articles that were (1) studies without controlled groups, (2) articles without available full-text versions, and (3) no available outcomes data.

**Selection criteria**

Two reviewers independently screened the titles and abstracts for eligibility criteria. Subsequently, the full text of the studies that potentially met the inclusion criteria were read, and the literature was reviewed to determine the final inclusion. Disagreement was resolved by consulting a third reviewer.
Quality assessment
According to whether the study is a randomized or non-randomized trial, the methodological index for non-randomized studies (MINORS) form was used to assess retrospective controlled trials [13]. Quality assessment for RCT was conducted according to a modification of the generic evaluation tool used by the Cochrane Bone, Joint and Muscle Trauma Group [14]. Disagreements were resolved by consensus or consultation with the senior reviewer.

Data extraction
Two researchers independently extracted the data from the included literature. The corresponding author was consulted for details in the case of incomplete data. The following information was extracted: first author name, year of publication, intervening measures, comparable baseline, sample size, and outcome measures. Other relevant parameters were also extracted from individual studies.

Data analysis and statistical methods
Pooling of data was analyzed by RevMan 5.1 (The Cochrane Collaboration, Oxford, UK). Heterogeneity was estimated depending on the value of $P$ and $I^2$ using the standard chi-square test. When $I^2 > 50\%$, $P < 0.1$ was considered to be a significant heterogeneity. Therefore, a random-effects model was applied for data analysis. A fixed-effects model was used when no significant heterogeneity was found. Subgroup analysis was performed to investigate sources in the case of significant heterogeneity. Mean difference (MD) and 95% confidence interval (CI) were presented for continuous outcomes. Risk difference (RD) and 95% CIs were calculated for dichotomous data.

Results
Search results
A total of 186 studies were identified as potentially relevant literature reports. By scanning title and abstract, 182 reports were excluded according to the eligibility criteria. No additional studies were obtained after the reference review. Ultimately, three RCT [11, 15, 16] and one non-RCT [12] were eligible for data extraction and meta-analysis. The search process is shown in Fig. 1.

Study characteristics
Demographic characteristics and details concerning the literature type of the included studies are summarized in Table 1. Statistically similar baseline characteristics were observed between both groups.

Risk of bias assessment
RCT quality was assessed based on the Cochrane Handbook for Systematic Review of Interventions (Fig. 2). For the non-RCTs, the MINORS score is 20. The methodological quality assessment is illustrated in Table 2.

Outcomes of meta-analysis
It was possible to perform a meta-analysis with nine outcomes (Table 3). There were statistically significant differences between topical TXA and control groups for total blood loss (MD $= -267.53$, $P = 0.00001$), drainage volume (MD $= -157$, $P = 0.00001$), length of hospital stay (MD $= -1.42$, $P < 0.0001$), and postoperative hemoglobin level (MD $= 0.95$, $P = 0.0003$). There were no statistically significant differences between topical TXA and control groups for blood transfusion rate (RD $= -0.18$, $P = 0.28$), wound hematoma (RD $= 0.00$, $P = 1.00$), wound infection (RD $= 0.00$, $P = 1.00$), DVT (RD $= 0.00$, $P = 1.00$), and PE (RD $= 0.00$, $P = 1.00$).

Discussion
The intravenous application of TXA has been confirmed as effectively decreasing blood loss and transfusion requirement in spinal surgery [6, 7]. Recently, topical TXA is widely established in hip and knee arthroplasty and successfully reduced postoperative blood loss and blood transfusion requirements [17, 18]. Astedt et al. [19] considered that TXA acts at the active bleeding and clot formation site and not within the circulation itself. But there have been limited studies reporting the efficacy of topical administration in spinal surgery. This is the first meta-analysis to evaluate the efficacy and safety of topical application of TXA in spinal surgery. The most important results of the present meta-analysis were that the topical application of TXA during spinal surgery decreased total blood loss, drainage volume, and length of hospital stay and preserved higher postoperative hemoglobin level. Moreover, no significant difference is noticeable regarding the occurrence of infection, hematoma, DVT, and PE.

Total calculated blood loss ranged from 650 to 2839 ml in adult spine fusion surgery, and transfusion requirements were 50 to 81% without plotting any strategy to reduce hemorrhage [20]. Pooled results indicated that total blood loss and drainage volume in the topical TXA group were significantly lower than that in the control group. Total blood loss included intra-operative blood loss (IBL), postoperative blood loss (PBL), and hidden blood loss (HBL). Xu et al. [15] performed an RCT evaluating the efficacy of topical tranexamic acid in posterior spinal fusion surgeries. They reported that IBL showed no significant difference between two groups. Most of current studies calculated PBL by measuring the amount of “blood” by wound drainage. All
included studies reported that topical TXA reduce post-operative drainage volume. These results were consistent with our meta-analysis. The mechanisms of HBL may be hemolysis [21, 22] and loss going into tissue compartments [23]. Smorgick et al. [24] reported that hidden blood loss accounts for 45% of total blood loss. Ren et al. [12] reported that topical TXA effectively reduce HBL following posterior lumbar interbody fusion (PLIF).

