Title Page

Title: A systematic review of Tranexamic acid in hip fracture surgery

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Running head: A systematic review of Tranexamic acid in hip fracture surgery

Keywords = Bleeding, femoral neck fracture, hip fracture, meta-analysis, Orthopaedics, surgery, systematic review, Tranexamic acid, transfusion, trauma.

STRUCTURED SUMMARY

Aim: To systematically examine and quantify the efficacy and safety of Tranexamic acid in hip fracture surgery.

Methods: A systematic literature search was conducted using Medline, EMBASE, AMED, CiNAHL, and the Cochrane Central Registry of Controlled Trials. Two assessors independently screened search outputs for potentially relevant articles which met the eligibility criteria. The primary outcome measure was requirement of post-operative blood transfusion. Risk of bias assessment was performed using the Cochrane Collaboration's risk of bias tool for RCT's and the ROBINS-I tool for observational studies. Meta-analysis was performed to estimate risk ratio (RR), risk difference (RD) and mean difference (MD) values for dichotomous and continuous data outcomes respectively. The interpretation of each outcome was made using the GRADE approach.

Results: Of 102 studies identified, seven met the inclusion criteria including a total of 770 participants (TXA: 341; Control: 429). On meta-analysis, intra-venous TXA resulted in a 46% risk reduction in blood transfusion requirement compared to a placebo/control group (RR:0.54; 95% CI: 0.35 to 0.85; I^2: 78%; Inconsistency (Chi^2) p=<0.0001; N=750). There was also a significantly higher post-operative haemoglobin for TXA versus placebo/control (MD:0.81; 95% CI: 0.45 to 1.18; I^2: 46%; Inconsistency (Chi^2) p=0.10; N=638). There was no increased risk of thromboembolic events (RD:0.01; 95% CI: -0.03, 0.05; I^2: 68%; Inconsistency (Chi^2) p=0.007, N=683).

Conclusion: There is moderate quality evidence that TXA reduces blood transfusion in hip fracture surgery, with low quality evidence suggesting no increased risk of thrombotic events. These findings are consistent with TXA use in other orthopaedic procedures.

Keywords: Bleeding, femoral neck fracture, hip fracture, meta-analysis, Orthopaedics, surgery, systematic review, Tranexamic acid, transfusion, trauma.

PROSPERO Registration: CRD42016036806

INTRODUCTION

Despite modern healthcare advances, hip fractures still remain a major risk group for in-hospital mortality, with figures as high as 15% [1, 2]. These deaths typically happen early in the post-operative period, with a mean of 11 days from admission [3].

Peri-operative blood loss is a common complication of hip fracture surgery that has been linked to post-operative mortality [4]. Blood loss in people who undergo hip fracture surgery is often significant [5], and is likely underestimated by standard intra-operative calculations [6]. In addition post-operative anaemia has been linked to increased impairment of functional ability, longer length of hospital stay and increased mortality [4, 7, 8].

Typical management of post-operative anaemia is through blood transfusion, Major orthopaedic surgery has been identified as the commonest indication for blood transfusion in surgical patients [9]. There is however concern regarding a significantly increased risk of serious bacterial infection in hip fracture patients undergoing allogenic blood transfusion [10]. The most recent Serious Hazards of Transfusion report (SHOT) found evidence for 15 transfusion-related deaths and 169 incidences of major morbidity associated with blood transfusion in 2014 within the UK alone [11].

One potential method of decreasing peri-operative blood loss and reducing post-operative transfusion is through the use of Tranexamic acid (TXA). This is an anti-fibrinolytic agent which blocks the lysine binding site of plasminogen [12]. Current evidence suggests that TXA reduces peri-operative blood loss and transfusion rates across a range of surgical disciplines without an increased risk of thrombosis [12-15].

Scientific rationale and supporting evidence suggests that TXA may be useful in reducing blood loss and transfusion rates in hip fracture surgery. Studies into TXA and hip fracture surgery have so far provided variable assessments of efficacy in reducing blood loss and thromboembolic risk with no clear consensus [16-19]. This topic has yet to be investigated in the form of a systematic review. 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 hip fracture surgery with quantification of effect through meta-analysis of relevant data.

METHODS

A systematic review and meta-analysis of the use of TXA in hip fracture surgery was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [20]. The review protocol was registered on the international prospective register of systematic reviews (PROSPERO) prior to commencement (Registration number CRD42016036806).

Search Strategy

Identification of relevant articles was undertaken through a search of Medline, EMBASE, AMED, CiNAHL, and the Cochrane Central Registry of Controlled Trials. A search of unpublished/grey literature databases was undertaken including: OpenGrey, Current Clinical Trials, the WHO registry of clinical trials and clinaltrials.gov. All electronic searches were undertaken from database inception to 18th June 2016. A full electronic search strategy for MEDLINE is shown in Supplementary Table 1. This was adapted for each individual database.

All reference lists from potentially eligible studies were reviewed. An additional online search was undertaken using the Google search engine to identify any papers which may have been omitted from the initial search and to cross-reference against the database search.

Eligibility Criteria

Studies were included if they: presented results evaluating the clinical outcomes and/or complications regarding the use of TXA in hip fracture surgery. We considered any form of

hip fracture surgery including: open reduction internal fixation (cannulated screws, dynamic hip screws, intramedullary devices), hemiarthroplasty and total hip arthroplasty (THA) for trauma. We excluded papers which were review articles and studies that included assessment of primary THA (elective), hip arthroscopy or any form of non-trauma hip surgery. We excluded non-English language publications but did not exclude studies based on study quality, age of publication or location of study origin.

Study Identification

Two assessors (LF, TS) independently screened the titles and abstracts of the search outputs for potentially relevant articles which met the eligibility criteria. For those papers which were deemed potentially eligible, their full-texts were evaluated to determine final eligibility.

