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Effectiveness and Safety of Tranexamic Acid Use in Acute Traumatic Injury in the Prehospital and In-hospital Settings: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background and Objectives: This systematic review and meta-analysis of randomized controlled trials (RCTs) aims to assess efficacy and safety of tranexamic acid (TXA) use in acute traumatic injuries.

Methods: PubMed and Cochrane libraries were searched for relevant RCTs published between January 2011 and January 3, 2021. Cohen's Q Test for heterogeneous effects was used to determine the appropriateness of fixed versus random effects models.

Results: Twenty-two studies met inclusion criteria. Meta-analysis of relative risk of mortality between treatment and placebo groups in the in-hospital, and perioperative settings was not significant. However, the risk of mortality is significantly lower in the treatment versus placebo group when TXA was given as loading dose only. Ten of the 11 studies evaluating perioperative use of TXA included in systematic review found significantly lower blood loss in the treatment compared with placebo groups, but results of meta-analysis showed no significant difference. Results of meta-analysis indicate that the risk of venous thromboembolism (VTE) in the in-hospital treatment group is greater than that of the placebo. In subset analysis of studies using only a single loading dose, there were no significant differences in VTE.

Conclusions: Systematic review supports TXA benefits are most evident when given shortly after injury and meta-analysis supports TXA reduces mortality as a single loading dose. Systematic review supports perioperative use of TXA when large volume blood loss is anticipated. Meta-results showed no significant difference in risk of thromboembolism in single-dose TXA treatment compared with placebo. These findings suggest that TXA is safe and effective for control of traumatic bleeding.

Keywords: tranexamic acid prehospital use, tranexamic acid in-hospital use, tranexamic acid perioperative use, acute trauma, outcomes measures

INTRODUCTION

Traumatic injury is the leading cause of death in the United States among those aged ≤45 years.[1,2] Most commonly, death is secondary to traumatic brain injury (TBI) or hemorrhage.[3,4] Tranexamic acid (TXA) inhibits fibrinolysis, strengthens clot formation, and reduces overall incidence of trauma-induced coagulopathy.[5] TXA is a competitive inhibitor of plasminogen, which stops enzymatic breakdown of fibrin by plasmin, thereby facilitating secondary hemostasis.[6]

The CRASH-2 and CRASH-3 trials showed a significant reduction in mortality with administration within 3 hours of injury.[7,8] However, concerns exist about the risk of venous thromboembolic (VTE) events (e.g., pulmonary embolism [PE], deep vein thrombosis [DVT]).[9] Prehospital TXA administration was evaluated in the STAAMP trial, which showed mortality benefit in patients with severe shock who received TXA within 1 hour of injury and benefit with dosages higher than standard.[10]

Objectives

This systematic review and meta-analysis aims to investigate the safety and efficacy of TXA use in acute traumatic injury through review of recent placebo controlled randomized clinical trials (RCTs) by assessing quantitative clinical outcomes in the pre-hospital, in-hospital, and perioperative settings.

Population, Intervention, Comparator, and Outcomes

PICO 1

In adult trauma patients without TBI, is prehospital use of TXA associated with lower incidence of mortality, complication rates, and blood loss?

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A.E. did study design and conception. S.R., A.L., I.Z., M.A., R.S., M.M., and A.E. did data collection, analysis, and interpretation. S.R., A.L., I.Z., M.A., R.S., M.M., and A.E. did article preparation and drafting. A.E., A.L., M.M., S.R., I.Z., R.S., and M.A. did critical revisions of article. All authors read and approved the final article.

S.R. and A.L. share first authorship on this work.

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PICO 2

In adult trauma patients without TBI, is in-hospital only use of TXA associated with lower incidence of mortality, complication rates, and blood loss?

PICO 3

In adult trauma patients without TBI, is perioperative only use of TXA associated with lower incidence of mortality, complication rates, and blood loss?

PICO 4

In adult trauma patients with TBI, is use of TXA associated with lower incidence of mortality, complication rates, and blood loss?

METHODS

Data Sources and Search Strategy

This study was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] PubMed and Cochrane databases were searched for studies published between January 1, 2011, and January 3, 2021. The following search keywords were included: "trauma" AND "tranexamic acid" AND "traumatic brain injury," "trauma" AND "tranexamic acid" AND "blunt," "trauma" AND "tranexamic acid" AND "penetrating" "trauma" AND "tranexamic acid" AND "prehospital." Studies not published in the English language were excluded. Studies were first screened by title and abstract, then by full text. A final literature search was performed on January 3, 2021.

Study Selection and Eligibility Criteria

There were no limits on country of publication, TXA administration setting, route, dosage, or patient follow up. While there were no limitations on patient age, included literature failed to report significant data regarding TXA administration in pediatric trauma patients. Studies were excluded if quantitative clinical outcomes were not reported. Surveys, editorials, commentary, and non-RCTs were excluded.

Risk of Bias and Quality of Evidence Assessment

Quality of evidence for all included studies was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.[12] GRADE criteria were also utilized to determine risk of bias.

Data Collection Process

The initial literature search was performed by S.E.R., A.E., I.Z., and A.L. and later screened by article title and abstract for exclusion. Authors S.E.R., A.E., I.Z., A.L., and M.A.A. performed secondary searches. The final literature search was conducted by A.E. and S.E.R. for data extraction from full-text RCTs. Any discrepancies in screened and selected articles were reviewed and resolved by A.E., M.M., and S.E.R. The extracted data included publication year, patient population, patient demographics, the setting, route, and dosage of TXA, fraction of patients with TBI, blood loss, units of transfused blood, Glasgow Coma Scale (GCS), Injury Severity Score (ISS), mortality, complications, and patient follow-up time.

Outcome Measures

Primary outcome is in-hospital and 30-day mortality. Secondary outcomes included complications such as DVT, PE, or stroke. Tertiary outcomes included blood loss. Outcomes were further analyzed to determine the effect of ISS, TXA administration setting/dosage, and by severity of TBI as evaluated by GCS.

