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Title:

Efficacy and Safety of Tranexamic Acid In Orthopedic Fracture Surgery: A Meta Analysis And Systematic Literature Review

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ABSTRACT

Background: Tranexamic acid (TXA) is an anti-fibrinolytic drug that has been shown to be effective in reducing blood loss and the need for transfusions after several orthopedic surgeries. However, the effectiveness of TXA use in orthopedic fracture surgeries still remains unclear. The purpose of this meta-analysis was to review existing literature with interest in the effectiveness and safety of TXA treatment in reducing total blood loss and transfusion rates for patients who underwent surgery for fracture repairs.

Methods: An electronic literature search of PubMed, Embase, OVID, and the Cochrane Library was conducted to identify studies published before December 2016. All randomized controlled trials and cohort studies evaluating the efficacy of TXA during fracture repair surgeries were identified. Primary outcome measures included the number of patients receiving a blood transfusion and peri-operative total blood loss. Data were analyzed using Comprehensive Meta Analysis (CMA) statistical software.

Results: Seven studies encompassing 559 patients met the inclusion criteria for the meta-analysis. Our meta-analysis indicated that when compared with the placebo control group, the use of TXA in fracture surgeries significantly reduced total blood loss by approximately 330 mL ($p=0.009$), reduced the transfusion rate with a relative risk of 0.54 ($p<0.001$), and decreased the drop of hemoglobin by 0.76 g/dL ($p<0.001$). There was no significant difference between the number of thrombo-embolic events among the study groups ($p=0.24$).

Conclusions: This study demonstrated that tranexamic acid may be used in orthopedic fracture surgeries to reduce total blood loss, transfusion rates, and the drop in hemoglobin level, without increasing risk of venous thrombo-embolism. A limitation to these findings is the small number of studies available. Further studies need to be conducted to confirm these findings.

Key Words: tranexamic acid;TXA;fracture repair;meta-analysis;systematic literature review;blood loss;transfusion rate

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.e

INTRODUCTION

Each year, there are over 16 million orthopedic fracture repair surgeries performed in the United States (1). Despite the recent advances in the technique and instrumentation of orthopaedic procedures, major orthopaedic surgeries are still commonly associated with substantial blood loss (2-4). Of all of the complications of surgery, hemorrhage is the number one preventable cause of death (1,3,5). In order to prevent anemia and hypovolemic shock, blood is often transfused. There are numerous complications that are associated with the transfusion of allogenic blood products including an increased rate of transmission of infectious diseases, a potentially acute life-threatening immune response, acute lung injuries, and an increased risk of postoperative infections (3, 5).

Several different techniques to reduce hemorrhage and the rate of transfusions have been utilized and include pharmacological therapy, anesthesia, and autologous transfusions (6-11). However, most of these methods are accompanied by their own complications. More recent efforts have focused on pharmacologic anti-fibrinolytic agents that minimize bleeding. One of the most common pharmacological agents used to control surgical blood loss is tranexamic acid (TXA). TXA is a synthetic derivative of the amino acid lysine, and functions by decreasing the rate of fibrinolysis (9,12-13). Previous studies indicate a significant reduction in the morbidity and mortality of patients who suffered from hemorrhage and who received TXA (9). Despite the world wide and multi-disciplinary proven efficacy in reducing blood loss, TXA is not routinely used in patients with fractures in the United States.

While TXA has been shown to be effective in certain orthopedic procedures, there is still uncertainty regarding the efficacy of TXA use in orthopedic fracture repair surgery. The use of a SR/MA can be very useful to summarize data across a number of trials. We believe that based on the scientific rationale of the drug and current published supporting evidence, TXA would be a useful agent in fracture repair surgeries. This topic has yet to be investigated in the form of a systematic review and a quantitative meta analysis. The purpose of this study was to address this limitation within the evidence and systematically examine the available literature regarding the potential risks and benefits of TXA use in fracture surgery with quantification of effect through meta- analysis of relevant data. Accordingly, with a systematic review of the current evidence, the aim of this investigation was to help determine the efficacy of TXA administration in reducing total blood loss and transfusion rates in orthopaedic fracture surgical patients by a meta-

analysis of the available literature.