Data Extraction

Data were extracted onto a pre-defined data extraction sheet by one reviewer (LF) and verified by a second (TS). Data included: study design, research aims, participants characteristics (age, gender, type of hip fracture, medical morbidity, fracture fixation, operative details), randomisation method (if applicable), intervention (TXA and control) and outcome data. Trial authors were contacted for any missing relevant data.

Outcome Measures

The primary outcome measure was frequency of post-operative blood transfusion. The secondary outcome measures were: post-operative haemoglobin, peri-operative blood loss, frequency of thromboembolic events, length of hospital stay and complications within the initial 90-days post-operatively. Outcomes were assessed as either intra-operative, short-term (hospital admission) or longer-term (post-hospital discharge).

Quality Assessment

Risk of bias assessment was performed by two reviewer independently (LF, TS) using the Cochrane Collaboration's risk of bias tool for RCT's [21] and the Risk of Bias in non-randomised studies – of interventions (ROBINS-I) tool [22] for observational studies. The ROBINS-I tool assesses bias across six domains including: confounding, participant selection, intervention classification, departure from intended interventions, missing data, measurement of outcomes and selection of reported results. For each domain an outcome of low, moderate, serious, critical and no information for risk of bias is recorded. An overall risk of bias judgement is then determined through combination of the six domains. The Cochrane Collaboration's risk of bias tool for RCT's comprises seven domains including: random sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. For each domain an outcome of low risk, unclear risk or high risk is recorded. There is no overall assessment of risk of bias.

During the study period any disagreements in quality assessment, study eligibility or data extraction were resolved through discussion between two reviewers (LF, TS).

Data Analysis

An assessment of clinical heterogeneity was made by analysing the completed data extraction form. When there was evidence of between-study heterogeneity in population characteristics, surgical intervention or trial intervention (i.e. TXA), a meta-analysis was deemed inappropriate and a narrative analysis of the evidence was undertaken. When there was clinical homogeneity in respect to population characteristics, surgical intervention and trial intervention, a meta-analysis was deemed appropriate and undertaken for those specific outcomes. All reported values are for Intravenous TXA unless otherwise stated.

When meta-analysis was undertaken, statistical heterogeneity was assessed using the inconsistency-value (I^2) and Chi-squared tests. When I^2 was ≤20% and Chi-squared equated to $p \geq 0.10$, a fixed-effects model meta-analysis was undertaken. When these were not

satisfied, a random-effects meta-analysis was undertaken [23]. For dichotomous outcomes including frequency of post-operative blood transfusion, thromboembolic events and 90-day complications, the relative risk (RR) or risk difference (RD) was estimated with 95% confidence intervals (CI). A risk difference was calculated if a zero number of events was reported for an outcome within an individual trial. The number needed to treat (NNT) was calculated for the primary outcome of post-operative blood transfusion using the inverse of the absolute risk reduction value. For all continuous outcomes including post-operative haemoglobin level, peri-operative blood loss and length of hospital stay, the mean difference (MD) was calculated with 95% CIs. In all analyses, $p<0.05$ denoted statistically significance. All analyses were undertaken by two reviewers (LF,TS) using Revman Version 5.3 [24]. All meta-analysis results are presented in the text as: outcome (RR/RD/MD); 95% CI; Inconsistency (I^2) value; Inconsistency (Chi^2) p value; Sample size (N).

A sensitivity analysis was conducted to analyse outcomes in trials without significant methodological limitation i.e. ambiguity on hip fracture type or surgical intervention. *A priori* subgroup analyses included comparison of the TXA intervention to control group on clinical outcomes stratified by mean age (less than 75 years versus 76 years and over), BMI group (less than or equal to BMI 40 versus BMI greater than 40), and hip fracture type (intracapsular vs extracapsular). Assessment was performed by excluding data from studies which did not meet the subgroup analysis requirements.

The analysis for each outcome was evaluated using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach by two reviewers (LF, TS) [25]. This was used to categorise the quality of evidence into four possible levels: high, moderate, low or very low quality. This approach evaluates the quality of evidence for each individual analysis (i.e. the body of the literature forming that particular analysis as opposed to the whole evidence irrespective of whether it was used in an analysis or not).

RESULTS

Search Results

A summary of the search results are presented in Figure 1. A total of 102 studies were identified. Sixteen of these underwent full-text assessment. Subsequently seven met the eligibility criteria. Two abstract only publications [26, 27] were not included due to incomplete data and lack of contact details in conference proceedings. A search of the grey/unpublished literature identified four ongoing trials at various stages of completion [28-31].

Characteristics of Included Studies

A summary of included study characteristics are shown in Table 1. A total of 770 patients were included in the analysis. The mean age was 72 years; 65% were female. Of these 341 patients received TXA (321 intravenous (IV) TXA; 20 topical TXA). There was a wide variation in the frequency and dose of TXA given peri-operatively. Of the seven studies, three did not differentiate fracture type or management; two studies examined patients undergoing intracapsular hip fracture treatment (hemi-arthroplasty) alone [17, 19] and two studies focused on extracapsular hip fractures (one utilised sliding hip screw fixation [18], the other a short intramedullary nail device [32]).

Quality Assessment

The seven articles identified as suitable for systematic review consisted of six double-blind RCTs [16-18, 32-34] and one retrospective cohort study [19]. Randomisation methods included utilisation of opaque sealed envelopes [32, 33], random number techniques [34] and a computer generated random number table [18]. One study [16] used a stratified sampling technique via a computer generated randomisation list to ensure equal distribution of patients undergoing osteosynthesis or hip arthroplasty. One study did not report their method of randomisation [17].

Risk of bias assessment was performed for individual studies with the results shown in Supplementary table 2. Determination of the risk of bias across studies was also performed for each outcome measured.

