Tranexamic acid in hip fracture surgery:  
A systematic review and meta-analysis

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Abstract
Aims: The primary objective of this review was to determine whether tranexamic acid (TXA) reduces transfusion rates in patients undergoing surgery for hip fractures. The secondary objective was to assess the effects of TXA on mortality and thromboembolic events in the same cohort. Methods: A systematic review of electronic databases was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We included randomized controlled trials comparing perioperative TXA in patients treated surgically for hip/proximal femoral fractures against placebo. The primary outcome was the proportion of patients requiring blood transfusion. Secondary outcomes were blood loss, mortality, and complications. Meta-analysis was performed using inverse variance and random effects model. Results: The pooled data from 10 studies involving 842 patients showed that the proportion of patients requiring blood transfusion was significantly less in the TXA group (risk ratio (RR) 0.72, 95% confidence interval (CI) 0.59–0.88). There was no difference between TXA and control groups when comparing mortality (RR 1.17, 95% CI 0.65–2.10), deep venous thrombosis (RR 1.14, 95% CI 0.43–3.06), pulmonary embolism (RR 0.53, CI 0.09–3.02), acute coronary syndrome (RR 1.52, CI 0.18–12.98), cerebrovascular events (RR 0.78, CI 0.16–3.68), or wound complications (RR 1.61, CI 0.51–5.13). Conclusion: There is evidence that TXA reduces the proportion of patients requiring blood transfusions when undergoing hip fracture surgery. However, the small sample size and low event rates for adverse effects preclude any definitive conclusions from being established regarding adverse effects. Future trials should be powered to further assess potential complications and determine the ideal dosage and regime.

Keywords
hip fracture, meta-analysis, orthogeriatrics, tranexamic acid

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Introduction
Hip fractures are common and debilitating, posing a significant burden to both the individual and society. There was an estimated 16,518 hip fractures among adult Australians in 2006–2007, and this incidence is expected to rise secondary to an aging population. Thus, evidence-based guidelines to direct optimal peri- and intraoperative management are crucial.1,2 Almost all these fractures are treated operatively and may result in significant blood loss. Increased surgical blood loss is associated with diminished functional recovery and increased long-term mortality (particularly in this susceptible subset of patients).3

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The etiology of blood loss is multimodal, with increased fibrinolytic activity implicated. Strategies to counteract bleeding include preoperative optimization; intraoperative hypotensive anesthesia, administration of antifibrinolytic agents, autologous reinfusion, and meticulous hemostasis; and postoperative transfusion. Many of the approaches aimed to reduce this risk remain cost-inefficient, supply-limited, and replete with their own adverse events (including cerebral sequelae, infection, and transfusion-related lung injury).

Tranexamic acid (TXA) is a simple and inexpensive antifibrinolytic agent. A synthetic derivative of the amino acid lysine exerts its action by reversibly blocking lysine-binding sites on plasminogen, reducing its conversion to the active metabolite plasmin and thus the dissolution of fibrin. TXA can be administered both topically and parenterally. Utilization of TXA has been shown to reduce allogenic blood transfusion in a range of surgical fields (including dental, cardiothoracic, urological, and arthroplasty procedures). A Cochrane review showed that in an emergency surgical setting, TXA reduced the probability of receiving an erythrocyte transfusion by 30% (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.52–0.94). Previous literature suggests that the use of TXA in hip fracture surgery diminishes blood transfusion requirement with low quality evidence, suggesting no increased risk of thrombotic events. However, limited numbers have limited interpretation of cause and effect.

Given its simplicity, wide availability, and cheapness, it is important to evaluate the effect of TXA in hip fracture patients, as diminished bleeding in this population may be greatly advantageous. Newer evidence should be incorporated to provide current best practice guidelines. Thus, this study analyzes the contemporary literature regarding the utility of TXA in hip fracture surgery and provides guidelines for future clinical use. The primary objective was to determine whether TXA reduces transfusion rates in patients undergoing surgery for hip fractures. The secondary objective was to assess the effects of TXA on mortality and thromboembolic events in this patient group.

Methods
A thorough systematic search was performed by two separate authors using electronic databases and references of relevant articles during December 2018 and updated in March 2019 in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The search was not limited by date, language, or publication status. Electronic databases search included the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, ISI Web of Science: Science Citation Index Expanded, and the WHO International Clinical Trials Registry Portal (refer Online Appendix 1 for search strategy). The references of all relevant articles were also screened.

Studies eligible for inclusion were randomized controlled trials comparing the effects of perioperative intravenous TXA (in any dosage or formulation) to a placebo or no TXA, in human patients greater than 18 years old treated surgically for hip/proximal femoral fractures (AO types 31-A and 31-B). All titles and abstracts were screened for potential eligibility. Full texts of relevant trials were
obtained and their bibliographies were screened. Authors of the trials were contacted for missing data. Authors of incomplete and unpublished trials were also contacted and asked for data.

The Cochrane collaboration’s risk of bias tool was used to assess the quality of included studies. The domains assessed for bias were sequence generation, allocation concealment, blinding, incomplete outcome data reporting, and selective outcome reporting.

The primary outcome assessed was the proportion of patients requiring a blood transfusion. Secondary outcomes included the number of units of blood transfused, mortality, and morbidity (including deep venous thrombosis, pulmonary embolism, acute coronary events, cerebrovascular events, and wound complications). Blood loss was initially intended to be included, but heterogeneity in the manner of collection and reporting precluded inclusion in this meta-analysis. Data were extracted from the text, tables, and
figures of all included studies. Statistical analysis was performed using review manager 5.3 (RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The RR and 95% CI were the measurement used for dichotomous outcomes, while mean difference with 95% CI was used for continuous data. Heterogeneity was assessed using a combination of visual inspection of the forest plot as well as the standard $\chi^2$ ($p$ value < 0.10) and the $I^2$ statistic. The data from the trials were pooled using the generic inverse variance method with random effects model.