Meta-analysis

Meta-analysis was performed in MS Excel 2010 and MATLAB 2019b using our internal formulas and functions.[13] In cases comparing occurrence rates of TXA-treated patients versus placebo, relative risk (RR) was chosen as the metric of comparison due to its relatively direct interpretation. In all cases, meta-analysis was performed only when more than three studies were included in a given subcategory. To properly assess RR, the number of events of interest in both TXA and Control groups needed to be at least one. In all cases, the Cohen's Q test for heterogeneous effects was used to determine the appropriateness of fixed versus random effects models. Finally, all significance levels were defined as $P < 0.05$ and all confidence intervals (CI) were calculated using 95% CI. Summary of population, intervention, comparator, and outcomes (PICO) questions and location of results are shown in Figure 1.

RESULTS

Systematic Review

Initial literature search of PubMed and Cochrane databases identified 1,205 publications. After removal of duplicates, 873 studies remained. Studies not published in English were excluded. After screening by title/abstract, there were 375 studies. Non-RCTs were excluded, resulting in 67 trials for full-text review. Twenty-two RCTs met inclusion criteria and were included for data extraction and meta-analysis (Fig. 2).[8,10,14–33]

Risk of Bias and Quality of Evidence Assessment

The quality of evidence was moderate (7 RCTs)[16,18,19,24,27,30,32] or high (15 RCTs)[10,12–15,17,20–23,25,26,28,29,31] (Table S1a, http://links.lww.com/AOSO/A85). The risk of bias was low: 3 RCTs reported small sample size, and 1 RCT reported 1 participant lost to follow up (Table S1b, http://links.lww.com/AOSO/A85).

Systematic Review of Prehospital and In-Hospital Use of TXA

There were only two studies which evaluated TXA given both prehospital and in-hospital.[10,14] One study assessed use in non-TBI trauma patients.[10] The other study included only patients with TBI (Table S2, http://links.lww.com/AOSO/A85).[14]

Systematic Review of Prehospital and In-Hospital Use of TXA in Non-TBI

Guyette et al analyzed the STAAMP trial, which evaluated the effect of prehospital TXA on mortality among trauma patients with risk of hemorrhage.[10] This large, multicenter RCT enrolled 903 patients (Table S2, http://links.lww.com/AOSO/A85) from four US level 1 trauma centers, and had either prehospital hypotension (SBP ≤ 90 mm Hg) or tachycardia (HR ≥ 110) <2 hours from injury.[10] Patients were randomized to receive either 1 g of TXA or placebo by EMS.[10] There was no difference in overall 30-day mortality (8.1% *vs* 9.9%, $P = 0.17$), but subgroup analysis showed statistically significant difference when TXA was given within 1 hour of trauma (4.6% *vs* 7.6%; $P < 0.002$) or in cases of severe shock (18.5% *vs* 35.5%; $P < 0.003$) (Table S3, http://links.lww.com/AOSO/A85).[10]

Systematic Review of Prehospital and In-Hospital Use of TXA in TBI

Rowell et al evaluated field-use TXA in TBI among 966 patients.[14] Participants with moderate-severe TBI without

