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## **Title**

Tranexamic acid use to decrease blood loss in primary shoulder and elbow replacement: a systematic review and meta-analysis

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#### **Conflicts of interest/Competing interests**

AWB and MRW disclose financial activities, all outside the submitted work. All authors have completed uniform disclosure forms.

#### **Availability of data and material**

Data extracted from individual papers are available from the corresponding author.

**Code availability**

Not applicable.

**Author contributions**

RLD, SKK and MRW designed the study. RLD and JRV contributed to data collection analysis, and interpretation. RLD wrote the first draft of the manuscript. All authors interpreted data, drafted, and reviewed the final manuscript. All authors approved the submitted manuscript.

**Ethics approval**

Not applicable.

**Consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Title**

Tranexamic acid use to decrease blood loss in primary shoulder and elbow replacement: a systematic review and meta-analysis

## **Abstract**

### *Purpose*

Tranexamic acid (TXA) is an inexpensive antifibrinolytic agent that significantly reduces peri-operative blood loss and transfusion requirements after total hip and knee replacement. This meta-analysis demonstrates the effects of TXA on blood loss in total shoulder replacement (TSR) and total elbow replacement (TER).

### *Methods*

We systematically searched MEDLINE, EMBASE and CENTRAL from inception to 03 September 2020 for randomised controlled trial (RCTs) and observational studies. Our primary outcome was blood loss. Secondary outcomes included the need for blood transfusion, and post-operative venous thromboembolic (VTE) complications. Mean differences (MD) and relative risks with 95% confidence intervals (CIs) were reported.

### *Results*

Four RCTs and five retrospective cohort studies (RCS) met eligibility criteria for TSRs, but none for TERs. RCT data determined that TXA administration significantly decreased estimated total blood loss (MD=-358mL), post-operative blood loss (MD=-113mL), change in haemoglobin (Hb) (MD=-0.71g/dL) and total Hb loss (MD=-35.3g) when compared to placebo. RCS data demonstrated significant association between TXA administration and decreased in post-operative blood loss, change in Hb, change in Hct and length of stay. There was no significant difference in transfusion requirements or VTE complications.

### *Conclusion*

TXA administration is safe and effective in patients undergoing primary TSR: it significantly decreases blood loss compared with placebo and is associated with shorter length of stay compared with no treatment. No significant increase in VTE complications was found. TXA administration should be routinely considered for patients undergoing TSR. Further research is needed to demonstrate the treatment effect in patients undergoing TER.

**Keywords (MeSH)**

Tranexamic Acid

Arthroplasty, Replacement, Shoulder

Blood Loss, Surgical

Venous Thromboembolism

Systematic Review

Meta-Analysis

## 1. Introduction

Total shoulder replacement (TSR) and total elbow replacement (TER) are effective treatments to relieve pain and improve function in patients. TSR is most commonly used to treat patients with osteoarthritis, cuff tear arthropathy and trauma, whereas TER is more commonly used to treat patients with trauma, inflammatory arthropathy and osteoarthritis[1, 2]. Both interventions have been performed in greater numbers year-on-year[3]. It is well established that joint replacements are associated with significant intra-operative blood loss, which increases the likelihood for allogenic blood transfusion[4, 5] and additional risk of morbidity and mortality[6-9].

Tranexamic acid (TXA) is an inexpensive and increasingly commonly-used antifibrinolytic agent that has been shown to significantly reduce peri-operative blood loss and transfusion requirements after total hip (THR) and knee replacement (TKR)[10-17] as well as other surgical procedures[18, 19]. Furthermore, TXA use has been associated with reduced surgical drain outputs, lower falls in haemoglobin (Hb) and haematocrit (Hct), lower incidence of periprosthetic joint infection and shorter length of stay. A recent meta-analysis that evaluated venous thromboembolism (VTE) outcomes following primary TSR and TER demonstrated that the pooled incidence across studies was less than 1% in the first three months, but the incidence can range from 0.04 to 16%[20]. Evidence also suggests that TXA administration does not increase the risk of VTE complications in patients undergoing total hip or knee arthroplasty but TSR and TER were not studied[21]. Hence, it will be useful to know whether the administration of TXA in patients undergoing TSR and TER procedures affects the risk of post-operative VTE events.

Previous meta-analyses, with the most recent in 2018, have demonstrated that TXA use in TSR can decrease total blood loss, Hb change, drain output and the need for blood transfusion[22-27]. However, five of these studies combined interventional with



observational data in their pooled analyses[[23-27](#)], which is methodologically incorrect, thus limiting the validity of their conclusions. Furthermore, these previous reviews were based on pooled analysis of very few trials, hence reducing power to make effective head-to-head comparisons. The most recent meta-analysis only pooled the results of three randomised controlled trials (RCTs) and three retrospective cohort studies (RCSs)[[22](#)]. Since the publication of the most recent review, new trials have been published. Similar evidence for the benefits of TXA in TER is notably lacking, with only one case series found by preliminary search[[28](#)]. There is a need to comprehensively summarise the evidence given that previous reviews are out of date or flawed with persisting uncertainties.

