Original Article



# Tranexamic acid use in breast surgery: a systematic review and meta-analysis

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**Background:** We aimed to determine if tranexamic acid (TXA) is safe to use in breast surgery and does it reduce haematoma and seroma formation.

**Methods:** Only high-quality randomized control trials (RCT's) were included for the meta-analysis. Databases searched included Embase, Medline, the Cochrane Central Register of Controlled Trials, Mednar and google scholar. RCT's study quality was assessed using the Cochrane risk of bias tool.

**Results:** Ten studies were identified, 5 RCT's and 5 non-RCT's. Overall the risk of thromboembolic events was not significantly greater after TXA administration (P=0.35) in 2,283 patients from 8 studies. 4 RCT's were included in the meta-analysis. For mastectomy patients with or without axillary surgery combined with mammoplasty procedures the rate of haematoma was unaffected [odds ratio (OR) =0.42, 95% confidence interval (CI): 0.19 to 0.76, P=0.30]. A small reduction in drainage volumes first 24 hours was observed [mean difference (MD) =−12 mL, 95% CI: −20.7 to −3.7, P=0.005], but no effect on late seroma formation (OR =1.04, 95% CI: 0.37 to 2.91, P=0.94).

**Conclusions:** The overall quantity and quality of evidence for TXA use in breast surgery is extremely limited. The current study suggests there is likely to be minimal benefit, at least for mastectomy and mammoplasty patients, with a still undefined risk of thromboembolic events. No RCT's were identified examining TXA use in breast reconstruction.

**Trial Registration:** Registration with PROSPERO online, study ID number 180806.

**Keywords:** Breast; surgery; tranexamic acid; systematic review; outcomes

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## Introduction

Tranexamic acid is a synthetic amino acid that blocks plasminogen being converted to the enzyme plasmin. Plasmin works by breaking down fibrin already formed in blood clots resulting in fibrinolysis and therefore clot lysis. The use of tranexamic acid (TXA) in breast surgical procedures has been controversial, however recently there has been increased interest in the subject. This interest has been curbed by the theoretical risk of thromboembolic events particularly for cancer patients and breast reconstruction involving micro-vascular anastomoses. Mastectomy with or without axillary surgery can infrequently be complicated by haematoma and seroma formation (1,2), haematoma is also a risk for aesthetic breast operation (3).

TXA has been extensively evaluated in several fields of medicine including trauma, orthopaedics, gynaecology and cardiothoracics (4-7) and has been shown to reduce bleeding and the need for blood transfusion when

administered intravenously or topically (8). Smaller studies have also demonstrated a reduction in seroma formation using TXA (9,10).

The aim of this review was to determine: (I) does tranexamic acid increase thromboembolic events in aesthetic, oncological or reconstructive breast surgical procedures and (II) does TXA reduce haematoma and seroma formation in breast surgical procedures. We present the following article in accordance to the PRISMA reporting checklist (11) (available at http://dx.doi.org/10.21037/abs-20-126).

## Methods

Prior to commencing the review, a protocol was established between all authors and uploaded to PROSPERO online, study ID number 180806.

### *Eligibility*

All randomized control studies, cohort studies and controlled before-after studies were included for assessment including prospective and retrospective studies. Review articles, expert opinion, case series, conference abstracts, posters, commentaries and non-English language articles were excluded. Studies were included if they performed breast surgery and compared tranexamic acid use to a control group. Studies were not excluded based on publication date.

### *Patient selection*

Inclusion criteria were all types of breast surgical procedures including mastectomy with or without axillary surgery, wide local excision with or without axillary surgery, breast reconstruction either immediate or delayed, mastopexy, breast augmentation or mammoplasty procedures. Exclusion criteria included patients with known thromboembolic disease, currently taking anticoagulant medications with known coagulation disorders and pregnant patients.

### *Patient interventions*

Patients receiving TXA as part of their surgical procedure versus either a placebo group or standard care. Administration of tranexamic acid could be intravenous, oral, topical or a combination of these routes.

### *Information sources*

Data was extracted by two independent reviewers from online libraries, including Embase, Medline, the Cochrane Central Register of Controlled Trials, Mednar and google scholar. Study period included from database inception to 1 May 2020. Identified full text articles were examined for additional references. Results of literature search were stored on endnote online.

### *Search strategy*

The previously mentioned libraries were reviewed using the search terms listed below and combined using Boolean operators AND and OR. Search terms used for Medline are listed in Appendix 1.