METHODS

We performed this systematic research and meta-analysis study according to the methods of the Cochrane Handbook for Systematic Reviews of Interventions (14). This systematic review and meta- analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) Statement (15). A study flow chart utilized from the PRISMA statement was constructed to show all literature search results.

Search strategy

We identified comparative studies comparing TXA with a placebo by searching Embase, PubMed, OVID, and the Cochrane Library. We used the following combined text and search terms: “tranexamic acid or TXA”, “fracture”, “orthopedic surgery” and “trauma”. There were no language restrictions. We also checked the bibliographies of identified reports and relevant review articles for other potentially relevant studies. We started from the earliest retrievable date of each database up until December 26 2016. In addition, reference lists of prior reviews of similar topics were searched for relevant studies.

Study selection:

Two authors independently conducted the initial search, deleted duplicate records, screened the titles and abstracts for relevance and identified papers. The study selection was performed according to the inclusive and exclusion criteria. The studies that met the following criteria were included: (1) the study evaluated the effect of TXA on blood loss in patients undergoing fracture repair surgery; (2) the study was a double blinded randomized controlled trial (RCT); (3) the study provided data on outcomes including total blood loss, post-operative drop in hemoglobin, rate of blood transfusions, and incidence of thromboembolic events. Articles were excluded from our meta- analysis if they were cohort studies, if they used animal or cadaver models, or if they did not have raw data for outcomes. The primary outcomes included absolute amount of total blood loss and the number of patients who required allogenic RBC transfusion peri-operatively. Secondary outcomes included post-operative hemoglobin concentration and the number of people who developed any thrombo-embolic event such as DVT.

Two investigators independently extracted data from the reports. For the studies evaluating multiple treatment arms, comparisons were made between TXA arm and standard of care or placebo arm only. For each article, data on the following study characteristics were collected when available: year of publication, total number of patients in study, number of patient in experimental arm, age of participants, intervention route, dosage of drug administered, number of patients, and length of follow-up. All primary and secondary outcomes reported.

Quality Assessment:

Two reviewers independently assessed the risk of bias of individual studies according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (16). See Table, Supplemental Digital Content 2, which shows the level of evidence of each study. This ranged from Level 1-Level 5 based on the judgments for the outcome regarding risk of bias, inconsistency, indirectness, and imprecisions.

Statistical Analysis:

The results of the meta-analysis were analyzed using CMA statistical software. We examined statistical homogeneity by using Cochrane's Q test and I^2 statistics, with $I^2 > 40\%$ considered significant heterogeneity. We anticipated that there will be sufficient homogeneity across studies to justify a pooled statistical synthesis. Data from all trials fulfilling the eligibility criteria will be pooled for meta-analysis using a random effects model to accommodate the anticipated heterogeneity among study results. Dichotomous outcomes (proportion of transfusion rates, and thromboembolic events) were calculated as the relative risk ration (RR) and the odds ratios (OR) respectively. Continuous outcome data (Hb concentration and total blood loss) were expressed as the mean difference (MD) or as the standardized MD (SMD). Group differences were also tested using unpaired *t*-tests of Mann-Whitney as appropriate with $p < 0.05$ signifying statistical significance.

RESULTS

Search Results:

The literature searches identified 150 publications that potentially met our criteria. Two additional studies were added using the references from other papers and abstract searches. After the initial screen of titles and abstracts, 13 articles remained for further investigation. The results for the screening algorithm implemented in shown in (**Figure 1)**. After detailed assessments, there were 7 eligible studies with 6 papers and one abstract consisting of 559 patients shown in Table, Supplemental Digital Content 2 (2, 8, 17-21).