The aims of this review are threefold: 1) to incorporate the latest evidence regarding the effects of TXA on blood loss in TSR into an updated meta-analysis that accounts for the shortcomings outlined above; 2) to synthesise evidence regarding TXA use in TER; and 3) to identify any gaps in the existing literature.

## **2. Materials and Methods**

### *2.1. Data sources and search strategy*

The review was registered *a priori* in the PROSPERO prospective register of systematic reviews (ID: CRD42020207353) and conducted according to a predefined protocol and in line with PRISMA guidelines. We searched for RCTs or observational study designs (prospective or retrospective case-control, prospective cohort, retrospective cohort, case-cohort and nested-case control) that compared TXA use with usual care/no treatment/placebo in adults undergoing primary TSR or TER. We systematically searched the databases of MEDLINE, EMBASE and CENTRAL from inception to 03 September 2020. There were no restrictions on language. The computer-based searches used a combination of free and MeSH search terms and keywords related to the population (e.g., “shoulder replacement,” “elbow replacement”), and intervention (e.g., “tranexamic acid”). We used a combined search strategy for both TSR and TER. The search was complemented by manually scanning the reference lists of retrieved articles and utilising the “Cited Reference Search” function in Web of Science to obtain any additional studies that were missed by the search strategy. Any previously published systematic reviews and meta-analyses were also screened for studies that met our eligibility criteria. The detailed search strategy has been provided in Appendix 1.

### *2.2. Eligibility criteria*

We included comparative RCTs or observational studies that compared TXA with no treatment/placebo/usual care in patient populations that underwent primary TSR (anatomic: “ATSR;” or reverse: “RTSR”) or primary TER and reported on blood loss and/or other outcomes. The primary outcome was blood loss. Secondary outcomes included the need for blood transfusion, change in Hb or Hct levels, drain output and VTE complications. We

excluded: revision arthroplasty; hemiarthroplasty; arthroscopic procedures; animal studies and cadaveric studies.

### *2.3. Study selection and data extraction*

Once the searches were completed, the results were imported into Rayyan[29], an online bibliographic tool. One reviewer (RLD) initially screened the titles and abstracts and removed any duplicates to provide a list of potentially relevant articles. Full-text screening of these articles was then performed independently by two reviewers (RLD, JRV) against predefined eligibility criteria. Any discrepancies regarding the eligibility of an article were discussed, and consensus was achieved through a third reviewer (SKK). One reviewer (RLD) independently extracted data and conducted quality assessments using a standardised data collection form. A second reviewer (JRV) independently repeated the process to verify the data. Data were extracted on the lead author, year of publication, geographical location, study design, number of participants, mean age, percentage of males, type of surgery, intervention and comparator/control, duration of follow-up, outcome measures and degree of adjustment for potential confounders. We also extracted data on relevant study characteristics to permit the risk of bias assessments. Authors of eligible studies were contacted to provide further information if there were missing data for the extracted fields.

### *2.4. Risk of bias assessment*

The risk of bias within individual RCTs was assessed using the Cochrane Risk of Bias (RoB 2) tool[30], a validated tool for assessing the quality of randomised studies. This tool assesses risk of bias for the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selective reporting. Each of these domains is assessed as low risk, some concerns or high risk, and then an overall judgement of the risk of

bias is provided for each study. The risk of bias within individual observational studies was assessed using the Cochrane Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) tool, a validated tool for assessing the quality of non-randomised studies[31]. This tool assesses the risk of bias for confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurements and selective reporting. Risk is quantified in each domain as low risk, moderate risk, serious risk or critical risk, then an overall judgement of the risk of bias is provided for each study.

### *2.5. Statistical analysis*

A meta-analysis was performed using RevMan 5.4 software (Cochrane Collaboration) and Stata version MP 16 (Stata Corp, College Station, Texas). Outcome data from RCTs and observational studies were analysed separately. Summary measures were presented as mean differences (95% confidence intervals, CIs) for continuous outcomes and relative risks (RRs) (95% CIs) for binary outcomes. For continuous data, if the mean or standard deviation (SD) was not reported, we estimated the mean and variance from the reported median, range, and sample size as recommended by Hozo *et al*[32], to facilitate a consistent approach to the meta-analysis. Relative risks were calculated from the extracted raw counts for the intervention and comparator. A narrative synthesis was performed for studies that could not be pooled.

Heterogeneity was assessed using the Cochrane  $\chi^2$  statistic and the  $I^2$  statistic. The inverse variance (IV) weighted method was used to combine pooled summary measures using random-effects (RE) models to minimise the effect of inter-study heterogeneity. Two-sided statistical significance of 0.05 was used. We planned to evaluate publication bias using funnel plots and Egger's regression symmetry tests if a sufficient number of studies met our

inclusion criteria. Subgroup analysis to explore the origins of heterogeneity using random-effects meta-regression was also planned.