### *Study selection*

Abstracts identified by the literature search were independently analyzed by two separate reviewers (AW and PM) looking for relevant articles for full text analysis. The above eligibility criteria were followed. Disagreements were resolved using a third party (BD). Studies were included if they met the following criteria: (I) studies involved comparison of the efficacy and safety of TXA usage in breast surgery and (II) studies included at least one of the outcome measures. All identified study authors were contacted for additional unpublished information.

### *Data extraction and quality assessment*

Extracted data was stored on excel. Two independent reviewers assessed articles for study design, type of surgical procedure, number of patients, age, patient demographics, exclusion criteria, randomization, blinding, types of controls, outcome data including haematoma rates, seroma rates, drain volumes and thromboembolic events.

Randomized controlled study quality was assessed using the Cochrane risk of bias tool (12). This tool examines 7 areas for bias including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete data, selective reporting and other bias. Each area is assigned a judgment score of low risk, unclear risk or high risk of bias. Studies including multiple areas of unclear risk of bias or an area of high risk were considered high risk of bias and excluded from the meta-analysis.

For non-randomized studies, quality was assessed using the methodological index for non-randomized studies (MINORS) (13) which is designed to assess the quality of non-randomized interventional studies. Studies were assessed independently by two reviews using the 12-question model. Each question can be assigned 0–2 points for a maximum score of 24. Zero points for unreported, one point for reported but inadequate, two points for reported and adequate. A score of ≥18 was considered high quality, 14–17 as moderate quality and ≤13 low quality. Non-RCT studies were excluded from the meta-analysis.

### *Statistical analysis*

The meta-analysis was conducted using Revman Review Manager 5.3 software. For dichotomous data, the odds ratio (OR) with 95% confidence intervals (CI) were used. For continuous outcomes, a weighted mean difference (MD) and 95% CI were used. If the above data points were missing, they were calculated from available data using Revman software. Heterogeneity of the studies was assessed using Cochran's Q test and a significance value (P) <0.10 was used. The $I^2$ test looking for observed total variation across studies due to real heterogeneity and not chance was also used. A value of 0% indicates no observed heterogeneity, whereas a larger value shows increased heterogeneity. The random effects model was used for all calculations due to variability in study design. In the random effect model, the true effect is assumed to vary between studies and the summary effect is the weighted average of the effects in the different studies. The assessment of publication bias and meta-regression was not conducted because at least 10 studies are usually required to perform these tests and the most frequent reported outcome, haematoma rate, was only reported in 4 included studies.

### *Ethical approval*

All analyses were based on previously published data, with no new patient contact and therefore ethical approval was not requested.

## Results

### *Search results*

A total of 2,038 abstracts were identified. This number was reduced to 1,705 after duplicates were removed: Medline [734], Embase [208], Cochrane [189], Mednar [572] and google [2]. After abstract review, we excluded 1667 as these abstracts were deemed irrelevant as they either related to breast surgery but not tranexamic acid, tranexamic acid but not breast surgery or neither tranexamic acid nor breast surgery. This left 38 papers for full text screening. One review article and two letters to the editor were excluded. Seventeen duplicate papers and five research projects either awaiting commencement or in progress but not completed, were excluded. Two abstracts were then excluded from the study and one commentary, leaving 9 articles. After liaising with one of the abstract authors his paper is since published and has been included in the review for a total of 10 papers. A flowchart of this is demonstrated in *Figure 1*. Five RCT's (10,14-17) and five non-RCT's including 2 prospective cohort studies (18,19), 2 retrospective cohort studies (20,21) and one controlled before-after study (22) were identified. Seven articles were located from Embase and Medline (10,14,15,18,20,21), 3 articles from grey databases (16,17,19). The characteristics of all included studies are shown in *Tables 1* and *2*.

### *Study quality*

The quality of RCT's are shown in *Figure 2*. Four studies were rated as low risk of bias (10,14-16) and one as a high risk of bias (17). In two studies the process of randomization was explicitly detailed (14,15), whereas in the other three randomization was stated but not fully explained (10,16,17). Blinding of patients and clinicians was universal, except in one study (17), however in three studies outcome assessors blinding could not be determined (10,16,17). In all studies due to short follow up periods dropout rates were minimal with good compliance and intention to treat analyses were performed. No co-interventions were introduced.