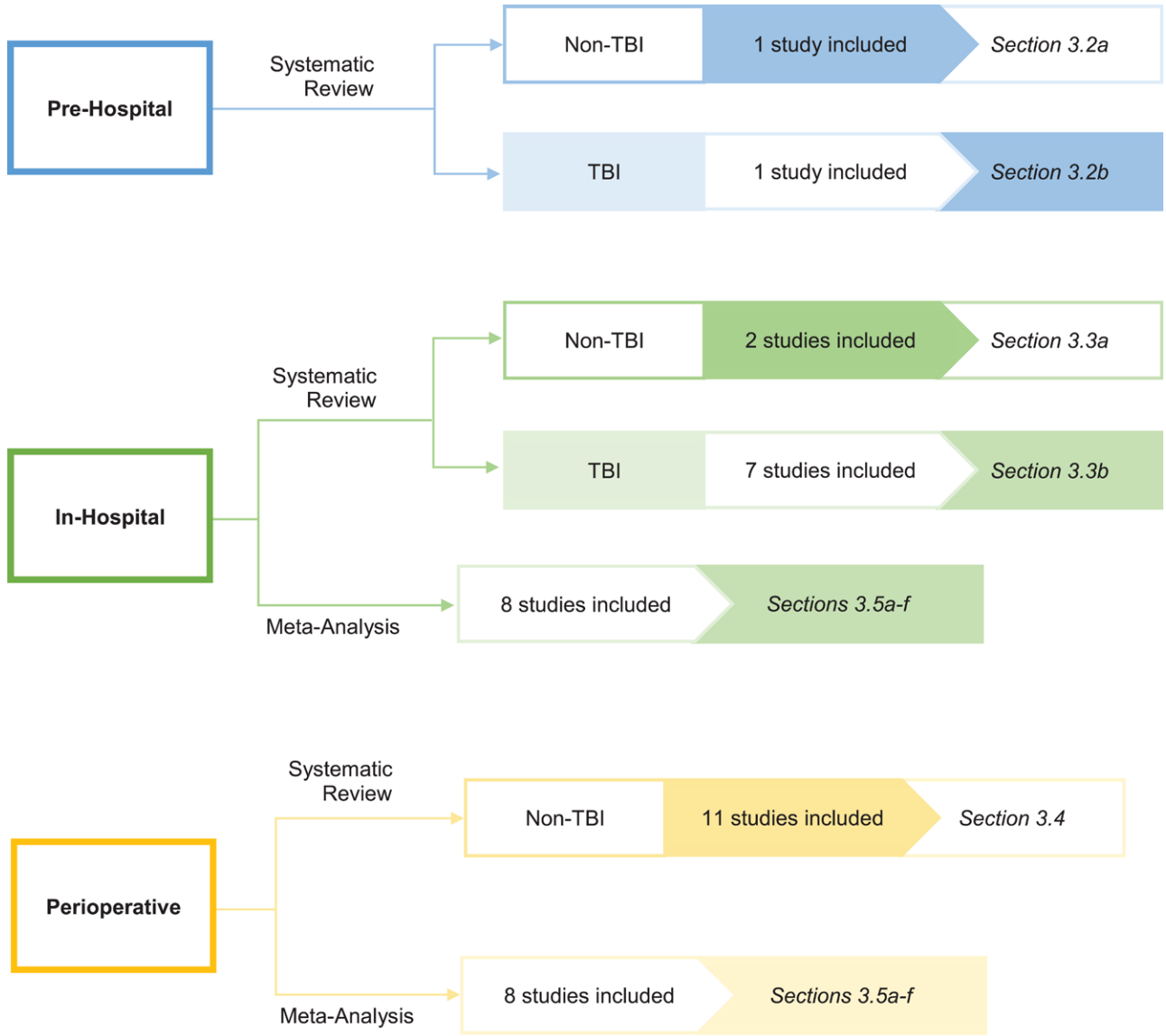

FIGURE 1. Summary of PICO questions and location of results. PICO, population, intervention, comparator, and outcomes.

shock were recruited to the double-blind RCT from 20 United States and Canadian trauma centers (Table S2, http://links.lww.com/AOSO/A85).[14] Participants were randomized into three cohorts to receive 1 g prehospital TXA bolus plus an 8 hours maintenance infusion (bolus plus maintenance group), 2 g prehospital TXA bolus plus placebo infusion (bolus only group), or placebo bolus prehospital plus placebo infusion (placebo group).[14] There was no statistically significant difference in positive neurological outcome (Glasgow Outcome Scale-Extended [GOSE] score > 4) at 6-month follow up (65% *vs* 62%; $P = 0.84$), in 28-day mortality (14% *vs* 17%; $P = 0.26$), or growth of intracranial hemorrhage (ICH) (16% *vs* 20%; $P = 0.16$) (Table S3, http://links.lww.com/AOSO/A85).[14]

Systematic Review of In-Hospital Use of TXA

Nine studies evaluated TXA in the hospital setting.[8,15,17,21–24,29,33] Of these, 7 evaluated use in patients with TBI (Table S2, http://links.lww.com/AOSO/A85).[8,15,17,21,23,29,33] The dosing protocol for most of these studies included a loading bolus followed by maintenance infusion. Two studies only administered a one-time bolus of TXA.[21,24]

Systematic Review of In-Hospital Use of TXA in Non-TBI

Monsef Kasmaei et al randomized 106 patients with pelvic trauma to either 1 g intravenous TXA loading dose followed by 3 doses every 8 hours *versus* placebo.[22] The main aim was blood loss reduction, evidenced by hemoglobin concentration (Tables S2 and S3, http://links.lww.com/AOSO/A85). There were significant differences in hemoglobin concentrations between TXA and control groups at 48 hours (11.58 *vs* 10.25; $P = 0.0001$) and 72 hours (11.45 *vs* 9.83; $P = 0.0001$) after admission.[22] No side effects were reported by either group after being discharged from the hospital.[22]

In the study conducted by Spinella et al, 149 patients were randomized to receive placebo, 2 g TXA, or 4 g TXA over 10 minutes.[24] There were no significant differences in baseline patient demographics, mortality ($P = 0.81$), or amount of blood products given after TXA administration ($P > 0.05$) between the groups.[24] However, the difference in thromboembolic events approached significance with increasing TXA dosage (placebo: 12.0%; 2 g: 26.5%; 4 g: 32.0%; $P = 0.05$).[24]

Systematic Review of In-Hospital Use of TXA in TBI

The CRASH-3 study examined the effect of TXA on TBI death in 9,127 patients randomly assigned to receive treatment or