All included studies were published between 2007 and 2016 and were reported in English. The route of TXA administration were all intravenous. The dose of TXA used varied from 10 mg/kg to 15mg/kg, while some studies used fixed doses of 500 mg to 1gm.

Quality Assessment:

Seven articles directly comparing intraoperative and postoperative blood management with and without the use of tranexamic acid administration in patients undergoing fracture repair surgery were included in this meta-analysis. The sample size of the included studies, which were only focused fracture repair surgeries, ranged from 60 to 110. TXA was the only type of anti-fibrinolytic agent used, although the doses varied between studies.

Of the seven total studies, six reported both an adequate sequence generation and allocation concealment. See Table, Supplemental Digital Content 3, which demonstrates the

methodological quality and the level of risk for bias of the RCTs. The amount of risk was assessed with regards to several factors including random sequence generation, allocation concealment, blinding, selective reporting, and other possible bias. Results for publication bias was assessed by funnel plot shown in Figure, Supplemental Digital Content 1.

Primary Outcomes:

Total blood loss

The data of total blood loss was reported in six studies (2,8, 17-19,21) involving 459 patients **Figure 2.** The pooled result revealed that the use of TXA significantly reduced total blood loss more than placebo ((Mean Difference (MD)= -330.00 mL; 95% CI -576.94 mL, -83.07 mL; p= 0.009). There was significant statistical heterogeneity (I^2 = 99 %).

Transfusion rates

The data of transfusion rates was provided in all seven studies **(**2, 8, 17-21**)** involving 559 patients **Figure 3.** Meta- analysis demonstrated that the use of TXA decreased the risk of transfusion rates more than placebo (RR= 0.54; 95% CI 0.398, 0.726; p<0.001)). There was very little statistical heterogeneity for this factors (I^2 = 26%).

Secondary Outcomes:

Hemoglobin levels:

The result of hemoglobin drop was assessed in five studies (8, 18-20, 21) involving 389 patients **Figure 4.** Meta-analysis showed that there was a significant difference in hemoglobin drop between the TXA and placebo groups (MD = -0.76 g/dL; 95 % CI -1.019, -0.498; p<0.001). The heterogeneity among studies was calculated (I^2 = 32 %).

Complications

The details of complication including thromboembolic events such as DVT was available in three studies (2, 19, 21) involving 242 patients **Figure** 5. Meta-analysis demonstrated that there were no statistical differences in DVT (OR= 2.55; 95% CI 0.936, 6.967; p=0.24) between the two groups with statistical heterogeneity of (I^2 = 36%).

DISCUSSION:

There is significant morbidity and mortality from traumatic fractures associated with peri-operative hemorrhage. The increased amount of blood loss can lead to a complications including anemia. The prevalence of perioperative anemia in hip fractured patients is as high as 80% (3). This meta analysis identified seven studies involving 559 patients with fractures who were treated with TXA. Based on these studies, the most important findings of this meta-analysis were that compared with placebo group, the use of intravenous TXA significantly reduced total blood loss, transfusion rates, and a decreased drop in the hemoglobin level. Another important finding

of this meta-analysis was that it demonstrated that TXA use did not significantly increase the risk of DVT compared with the placebo groups, which corresponds with current literature studying thromboembolic events with the use of post-operative TXA (7-8, 22-29). Previous studies also demonstrated reduced probability of mortality, and decreased blood transfusions by approximately 30 percent (6,7, 12, 22-27). Thus the results of this meta-analysis were consistent with the results seen for TXA administration in other surgical procedures.

Due to the limited number of studies available in the literature, significant variability was observed in the studies used. A few studies demonstrated that there was a significant reduction in the intra-operative blood loss with the use of TXA compared to placebo. Several studies demonstrated that in patients undergoing hip fracture surgery, the administration of tranexamic acid produced a significant relative risk reduction in the incidence of blood transfusions compared with placebo mostly due to a reduction in post-operative blood loss (2, 8).