The quality of non-randomized studies (18-22) (non-RCT) are shown in *Table 3*. One study (19) had a MINORS score of ≥18 and was deemed high quality, three studies moderate quality (18,20,21) and one study was low quality (22) with a score of ≤13 or less. Two studies collected data prospectively, while the others were retrospective. None of the non-RCT's used blinding of study outcomes and none of the studies made a prospective calculation of study size. Most had adequate control groups, however one study (22) did incorporate variations in surgical technique and the use of pressure dressings post operatively, as well as TXA to the intervention group. Two studies used historical data as a control group (21,22), rather than contemporary

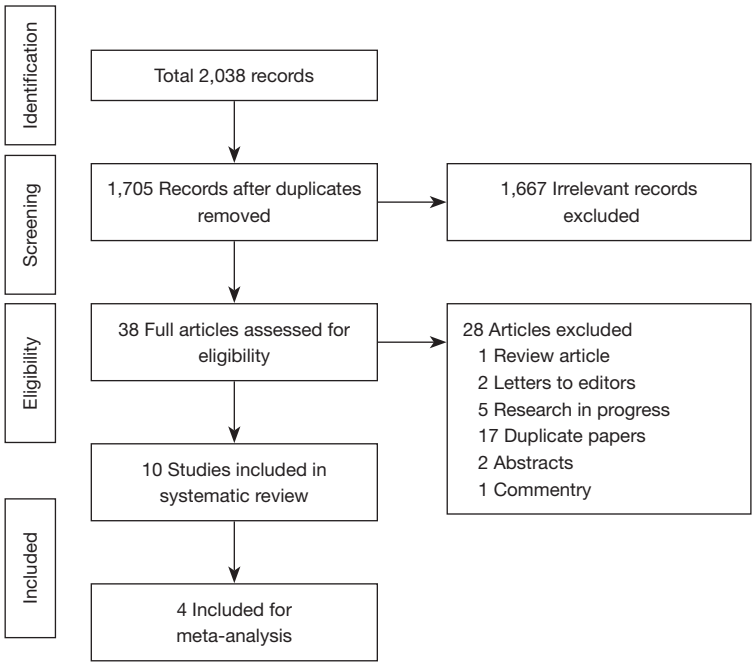


**Figure 1** PRISMA flowchart.

**Table 1** Randomized controlled trials

| Study | Patients (TXA/ control) | Age (TXA/ control) | Study design | Surgical procedure | Intervention | Control | BMI (TXA/ control) | Neo-adjuvant Chemo (TXA/control) (%) | Prophylatic anticoagulation (TXA/control) (%) | Additional interventions (TXA/control) (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Oertli, 1994, (10) | 79/81 | 58.1/59.4 | RCT | WLE or mastectomy +/– ALND | 3× 1 g IV TXA day 1 in 100 mL NS, then 3 g oral for 4/7 | 100 mL NS | NR | – | NR | ALND 79.1/81.3 |
| Gogna, 2015, (17) | 25/25 | 47/46.1 | RCT | Mastectomy + ALND | 1 g TXA IV TDS 5/7 | Nil | NR | 28/36 | NR | Nil |
| Pathak, 2016, (16) | 25/25 | 43/43 | RCT | Bil reduction mammoplasty | 20 mL TXA 25 mg/mL topical | 20 mL NS | NR | – | Nil | Nil |
| Ausen, 2015, (14) | 28/28 | 45/45 | RCT | Bil reduction mammoplasty | 20 mL TXA 25 mg/mL topical | 20 mL NS | NR | – | Nil | Nil |
| Ausen, 2020, (15) | 101/101 | 66.2/62.3 | RCT | Mastectomy +/– ALND | 20 mL TXA 25 mg/mL topical | 20 mL NS | 26.9/27.1 | 31.7/40.6 | 31.7/36.6 | ALND 33.7/30.7 |

TXA, tranexamic acid; IBR, immediate breast reconstruction; ALND, axillary lymph node dissection; NS, normal saline; NR, not recorded; pro-, prospective; BMI, body mass index; WLE, wide local excision; RCT, randomized controlled study; BAS, before after study; Bil, bilateral; IV, intravenous.

