

Article

# THE EFFICACY OF TOPICAL TRANEXAMIC ACID IN BREAST SURGERY EVALUATING THE DRAIN OUTPUT AND COMPLICATIONS REDUCTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## ABSTRACT

**Introduction :** The topical administration of Tranexamic Acid (TXA) has gained significant attention for its potential advantages in various plastic surgery procedures. This study aims to conduct a systematic review and meta-analysis focusing on the use of topical TXA in breast surgery, analysing its impact on postoperative drain output and complications.

**Method :** PubMed, Embase and the Cochrane Library databases were systematically searched to identify relevant studies. The data synthesis utilized random-effects models and the findings were presented as a mean difference and weighted odds ratio along with the corresponding 95% confidence interval.

**Results :** Seven studies including four RCTs and three observational studies, comprising 1,553 breasts undergoing surgery were included. The average age of participants was 46 years; mean body mass index (BMI) was 26.1 kg/mm<sup>2</sup>. Of the breasts studied, 764 (49%) received topical TXA and 789 (51%) received normal saline as placebo. Overall, topical TXA was associated with a lower drain output in the first 24 hours postoperative (MD -25.87; p=0.00001) and a lower cumulative drain output (MD -59.72; p<0.00001). The rate of hematoma is significantly lower in the topical TXA group compared to the control group (OR 0.19; p=0.0009). There were no significant differences in rates of seroma, infection, thromboembolic events and time to drain removal between groups.

**Conclusion:** Evidence of this study suggests that administration of topical TXA significantly reduces the drain output production and hematoma in breast surgery. The use of topical TXA not significantly affecting rates of seroma, infection and postoperative duration with drain.

**Keywords:** *Tranexamic acid; Breast; Reduction mammoplasty; Mastectomy; Antifibrinolytic agents*

**Latar Belakang:** Pemberian Tranexamic Acid (TXA) secara topikal telah menarik perhatian yang signifikan karena potensi keuntungannya dalam berbagai prosedur bedah plastik. Studi ini bertujuan untuk melakukan tinjauan sistematis dan meta-analisis yang berfokus pada penggunaan TXA topikal dalam bedah payudara, menganalisis dampaknya terhadap produksi drainase pascaoperasi dan komplikasinya.

**Metodologi:** Penelusuran melalui PubMed, Embase and the Cochrane Library databases dilakukan secara sistematis untuk mengidentifikasi studi yang relevan. Sintesis data menggunakan random-effects models dan hasilnya ditemukan perbedaan bobot rata-rata dan rasio odds dalam interval kepercayaan 95%.

**Hasil:** Tujuh studi termasuk empat RCT dan tiga studi observasional, yang mencakup 1.553 payudara yang menjalani operasi, telah disertakan. Usia rata-rata peserta adalah 46 tahun; rata-rata indeks massa tubuh (BMI) adalah 26,1 kg/mm<sup>2</sup>. Dari payudara yang diteliti, 764 (49%) menerima TXA topikal dan 789 (51%) menerima larutan normal saline sebagai plasebo. Secara keseluruhan, TXA topikal berhubungan dengan produksi drainase yang lebih rendah dalam 24 jam pertama pascaoperasi (MD -25,87; p=0,00001) dan produksi drainase kumulatif yang lebih rendah (MD -59,72; p<0,00001). Tingkat hematoma secara signifikan lebih rendah di kelompok TXA topikal dibandingkan dengan kelompok kontrol (OR 0,19; p=0,0009). Tidak ada perbedaan signifikan dalam tingkat seroma, infeksi, peristiwa tromboemboli, dan waktu pengangkatan drainase antara kelompok.

**Kesimpulan:** Bukti dari studi ini menunjukkan bahwa pemberian TXA topikal secara signifikan mengurangi produksi drainase dan hematoma dalam bedah payudara. Penggunaan TXA topikal tidak signifikan memengaruhi tingkat seroma, infeksi, dan durasi pascaoperasi dengan drainase.

**Kata Kunci:** *Tranexamic acid; Payudara; Reduksi mammoplasti; Mastektomi; Agen antifibrinolitik*

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**Conflicts of Interest Statement:**

The author(s) listed in this manuscript declare the absence of any conflict of interest on the subject matter or materials discussed.