### **3. Results**

#### *3.1. Study selection*

Our search strategy identified 455 potentially relevant citations, and this was reduced to 368 after duplicates were removed. After the initial screening of titles and abstracts, 19 full-text articles remained for further evaluation, and a further five were obtained by manually scanning the reference lists of the retrieved articles. Fifteen papers failed to meet the eligibility criteria. Therefore, nine studies were deemed eligible for inclusion in this systematic review and meta-analysis[[33-41](#)]. A PRISMA flow chart is provided in Figure 1.

#### *3.2. Study characteristics*

Table 1 provides a summary of the characteristics of the included studies. Four included studies were RCTs (three in the USA, one in Austria) and five were RCSs (four in the USA, one in South Korea). All studies compared TXA (intravenous in eight studies, topical in one RCT) to either no treatment or placebo (normal saline). Six studies assessed blood loss in patients undergoing both ATSR and RTSR (three RCTs, 3 RCSs), two studies assessed RTSR only (one RCT, one RCS) and one study assessed ATSR only (one RCS). Most studies were not explicit regarding the duration of their follow up periods beyond the time the patients were discharged from the hospital. All four RCTs compared TXA (n=188) against placebo (n=187), and all five RCSs compared TXA (n=370) against no treatment (n=288). Additional comparators within individual studies (e.g., topical thrombin) were not included in our analysis. Across the nine included studies, 1033 procedures were performed: 522 ATSR and 511 RTSR. No studies that compared TXA administration to no treatment/placebo/usual care for patients undergoing TER were identified. Missing outcome data and/or clarifications were sought from authors where required, but no responses were returned.

### *3.3.Risk of bias*

According to the RoB 2 risk of bias tool, three RCTs were deemed to be of low risk of bias, and one was deemed to have some concerns. The ROBINS-I tool indicated that all five RCSs were assessed to be of moderate risk of bias. The risk of bias and quality assessments for individual articles are included in Appendices 2 (RCTs) and 3 (RCSs).

### *3.4.Estimated total blood loss*

Total blood loss was reported in four TSR studies[[33](#), [34](#), [40](#), [41](#)]. RCT data showed total blood loss to be significantly lower in the TXA group than the placebo group (MD = -357.92mL; 95% CI: -504.27, -211.58;  $p < 0.00001$ ; Figure 2 top). RCS data showed total blood loss to be lower in the TXA group compared with no treatment, but the difference was not statistically significant (MD = -132.78mL; 95% CI: -275.12, 9.56;  $p = 0.07$ ; Figure 2 bottom).

### *3.5.Drain output (post-operative blood loss)*

Drain output was used as a surrogate marker of post-operative blood loss, and this was reported in six TSR studies[[33](#), [36](#), [38-41](#)]. RCT data showed drain output to be significantly lower in the TXA group than the placebo group (MD = -113.34mL; 95% CI: -168.49, -58.20;  $p < 0.0001$ ; Figure 3 top). RCS data also showed post-operative blood loss to be significantly lower in the TXA group compared with no treatment (MD = -130.26mL; 95% CI: -207.03, -53.50;  $p = 0.0009$ ; Figure 3 bottom).

### *3.6.Change in Hb*

Change in Hb was reported in four TSR studies[[33](#), [38](#), [39](#), [41](#)]. RCT data showed the change in Hb to be significantly lower in the TXA group than the placebo group (MD = -0.71g/dL; 95% CI: -1.07, -0.36;  $p < 0.0001$ ; Figure 4 top). RCS data also showed the change in Hb to be significantly lower in the TXA group compared with no treatment (MD = -0.70mg/dL; 95% CI: -0.93, -0.48;  $p < 0.00001$ ; Figure 4 bottom).

### *3.7. Change in Hct*

Change in Hct was reported in two TSR RCSs[[33](#), [39](#)], but no RCTs. The data showed the change in Hct to be significantly lower in the TXA group compared with no treatment (MD = -1.86%; 95% CI: -2.47, -1.25;  $p < 0.00001$ ).

### *3.8. Total Hb loss*

Total Hb loss was reported in two TSR RCTs[[36](#), [41](#)], but no RCSs. The data showed the total Hb loss to be significantly lower in the TXA group compared with the placebo group (MD = -35.25g; 95% CI: -54.54, -15.96;  $p = 0.0003$ ).

### *3.9. Length of stay*

Length of stay was reported in four TSR studies[[34](#), [36](#), [37](#), [41](#)]. RCT data showed a slight increase in length of stay in the TXA group compared with the placebo group (MD = 0.11 days; 95% CI: -0.16, 0.39;  $p = 0.43$ ), which was not significant. RCS data also showed a decrease in length of stay in the TXA group compared with no treatment (MD = -0.19 days; 95% CI: -0.35, -0.03;  $p = 0.02$ ), which was significant.