Synthesis of results

Primary outcome: Post-operative blood transfusion requirement

All seven studies reported the requirement for post-operative blood transfusion [16-19, 32-34]. Meta-analysis showed there was a 46% lower risk of blood transfusion requirement in those who received intra-venous TXA compared to a placebo/control group (RR: 0.54; 95% CI: 0.35 to 0.85; I^2: 78%; Inconsistency (Chi^2) p=<0.0001; N=750; Figure 2). The NNT for this primary outcome was 8. The funnel plot for the primary outcome is shown in Figure 3.

Secondary outcome: Post-operative haemoglobin level

Six studies reported the requirement for post-operative haemoglobin level [17-19, 32-34]. On meta-analysis, post-operative haemoglobin was greater in those who received intra-venous TXA compared to a placebo/control group (MD: 0.81; 95% CI: 0.45 to 1.18; I^2: 46%; Inconsistency (Chi^2) p=0.10; N=638; Figure 4).

Secondary outcome: Total post-operative blood loss within the initial post-operative day

Five studies reported the requirement for post-operative blood loss [16, 17, 32-34]. Data were available to pool outcomes from three studies [17, 33, 34]. On this meta-analysis, post-operative total blood loss was less in those who received intra-venous TXA compared to the placebo/control group (MD: -341; 95% CI: -672 to -9.87; I^2: 100%; Inconsistency (Chi^2) p<0.00001; N=197; Supplementary Figure 1).

There was insufficient data in Zuffery et al [16] to be included in the meta-analysis as post-operative blood loss was only reported at Day 8. They reported no statistically significant

difference between TXA and placebo groups (444mls; 95% CI: 116 to 804 vs. 307mls; 95% CI: 90 to 526; respectively; p=0.07). Tengberg et al [32] also only provided data for post-operative blood loss at Day 4, where there was a statistically significant higher blood loss for control versus TXA (MD: 571; 95% CI: 61.7 to 1080; p=0.029)

Secondary outcome: Peri-operative blood loss

Three studies reported peri-operative blood loss [16, 32, 34]. Meta-analysis showed a significantly lower blood loss for TXA versus control (MD: -190; 95% CI: -495 to 115; I^2: 91%; Inconsistency (Chi^2) p<0.00001; N=249; Supplementary Figure 2).

Secondary outcome: Total Length of Hospital Stay

Two studies reported hospital length of stay [19, 34]. There was no significant difference between the TXA and placebo/control groups for this outcome (MD: 0.26; 95% CI: -4.05 to 4.56; I^2: 77%; Inconsistency (Chi^2) p=0.04; N=338; Supplementary Figure 3).

Post-operative complications

Meta-analysis was only possible for six post-operative complications: 30-day mortality; 90 day mortality; stroke; overall thromboembolic events; pulmonary embolism and deep vein thrombosis. The results of these analyses are shown in table 2. The forest plot for thromboembolic events is presented in Figure 5. All other forest plots for post-operative outcomes are displayed in the supplementary material (Supplementary Figures 4 to 8). There were no statistically significant differences comparing TXA to placebo across the six analyses.

Zufferey et al [16] reported on a number of other post-operative complications. There were no significant differences observed for TXA compared to placebo for major bleeding (inclusion criteria not defined), bacterial infection, pneumonia, lower respiratory tract infection, urinary tract infection, superficial wound infection, deep wound infection and acute coronary syndrome.

GRADE Assessment

The quality of evidence for each eligible outcome was assessed using the GRADE approach. The results of this are presented in Table 2. These indicated that whilst the quality of evidence was high the outcome of post-operative haemoglobin level, it was moderate for those of requirement of post-operative blood transfusion and 30-day mortality. All other outcomes were either of low or very low quality.

Subgroup analysis

Subgroup analysis was performed as planned where data permitted. There were five observed alterations to meta-analysis outcomes. This included a lack of statistical significance in transfusion rate for TXA versus placebo in those age ≥76 (RR 0.67 (0.37, 1.22); I^2: 84%; Inconsistency (Chi^2) p=0.002; N=453), in those BMI ≤40 (RR 0.73 (0.49, 1.11); I^2: 68%; Inconsistency (Chi^2) p=0.02; N=289), and where extracapsular hip fractures were examined alone (RR 0.67 (0.24, 1.87); I^2: 88%; Inconsistency (Chi^2) p=0.004; N=172). When considering peri-operative blood loss there was a lack of significance for TXA versus placebo in those age ≥76 (MD -47.6 (-127, 31.5); I^2: 0%; Inconsistency (Chi^2) p=0.97; N=182). There was also a lack of significance in post-operative haemoglobin for TXA versus placebo when examining intracapsular hip fractures alone (MD 0.93 (-0.04, 1.91); I^2: 79%; Inconsistency (Chi^2) p=0.06; N=309). Results for all other subgroup analyses are presented in Table 3.

A sensitivity analysis was undertaken removing the results of Lee et al [19] to examine the influence of any bias inherent in the design of this study. Due to ambiguity regarding the number of femoral shaft fractures included in their study a similar assessment was also performed with Vijay et al [33] removed. There were no significant differences in meta-analysis outcomes for either cohort. Results are again presented in Table 3.

DISCUSSION

Our systematic review and meta-analysis found moderate-quality evidence that the use of TXA in hip fracture surgery reduces the absolute risk of requiring a post-operative blood transfusion by 12%. The NNT for this primary outcome was low at 8.

There is associated high-quality evidence for a higher post-operative haemoglobin level with TXA and moderate quality evidence for no difference in 30 day mortality. The use of TXA was not associated with an increase in post-operative stroke, pulmonary embolus, DVT or composite thromboembolic events. However, the quality of evidence was judged as low for these outcomes. There is also low quality evidence to suggest a decreased level of post-operative and peri-operative blood loss with TXA and very low quality evidence suggesting no difference in length of hospital stay. These findings are in keeping with evidence from other systematic reviews examining the use of TXA in hip and knee arthroplasty [12], as well as other surgical procedures [13].