**INTRODUCTION**

In the realm of breast surgical interventions, a paramount emphasis is placed on achieving effective hemostatic control to mitigate the risk of bleeding complications. The occurrence of postoperative hematoma after mastectomy with immediate breast reconstruction ranges from 2% to 7%. Simultaneously, the rates of seroma vary, ranging from 1% to 80% in breast reconstruction.<sup>1,2</sup> Researchers and healthcare professionals have recently shown interest in the application of topical tranexamic acid (TXA) in breast surgery, recognizing its possible influence on hemostasis and postoperative results.<sup>3</sup> Although the systemic administration of TXA has demonstrated effectiveness in minimizing blood loss, the specific ramifications of its topical application warrant further exploration.<sup>4</sup> TXA functions as a synthetic reversible competitive inhibitor targeting the lysine receptor present on plasminogen. This inhibitory action prevents the activation of plasmin, hindering its binding to the fibrin matrix and ultimately leading to the stabilization of the fibrin structure.<sup>5</sup> TXA has proven effective in reducing blood loss in a range of surgical procedures, including those related to the breast.<sup>6</sup> In the realm of breast reconstruction, standard practice includes the incorporation of drainage systems to mitigate potential complications such as seroma, hematoma, and the accumulation of excessive fluids during the healing phase.<sup>7</sup> However, prolonged elevation in drain output levels may extend the duration of drainage, thereby heightening the risk of infection and serving as a potential indicator for late complications.<sup>8</sup>

While there is a substantial body of existing research on the role of TXA in breast surgery, numerous meta-analyses have primarily concentrated on its systemic administration.<sup>4,9</sup> To mitigate existing uncertainties, our meta-analysis aims to comprehensively investigate and synthesize the current corpus of evidence regarding the utilization of topical TXA in breast surgery. Through a meticulous assessment of pertinent research, our objective is to offer a more distinct and nuanced comprehension of the benefits and potential risks associated with the adoption of this methodology. This analysis is poised to offer practical insights for clinicians,

addressing gaps in knowledge and facilitating evidence-based decision-making in breast surgical interventions.

**METHOD**

This systematic review and meta-analysis were conducted and documented following the guidelines outlined in the Cochrane Collaboration Handbook for Systematic Review of Intervention and adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.<sup>10,11</sup>

**Ethical Approval**

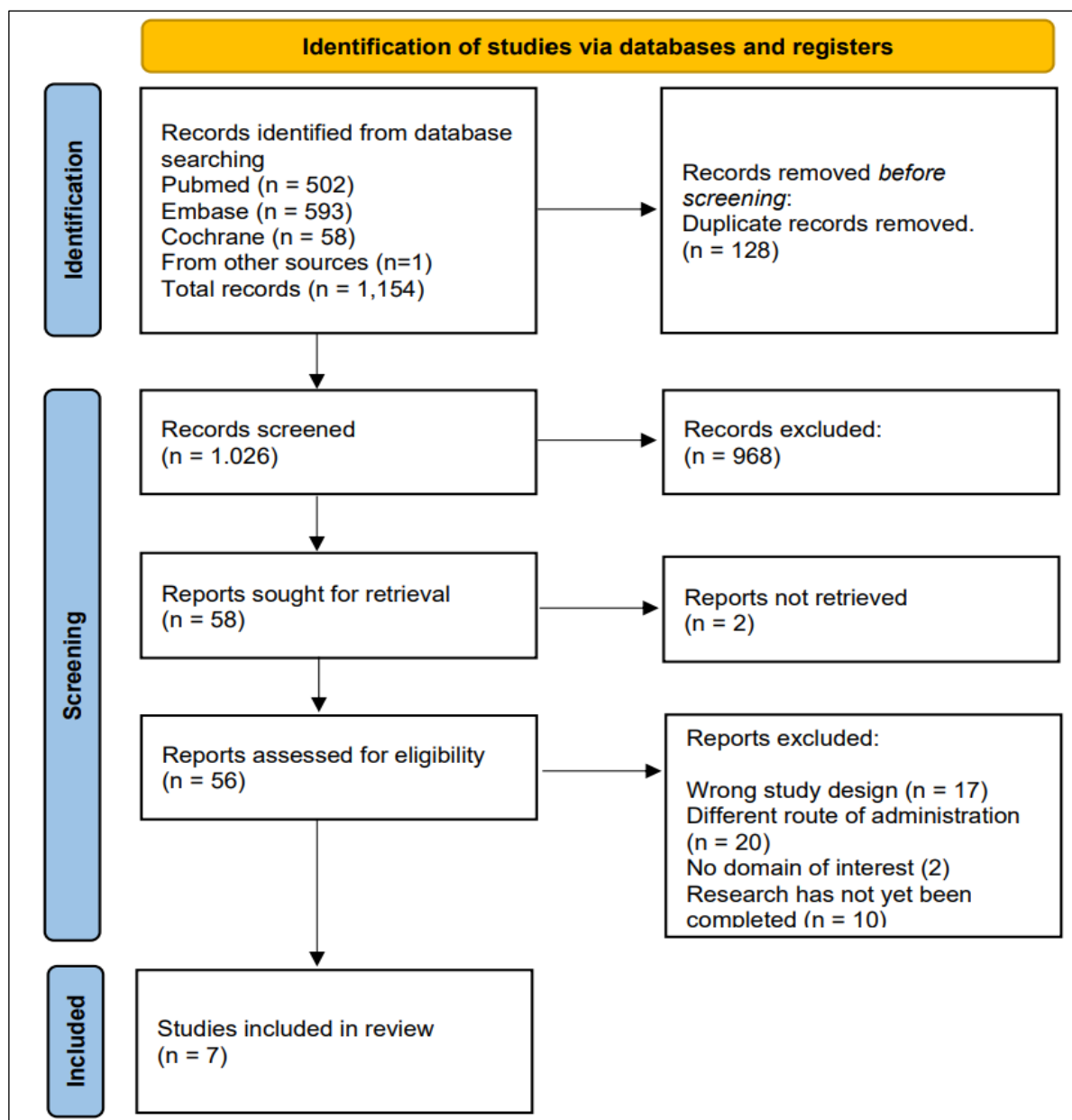
The research did not involve trials on humans or animals, thereby eliminating the necessity for ethical board approval.