**Table 2** – Non-randomized studies

| Study | Patients (TXA/ control) | Age (TXA/ control) | Study design | Surgical procedure | Intervention | Control | BMI (TXA/ control) | Neo-adjuvant Chemo (TXA/control) (%) | Prophylatic anticoagulation (TXA/control) (%) | Additional interventions (TXA/control) (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Eldesouky, 2019, (19) | 65/50 | 50/47.9 | Cohort pro | mastectomy + ALND | 20 mL TXA 25 mg/mL topical | Nil | 32.4/33.0 | 24.6/22 | NR | Nil |
| Weissler, 2020, (20) | 217/651 | 51/50 | Cohort retro | mastectomy + IBR | 1 g pre/1 g post TXA IV | Nil | 26.1/25.6 | 30.4/27.2 | ALL | Nil |
| Lardi, 2018, (21) | 50/33 | 51.4/50.6 | Cohort retro | matectomy + free tissue transfer breast recon | 1–3 g TXA IV day of surgery depending on blood loss | Nil | 22.7/21.7 | 12/6.1 | ALL | Nil |
| Lohani, 2020, (18) | 47/46 | 49.7/48.8 | Cohort pro | WLE or mastectomy + ALND | 15 mg/kg TXA IV induction, then 500 mg BD for 4/7 | Nil | NR | 48.9/52.1 | NR | Mastectomy 70.2/67.4 |
| Wolter, 2018, (22) | 366/346 | 27.4/28.6 | Controlled BAS | FTMM (mastectomy/ mastopexy/ multiple) | 1–2 g TXA IV + BP elevation + pressure dressing | Nil | 22.5/24 | – | ALL | Nil |

TXA, tranexamic acid; IBR, immediate breast reconstruction; ALND, axillary lymph node dissection; NS, normal saline; NR, not recorded; pro-, prospective; BMI, body mass index; WLE, wide local excision; RCT, randomized controlled study; BAS, before after study; IV, intravenous; BP, blood pressure; FTMM, female to male mastectomy.

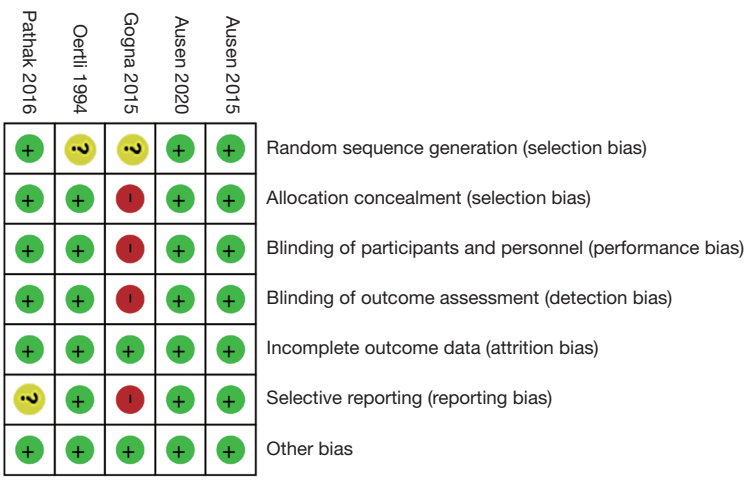


**Figure 2** Risk of bias summary for RCT's: review authors' judgements about risk for individual studies.

groups. Three studies (20-22) had significant differences between the groups at baseline which may have affected outcomes. Most studies had adequate follow up and retention, except one (19) which had a 5% loss to follow up for the main outcome.

### *Studies included in meta-analysis*

Of the four RCT's (10,14-16) two studies included WLE or mastectomy patients with or without axillary surgery (10,15). This included 180 breasts in the TXA groups and 182 in the control groups. Two other studies (14,16) looked at bilateral

 

**Table 3** Study quality for non-RCT's

| Methodological items for non-randomized studies | Weissler 2020, (20) | Lardi 2018, (21) | Lohani 2020, (18) | Eldesouky 2019, (19) | Wolter 2017, (22) |
|---|---|---|---|---|---|
| A clear stated aim | 2 | 2 | 2 | 2 | 2 |
| Inclusion of consecutive patients | 2 | 1 | 2 | 2 | 2 |
| Prospective collection of data | 0 | 0 | 2 | 2 | 0 |
| Endpoints appropriate to aim of study | 2 | 2 | 1 | 2 | 2 |
| Unbiased assessment of the study endpoints | 0 | 0 | 0 | 0 | 0 |
| Follow up period appropriate to outcomes | 2 | 2 | 2 | 2 | 2 |
| Loss to follow up less than 5% | 2 | 2 | 0 | 2 | 2 |
| Prospective calculation of the study size | 0 | 0 | 0 | 0 | 0 |
| An adequate control group | 2 | 2 | 2 | 2 | 1 |
| Contemporary group | 2 | 0 | 2 | 2 | 0 |
| Baseline equivalence of the groups | 2 | 1 | 2 | 2 | 1 |
| Adequate statistical analyses | 2 | 2 | 1 | 1 | 1 |
| TOTAL (24 maximum score) | 18 | 14 | 16 | 19 | 13 |
| Additional data obtained from author's | x | | | | x |

reduction mammoplasties and compared one side to the other, they included 53 patients and 106 breasts.