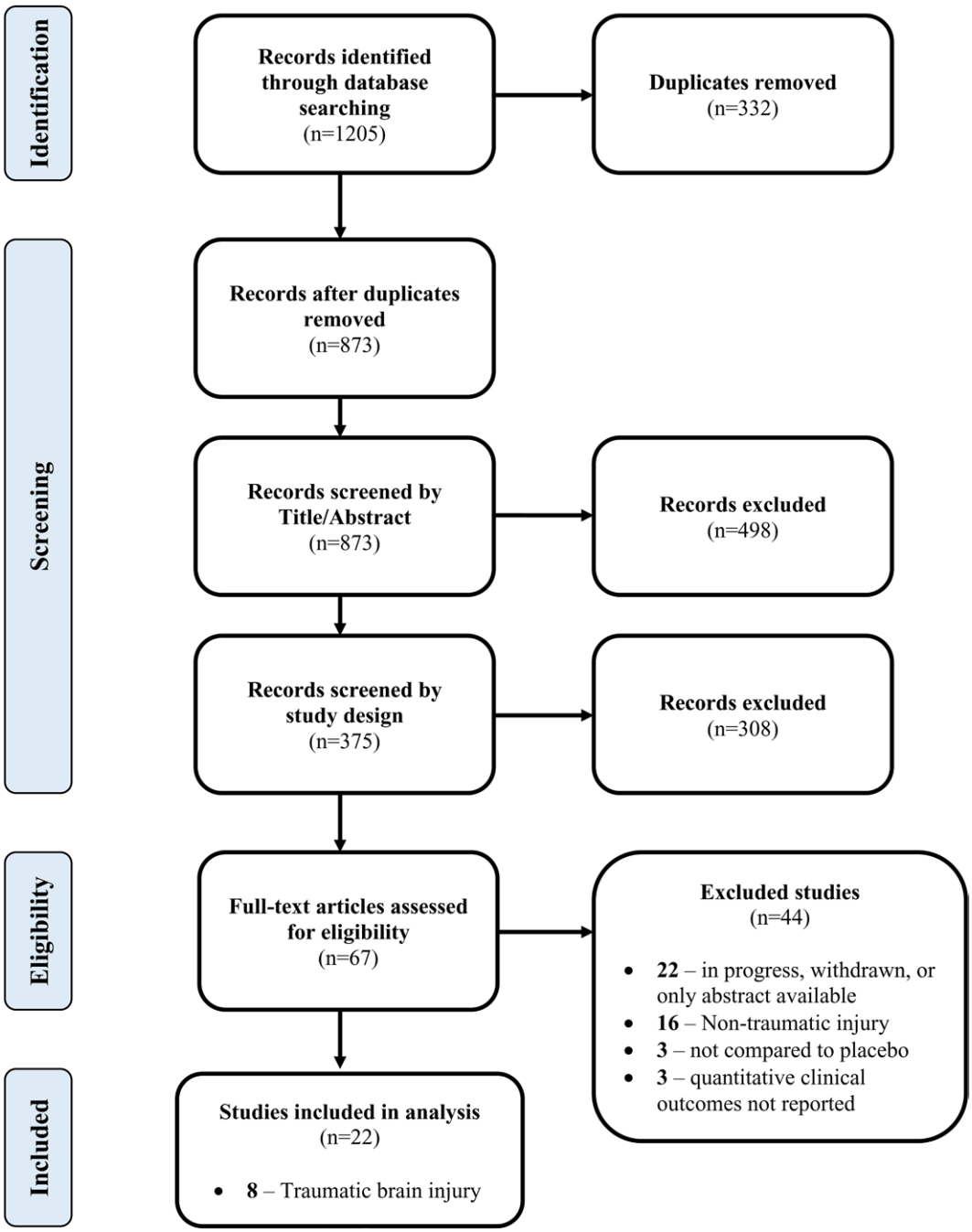

FIGURE 2. PRISMA flow chart for randomized controlled trials included in the systematic review and meta-analysis.

placebo within 3 hours of injury. They found no evidence of heterogeneity in the effect of TXA by patient age (P = 0.45).[8] Among the patients, the risk of head injury-related death was 18.5% in the TXA group *versus* 19.8% with placebo (855 *vs* 892 events, RR: 0.94; 95% CI: 0.86, 1.02).[8] In sensitivity analysis, which excluded patients with a GCS=3 or bilateral unreactive pupils at baseline, the risk was 12.5% *versus* 14% (485 *vs* 525 events, RR: 0.89; 95% CI: 0.80, 1.00).[8] Additionally, the CRASH-3 study found a reduction in the risk of head injury-related death with TXA in patients with mild-moderate head injury (RR: 0.78; 95% CI: 0.64, 0.95), but in patients with severe head injury they found no clear evidence of risk reduction (RR: 0.99; 95% CI: 0.91, 1.07) (Tables S2 and S3, http://links.lww.com/AOSO/A85).[8]

Early treatment was more effective than later treatment in patients with mild-moderate head injury (P = 0.005), but no obvious difference in patients with severe head injury (P = 0.73) was found.[8] In a regression analysis, when the effect of baseline GCS was examined, they found TXA was more effective in less severely injured patients (P = 0.007) and reduced head injury-related deaths in those with reactive pupils (RR: 0.87; 95% CI: 0.77, 0.98).[8] Overall, when stratified by time to treatment, no evidence of heterogeneity (P = 0.96) was recorded.[8] The RR of head injury-related death, regardless of injury severity, with TXA was 0.96 (95% CI: 0.79, 1.17), 0.93 (95% CI: 0.85, 1.02), and 0.94 (95% CI: 0.81, 1.09) in patients randomly assigned to receive treatment within 1 hour, between 1 hour and 3 hours, and over 3 hours after injury, respectively.[8]

Regarding complications, the CRASH-3 study did not find evidence of TXA increasing fatal or nonfatal stroke (RR: 1.08; 95% CI: 0.71, 1.64). Risk of seizure was similar between TXA and placebo groups (RR: 1.09; 95% CI: 0.90, 1.33) (Table S3, http://links.lww.com/AOSO/A85).[8]

Jokar et al evaluated the effect of TXA on ICH 48 hours after injury in TBI with GCS > 8 (Table S2, http://links.lww.com/AOSO/A85). Eighty patients were enrolled in the study and randomly assigned to be given either placebo or TXA (1 g bolus plus 1 g over 8 hours), and ICH was measured by CT scan. ICH volume expansion was significantly less in the TXA group (1.7 *vs* 4.3 mL; $P < 0.001$).[17] Mortality was not reported (Table S3, http://links.lww.com/AOSO/A85).

Participants in the study conducted by Mojallal et al received either 1 g TXA or placebo over 1 hour after admission and head CT (n = 120), within 8 hours of the trauma (Table S2, http://links.lww.com/AOSO/A85).[21] There was no significant difference in mean cerebral hemorrhage volume at admission and after 24 hours between treatment and placebo groups ($P = 0.207$ and $P = 0.824$, respectively) (Table S3, http://links.lww.com/AOSO/A85).[21] Similarly, there was no significant difference in in-hospital mortality ($P = 0.236$).[21] It should be noted, however, that baseline ICH bleed types were not similar and 16 patients were lost to follow up in the TXA group and four in the control group.