**Eligibility criteria**

The meta-analysis exclusively incorporated studies that met the following criteria: (1) randomized trials or non-randomized cohorts; (2) conducted within the last decade; (3) entailed a comparison between topical TXA and a placebo; (4) enrolled patients who underwent breast surgery; (5) included participants aged 18 years or older; (6) featured a follow-up period lasting at least 2 weeks. Additionally, studies were deemed eligible only if they presented pertinent clinical outcomes. Studies were excluded if they satisfied any of the following criteria: (1) involved participants below the age of 18; (2) lacked a control group; (3) employed intravenous TXA in both groups; (4) were in a language other than English; (5) had no full-text availability; and (6) included letters, meeting proceedings, or case reports.

**Search strategy and data extraction**

We conducted a thorough search of relevant literature using PubMed, Scopus, and Cochrane Central Register of Controlled Trials, covering the period from inception to December 2023. The search terms employed were 'topical,' 'tranexamic acid,' and 'breast.' Additionally, we manually reviewed the references of the included studies, prior systematic reviews, and meta-analyses to identify any additional relevant studies.



**Fig 1.** Flow diagram of literature search and selection of studies (search date, December

Data extraction and quality assessment were carried out independently by two authors (J.P.S. and I.F.S.) based on pre-established search criteria. The prospective meta-analysis protocol was officially registered on PROSPERO on December 17, 2023, with the assigned protocol number #CRD42023489290.

#### Endpoints and sub-analyses

The primary findings included the quantity of drainage within the first 24 hours and the cumulative drainage output after surgery.

Secondary endpoints comprised the occurrence of hematoma, seroma, surgical-site infection, capsular contracture, thromboembolic events, and the duration until drain removal. Predefined sub-analyses were conducted, focusing on data specific to different types of breast surgeries (mastectomy versus reduction mammoplasty).