Three studies (14-16) examined topical application of TXA to the wound bed, including 154 breasts in the TXA groups and 154 breasts in the control groups, the other studies regime (10) involved IV TXA initially followed by oral TXA for four days including 79 patients in the TXA groups and 81 in the control groups.

### *Excluded studies from meta-analysis*

One study (17) was excluded from the analysis due to the high risk of bias. No placebo was not given, unlike the other studies, and therefore blinding for staff and patients was unlikely.

### *Effects of interventions*

*Figure 3* is a summary of findings for the main outcomes.

### *Thromboembolic events*

Due to a low number of events a meta-analysis could not be performed for this outcome. Excluding the 2 papers on patients with bilateral mammoplasties used as their own controls. In eight studies in the review only one thrombotic event was recorded in the control group for a venous anastomosis in a free flap patient (21). Zero patients out of 950 patients in the TXA group and 1 patient out of 1,333 patients in the control group (P=0.35). TXA did not increase the risk of thromboembolic events.

### *Haematoma rates*

Three studies (10,14,15) compared haematoma rates. In the TXA group 6/208 breasts versus 13/210 breasts in the control group. Overall the studies had moderate heterogeneity (P=0.15, $I^2$=48%), *Figure 4*. The pooled results suggest no effect on haematoma rates after TXA (OR =0.42, 95% CI: 0.19 to 0.76, P=0.30).

### *Drain fluid and seroma*

**Drain volume over 1st 24 hour's**

Three studies (14-16) reviewed seroma fluid drainage over the first 24 hours after surgery. Both arms included 154 breasts. Mean drain volume was 102 mL for the control group and 90 mL for the TXA group. Heterogeneity between studies was moderate (P=0.19, $I^2$=40%, *Figure 5*). The overall result was significant favouring TXA group (MD =–12 mL, 95% CI: –20.7 to –3.7, P=0.005).

**TXA compared to controls in breast surgery. A systematic review and meta-analysis.**

**Patient or population:** breast surgery. A systematic review and meta-analysis.
**Setting:**
**Intervention:** TXA
**Comparison:** controls

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with controls | Risk difference with TXA |
| TXA vs control Thromboembolic events | 2283 (8 observational studies) | ⨁◯◯◯ LOW | **OR 0.21** (0.01 to 5.43) | 1 per 1,000 | **1 fewer per 1,000** (1 fewer to 3 more) |
| Haematoma rates | 418 (3 RCTs) | ⨁⨁⨁◯ MODERATE | **OR 0.42** (0.08 to 2.20) | 62 per 1,000 | **35 fewer per 1,000** (57 fewer to 65 more) |
| TXA vs control drain output 1st 24 hours | 308 (3 RCTs) | ⨁⨁⨁⨁ HIGH | - | The mean drain output 1st 24 hours was **102** mls | MD **12.18 mls lower** (20.67 lower to 3.69 lower) |
| TXA vs controls Total drain output | 362 (2 RCTs) | ⨁⨁⨁◯ MODERATE | - | The mean Total drain output was **311** mls | MD **80.55 mls lower** (201.41 lower to 40.3 higher) |
| TXA vs Controls Late seroma requiring intervention | 362 (2 RCTs) | ⨁⨁⨁◯ MODERATE | **OR 1.04** (0.37 to 2.91) | 467 per 1,000 | **10 more per 1,000** (222 fewer to 251 more) |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference **TXA:** Tranexamic acid

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Figure 3** Summary of findings.