Perel et al performed post-hoc analysis of 270 CRASH-2 TBI participants from 10 hospitals.[23] Fewer patients in the TXA group had poor outcomes (significant hemorrhage growth, new intracranial hemorrhage, new focal cerebral ischemic lesions, need for neurosurgery, or death) compared with the placebo group (OR: 0.59; 95% CI: 0.37, 0.96).[23] The adjusted OR for poor outcome was 0.57 (95% CI: 0.33, 0.98).[23] Furthermore, there were no adverse events related to the study treatment.[23]

Yutthakasemsunt et al performed a 238-patient double-blinded RCT evaluating TXA in reducing ICH for moderate-severe TBI (GCS 4-12).[29] Patients (≥16 years) were divided into a TXA arm (n = 120) receiving a 1 g loading dose over 30 minutes and a maintenance dose of 1 g over 8 hours, and a placebo group with (n = 118).[29] Primary outcome was ICH expansion. Progression of ICH, GOSE, and death were not significantly different between the groups.[29]

Fakharian et al analyzed TXA (n = 74) *versus* placebo (n = 75) in TBI patients aged ≥ 15 (Tables S2 and S3, http://links.lww.com/AOSO/A85).[15] The TXA group received an in-hospital loading dose of 1 g and 1 g over 8 hours. There was no statistical difference in new bleeds ($P = 0.210$), hematoma expansion (RR: 0.89; 95% CI: 0.55, 1.74), or need for surgery (RR: 0.67; 95% CI: 0.29, 1.55).[15] Unfavorable outcomes at discharge (RR: 0.62; 95% CI: 0.22, 1.46) and at 3 months (RR: 0.46; 95% CI: 0.16, 1.26) were similar.[15] Finally, mortality between both groups was similar (RR: 0.67; 95% CI: 0.12, 3.93).[15] There was, however, a significant difference in the change in hemorrhage volume, with 68.5% of the TXA patients experiencing a decrease compared with 50.7% in placebo ($P = 0.03$).[15]

Chakroun-Walha et al assessed TXA use in 180 TBI patients with no extracranial hemorrhage.[33] Ninety-six patients were randomized to receive a loading dose of 1 g TXA, followed by 1 g over 8 hours, but only 10% received TXA within 3 hours of injury.[33] Transfusion requirements were similar through hospital day 7, and there was no significant difference in need for neurosurgical intervention, mortality, or GOSE at 28 days.[33] There was a significantly higher rate of PE in the TXA group (11.5% *vs* 2.4%; $P = 0.02$).[33]

Systematic Review of Perioperative Use of TXA

A total of 11 studies evaluated perioperative TXA use (Tables S2 and S3, http://links.lww.com/AOSO/A85).[16,18–20,25–28,30–32] Of these, seven administered only one preoperative TXA bolus.[16,18,20,26,28,31,32] Three administered two identical doses of TXA.[25,27,30] One gave a loading dose followed by maintenance dose of TXA.[19]

Tengberg et al recruited 72 patients to their RCT evaluating perioperative TXA in unstable extracapsular hip fractures.[26] Patients were randomized to receive TXA (n = 33) or placebo (n = 39).[26] The TXA cohort was given a preoperative bolus of 1 g TXA and a postoperative infusion of 3 g over 24 hours.[26] The TXA cohort had a 90-day mortality rate of 39% and the placebo cohort had a mortality rate of 10.2% ($P = 0.07$).[26] The TXA cohort had a recorded blood loss of 1,529.6 mL while the placebo cohort had a recorded blood loss of 2,100.4 mL ($P = 0.029$).[26]

Watts et al evaluated perioperative TXA use in 138 patients undergoing arthroplasty for low energy isolated femoral neck fracture, divided into TXA (n = 69) or placebo (n = 69) groups (Table S2, http://links.lww.com/AOSO/A85).[27] The TXA cohort received a perioperative dose of 15 mg/kg TXA and a second dose after wound closure.[27] Blood loss in the TXA cohort was lower throughout postoperative days (POD) 1 (731 *vs* 973 mL; $P = 0.01$), 2 (830 *vs* 1124 mL; $P = 0.0002$), and 3 (902 *vs* 1205 mL; $P = 0.0005$) (Table S3, http://links.lww.com/AOSO/A85).[27]

Xie et al assessed TXA in patients undergoing calcaneal fracture surgery, randomized into 2 cohorts of 45 patients.[28] The treatment group received a perioperative dose of 15 mL/kg.[28] The control group demonstrated lower incidence of wound complications (3 *vs* 10 patients, 7.3% *vs* 23.8%, $P = 0.036$).[28] Vascular events such as DVT, MI, and CVA were similar (Table S3, http://links.lww.com/AOSO/A85).[28] There were significant differences in postoperative blood loss between the two groups (110.0 mL in TXA *vs* 320.0 mL placebo; $P < 0.001$).[28]

Zhang et al evaluated TXA use in patients receiving nail fixation of intertrochanteric femur fractures.[30] They recruited 122 participants, randomized into two groups of 61. The treatment group received two doses of 1 g TXA over 10 minutes.[30] There was no significant difference in mortality between TXA and placebo (1.6% *vs* 3.3%; $P = 1.000$). The TXA group had lower blood loss (712.11 mL) compared with the placebo group (1,103.5 mL; $P < 0.001$).[30]

Zhou et al also evaluated TXA in intertrochanteric fractures.[31] Fifty patients were randomized to receive 1 g TXA before proximal femoral surgery and 50 received placebo.[31] There were no statistical differences between the groups for DVT ($P = 0.65$) or PE ($P = 0.31$). Blood loss was significantly lower in TXA group (563.37 *vs* 819.25 mL, 95% CI: −349.49, 162.27; $P < 0.01$) (Table S3, http://links.lww.com/AOSO/A85).[31]