Table 1. Baseline Characteristics of the Included Studies

| First Author and Year | Country       | Level of Evidence | Study design  | Study of Period | Surgery Type                                             | Follow-up | Timing of Topical TXA Administration            | TXA Dose per Breast                                                           | Number of breasts |     | Age (yr) |      | BMI (kg/m <sup>2</sup> ) |      | History of Smoking |      | Weight of Tissue |      |     |     |
|-----------------------|---------------|-------------------|---------------|-----------------|----------------------------------------------------------|-----------|-------------------------------------------------|-------------------------------------------------------------------------------|-------------------|-----|----------|------|--------------------------|------|--------------------|------|------------------|------|-----|-----|
|                       |               |                   |               |                 |                                                          |           |                                                 |                                                                               | TXA               | Co  | TXA      | Co   | TXA                      | Co   | TXA                | Co   | TXA              | Co   | TXA | Co  |
| Bae, 2023             | South Korea   | III               | Retrospective | 2021-2022       | Mastectomy + Implant based reconstruction                | 3 months  | Topically administered before implant placement | 10 ml of TXA 100 mg/ml mixed with 100 mL of normal saline                     | 251               | NR  | NR       | 43.7 | 44.6                     | 22.3 | 22.1               | NR   | NR               | NR   | 316 | 311 |
| Yao, 2023             | United States | I                 | RCT           | 2021-2022       | Reduction mammoplasty                                    | 1 month   | Topically administered before closure           | 10 ml of TXA 100 mg/ml mixed with 90 mL of normal saline                      | 98                | 98  | 98       | 34.2 | 34.2                     | 31.5 | 31.5               | NR   | NR               | NR   | NR  | NR  |
| Safran, 2023          | Canada        | I                 | RCT           | 2020-2023       | Nipple-sparing Mastectomy + Implant based reconstruction | 6 months  | Topically administered before implant placement | 30 ml of TXA 100 mg/ml mixed with 70 mL of normal saline                      | 53                | 53  | 53       | NR   | NR                       | NR   | NR                 | 0(0) | 0(0)             | NR   | NR  | NR  |
| Sipos, 2023           | Finland       | III               | Retrospective | 2019-2021       | Reduction mammoplasty                                    | 2 weeks   | Topically administered before wound closure     | 10 ml of TXA 100 mg/ml mixed with 40 mL of normal saline (given 25 ml/breast) | 168               | 208 | 168      | 46   | 46                       | NR   | NR                 | 8    | 10               | NR   | NR  | NR  |
| Ausen, 2020           | Norway        | I                 | RCT           | 2016-2018       | Mastectomy ≠ ALND                                        | 3 months  | Topically administered before wound closure     | 5 ml of TXA 25 mg/ml mixed with 15 ml of normal saline (given 20 ml/breast)   | 101               | 101 | 98       | 66.2 | 62.3                     | 26.9 | 27.1               | 19   | 13               | (13) | 780 | 746 |
| Eldesouky, 2019       | Egypt         | II                | Prospective   | 2016-2018       | Mastectomy                                               | 1 month   | Topically administered on wound                 | 5 ml of TXA 100 mg/ml mixed with 15 ml of normal saline                       | 65                | 50  | 65       | 55   | 46                       | 48   | 32                 | 33   | NR               | NR   | NR  | NR  |
| Ausen, 2015           | Norway        | I                 | RCT           | 2013-2014       | Reduction mammoplasty                                    | 3 months  | Topically administered before wound closure     | 5 ml of TXA 25 mg/ml mixed with 15 ml of normal saline (given 20 ml/breast)   | 28                | 28  | 28       | NR   | NR                       | NR   | NR                 | NR   | NR               | NR   | NR  | NR  |
| Total                 |               |                   |               |                 |                                                          |           |                                                 |                                                                               | 764               | 789 | 510      | 542  | 45.7                     | 47   | 26.2               | 26   | (8)              | (6)  | 449 | 436 |

Co, control; DM, diabetes mellitus; NR, not reported.

### Quality assessment

Two assessors (J.P.S and I.F.S.) independently conducted the assessment of bias risk utilizing the Risk of Bias tool for Randomized Trials (ROB-2) and the Risk of Bias in Non-randomized Studies (ROBINS-I) tools, as prescribed by Cochrane.<sup>12,13</sup> Any conflicting viewpoints were harmoniously addressed through consensus following a thorough deliberation on the rationales behind the disparities. To explore potential publication bias, an analysis using a funnel plot of point estimates in relation to study weights was executed.

### Statistical analysis

Odds ratios (OR) along with 95% confidence intervals (CI) were utilized to assess the treatment effects concerning categorical endpoints. Mean differences (MD) were applied to contrast continuous outcomes. Heterogeneity was evaluated through I<sup>2</sup> statistics and Cochran's Q test, acknowledging significance for heterogeneity when p-values were less than 0.10 and I<sup>2</sup> exceeded 25%.

Our analysis employed the DerSimonian and Laird random-effects model. Furthermore, two sensitivity analyses were executed: (1) exclusion of each individual study from the outcome assessment, and (2) utilization of adjusted risk estimates from non-randomized studies, when available. Statistical analysis was performed using Review Manager 5.4.1, developed by the Cochrane Center in collaboration with The Cochrane Collaboration, Denmark.<sup>14</sup>

## RESULTS

### Study selection and characteristics

As illustrated in Supplementary Figure 1, the preliminary exploration identified 1,154 studies located through the database search, with 128 duplicates identified. Subsequent screening revealed an additional 1,026 studies. Following the evaluation of abstracts, 968 studies were excluded. Out of the remaining 58 publications, 49 were excluded due to non-alignment with the inclusion criteria, and two were eliminated as full texts were inaccessible (only abstracts were accessible). The final analysis incorporated seven studies. Figure 1 presents a schematic diagram outlining the process of study identification.