There is a potential financial benefit associated with the use of TXA in hip fracture surgery when considering blood transfusion. Our estimates suggest that when considering two peri-operative doses of 1g IV TXA, with a cost of £1.50 per 5ml (100mg/ml) for TXA , £635 per transfusion , and an NNT of 8, this would equate to a saving of approximately £74.13 per patient who undergo hip fracture surgery on transfusion costs alone. Further cost-benefit analyses are warranted to estimate the potential value (or not) of TXA on the entire patient pathway following hip fracture to test whether these suggested benefits are repeatedly evident following hip fracture surgery.

Subgroup analysis was performed to identify any potential patient or external factors which may have influenced study findings. A number of differences in the significance of outcome results were identified. Firstly, a lack of significance was noted for TXA versus placebo regarding the transfusion rate in those studies with mean age ≥76. This finding could be explained by previously acknowledged heightened levels of pre-operative anaemia with

increasing age [35] amplifying the likelihood of transfusion in both groups. Secondly, there was a lack of significance in transfusion rate for those BMI ≤40. One potential explanation for this result could relate to greater blood loss in both groups influencing the difference in transfusion rate. Such higher levels of blood loss of those with a lower BMI would be in keeping with findings in other orthopaedic surgical procedures [36]. There was also a lack of significance in transfusion rate with TXA identified for extracapsular hip fractures. Again this could be explained by recognised greater blood loss and higher levels of pre-operative anaemia compared to intracapsular fractures [5]. Finally there was a lack of significance for peri-operative blood loss in those age ≥76 which was felt to relate to the very wide confidence intervals of the studies used in this analysis.

Sensitivity analysis with data from Vijay et al [33] and Lee et al [19] excluded did not have a significant effect on any of the results and therefore neither were felt to have a negative impact on the overall study outcome.

A number of limitations identified with this study related to the current evidence-base. Firstly, it was not possible to analyse the potential impact of variation in the dose and timing of TXA across studies. This was poorly reported and may relate to a current paucity of data regarding the optimum therapeutic regimen for TXA. The small number of trials presented meant that sub-group analysis to establish differences between TXA protocols was not possible. Secondly, major inter-study variation in the transfusion protocol used may explain some of the differences in outcomes across studies. It is notable that both of the studies with identified low transfusion thresholds (Hb<9-10 g/dl) [16, 32] did not find a statistically significant difference in post-operative transfusion rate between TXA and placebo. This is compounded by the fact that in the Tengberg et al [32] study the TXA group had significantly lower haemoglobin at admission than the placebo group (11.92 [SD 1.61] vs 12.89g/dl [SD 1.45] respectively; p=0.024). Finally, the GRADE analysis identified a number of the secondary outcomes as having low or very low quality evidence. This was mainly due to high heterogeneity across studies, low event numbers and wide confidence intervals. This

unfortunately limits the conclusions that can be drawn from the evidence and the identified results for these outcomes must be interpreted with caution.

Four key aspects for future research have been highlighted by this study. Firstly, understanding the thrombotic risk associated with TXA use in hip fracture surgery is of paramount importance to determining its clinical utility. Future studies must ensure that safety outcomes are assessed. Only large studies are likely to provide sufficient cohort size to accurately determine thrombosis risk. Verification of the optimum timing and dosage of Intravenous TXA to reduce study heterogeneity would likely be of benefit in this regard.

Secondly, the use of topical TXA in hip fractures is another potential research area of interest. Only one study [17] examined topical TXA as a treatment option. Their results indicated an efficacy similar to that of Intravenous TXA when compared to placebo, but with an improved safety profile. A lack of systemic absorption with topical TXA is one suggested reason for such an effect. Comparable results have previously been identified with topical TXA in hip and knee arthroplasty [37-39]. Caution should however be taken when considering use in hemiarthroplasty as recent research has identified a potential cytotoxic effect on chondrocytes in an animal model [40]. There is however no suggestion for an adverse effect with artificial joint materials [41].

Thirdly, evaluation of treatment effect differences between different hip fractures and treatment options may also be of benefit. Extracapsular hip fracture management has previously been shown to have a higher amount of blood loss than intracapsular hip fractures [5, 6]. The complexity and length of THA for hip fracture compared to hemiarthroplasty has also been shown to lead to a higher degree of blood loss [42]. The beneficial effects of TXA may be more pronounced in such high-risk groups.

Finally the impact of TXA administration at hospital admission should also be examined. This approach is already heavily utilised in trauma patients based on results of the landmark CRASH-2 trial [43]. Hip fractures have been associated with a high initial blood loss that may

not be apparent on initial haemoglobin testing [5, 44]. Early TXA may provide one method of reducing pre-operative anaemia, which has previously been identified as risk-factor for mortality [45].

CONCLUSIONS

The clinical importance and financial impact of post-operative blood transfusion requirement and post-operative anaemia in hip fracture surgery is already well established. Our systematic review and meta-analysis confirms that TXA is effective at reducing both of these adverse outcomes in this setting. The presence of an associated thromboembolic risk with TXA use remains unclear.

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481 years; no other relationships or activities that could appear to have influenced the submitted
482 work”

483 **AUTHOR CONTRIBUTIONS**

484 LF developed the research idea. He performed the review literature search as well as
485 primary data extraction and data analysis. He wrote the structured summary, introduction,
486 results, discussion and conclusion sections of the manuscript.

487 TS performed the review literature search as well as secondary data extraction and data
488 analysis. He provided guidance on design of the manuscript and wrote the methods section.
489 He also provided critical appraisal of the manuscript prior to submission.

490 GA provided expertise in the clinical interpretation and application of the results. He also
491 performed critical appraisal of the manuscript prior to submission.