### *3.10. Operative time*



Operative time was reported in two TSR RCSs[[34](#), [37](#)], but no RCTs. The data demonstrated a slight decrease in operative time in the TXA group compared with no treatment, which was not significant (SMD = -0.19 minutes; 95% CI: -0.79, 0.41;  $p = 0.53$ ). This finding was echoed in one RCT[[41](#)], which also found no significant difference in operative time ( $p = 0.527$ ).

### *3.11. Transfusion requirements*

The overall proportion of patients requiring transfusions in each treatment arm was low. Transfusion requirements were reported in all nine TSR studies[[33-40](#)]. RCT data showed a decrease in the number of blood transfusions in the TXA group compared with the placebo group (RR = 0.50; 95% CI: 0.16, 1.54;  $p = 0.919$ ; Figure 5 top), but this was not significant. Similarly, RCS data also showed a non-significant decrease in the number of blood transfusions in the TXA group compared with no treatment (RR = 0.30; 95% CI: 0.13, 0.69;  $p = 0.511$ ; Figure 5 bottom).

### *3.12. VTE complications*

VTE complications were only reported in two RCTs[[36](#), [41](#)], but no RCSs. The data showed VTE complications to be lower in the TXA group compared with the placebo group (RR = 0.52; 95% CI: 0.05, 5.62;  $p = 0.705$ ), but this was not significant.

### *3.13. Publication bias and Subgroup analysis*

It was not possible to assess publication bias due to the small number of included studies. Subgroup analysis to explore the origins of heterogeneity was not possible due to limited data.

#### 4. Discussion

To our knowledge, this is the largest, most comprehensive and up to date systematic review and meta-analysis on the use of TXA compared with no treatment/placebo/usual care in patients undergoing primary TSR (anatomic or reverse) to date. The search strategy did not yield any relevant studies to investigate the intervention effect in patients undergoing TER, and we have identified this as an area that requires research in the future. Four RCTs and five RCSs of TSRs were eligible for inclusion in this review, and all were deemed to be of low-to-moderate risk of bias.

Interventional data in this meta-analysis demonstrates that the administration of peri-operative TXA significantly decreases estimated total blood loss, post-operative blood loss (drain output), change in Hb and total Hb loss when compared to placebo. Observational data also demonstrated a significant association between peri-operative TXA administration and decreases in post-operative blood loss (drain output), change in Hb, change in Hct and length of stay. Whilst a decrease in transfusion requirements and VTE complications were noted, these were not significantly lower.

Previous meta-analyses in this field have been published between 2017-2018, with the number of included studies ranging from four to six. TXA was demonstrated to be beneficial in terms of total blood loss by five studies[[22](#), [24-27](#)], drain output by five studies[[22-25](#), [27](#)], change in Hb by six studies[[22-27](#)], and transfusion requirements by two studies[[22](#), [26](#)]. However, these earlier meta-analyses inappropriately pooled the results of RCTs and observational studies, two different study designs that are methodologically incorrect to pool. This approach has a detrimental influence on the levels of heterogeneity, bias, confounding and the accuracy of assessment of the treatment effect size, hence results may be misleading. We avoided this approach in our review and also incorporated studies that had not been included in previous reviews. Previous studies also acknowledged that the small numbers

included limited their analysis of the effects of TXA administration on the risk of VTE complications. With the addition of new evidence, we had increase power to demonstrate that TXA administration did not increase the risk of VTE events, and this is in keeping with the results of a recent meta-analysis which showed that TXA administration did not increase the risk of VTE complications in patients undergoing total hip and knee arthroplasty[21].

As the incidence of TSR continues to increase, it is important to utilise cost-effective treatments such as TXA as part of wider blood management and outcome optimisation strategies. This should, in turn, reduce the need for allogenic blood transfusion, and therefore reduce the risk of associated peri-operative morbidity and mortality[6-9] to patients undergoing this procedure, albeit this association is yet to be investigated in the literature for patients undergoing TSR. This need to control blood loss and minimise blood transfusions is of particular importance in procedures such as TSR where alternative strategies, such as the application of a tourniquet proximally to the operation site, cannot be used.

The current National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom (UK) in June 2020 advocate utilising intravenous TXA in adults undergoing primary THR and TKR, but only that it should be “considered” in patients undergoing primary TSR[42]. They also recommend that all patients undergoing THR, TKR and TSR receive topical TXA diluted in saline after the final wound washout before wound closure (assuming the patient does not suffer from renal impairment), and that the total intravenous and topical combined dose should not exceed 3 grams. The rationale provided explains that there is good evidence for combined TXA treatments in patients undergoing TKR and THR, but not in patients undergoing TSR.

Of note, our literature search did yield one small RCT which compared intravenous TXA versus topical TXA versus combined intravenous and topical TXA administration in patients undergoing reverse TSR, which was published in June 2020[43]. We excluded this paper

from the meta-analysis on the basis that there was no placebo/no treatment group.