A combined total of seven investigations involving 1,553 breast cases were included in the

analysis, comprising four randomized controlled trials (RCTs) and two non-randomized observational cohort studies. Among this cohort, 764 breasts (49%) were subjected to topical, there were variations among the studies regarding the dose of topical TXA administered per breast and the timing of such administration. Administration of topical TXA varied between 20 ml and 110 ml per breast, and the doses administered intraoperatively ranged from 6.25 mg/ml to 30 mg/ml.

All other baseline characteristics were evenly distributed among the treatment groups, including age (with a weighted mean of 45.7 years in the TXA group and 47 years in the control group), BMI (26.2 kg/m<sup>2</sup> in the TXA group and 26 kg/m<sup>2</sup> in the control groups), smoking history (8% in the TXA group and 6% in the control group), and tissue resection weight (449 g in the TXA group and 436 g in the control group). Further details regarding study type, level of evidence, surgery type, timing and dosage of TXA administration, and patient characteristics are provided in Table 1.

### Pooled analysis of all studies

#### Primary Outcome

In individuals who were administered topical TXA, a general inclination towards reduced drainage output within the initial 24 hours postoperative was observed in three studies (MD -25.87, 95% CI -33.78 to -17.96; p<0.00001; I<sup>2</sup>=96%; depicted in Figure 2). Moreover, there was a significant decrease in the cumulative drainage output, as reported in three studies (MD -59.72; p<0.00001; 95% CI -95.57 to -17.96; I<sup>2</sup>=97%; illustrated in Figure 3).

In the study conducted by Safran in 2023, a patient noted an elevated drainage output within the TXA group in comparison to the control group. The research by Bae in 2023, being a retrospective cohort study, is susceptible to bias. Given the notable impact of Bae's research on the results presented in Figure 2, we conducted an inquiry to assess the robustness of the findings by examining the mean drain output 24 hours postoperatively while retaining this study in our analysis. The average drain production in the first 24 hours postoperative was found to be significantly lower in the TXA group, albeit with a diminished level of statistical significance (MD -24.38, 95% CI -44.63 to -4.13; p=0.02; I<sup>2</sup>=93%).