Lack et al evaluated perioperative TXA in open reduction and internal fixation (ORIF) of acetabular fractures.[19] They recruited 88 patients from 2 US level 1 trauma centers, randomized to receive either TXA (n = 42) or placebo (n = 46) in a 10 mg/kg bolus 30 minutes before surgery, plus 10 mg/kg IV intraoperatively (Tables S2 and S3, http://links.lww.com/AOSO/A85).[19] There was no significant difference in blood loss (753 *vs* 533 mL; $P = 0.061$), transfusion rate (50% *vs* 32.6%; $P = 0.097$), or transfusion requirements (average of 2.65 *vs* 2.36 units; $P = 0.522$) (Table S3, http://links.lww.com/AOSO/A85).[19]Khiabani et al examined perioperative TXA in ORIF for bilateral displaced mandibular fractures[18] from a center in Iran (Table S2, http://links.lww.com/AOSO/A85). Participants were randomized into equal-sized cohorts receiving either 20 mg/kg of TXA or placebo prior to surgery.[18] They found that mean blood loss was significantly lower in the TXA group (360.57 ± 173.5 mL and 560.9 ± 248.07 mL, respectively; $P = 0.008$) (Table S3, http://links.lww.com/AOSO/A85).[18]

Lei et al evaluated perioperative TXA in surgical repair of traumatic intertrochanteric fracture; 77 participants were recruited to this single-blind study and randomized to receive either 1 g of TXA or placebo.[20]. There was significantly lower

estimated blood loss on POD-3 (279.35 ± 209.11 *vs* 417.89 ± 289.5; $P = 0.049$) and transfusion rate (28.20% *vs* 56.09%; $P = 0.01$) in the TXA group (Table S3, http://links.lww.com/AOSO/A85).[20]

Spitler et al randomized patients to receive either TXA or placebo for hip or pelvis ORIF; patients received a 15 mg/kg preoperative loading dose and a 15 mg/kg dose 3 hours after initial dose.[25] When excluding cell saver, total blood loss was higher in the control group (952 *vs* 1,325 mL; $P = 0.028$) (Table S3, http://links.lww.com/AOSO/A85).[25] When including cell saver volumes, total blood loss remained higher in the control group (1,048 *vs* 1,396 mL; $P = 0.046$).[25] The average drop in hematocrit from preoperative to POD-1 was greater ($P = 0.021$) in the control group.[25] The average drop from preoperative to POD-2 was also greater in the control group ($P = 0.026$; TXA = 25.37, placebo = 27.97).[25] There were no differences in major complications.[25]

Batibay et al analyzed the safety and effectiveness of TXA *versus* placebo administration in the setting of isolated traumatic tibial-fibular fractures requiring fixation via intramedullary nailing.[32] This study excluded polytrauma, those requiring open reduction or other orthopedic intervention, Gustilo/Anderson type 2 or 3 open fractures, any abnormal INR, and coagulopathies.[32] The study included 35 patients in both the control and TXA cohorts who were evaluated over a 12-week follow-up period.[32] The TXA cohort received a 10 mg/kg IV bolus 30 minutes prior to first incision.[32] The Hb levels at 24 hours (11.38 *vs* 10.34; $P = 0.0067$) and 48 hours (10.78 *vs* 9.98; $P = 0.0023$) were significantly higher in the TXA group.[32]

Dakir et al assessed the effectiveness of a single 10 mg/kg dose of TXA *versus* placebo 15 minutes preoperatively in minimizing blood loss in patients undergoing maxillofacial traumatic fractures.[16] Their RCT measured Hb preoperatively and postoperatively at 4, 24, and 48 hours intervals, and both intra and postoperative blood loss in 12 male patients (ages 20–40 years).[16] They reported statistically significant reduction in blood loss in the TXA group (489.17 *vs* 900.83 mL; $P < 0.001$) (Table S3, http://links.lww.com/AOSO/A85).[16]

Meta-Analysis

Meta-Analysis of Mortality Risk

Only two studies had the treatment cohort receive both pre- and in-hospital TXA.[10,14] This was insufficient to perform a meaningful meta-analysis. Thus, only in-hospital and perioperative mortality rates underwent meta-analysis (Tables 1 to 4). In both, Cohen's Q was not significant (Table 1), indicating a fixed effects model was sufficient. There is insufficient evidence to conclude a difference between TXA and placebo mortality rates in either setting (in-hospital 95% CI: 0.86, 1.02, perioperative 0.76–2.45) (Figure S1a, http://links.lww.com/AOSO/A84). Considering only in-hospital TBI studies, this does not change. A direct comparison of the means of the two meta-groups was not significant (Z-test, $P = 0.2124$), indicating there is not sufficient evidence to show a difference in RR between in-hospital and perioperative settings (Figure S1a, http://links.lww.com/AOSO/A84).

In both single-dose and loading and maintenance subcategories, Cohen's Q was not significant, indicating a fixed effects model was sufficient. There is sufficient evidence the risk of mortality in TXA-administered patients is smaller than that of the placebo (95% CI: 1.09, 2.04) (Table 1).[16,18,20,21,24,26,28,31,32] However, in the Loading and Maintenance subcategory, there is insufficient evidence of a difference between TXA and placebo mortality rates (95% CI: 0.87, 1.02).[8,14,15,17,19,22,23,29,33]

When all studies are considered irrespective of setting or administration, no significant difference in mortality was found between Placebo and TXA.

Meta-Analysis of Risk of General Complications

For the same reasons as above, only differences between in-hospital and perioperative settings were considered. In perioperative, Cohen's Q was not significant, indicating a fixed effects model was sufficient (Table 2). However, for in-hospital, Cohen's Q was significant, indicating a random effects model was needed. There is insufficient evidence to conclude a difference between TXA and placebo complication rates in both settings (in-hospital 95% CI: 0.26, 1.31; perioperative 95% CI: 0.86, 2.11) (Figure S1b, http://links.lww.com/AOSO/A84). A direct comparison of the means of the two meta-groups was not significant (Z-test, $P = 0.0779$), indicating there is insufficient evidence to show a difference in RR between the in-hospital and perioperative settings.