Concerns regarding TXA revolve around a feared complication of thromboembolic events. Previous studies discuss the potential benefits of using TXA administered locally during joint replacement as a safer method of administration when compared to its systemic administration; lower systemic absorption would lead to a lower risk of thromboembolic complications (6, 23-25). Current available literature show that TXA does not increases the risk of thrombotic complications, namely PE and DVTs. In our meta-analysis, of the seven included studies, three studies reported the incidence of DVT after the fracture surgery repair. There was no significant statistical difference in the number of thromboembolic events for patients who had TXA compared to controls. Zufferey et. al, found a threefold increased risk of vascular events with

the use of tranexamic acid when compared with placebo (2). Another study by Emara et. al, found that while TXA significantly reduced the amount of blood loss and decreased drop in hemoglobin compared to controls, there was a significantly increased the risk of thromboembolic events including DVT and PE in hip hemi-arthroplasties (19). This is contrary to what all other studies with available data demonstrated and contrary to the previous findings of elective hip or knee arthroplasty, where the use of tranexamic acid did not increase the risk of venous or arterial thrombosis. In addition, another meta-analysis investigating the safety of TXA and it similarly indicated that there was no significant difference in the rate of thromboembolic events such as DVT between the TXA group and the control group (24). The consensus from this literature is in favor of administration of TXA given the decrease in blood loss, transfusion rates and cost. Although a few individual studies have found increased risk of thromboembolic events in groups receiving TXA, larger studies and meta-analyses have uniformly found no increased risk of thrombosis. Although other studies have demonstrated these results in elective orthopedic procedures, such as TKA and THA, this analysis assessed these factors in an unpredictable traumatic fracture repair. Although this meta-analysis focused on the IV administration of TXA, other routes of administration have also been deemed to be as effective.

Several factors increased the power this study. Extensive searches of all available studies meeting the topic was performed including the inclusion of unpublished abstracts. The methods and procedures of the study were strictly conducted utilizing both the Cochrane Handbook for Systematic Reviews of Interventions and PRISMA statement, thus ensuring the methodological reporting quality of this study. The need for a meta-analysis to combine and evaluate all existing literature on TXA administration in fracture repair surgeries was warranted to bring additional

clarity to the efficacy to its administration and to potentially establish additional indication for the drug in fracture repair surgery. Unlike the previously cited meta-analyses which focused on the effectiveness and safety of TXA in TKAs, THAs, and spinal surgeries, this meta analysis focused primarily on TXA use in fracture associated surgeries. To our knowledge, this is the first meta-analysis of studies comparing the effectiveness and safety of TXA use in patients undergoing surgical repair of fractures.

Limitations to this study are intrinsic to all similar meta-analyses. These include a small sample size of available studies and thus number of patients. In addition, there was a significant amount of heterogeneity among several of the outcomes. This is primarily due to the limited amount of available literature to analyze. Variations in methodology, different routes of administration, and different doses of TXA among the different trials may account for the heterogeneity. Due to the limited number of available studies, it was difficult to analyze all of the variables discussed in this study since many of the studies did not report such information. For example, of the seven studies included in this study, only three reported results regarding thromboembolic events. In addition, one of the primary outcome variables evaluated in this study, total blood loss has both high inter- and intra-observer variability. Another limitation is the decreased amount of power from this study due the evaluation of certain outcomes with very low event rates due to the limited number of patients. Thus, the data needs to be evaluated with caution since these parameters typically require larger studies. A power analysis was performed to determine the sample size required for a study to have adequate power. Considering a 10% difference in the proportion of the patients and a power of 80% and a confidence interval of 95%, a study would need a sample size of roughly 430 patients. Finally, the funnel plot created demonstrated that

publication bias could have existed in this study due to the asymmetric nature of the chart. Further randomized control trials are needed to further confirm the results of this meta-analysis.