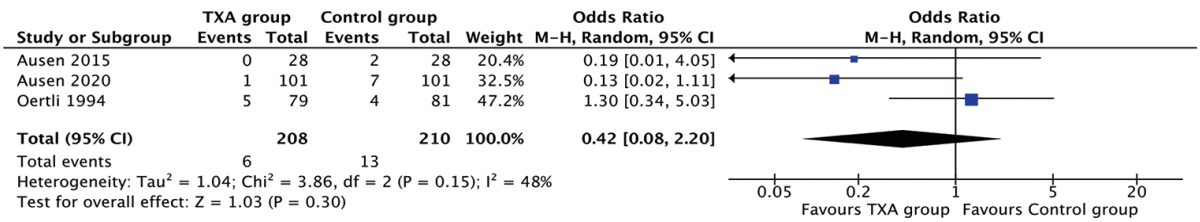


**Figure 4** Forrest plot of comparison: tranexamic acid (TXA) versus controls, outcome: Haematoma.

### Total drain volume

Two studies (10,15) looked at total drainage volume prior to removal. This included 180 patients in the TXA group with mean drainage of 230 mL versus the control group with 182 patients and 310 mL. Heterogeneity was high (P=0.003, $I^2$=89%, *Figure 5*). The overall result suggests no difference with TXA (MD =–80.5, 95% CI: –201.4 to 40.3, P=0.19).

### Late seroma requiring intervention

Two studies (10,15) looked at late seroma rates, defined as requiring aspiration or further intervention at least once. In the TXA group 89/180 required an intervention versus 85/182 in the control arm. Heterogeneity was noted to be high (P=0.02, $I^2$=81%, *Figure 5*). The overall results suggest no significant effect from TXA, (OR =1.04, 95% CI: 0.37–2.91, P=0.94).

### *Long term outcomes*

None of the included studies looked at long term outcomes.

## Discussion

### *Summary of main results*

For mastectomy patients with or without axillary surgery combined with mammoplasty no effect on haematoma formation, overall drainage or late seroma formation was seen. A reduction in drainage fluid at 24 hours after surgery was noted.

### *Overall completeness and applicability of evidence*

The results of this review need to bear in mind that

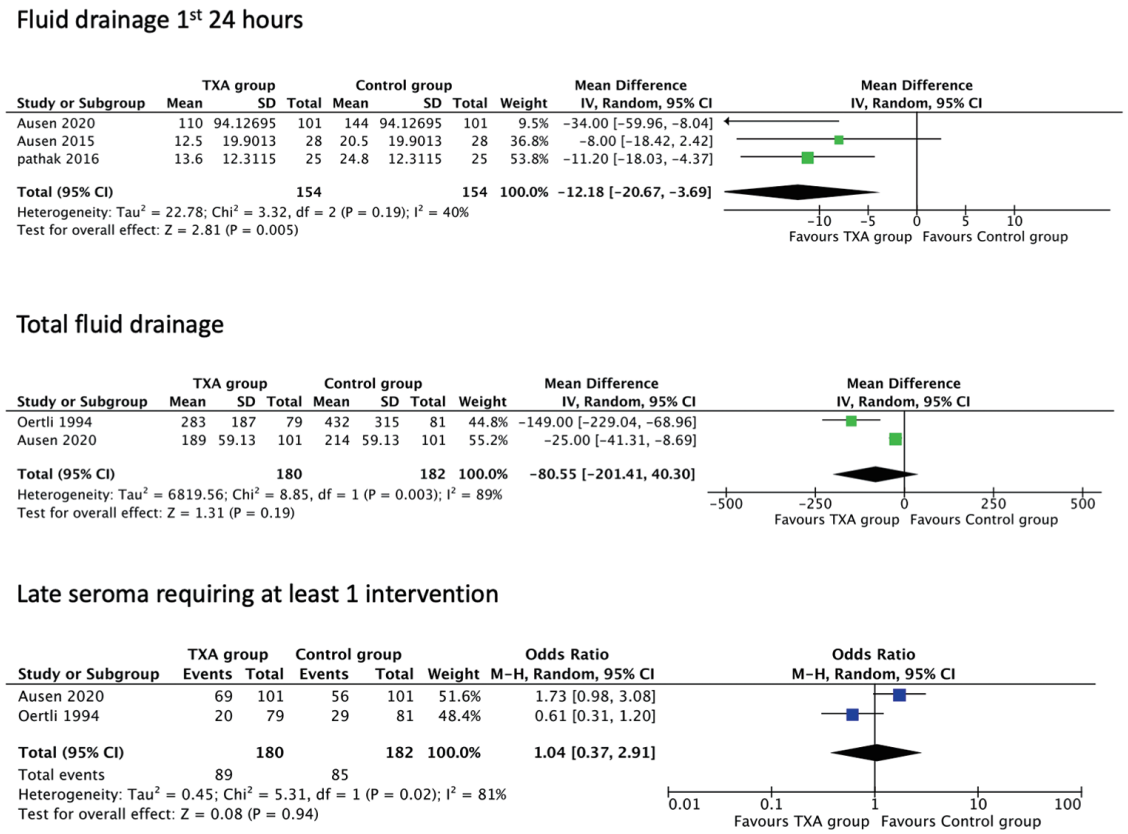


**Figure 5** Forest plot of comparison: tranexamic acid (TXA) versus controls, outcomes: Drain volumes first 24 hours, Total drain volumes and Late Seroma.