In the single-dose subcategory, Cohen's Q was not significant, indicating a fixed effects model was sufficient. However, for the Loading and Maintenance subcategory, Cohen's Q was significant, indicating a random effects model was needed. In both cases, there is not sufficient evidence to conclude a difference between TXA and placebo general complication rates in either dosing subcategory (single-dose 95% CI: 0.65, 1.70, loading and maintenance 0.33–1.27) (Table 2; Figure S1b, http://links.lww.com/AOSO/A84). A direct comparison of the means of the two meta-groups was not significant (Z-test, $P = 0.2536$), indicating there is not sufficient evidence to show a difference in RR between the dosing subcategories.

When all studies are considered irrespective of setting or administration, no significant difference in incidence of complications was found between placebo and TXA.

Meta-Analysis of Risk of Venous Thromboembolism

In both cases, Cohen's Q was not significant, indicating a fixed effects model was sufficient. The 95% CI for the In-Hospital setting is entirely below one (95% CI: 0.44, 0.90), indicating there is sufficient evidence the risk of VTE in TXA-administered patients is greater than in the placebo (Figure S1c, http://links.lww.com/AOSO/A84). There is insufficient evidence for that conclusion in the perioperative setting (95% CI: 0.43, 1.83) (Table 3).

There were sufficient studies reporting VTE rates for meta-analysis only in the single-dose subcategory. Cohen's Q was not significant, indicating a fixed effects model was sufficient. The meta-analysis 95% CI contains one (95% CI: 0.54, 1.09), indicating that there is insufficient evidence to conclude a difference between TXA and placebo general complication rates in this dosing subcategory (Figure S1c, http://links.lww.com/AOSO/A84).

When all studies are considered irrespective of differences in setting or administration, with the risk of VTE in placebo patients was found to be 0.68 times that of TXA-administered patients (95% CI: 0.49, 0.93).

Meta-Analysis of Risk of Infection

When all studies are considered irrespective of setting or administration, no significant difference in incidence of infection was found between placebo and TXA. Due to insufficient number of usable trials, we were unable to perform any comparison meta-analyses of pre- versus in-hospital timing or dose on infection risk.

Meta-Analysis of Risk of Stroke

There was an insufficient number of usable trials to perform comparison meta-analyses on stroke risk. When all studies are considered irrespective of setting or administration, no significant difference in stroke incidence was found between placebo and TXA.

TABLE 1.

Metaestimated Mortality Risk of Placebo/TXA in In-hospital and Perioperative Settings, and in Single and Loading and Maintenance Dosing

Category	Subcategory	Number of Studies	Total Number Treatment	Total Number Control	Cohen's Q *P* Value	Estimated Relative Risk, Mortality, Placebo/TXA	95% Confidence Intervals
All studies		12	5427	5320	0.2171	0.94	(0.87, 1.02)
Administration Site	In-hospital	8	5227	5111	0.4839	0.94	(0.86, 1.02)
	In-hospital, TBI only	6	5128	5011	0.2912	0.94	(0.86, 1.02)
	Perioperative	4	200	209	0.1001	1.36	(0.76, 2.45)
Dosing	Single dose	6	570	532	0.2393	1.49	(1.09, 2.04)
	Loading and maintenance	6	5384	5276	0.5038	0.94	(0.87, 1.02)

TXA indicates tranexamic acid.

TABLE 2.

Metaestimated Complication Risk of Placebo/TXA in In-Hospital and Perioperative Settings, and in Single and Loading & Maintenance Dosing

Category	Subcategory	Number of Studies	Total Number Treatment	Total Number Control	Cohen's Q *P* Value	Estimated Relative Risk, Any Complication, Placebo/TXA	95% Confidence Interval
All studies		9	683	674	0.0127	0.61	(0.32, 1.16)
Administration site	In-hospital	4	423	414	0.0038	0.59	(0.26, 1.31)
	Perioperative	5	260	260	0.8724	1.34	(0.86, 2.11)
Dosing	Single dose	4	475	439	0.0823	1.05	(0.65, 1.7)
	Loading and maintenance	5	735	723	0.0080	0.65	(0.33, 1.27)

TXA indicates tranexamic acid.

TABLE 3.

Metaestimated Venous Thromboembolism Risk of Placebo/TXA in In-Hospital and Perioperative Settings, and in Single and Loading and Maintenance Dosing

Category	Subcategory	Number of Studies	Total Number Treatment	Total Number Control	Cohen's Q *P* Value	Estimated Relative Risk, VTE, Placebo/TXA	95% Confidence Interval
All studies		9	5106	5002	0.4698	0.68	(0.49, 0.93)
Administration site	In-hospital	4	4844	4737	0.1649	0.63	(0.44, 0.9)
	Perioperative	5	262	265	0.7684	0.89	(0.43, 1.83)
Dosing	Single dose	6	576	544	0.2269	0.76	(0.54, 1.09)

TXA indicates tranexamic acid; VTE, venous thromboembolism.

Meta-Analysis of Blood Loss

All studies with Blood Loss values that included standard deviations were in the Perioperative setting.[16,18–20,26,28,30,31] Cohen's Q was significant ($P < 0.0001$), indicating the need for a random effects model. The 95% CI for the resulting difference between the placebo and TXA means contains zero (95% CI: –22, 344), indicating there is insufficient evidence to show that blood loss for the TXA group differs from the placebo group (Table 4; Figure S1d, http://links.lww.com/AOSO/A84). Analysis of the five studies that evaluated TXA use in surgical treatment of traumatic hip or pelvic fractures showed meta-CI containing zero (95% CI: –20, 367). When considering the single-dose subset of these studies, the result does not change. No other dosing subsets had enough for meaningful meat-analysis.

DISCUSSION

This systematic review and meta-analysis included 22 RCTs evaluating TXA use in prehospital, in-hospital, and perioperative settings. Main outcomes assessed were mortality, complications, and blood loss.