CONCLUSION

This meta-analysis of the current literature indicates that TXA administration in orthopaedic fracture surgery patients leads to a statistically significant reduction in total blood loss, transfusion rate and with less of a drop in hemoglobin level, with no increased risk of thromboembolic complications. Further study is required to elucidate the clinical outcomes, optimal dosage, and optimal drug administration route used in patients undergoing surgical repair of fractures.

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LEGENDS:

Figure 1: The flow chart summary for the screening and exclusion summary for the studies.

Figure 2: The forest plot and tabulated data illustrating the MD in the total blood loss between the TXA and placebo group, showing that TXA administration significantly decreased the total amount of blood loss.

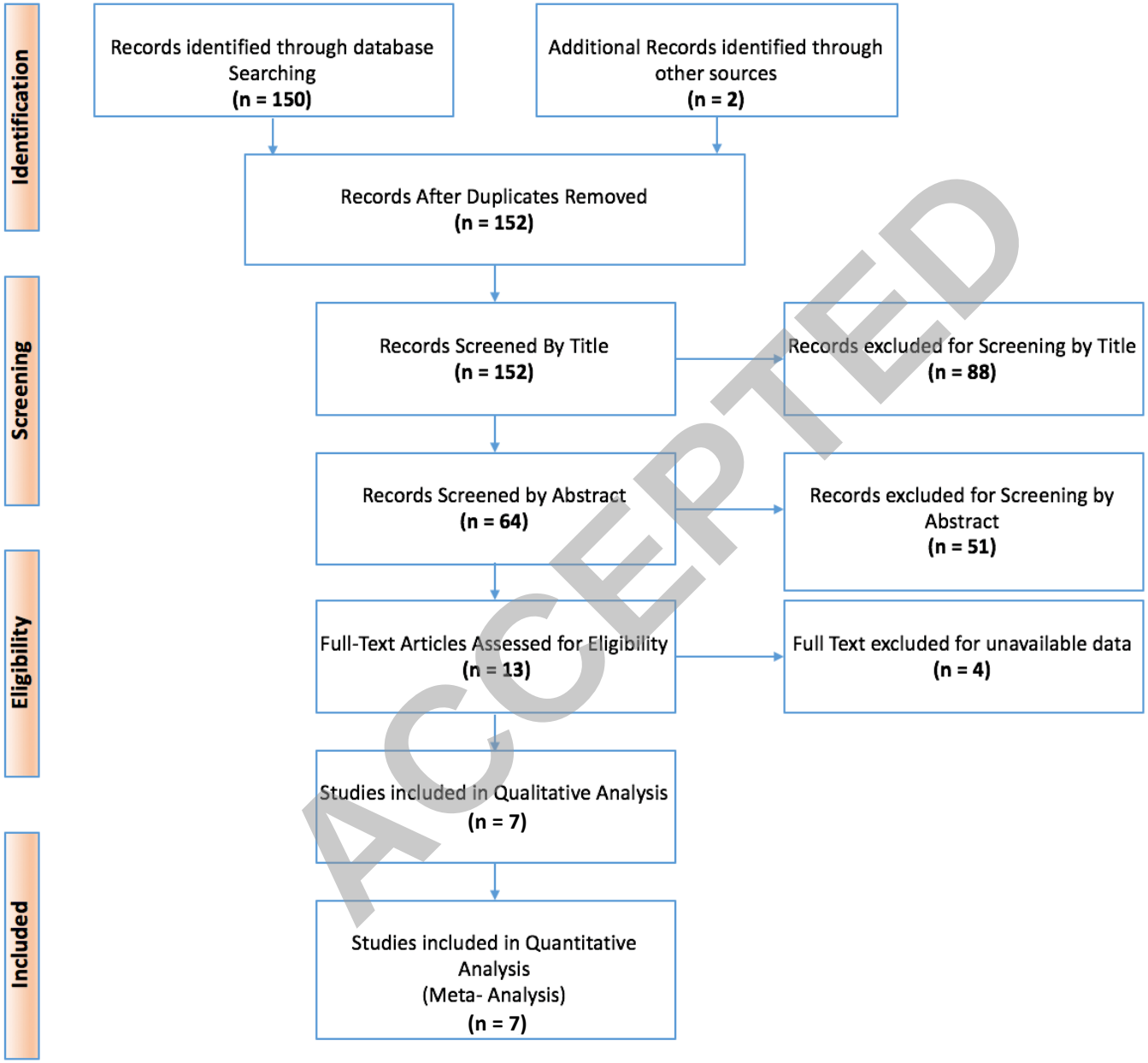
Figure 3: This figure illustrates the forest plot and tabulated data illustrating the RR in the allogenic rate of transfusion between the TXA and placebo group, showing that TXA administration significantly decreased the total number of allogenic blood transfusion.