Nevertheless, this RCT demonstrates no significant differences between all treatment arms in terms of change in Hb, post-operative blood loss (drain output) and transfusion rate, albeit the combined TXA group had the fewest blood transfusions.

Due to the small number of included papers (4 RCTs and 5 RCSs), publication bias could not be adequately assessed. For similar reasons and because heterogeneity was not substantial in the majority of the pooled comparisons, sub-group analysis was not performed.

This study has several limitations that must be taken into account. First, there was variation in the route of TXA administered (intravenous and topical), the doses of TXA and placebo administered (fixed-dose and weight-based dose) and also the frequency of administration of the doses; therefore, whilst this study can report an overall treatment effect in favour of utilising TXA, we are unable to suggest whether a particular route of administration or dosage is optimal. Second, five out of the nine included studies were observational, which provided us with estimates of associations but not causality. In particular, the observational data increases the risk of confounding and selection bias. However, data from the few RCTs confirmed these findings. Third, whilst the overall sample size was large (1151 TSRs), the sample sizes for individual outcome analyses were much smaller due to variation in the reported outcomes and available data in individual studies. Other variables that were not controlled for included variation in post-operative VTE prophylaxis, variation in the duration of participant follow-up and heterogeneity amongst transfusion protocols – all of which could affect the outcomes considered. It is also worth commenting on the absence of published data comparing the administration of TXA in patient undergoing TER to placebo or no treatment. Moreover, our literature only yielded one small case series<sup>[28]</sup> of ten patients who underwent TER and all were administered TXA. Despite the differences when compared to THR, TKR and TSR, patients undergoing TER

remain at risk of bleeding that would be amenable to mitigation through an appropriate dose of TXA – but the effect and safety of this should be adequately researched. If the benefits of TXA in TER are similar to that of THR, TKR and TSR, then it would reduce post-operative bleeding, reduce transfusion requirements and may reduce the need for a tourniquet. Finally, many studies excluded patients with a history of VTE events, therefore the safety profile and efficacy of TXA in these populations remain unclear.

We suggest that future research should focus on the optimal dose, frequency and route of administration of TXA in TSR, given that most of the studies to date have shown variation in practices. Homogenisation of transfusion protocols and follow-up periods would improve our ability to compare complications rates (e.g., VTE events, surgical site infections, periprosthetic joint infections, etc.) and transfusion rates. Further assessment of the treatment effect of TXA in patients undergoing TER is warranted, as outlined above.

## **5. Conclusions**

This contemporary systematic review and meta-analysis on the use of TXA in primary TSR has demonstrated that it is effective at significantly decreasing blood loss and change in Hb when compared to placebo, and that it is associated with lower blood loss and shorter length of stay when compared to no treatment. No significant reductions in transfusion requirements or VTE complications were determined by our analysis. Hence, our review demonstrates that TXA is an effective intervention to reduce surgical blood loss without increasing the risk of VTE events in patients undergoing TSR. TXA is an inexpensive and commonly used medication which has been demonstrated to reduce blood loss in TSR in a similar fashion to that seen in hip and knee replacement. We advocate the administration of TXA in patients undergoing TSR as part of a wider blood management strategy to minimise peri-operative

blood loss and blood transfusion requirements. Further research is needed to demonstrate if a similar treatment benefit exists in patients undergoing TER.