The systematic review found that in adults with non-TBI traumatic injury, prehospital TXA showed significant mortality benefit when given ≤1 hour after injury.[10] In the lone study of TXA in TBI given prehospital, there was no significant difference in outcome, mortality, or ICH volume.[14] The CRASH-3 trial showed significant mortality benefit with early administration of TXA in mild-moderate, but not severe, TBI.[8] There was no significant difference in in-hospital mortality between TXA and placebo groups.[21,33]

We also found that most studies assessing perioperative TXA found significant reduction in intraoperative blood loss compared with placebo.[16,18,20,25–28,30–32] One study reported no significant difference in blood loss.[19] Meta-analysis showed a 178 mL difference between the Control and TXA, with a 95% Student's t CI of (–21.6, 343.5), indicating there is not sufficient evidence to show the blood loss for the TXA group differs from the placebo group. There was a variable effect on ICH volume expansion in TXA compared with placebo. Two studies reported significantly less ICH expansion, while two others reported no significant difference.[15,17,23,29]

Meta-analysis of comparison of RR of mortality between treatment and placebo groups in in-hospital and perioperative settings was not significant. However, when considering studies which only administered one loading TXA bolus, the meta-CI was >1, indicating risk of mortality is significantly lower in the treatment group.

Meta-analysis results indicate the risk of VTE in the treatment group is greater than in the placebo in in-hospital setting. However, there is not sufficient evidence for that conclusion in perioperative setting, nor is there sufficient evidence to show a difference in RR between in-hospital and perioperative settings. There was no significant difference in RR in single-dose TXA,

TABLE 4.

Metaestimated Difference in Blood Loss of Placebo/TXA in In-Hospital and Perioperative Settings, and in Single and Loading and Maintenance Dosing

Category	Subcategory	Number of Studies	Total Number Treatment	Total Number Control	Cohen's Q *P* Value	Estimated Difference in Blood Loss, Placebo—TXA (mL)	95% Confidence Interval
All studies		8	299	312	< 0.0001	178	(-21.6, 343.54)
Administration site	Perioperative	8	299	312	< 0.0001	178	(-21.6, 343.54)
Dosing	Single Dose	6	196	205	< 0.0001	192	(-57.32, 382.97)
Fracture type	Hip/Pelvis	5	223	236	0.0006	207	(-20.11, 366.95)

TXA indicates tranexamic acid.

regardless of setting. Unfortunately, there were not enough studies reporting VTE rate in other dosing protocols.

While a few prior studies have analyzed the combined results of recent TXA RCTs, to our knowledge this is the largest systematic review and meta-analysis of 22 studies. Other reviews include up to 12 studies.[34–39] This study includes comparative analysis of administration setting/dosing and type of injury. Although other systematic reviews and meta-analyses, such as the publication by Almuwallad et al, have attempted to elucidate the effect of prehospital TXA use, to our knowledge, no other study includes only randomized controlled trials (RCTs).[40] Almuwallad et al included a total of four studies: only one RCT, one retrospective cohort, and two prospective cohorts.[40]

Current recommendations and guidelines are often vague and inconclusive, partly due to gaps in the literature reporting strong and consistent evidence for TXA in various traumatic settings and injury types. Furthermore, because trials like the CRASH studies were conducted outside the United States, similar studies should be conducted in the United States to draw more conclusive evidence and provide clearer guidelines. The 2017 Eastern Association for the Surgery of Trauma (EAST) guidelines for damage control resuscitation and severe traumatic hemorrhage recommended TXA for in-hospital use.[41]

The findings of the systematic review suggest there is some mortality benefit associated with early TXA in trauma. These results highlight the need for clear, concordant guidelines for TXA in trauma. The inclusion of only RCTs provides stronger evidence and limits risk of bias. Understanding the importance of TXA with factors such as setting, demographics, GCS, dosage, and timing is crucial.[40] Identification of key injury patterns and development of detailed guidelines may significantly improve patient outcomes. This study may assist in valuation of TXA in trauma, or at least provide indications for further research.

Limitations

There is a large heterogeneity present for numerous data points reported within the RCTs in this systematic review and meta-analysis; notably, variation in VTE screening and mixed reporting and variability of the inclusion criteria. While this has been accounted for in our meta-analysis, there remains some degree of discrepancy in the reporting criteria and technical definitions of VTE in general. Furthermore, analysis of variables such as race, ISS, GCS, LOS, follow up, and factors related to blood loss, such as mean units of blood transfused, was not feasible due to underreporting. Similarly, analysis of mechanism of injury was not feasible due to low reporting. Heterogeneity in injury type also exists; while this has some advantage, in that it may allow our findings to be more generalizable in a variety of trauma situations, the inconsistency in reporting mechanism of injury makes sophisticated analysis difficult. Additionally, only two studies evaluated prehospital TXA, which limited robust assessment. Outcome reporting among the included studies varied; some reported overall adverse events while others assessed specific complications. Intrinsic limitations of contributing studies such as, but not limited to, lack of diversity in age, race, and gender may have led to findings which cannot be attributed to TXA use. Moreover, mortality included deaths occurring within 30 days of intervention in some studies while others only reported in-hospital mortality. Of note, included RCTs were published in various international journals, with varying impact factors. There were also differences in the number of patients within studies. Despite our aim to include all RCTs on TXA use in traumatic injury, studies such as the CRASH-3 trial enrolled patients on a much larger scale than others. Consequently, a larger proportion of patients and results were obtained from the CRASH-3 trial.

CONCLUSIONS

The systematic review of TXA indicates the benefits of this intervention appear most evident when given shortly after traumatic injury. The systematic review also supports the value of TXA in reducing intraoperative blood loss and evidence indicates it could provide more favorable outcomes when used in emergent settings in which large volumes of blood loss are anticipated. The meta-analysis showed TXA used as a single dose was associated with improved mortality. Meta-analysis of TXA used in a single dose showed no significant difference in risk of VTE or other complications compared with placebo. Cohesive guidelines on the use of TXA are lacking; the findings of this study may aid in the development of algorithms for identifying patients who may benefit from TXA use.

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