Figure 4: The forest plot and tabulated data illustrating the OR in the level of hemoglobin between the TXA and placebo group, showing that TXA administration significantly decreased the drop in hemoglobin during the fracture repair surgery.

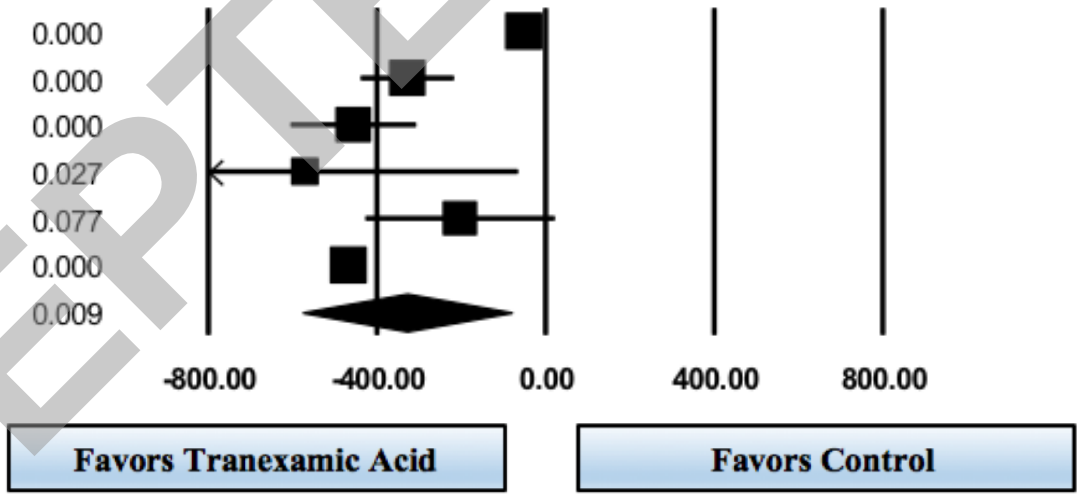
Figure 5: The forest plot and tabulated data illustrating the effect of TXA on the rate of DVT, showing that the ratio of DVT in the two administrations are not significantly different.