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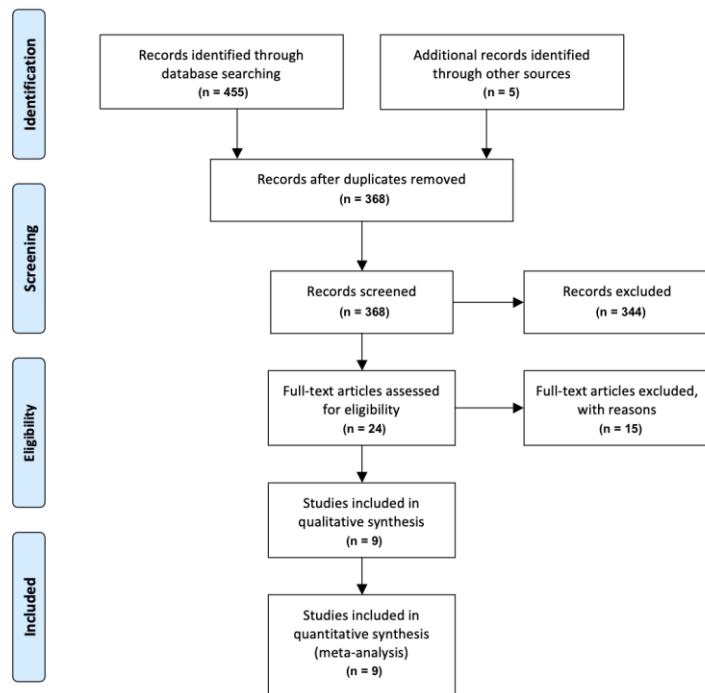
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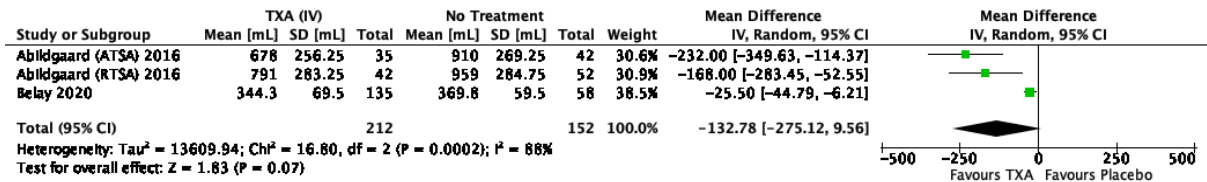
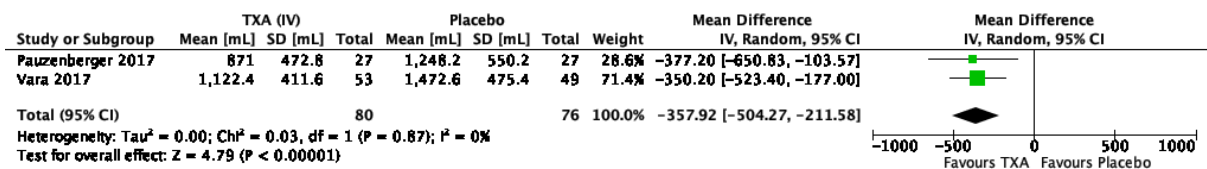
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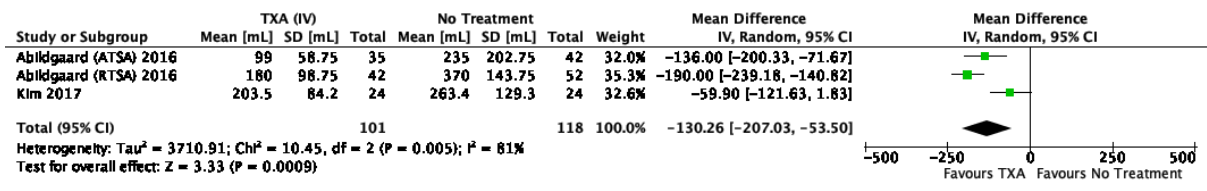
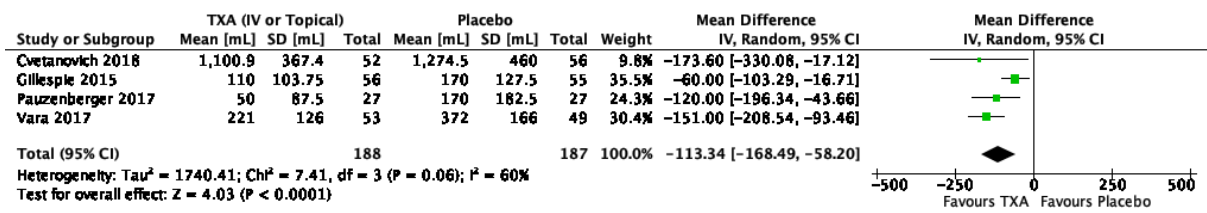


**Figure 1: PRISMA flow chart**

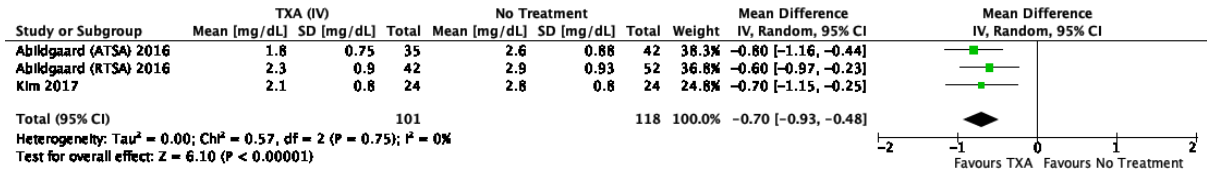
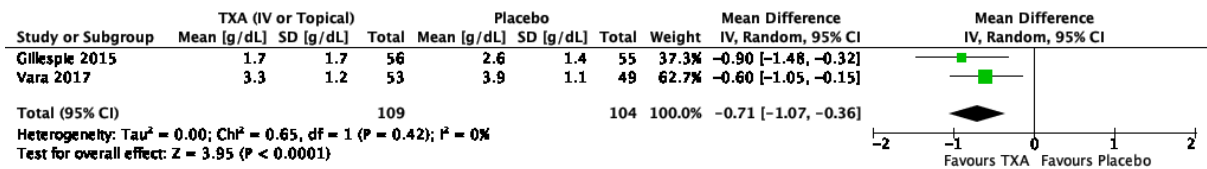