they are derived from a small number of individually underpowered studies with few patients. Small studies may be powered enough to detect differences in drain volumes, but underpowered to detect differences in haematoma rates, a complication seen in <5% of patients. Many of the studies in this field are non-randomized studies that may over-estimate treatment effects, with few RCT's remaining. Unfortunately, no reconstructive papers were included in the final meta-analysis so the conclusions of this study cannot be applied to immediate or delayed breast reconstructive procedures or aesthetic surgical procedures including mastopexy or augmentation.

### *Agreement and disagreement with other studies and reviews*

TXA use has been extensively reviewed in the setting of major surgery and trauma where it has been shown to reduce bleeding, the need for blood transfusion and death (7,23) and is now recommended as an early intervention. Orthopaedic studies looking at the safety of TXA in hip and knee joint replacement surgery found no increased risk of thromboembolic events compared to controls (24,25). In contrast, the recent HALT-IT study (26) found an increase in deep vein thrombosis and pulmonary embolism with TXA use in acute gastrointestinal bleeding amongst 12,009 patients, with no benefits to mortality, bring in to question the safety of TXA. An increased risk of venous thromboembolism in 21,931 trauma patients was demonstrated in a retrospective propensity matched study (27), again with no associated gain in survival. Potentially this increased in thromboembolic risk is only seen in large studies due to the rarity of the event. Less is known about the benefits of TXA in surgery where major haemorrhage is less common. In 2015 the journal of military medicine published a retrospective cohort study (28) which found no increased risk of thromboembolic events, including flap thrombosis, for patients undergoing extremity reconstructions in combat care treated with TXA. In plastic surgery TXA was found to decrease blood loss

in liposuction (29) and reduce oedema and ecchymosis in septorhinoplasty patients (30).

### *Limitations*

The major limitations for this review include four main factors: (I) the lack of randomized controlled trials, (II) the types of surgical interventions, (III) the routes of TXA administration and (IV) outcome measures.

#### Lack of randomized trials

Many of the questions this review hope to answer could not be due to a lack in randomized trials. Only patients who underwent wide local excision or mastectomy with or without axillary surgery (10,15), as well as mammoplasty patients (14,16) were included in the meta-analysis. Two non-RCT papers examining breast reconstruction were excluded, one on implant-based reconstruction (20) and another on autologous reconstruction (21). The implant reconstruction paper did demonstrate a reduction in haematoma rates for the TXA group controlled for age, hypertension and implant position (pre-pectoral versus subpectoral) and mastectomy type (nipple versus skin sparing mastectomy) in 868 patients (P=0.018). They also noted a non-significant reduction in seroma formation. The free-flap autologous reconstruction paper included 83 patients noting no effect on haematoma formation (P=0.332), but a significant reduction in blood loss, 70 mL on average (P<0.001).

#### Variation in surgical interventions

Even in the small number of papers included in the final meta-analysis variations in surgical procedures is a major limiting factor. The difference in volumes of drained fluid from a wide local excision versus a mastectomy complicated by variations in axillary surgery is self-evident. Lack of benefit or benefits may be masked by grouping such procedures together, even with randomization. Bilateral mammoplasty provides an excellent control for studies, however the volume of fluid drained and the risk of late seroma are far less then compared to mastectomy.

#### Route of administration of TXA.

In the meta-analysis three studies (14-16) reviewed topical TXA as a single dose at the time of surgery and one study (10) three IV TXA doses in the first 24 hours followed by oral doses for a further 4 days. Bilateral mammoplasty acts as an excellent control group when topical TXA is administered but currently the effects systemically from this are not known and may affect the overall results. The best methods of administration of TXA for surgical patients is still debated and varies depending on the indications. One review (31) noted a reduction in blood loss and transfusion requirements with the majority of patients receiving a single IV dose of 15 mg/kg of TXA. The beneficial effects of topical TXA on blood loss and transfusion requirement have also been studied and confirmed by a meta-analysis of surgical patients including 71 trials and 7,539 patients (8). They noted no increase in adverse events including mortality, pulmonary embolism, myocardial infarction, deep vein thrombosis or stroke. Fatima *et al*. (32) reviewed topical tranexamic acid versus placebo in spinal deformity surgery and demonstrated no difference in complications between the two groups but noted a decrease in drain output for the TXA group and hospital stay. The best method of administration in breast surgery is still to be determined.