The indications for blood transfusion were based on postoperative hemoglobin levels and clinical symptoms of anemia. Although present meta-analysis showed that blood transfusion rate in topical TXA group is lower, there was no significant difference found between the two groups. The reason could be that transfusions trigger varied from different studies. Length of hospital stay is another element in determining the effectiveness of THA and TKA. Recently, two RCTs [11, 15] have reported that topical administration of TXA reduces length of hospital stay in PLIF. This was consistent with our meta-analysis results. The decreased blood loss contributes to not only a lower risk of anemia but also better recovery and shorter hospitalization.

DVT is a common complication following spine surgery, may develop to PE and result in serious complications. In theory, the intravenous application of TXA may enhance the possibility of venous thromboembolism. Present meta-analysis showed that topical application of TXA did not increase the risk of DVT or PE. Bleeding may still occur after wound closed and result in wound hematoma or infection. Topical application of TXA is simple and provides a maximum concentration of TXA at the bleeding field. Present meta-analysis showed that topical TXA did not increase the risk of wound hematoma or infection. Taking these findings together, we conclude that topical TXA is safe in spine surgery.

Several potential limitations should be noted. (1) Only four studies with relatively small sample size were included; (2) subgroup analysis was not performed because of the limited number of included studies, and we could
not determine the source of heterogeneity; (3) methodological weaknesses exist in studies; and (4) several outcome parameters were not fully described so that we failed to perform a meta-analysis.

**Conclusion**

The present meta-analysis indicated that the topical application of TXA in spinal surgery decreases the total blood loss and drainage volume and preserves higher postoperative hemoglobin level without increasing the risk of infection, hematoma, DVT, and PE. More high-quality randomized controlled trials are required due to the limited quality and data in the evidence currently available.

**Abbreviations**

CI: Confidence interval; DVT: Deep vein thrombosis; HBL: Hidden blood loss; IBL: Intra-operative blood loss; MD: Mean difference; MINORS: Methodological index for non-randomized studies; PBL: Post-operative blood loss; PE: Pulmonary embolism; PLIF: Posterior lumbar interbody fusion; RCTs: Randomized controlled trials; RD: Risk difference; TKA: Total knee arthroplasty; TXA: Tranexamic acid

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**Availability of data and materials**

As this paper is a meta-analysis, there are no patient data sets. The search strategy for the study selection supports the conclusion of the meta-analysis.

**Authors’ contributions**

WL and RXS conceived the study. WL and XLM searched the literature and collected the data. WL, RXS, HJ, and XLM performed the statistical analysis. WL and RXS drafted the manuscript. XLM reviewed the manuscript. WL, RXS, HJ, and XLM revised the manuscript. All authors have read and approved the final paper.

**Ethics approval and consent to participate**

Not applicable. This meta-analysis does not involve research on humans.

**Competing interests**

The authors declare that they have no competing interests.

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**Table 3 Meta-analysis results**

| Outcome                                | Studies | Groups (A/C) | Overall effect | Effect estimate | 95% CI      | p value  | Heterogeneity | 
|----------------------------------------|---------|--------------|----------------|-----------------|-------------|-----------|--------------|
| Total blood loss                       | 2       | 66/64        |                | 267.53          | −0.373, 106.02| 0.000001  | 0.38         |
| Drainage volume                        | 4       | 136/134      |                | 157.00          | −0.191, 122.84| 0.00001   | 0.16         |
| Blood transfusion rate                 | 4       | 136/134      |                | 0.18            | −0.51, 0.15   | 0.28      | 0.00001      |
| Postoperative hemoglobin level         | 2       | 80/80        |                | 0.95            | 0.44, 1.47    | 0.0003    | 0.43         |
| Hematoma                               | 3       | 120/120      |                | 0.00            | −0.03, 0.03   | 1.00      | 1.00         |
| Infection                              | 3       | 120/120      |                | 0.00            | −0.03, 0.03   | 1.00      | 1.00         |
| Deep Vein Thrombosis                   | 2       | 90/90        |                | 0.00            | −0.03, 0.03   | 1.00      | 1.00         |
| Pulmonary embolism                      | 2       | 90/90        |                | 0.00            | −0.03, 0.03   | 1.00      | 1.00         |
| Length of hospital stay                | 2       | 70/70        | −1.42          | −0.93           | 0.00001      | 79        | 0.03         |

* A: aminocaproic acid, C: control, CI: confidence interval

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