**Figure 2: Forest plot for estimated total blood loss (top = RCT data only; bottom = RCS data only)**

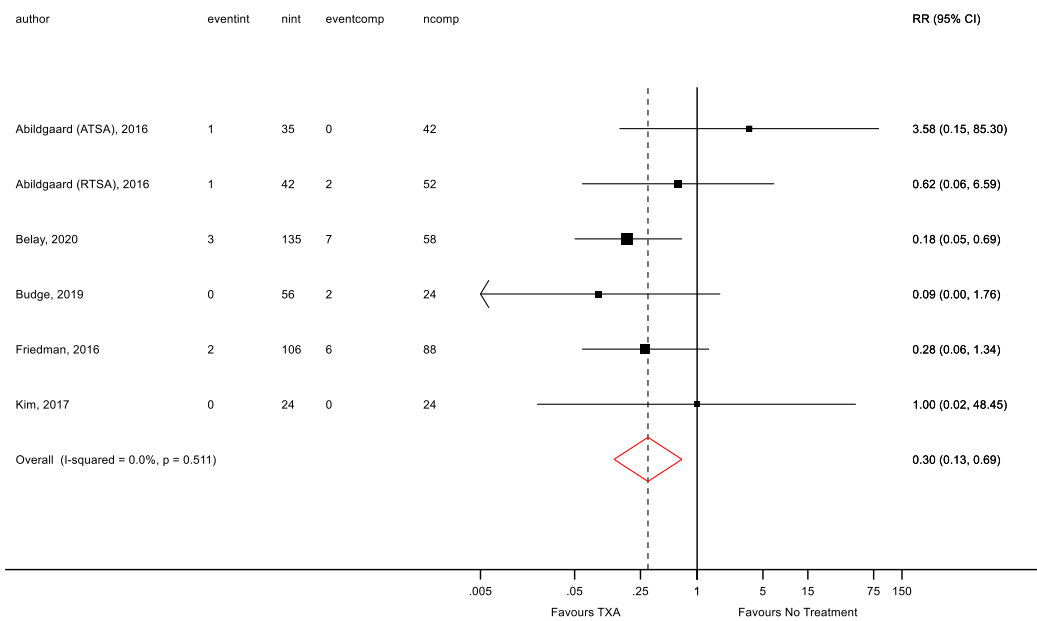
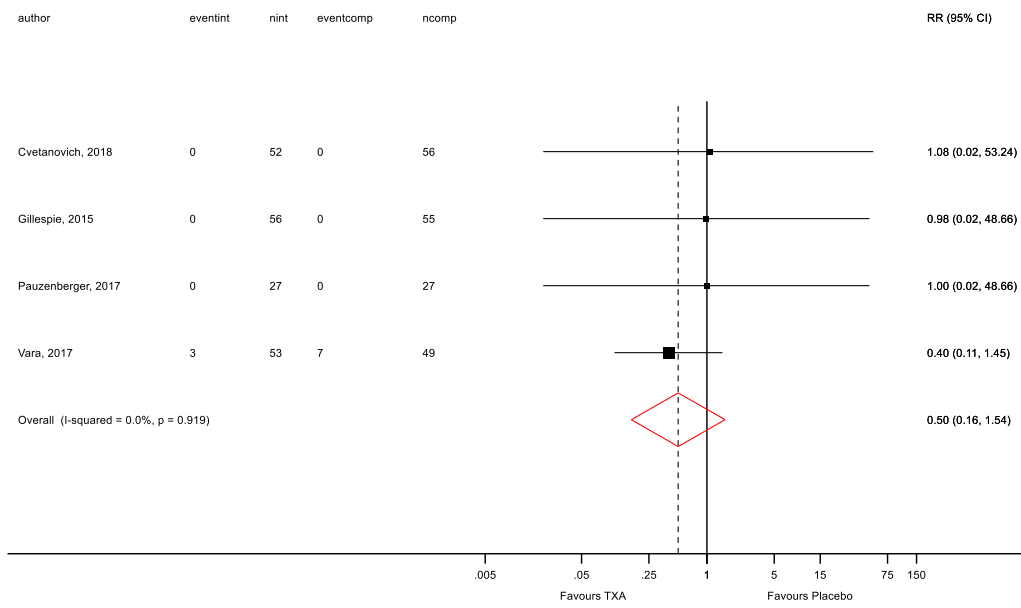