#### Outcome measures

Late seroma formation requiring at least one intervention is unaffected in this meta-analysis from limited studies, however from this data we do not know if the number of interventions required by the patient is affected by TXA.

### *Quality of evidence and Grade*

This study has demonstrated that TXA may have no effect on thromboembolic risk for breast surgery patients, but the certainty of evidence is low due to numbers of patients, mixed operation types and incorporating non-RCT's for this outcome. For mastectomy patients with or without axillary surgery and mammoplasty patients the rate of haematoma formation, after TXA, probably results in little to no difference with moderate certainty. Drain fluid output in the first 24 hours is reduced with high certainty, but the effect is small and may not be important overall to the patient. Drain production overall is lower but does not reach significance with moderate certainty and may not be important. Seroma formation requiring at least one intervention is unaffected by TXA to moderate certainty for mastectomy patients with or without axillary surgery.

## Conclusions

The overall benefits and risks of TXA remain uncertain in breast surgery. Further larger scale RCT's are required to

determine the real benefit from TXA in breast surgery, what dose, the best route of administration and in which surgical procedures. Two incomplete studies were identified during the literature search on clinicialtrials.gov, one "Tranexamic acid for bleeding in breast surgery (TABBS)" (33), which had so far failed to secure funding, and the second "Seroma Reduction pOst Mastectomy (SEROMA study)" (34) which is in recruitment and may provide addition information on this subject.

## Acknowledgments

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## Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/abs-20-126

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/abs-20-126). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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Supplementary

## Appendix A Search terms

Tranexamic acid OR cyklokapron OR lysteda OR transamin OR ugurol OR spotof OR anvitoff OR amchafibrin OR exacyl OR amca OR amcha OR t-cmcha OR trans-4-(aminomethyl)cyclohexanecarboxylic acid OR HAKU AND Breast OR breast surgery OR mastectomy OR simple mastectomy OR modified mastectomy OR radical mastectomy OR mastopexy OR mammoplasty OR breast reduction OR breast reconstruction OR immediate OR delayed OR breast cancer OR breast implant OR breast implants OR mastectomies OR mammectomy OR mammectomies OR breast implantation OR breast reconstructions OR mamoplasty OR mamoplasties OR reconstruction, breast OR reconstruction, breasts OR breast conservative therapies OR breast conservative therapy OR breast conserving surgery OR breast conserving surgeries OR breast quadrantectomies OR breast quadrantectomies OR breast quadrantectomy OR breast sparing surgery OR breast-conserving surgery OR breast sparing surgeries OR conservative therapy, breast OR conservative therapies, breast OR lumpectomy OR lumpectomies OR mastectomies, partial OR mastectomies, segmental OR mastectomy, partial OR mastectomies, segmental OR partial mastectomy OR partial mastectomies OR quadrantectomy, breast OR quadrantectomy, breasts OR segmental mastectomies OR segmentectomy OR segmentectomies OR surgery, breast conserving OR surgeries, breast sparing OR surgery, breast conserving OR surgery, breast-conserving OR surgery, breast sparing OR perforator flap OR perforator flaps OR flap, perforator OR flaps, perforator OR surgical flaps OR surgical flaps OR pediculed flaps OR pediculed flap OR free flaps OR free flap OR flaps, free OR flap, free OR flap, free tissue OR flaps, free tissue OR flap, microsurgical free OR flaps, microsurgical free OR free flap, microsurgical OR free flaps, microsurgical OR free tissue flap OR free tissue flaps OR microsurgical free flaps OR microsurgical free flap OR free tissue transfer flap OR tissue transfer flaps OR free OR tissue flap OR tissue flaps OR lymph node dissection OR lymph node dissections OR lymph node excision OR sentinel lymph node biopsy OR dissection, lymph nodes OR excision, lymph nodes OR lymphadenectomy OR node dissection, lymph AND outcomes OR post-operative outcomes OR outcomes, post-operative OR seroma OR haematoma OR bleeding OR haemostasis OR thrombosis OR deep vein thrombosis OR pulmonary embolism OR myocardial infarction OR stroke OR thromboembolic event OR clot OR complications


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