**Results**

**Search results**

The search yielded 235 unique results. Following full-text screening, 10 studies were deemed appropriate for inclusion in this study13–22 (refer Figure 1). All trials had a predetermined transfusion protocol and these also differed (Table 1).

A total of 842 patients were included in the 10 trials eligible for meta-analysis, with 415 patients receiving TXA and 427 patients receiving placebo or control. Refer to Online Appendix 2 for forest plots of all analyses included below. Cochrane Risk of Bias demonstrated largely low risk, with high risk in select studies with relation to blinding and incomplete data (Figure 2 and 3).

**Transfusion**

Patients who received TXA had a statistically significantly lower risk of requiring transfusion (RR 0.72, CI 0.59–0.88, $p = 0.002$). Only one trial measured units of blood transfused in a manner able to be included, but this was not statistically significant (RR 0.79, CI 0.60–1.03, $p = 0.09$) (Table 2).

**Blood loss**

Total blood loss was significantly lower in the TXA group compared to placebo patients (mean difference $-266.75$, CI $-367.8$ to $-165.8$, $p < 0.0001$; Table 2).

**Mortality**

Mortality at any timepoint was not statistically significantly different when comparing TXA and placebo patients (OR 1.17, CI 0.65–2.10, $p = 0.59$; Table 2).

**Thromboembolic sequelae**

**Deep vein thrombosis.** Rates of deep vein thrombosis were not statistically significant between TXA and placebo (RR 1.14, CI 0.43–3.06, $p = 0.79$).

**Figure 2.** Cochrane risk of bias tool summary.

**Pulmonary embolism.** Rates of pulmonary embolism were not statistically significant between TXA and placebo (RR 0.53, CI 0.09–3.02, $p = 0.48$).

**Acute coronary syndrome.** Rates of acute coronary syndrome were not statistically significant between TXA and placebo (RR 1.52, CI 0.18–12.98, $p = 0.70$).

**Cerebrovascular accident.** Rates of cerebrovascular accidents were not statistically significant between TXA and placebo (RR 0.78, CI 0.16–3.68, $p = 0.75$; Table 2).
Wound complications. The rate of wound complications was not significantly different between the two groups (RR 1.61, CI 0.51–5.13, \( p = 0.42 \); Table 2).

Discussion
Minimization of blood loss in the particularly susceptible population of the elderly undergoing surgical management of proximal femoral fractures is crucial. Although many trials have demonstrated a significant reduction of transfusion rates in elective hip surgery postutilization of TXA, little research has been performed in those undergoing emergency hip surgery. Hip fracture patients are very different from those undergoing elective hip surgery—they tend to be older and at higher risk of postoperative complications. Additionally, data regarding complications of TXA usage in any surgery are scarce (due to low occurrence rates), and it has been suggested that future trials be powered to focus on complications, rather than the established benefits.6

This review found a significant reduction in transfusion requirements in patients, where TXA was utilized, by 25%. A nonsignificant reduction in mean units transfused per patient was also noted, with no significant difference in mortality, thromboembolic events, or wound complications. These results are in keeping with prior research pertaining to elective hip surgery and all emergency operations.11,23

No significant differences in complications were noted between those receiving TXA and those that did not. Although not significant, a trend toward more frequent deep vein thrombosis, acute coronary syndromes, cerebrovascular events, and wound complications was noted in the TXA group; however, mortality and pulmonary emboli were diminished in this group. These results challenge previous suggestions that the utilization of TXA may promote a hypercoagulable state if used in hip fracture patients.21 Furthermore, it is unclear as to whether patients who did indeed suffer venous thromboembolic events had predisposing characteristics—future studies should aim to clarify this. Given their relatively low incidence, conclusions regarding these complications and the use of TXA are likely best drawn from registry-style studies.

A prior systematic review was identified, which reported moderate quality evidence that TXA reduces blood transfusion in hip fracture surgery, with low quality evidence, suggesting no increased risk of thrombotic events.24 However, low numbers do limit interpretation of cause and effect, and the current review has included a number of further studies that have since been published.

This systematic review is not without its limitations. Small sample size and low event rates limit the power of this review as well as the establishment of definitive recommendations. Although all included studies were randomized controlled and double blinded, only two performed an intention to treat analysis. Mortality and complications were included as secondary outcomes in only a subset of studies. Several papers reported incomplete outcome data, with resultant increased attrition bias. The dosage and frequency of TXA varied between trials, as did predetermined transfusion protocols and chemical thromboprophylaxis, which inevitably may have skewed the number of patients receiving transfusion. No mention was made of implementation of other blood minimization strategies (cell savers, and so on). Additionally, data were excluded from ongoing current trials, due to lack of communication from the authors, and may have altered the analysis.

Despite these limitations, this systematic review and meta-analysis demonstrate a significant reduction in transfusion requirements when TXA is utilized. Nonsignificant reductions in mean units transfused, mortality, deep venous thrombosis, and pulmonary emboli were also noted. This review supports the usage of TXA as an adjunct in the peri- and intraoperative management of patients with proximal femoral fractures. Future trials should be powered to further assess potential complications and determine the ideal dosage and regime.
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Supplemental material
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