**Figure 3: Forest plot for drain output (post-operative blood loss) (top = RCT data only; bottom = RCS data only)**



**Figure 4: Forest plot for change in Hb (top = RCT data only; bottom = RCS data only)**



**Figure 5: Forest plot for transfusion rates (top = RCT data only; bottom = RCS data only)**

1 **Table 1: Characteristics of the included studies**

2

<b>Author</b> Year <i>Location</i>	<b>Study</b> <b>Type</b>	<b>Participants</b> <b>(n)</b>	<b>Age (years)</b> Mean $\pm$ SD (range)	<b>Gender</b>	<b>Surge</b> <b>ry</b>	<b>Intervention</b>	<b>Comparator 1</b>	<b>Comparator 2</b>	<b>Outcomes</b> <u>Primary</u> Secondary	<b>Length of Follow-Up</b>
<b>Abildgaard</b> 2016 <i>USA</i>	RCS	171	ATSR: 70 (53 – 87)  RTSR: 71.1 (53 – 90)	100  M  71 F	77  ATSR  94  RSTR	IV TXA  n=77  35 ATSR /  42 RTSR	No  treatment  n=94  42 ATSR /  52 RTSR	N/a	<u>Total blood loss</u>  Change in Hb; Change in Hct;  Drain output; Transfusion rate	Not stated
<b>Belay</b> 2020 <i>USA</i>	RCS	283	IV TXA: 65.7 $\pm$ 10.1  Topical thrombin:  68.2 $\pm$ 8.2  No treatment: 68.8 $\pm$ 9.1	138  M  146  F	283  ATSR  135 ATSR	IV TXA  n=135  135 ATSR	No  treatment  n=58  58 ATSR	Topical  thrombin  n=90  90 ATSR	<u>Post-op Hb</u>  Operative time; Total blood loss; Transfusion rate; Length of stay; Readmission rate	Not stated

<b>Budge</b> 2019 <i>USA</i>	RCS	80	IV TXA: 69 Topical TXA: 68 No treatment: 71	41 M 39 F	51 ATSR 29 RSTR	IV TXA n=28 <i>17 ATSR /</i> <i>11 RTSR</i>	Topical TXA n=28 <i>15 ATSR /</i> <i>13 RTSR</i>	No treatment n=24 <i>19 ATSR /</i> <i>5 RTSR</i>	<u>Change in Hb</u> Transfusion rate; Length of stay; Wound complications; VTE complications; Discharge destination	Not stated
<b>Cvetanovich</b> 2018 <i>USA</i>	RCT	108	66.4 ± 10.1	51 M 57 F	49 ATSR 59 RSTR	IV TXA n=52 <i>23 ATSR /</i> <i>29 RTSR</i>	Placebo n=56 <i>26 ATSR /</i> <i>30 RTSR</i>	N/a	<u>Total blood loss</u> Transfusion rate; Hb loss (weight); Estimated blood loss; Length of stay; VTE complications; Readmission rate; Infection; Return to theatre	90 days
<b>Friedman</b> 2016 <i>USA</i>	RCS	194	Not stated	79 M 115 F	97 ATSR 97 RTSR	IV TXA n=106 <i>54 ATSR /</i> <i>52 RTSR</i>	No treatment n=88 <i>43 ATSR /</i> <i>45 RTSR</i>	N/a	<u>Change in Hb</u> Change in Hct; Transfusion rate; Length of surgery; Duration in recovery; Length of stay	Not stated

<b>Gillespie</b> 2015 <i>USA</i>	RCT	111	67 (41 – 86)	49 M 62 F	44 ATSR 67 ATSR	Topical TXA n=56 22 ATSR / 34 RTSR	Placebo n=55 22 ATSR / 33 RTSR	N/a	<u>Drain output</u> Change in Hb; Transfusion rates Complications	Not stated
<b>Kim</b> 2017 <i>South Korea</i>	RCS	48	IV TXA: 73.2 ± 4.4 No treatment: 74.2 ± 4.4	9 M 39 F	48 RTSR	IV TXA n=24 24 RTSR	No treatment n=24 24 RTSR	N/a	<u>Hb change</u> Hct change; Drain output; Complications	12 months
<b>Pautzenberger</b> 2017 <i>Austria</i>	RCT	54	IV TXA: 70.3 ± 9.3 (46.3 – 87.8) Placebo: 71.3 ± 7.9 (53.7 – 84.3)	38 M 16 F	26 RTSR 28 RTSR	IV TXA n=27 15 ATSR / 12 RTSR	Placebo n=27 11 ATSR / 16 RTSR	N/a	<u>Drain output</u> Change in Hb; Change in Hct; Total blood loss; Transfusion rate; Haematoma rate; Pain score (VAS); Complications	Not stated
<b>Vara</b> 2017 <i>USA</i>	RCT	102	IV TXA: 67 ± 9 Placebo: 66 ± 9	42 M 60 F	102 RTSR	IV TXA n=53 53 RTSR	Placebo n=49 49 RTSR	N/a	<u>Total blood loss</u> Operative time; Change in Hb; Change in Hct; Drain output;	6 weeks

									Complications (any); VTE complications; Infections	
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3

4 **Key (alphabetical):**

- 5 ATSR=anatomic total shoulder replacement; Hb=haemoglobin; Hct=haematocrit; HSD=honest significant difference; IV=intravenous; NSAIDs=non-steroidal  
6 anti-inflammatory drugs; RCS=retrospective cohort study; RCT=randomised controlled trial; RTSR=reverse total shoulder replacement; TXA=tranexamic acid;  
7 VAS=Visual Analogue Score; VTE=venous thromboembolism