492 PM oversaw development and design of the study as well as providing critical appraisal of
493 the manuscript prior to submission.

494

495 **FIGURE LEGENDS**

496 **Figure 1.** Flow diagram depicting the study selection process
497
498 **Figure 2.** Forest-plot of TXA versus control for requirement for blood transfusion
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500 **Figure 3.** Funnel plot of TXA versus control for requirement for blood transfusion.
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502 **Figure 4.** Forest-plot of TXA versus control for post-operative haemoglobin
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506 **SUPPLEMENTARY FIGURE LEGENDS**

507 **Supplementary Figure 1.** Forest-plot of TXA versus control for total blood loss
508
509 **Supplementary Figure 2.** Forest-plot of TXA versus control for Peri-operative blood loss
510
511 **Supplementary Figure 3.** Forest-plot of TXA versus control for length of stay

Supplementary Figure 4. Forest-plot of TXA versus control for 90 day mortality

Supplementary Figure 5. Forest-plot of TXA versus control for Stroke

Supplementary Figure 6. Forest-plot of TXA versus control for Pulmonary Embolus

Supplementary Figure 7. Forest-plot of TXA versus control for DVT

Supplementary Figure 8. Forest-plot of TXA versus control for 30 day mortality

522 **Table 1.** Characteristics of included studies

Paper	Study	N	Gender (M/F)	Mean age (years)	ASA grade (3 or 4)	Fracture type	Fracture surgical management	Duration of surgery (minutes)	Intervention	Control
Lee et al 2015 [19]	RCS	271	Interv: 32/52 Control: 53/134	Interv: 86.0 Control: 84.7	Interv: 57 Control: 137	Hip Fracture	Hemiarthroplasty: 271	Not documented	(N: 84) 1g IV TXA given at induction.	(N:187) No treatment control.
Sadeghi & Mehr - Aein 2007 [34]	DBL blind RCT	67	Interv: 17/15 Control: 24/11	Interv: 51.8 Control: 44.4	Not documented	Hip Fracture	Not documented	Not documented	(N:32) Single bolus of 15mg/kg IV TXA given at induction.	(N:35) Same volume of IV normal saline given to controls.
Zuffery at al. 2010 [16]	DBL blind RCT	110	Interv: 10/47 Control: 4/49	Interv: 81 Control: 82	Interv: 19 Control: 20	Cervical: 45 Trochanteric: 19 Unstable trochanteric/inter/subtrochanternic: 46	THR: 45 Hemiarthroplasty: 2 SHS: 41 IMN: 22	Interv: 64.0 Control: 64.0	(N:57) Two doses of IV TXA – 15mg/kg given at induction then another 3 hours later.	(N:53) Control group received 2 doses of IV placebo at same intervals.
Emara 2014 [17]	DBL blind RCT	60	Interv (IV): 12/8 Interv (Topical): 10/10 Control: 14/6	Interv (IV): 56.5 Interv (Topical): 55 Control: 56	Not documented	Hip Fracture	Hemiarthroplasty: 60	Interv (IV): 2.3 hrs Interv (Topical): 2.3 hrs	(N:20) IV TXA 10mg/kg as bolus pre incision then 5mg/kg/h infusion until end (N:20) Topical TXA 100mls NS with 1.5g TXA poured into surgical field for 5 mins	(N:20) Control received 20ml of normal saline pre-incision and 80ml/h of normal saline until end.100ml of normal saline poured into surgical field for 5 mins
Mohib et al. 2015 [18]	DBL blind RCT	100	Interv: 21/29 Control: 24/26	Interv: 69.0 Control: 70.0	Not documented	Intertrochanteric: 100	SHS: 100	Interv: 112.9 Control: 112.3	(N: 50)Two doses of IV 10mg/kg TXA at induction and 3 hours later.	(N:50) Controls: same amount saline.
Vijay et al 2013 [33]	DBL blind RCT	90	Interv: 10/35 Control: 10/35	Interv: 49.3 Control: 48.8	Interv: 0 Control: 0	Hip and Femoral fracture. No further details provided.	ORIF; hemiarthroplasty; THR. Frequencies not documented.	Interv: 118.7 Control: 117.3	(N: 45) 10mg/kg body weight IV TXA given 15min prior to incision.	(N:45) Controls: 1mg/kg body weight IV saline.
Tengberg et al 2016 [32]	DBL blind RCT	72	Interv: 7/26 Control: 14/25	Interv: 79.8 Control: 75	Interv: 5 Control: 12	Extracapsular (AO type 31-A2.2 to 31-A3): 72	Short intramedullary nail: 72	Not documented	(N: 33) 1g IV TXA as bolus pre incision then post-op 24hr infusion of 3g TXA	(N: 39) Controls: 5ml saline given pre incision and then 24 hour infusion of 1litre IV saline

523 Abbreviations: DBL = Double; RCT = Randomised controlled trial; RCS = Retrospective cohort study; Interv = Intervention group; THR = Total Hip replacement; SHS = Sliding
524 hip screw; IMN = Intramedullary nail; ORIF = Open reduction internal fixation
525

Table 2. Synthesis of results for all outcomes & GRADE assessment: summary of findings