Figures

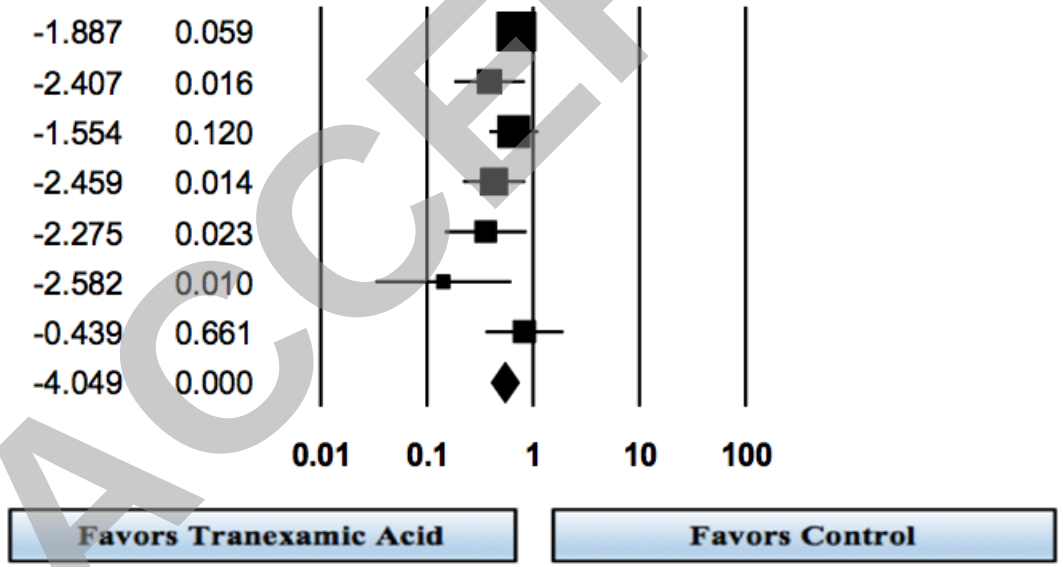
(Figure Legends in Notes section)



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Vijay, 2013	-51.800	3.026	9.154	-57.730	-45.870	-17.121	0.000
Moghaddam, 2011	-328.000	56.617	3205.467	-438.967	-217.033	-5.793	0.000
Sadeghi, 2007	-456.000	76.245	5813.318	-605.438	-306.562	-5.981	0.000
Tengberg, 2016	-570.800	258.019	66573.793	-1076.508	-65.092	-2.212	0.027
Zufferey, 2010	-203.000	114.864	13193.625	-428.128	22.128	-1.767	0.077
Emara, 2014	-467.500	8.216	67.500	-483.603	-451.397	-56.902	0.000
	-330.002	125.989	15873.316	-576.937	-83.067	-2.619	0.009



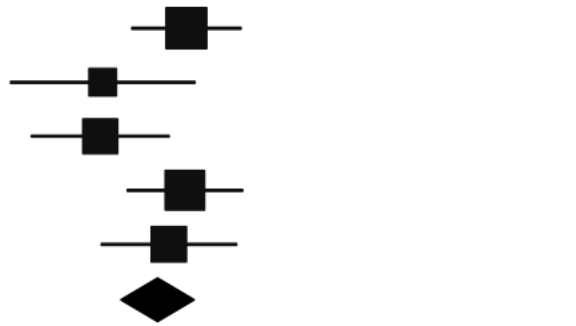
Study name	Statistics for each study				
	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Zufferey, 2010	0.697	0.480	1.014	-1.887	0.059
Vijay, 2013	0.389	0.180	0.839	-2.407	0.016
Sadeghi, 2007	0.656	0.386	1.116	-1.554	0.120
Mohib, 2015	0.429	0.218	0.842	-2.459	0.014
Moghaddan, 2011	0.357	0.147	0.867	-2.275	0.023
Emara, 2014	0.143	0.033	0.626	-2.582	0.010
Tengberg, 2016	0.827	0.355	1.930	-0.439	0.661
	0.538	0.398	0.726	-4.049	0.000



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Mohib, 2015	-0.542	0.204	0.041	-0.941	-0.143	-2.660	0.008
Emara, 2014	-1.140	0.341	0.116	-1.809	-0.472	-3.345	0.001
Tengberg, 2016	-1.158	0.255	0.065	-1.658	-0.657	-4.532	0.000
Vijay, 2013	-0.552	0.215	0.046	-0.973	-0.131	-2.571	0.010
Sadeghi, 2007	-0.667	0.251	0.063	-1.159	-0.174	-2.653	0.008
	-0.759	0.133	0.018	-1.019	-0.498	-5.711	0.000

Statistics for each study

Std diff in means and 95% CI



Favors Tranexamic Acid

Favors Control