Outcomes	Intervention	Control	Relative effect (95% CI)	Inconsistency value (I^2)	Inconsistency (Chi^2) p value	Number of participants [Studies]	Quality of evidence	Comments
Post-operative blood transfusion	85 of 321	166 of 429	RR 0.54 (0.35, 0.85)	78%	p<0.0001	750 [16-19, 32-34]	Moderate	Serious imprecision
Post-operative haemoglobin	10.5 g/dl	10.0 g/dl	MD 0.81 (0.45, 1.18)	46%	p=0.10	638 [17-19, 32-34]	High	
Blood loss on 1st post-operative day	467mls	780mls	MD -341 (-672, -9.87)	100%	p<0.0001	197 [17, 31, 34]	Low	Serious inconsistency & serious imprecision
Peri-operative blood loss	415mls	568mls	MD -190 (-495, 115)	91%	p<0.0001	249 [16, 32, 34]	Low	Serious inconsistency & serious imprecision
Length of hospital stay	16.4 days	16.1 days	MD 0.26 (-4.05, 4.56)	77%	p=0.04	338 [19, 34]	Very low	Serious risk of bias, serious inconsistency & serious imprecision
Post-operative complications: 30 day mortality	9 of 206	11 of 314	RR 1.33 (0.53, 3.34)	0%	p=0.48	520 [16,19, 32, 34]	Moderate	Serious risk of bias
Post-operative complications: Stroke	2 of 110	1 of 112	RR 1.49 (0.24, 9.25)	0%	p=0.60	222 [16, 17, 32]	Low	Very serious imprecision
Post-operative complications: Thromboembolic events	16 of 289	10 of 394	RD 0.01 (-0.03, 0.05) *	68%	p=0.007	683 [16-19, 32, 31]	Low	serious inconsistency & serious imprecision
Post-operative complications: Pulmonary embolus	0 of 205	0 of 207	RD 0.00 (-0.02, 0.02) *	0%	p=1.00	412 [16-18, 32, 33]	Low	Very serious imprecision
Post-operative complications: DVT	10 of 172	4 of 168	RD 0.01 (-0.03, 0.04) *	43%	p=0.13	412 [16-18, 32, 33]	Low	Serious inconsistency & serious imprecision

Abbreviations: GRADE = Grading of Recommendations Assessment, Development and Evaluation;
CI =Confidence interval; RR =Relative risk; RD = Risk difference; MD = Mean difference. * risk difference calculated given zero-events were reported in some studies.

Table 3. Subgroup & Sensitivity analysis

Subgroup Analysis	Variable [Studies]	Transfusion	Post-operative haemoglobin	Day 1 post-operative blood loss	Peri-operative blood loss	Total Length of Hospital Stay	Thromboembolic events	30 day mortality	90 day mortality	PE	DVT	Stroke
Age	≥76 [16,19,32]	RR 0.67 (0.37, 1.22); I^2: 84%; Inconsistency Chi^2 p=0.002; N=453 *	MD 0.50 (0.10, 0.89); I^2: 0%; Inconsistency Chi^2 p=0.87; N=341		MD -47.6 (-127, 31.5); I^2: 0%; Inconsistency Chi^2 p=0.97; N=182 *		RD 0.00 (-0.07, 0.08); I^2: 69%; Inconsistency Chi^2 p=0.04; N=453	RR 1.61 (0.64, 4.03); I^2: 0%; Inconsistency Chi^2 p=0.41; N=453		RD 0.00 (-0.03, 0.03); I^2: 0%; Inconsistency Chi^2 p=1.00; N=182	RD 0.01 (-0.06, 0.07); I^2: 9%; Inconsistency Chi^2 p=0.29; N=182	RD 0.04 (-0.04, 0.04); I^2 0%; Inconsistency Chi^2 p=0.32; N=182
	≤75 [17,18,33,34]	RR 0.48 (0.33, 0.72); I^2: 10%; Inconsistency Chi^2 p=0.35; N=297	MD 1.03 (0.46, 1.60); I^2: 64%; Inconsistency Chi^2 p=0.0004; N=297				RD 0.03 (-0.06, 0.12); I^2: 84%; Inconsistency Chi^2 p=0.002; N=230					
BMI	≤40 [16,17,32,34]	RR 0.73 (0.49, 1.11); I^2: 68%; Inconsistency Chi^2 p=0.02; N=289 *	MD 1.34 (0.76, 1.93); I^2: 0%; Inconsistency Chi^2 p=0.79; N=179	MD: -461 (-478, -444); I^2: 0%; Inconsistency Chi^2 p=0.43; N=107			RD 0.08 (-0.10, 0.26); I^2: 82%; Inconsistency Chi^2 p=0.003; N=222	RR 2.26 (0.48, 10.63); I^2: 0%; Inconsistency Chi^2 p=0.42; N=247		RD 0.00 (-0.03, 0.03); I^2: 0%; Inconsistency Chi^2 p=1.00; N=222	RD 0.04 (-0.02, 0.11); I^2: 65%; Inconsistency Chi^2 p=0.20; N=222	
	>40											
Hip fracture type	Intracapsular [17,19]											
	Extracapsular [18,32]	RR 0.67 (0.24, 1.87); I^2: 88%; Inconsistency Chi^2 p=0.004; N=172 *	MD 1.40 (-0.79, 2.01); I^2: 0%; Inconsistency Chi^2 p=0.85; N=212				RD -0.02 (-0.07, 0.04); I^2: 40%; Inconsistency Chi^2 p=0.20; N=172			RD 0.00 (-0.03, 0.03); I^2: 0%; Inconsistency Chi^2 p=1.00; N=172	RD -0.01 (-0.05, 0.03); I^2: 0%; Inconsistency Chi^2 p=0.49; N=172	

Subgroup Analysis	Variable [Studies]	Transfusion	Post-operative haemoglobin	Total post-operative blood loss	Peri-operative blood loss	Total Length of Hospital Stay	Thromboembolic events	30 day mortality	90 day mortality	PE	DVT	Stroke
Vijay et al. 2013 removed	[16-19,32,34]	RR 0.58 (0.36, 0.92); I^2: 78%; Inconsistency Chi^2 p=0.0003; N=660	MD 1.01 (0.50, 1.51); I^2: 43%; Inconsistency Chi^2 p=0.14; N=548	MD: -461 (-478, -444); I^2: 0%; Inconsistency Chi^2 p=0.43; N=107			RD 0.02 (-0.04, 0.08); I^2: 75%; Inconsistency Chi^2 p=0.0003; N=593			RD 0.02 (-0.02, 0.02); I^2: 0%; Inconsistency Chi^2 p=1.00; N=322	RD 0.03 (-0.02, 0.08); I^2: 58%; Inconsistency Chi^2 p=0.07; N=322	
Lee et al. 2015 removed	[16-18,32-34]	RR 0.60 (0.39, 0.92); I^2: 76%; Inconsistency Chi^2 p=0.001; N=479	MD 1.00 (0.47, 1.54); I^2: 53%; Inconsistency Chi^2 p=0.08; N=369				RD 0.02 (-0.04, 0.09); I^2: 77%; Inconsistency Chi^2 p=0.001; N=412	RR 2.26 (0.48, 10.63); I^2: 0%; Inconsistency Chi^2 p=0.42; N=479				

Abbreviations: CI = confidence intervals; I^2 = inconsistency value; N = number of cases; RR = Risk ratio; RD = risk difference (calculated given zero-events were reported in some studies). * denotes result that has ceased to become statistically significant after subgroup analysis.

Supplementary Table 1. Search strategy

1. Tranexamic acid
2. hip fracture
3. femoral fracture
4. neck of femur
5. extracapsular
6. intracapsular
7. subcapital
8. transcervical
9. basicervical
10. intertrochanteric
11. subtrochanteric
12. hemiarthroplasty
13. total hip arthroplasty
14. sliding hip screw
15. dynamic hip screw
16. intramedullary nail
17. femoral nail
18. cannulated screws
19. open reduction internal fixation
20. OR/1-11
21. OR/12-19
22. AND/1,20,21

Supplementary table 2. Risk of bias assessment for individual studies

RCT Studies	**Random sequence generation**	**Allocation concealment**	**Blinding of participants & personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other bias**	**Other bias explanation**
Emara et al 2014 [17]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk	Low risk	
Mohib et al 2015 [18]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Sadeghi et al 2007 [34]	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	High risk	Low risk	
Vijay et al 2013 [33]	High risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	High risk	unclear frequency of distal or proximal femoral fracture
Zufferey et al 2010 [16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Tengberg et al 2015 [32]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Significant baseline differences in treatment groups
Observational studies	**Bias due to confounding**	**Bias in participant selection**	**Bias in classification of interventions**	**Bias due to departures from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall bias**
Lee et al 2015 [19]	Serious risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk	Serious risk

Risk of bias assessment was performed using the Cochrane Collaboration's risk of bias tool for RCT's. Each domain was classified as either unclear, low or high risk. The Risk of Bias in non-randomised studies – of interventions (ROBINS-I) tool was used for observational studies. Each domain was classified as low risk, moderate risk, serious risk, and critical risk or not interpretable. An overall bias assessment was then made using the same scale.

Figure 1. Flow diagram depicting the study selection process

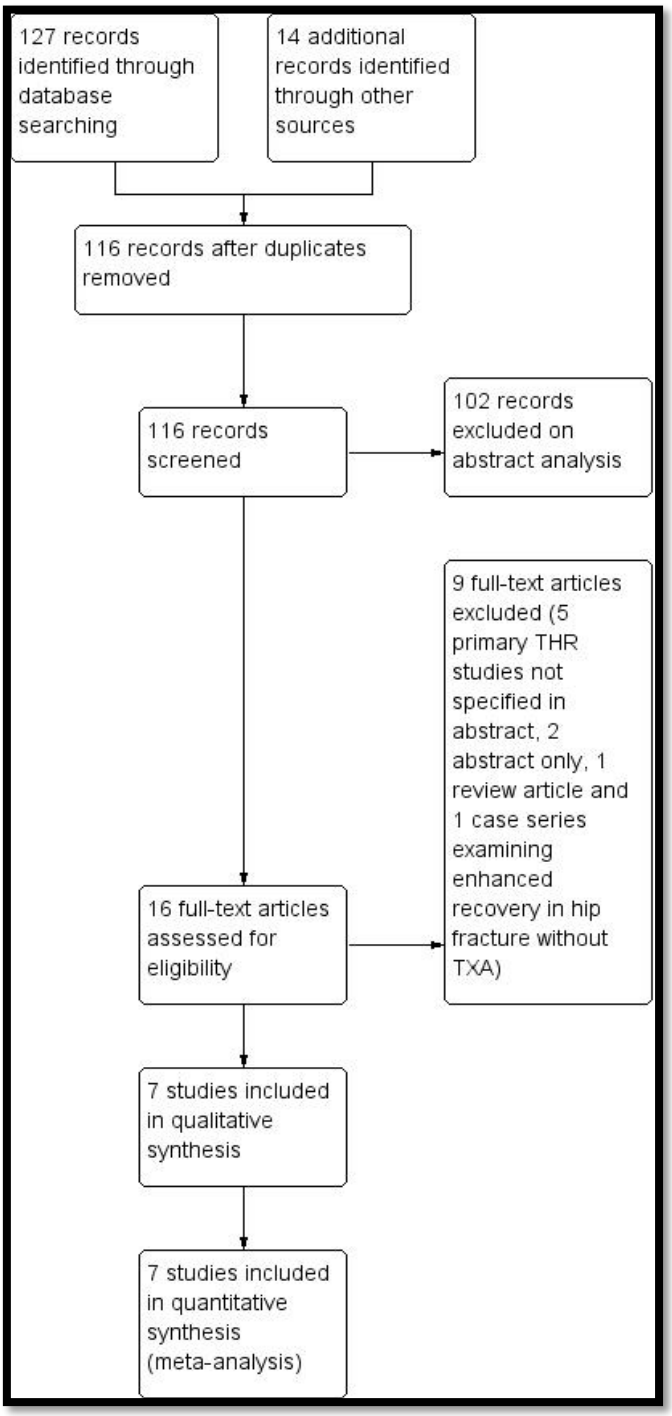

Figure 2. Forest-plot of TXA versus control for requirement for blood transfusion

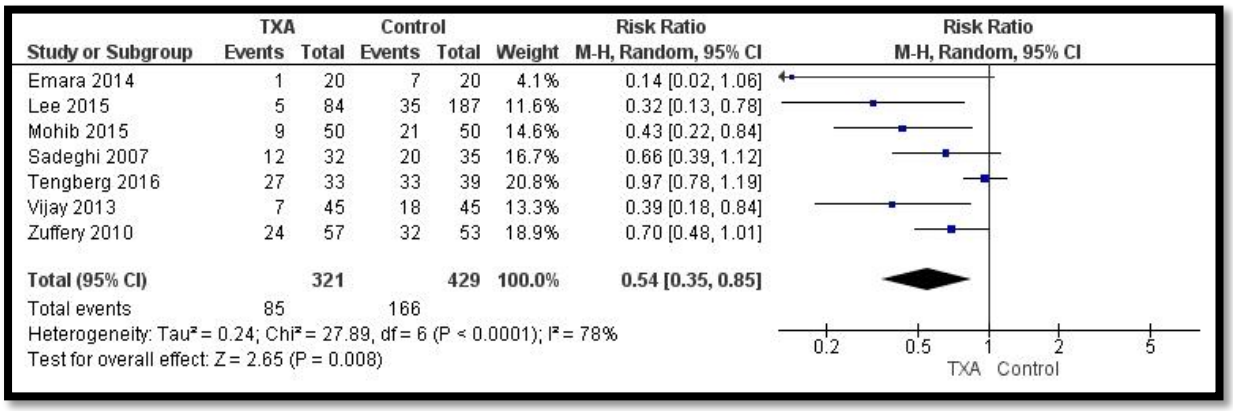

Figure 3. Funnel plot of TXA versus control for requirement for blood transfusion.

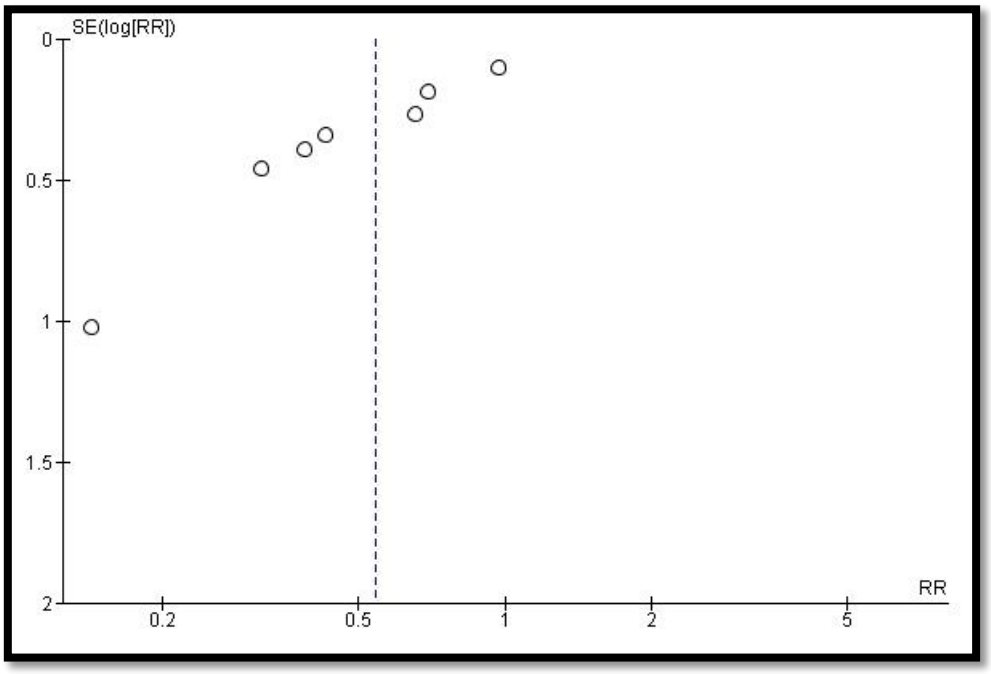

Figure 4. Forest-plot of TXA versus control for post-operative haemoglobin

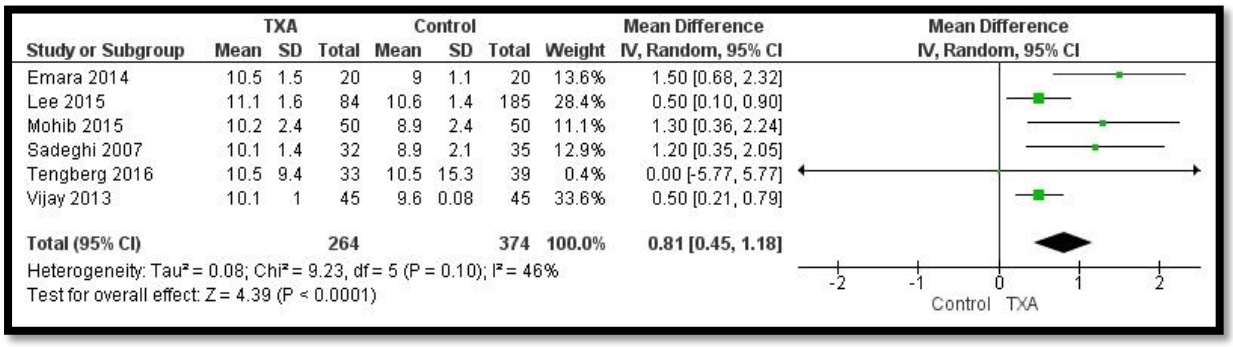

Figure 5. Forest-plot of TXA versus control for thromboembolic events