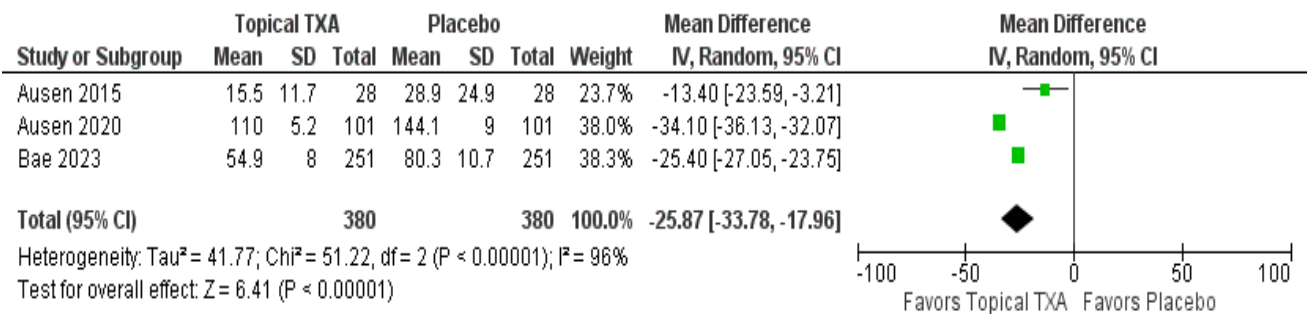


Fig. 2. Drain Output in 24 hours Postoperative

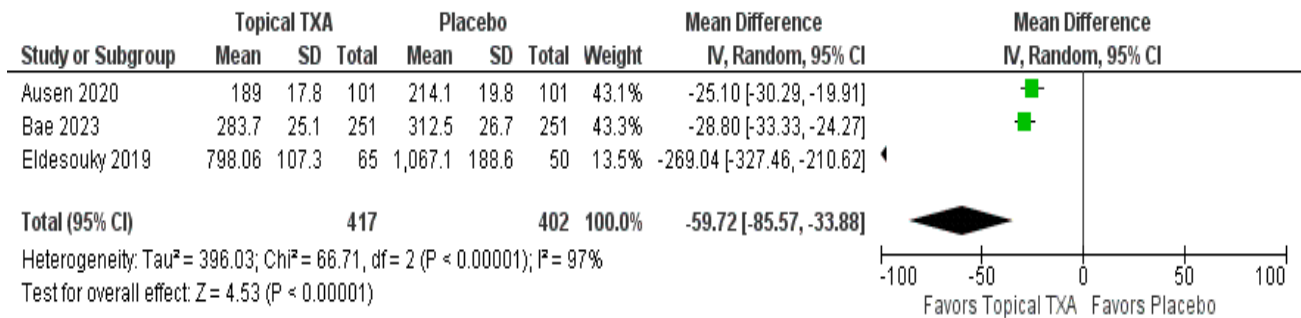


Fig. 3. Cumulative Drain Output

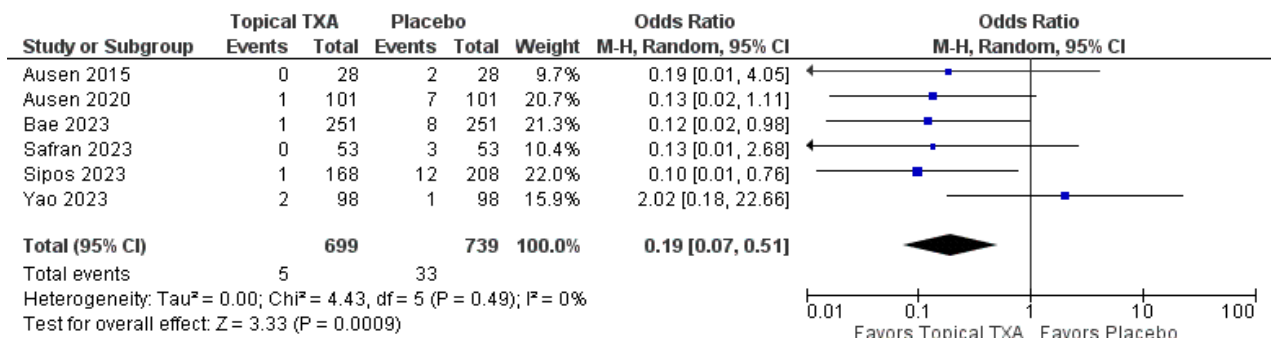


Fig. 4. Postoperative Hematoma Formation

**Secondary Outcome**

*Postoperative Hematoma Formation*

The incidence of hematomas was notably reduced when utilizing topical TXA in contrast to the control group (OR 0.19; 95% CI 0.07-0.51; p=0.0009; I<sup>2</sup>=0%; Figure 4). As documented in two distinct studies by Ausen, nine individuals necessitated reoperation and hematoma evacuation. Due to the limited occurrence of such events, sensitivity analyses incorporating adjusted risk estimates for significant hematomas requiring evacuation could not be conducted.<sup>3,20</sup>

The results in Fig. 2 were significantly influenced by Bae 2023 and Sipos 2023. To assess

the robustness of the findings, postoperative hematoma events were evaluated without considering these two investigations (15,19). The research indicated that there was no notable variance in postoperative hematoma rates among the different groups (OR 0.34, 95% CI 0.06 to 2.08; p=0.24; I<sup>2</sup>=36%).

*Seroma Formation*

The incidence of seroma accumulation was examined across five studies subsequent to the application of topical TXA. The seroma rates were found to be similar, as indicated by the recorded occurrences in each study. Statistical analysis revealed no significant difference between the

groups in relation to the formation of seromas (OR 1.04; 95% CI 0.68–1.60;  $p=0.85$ ;  $I^2=16\%$ ).

### Surgical Site-Infection

Surgical site infections were reported in four studies, and no significant difference was found between the two groups (OR 0.65; 95% confidence interval 0.30–1.39;  $p=0.27$ ;  $I^2=7\%$ ). This outcome encompasses data from two cohort studies, Bae 2023 and Sipos 2023, both of which are susceptible to bias. The results also encompassed the incidence of breast pocket infections as reported by Safran 2023.<sup>16</sup>

### Time to Drain Removal

Two investigations documented the duration for drain removal by presenting it as either the median or mean number of days. The duration of drain placement did not exhibit a significant distinction among the various groups (MD -0.87, 95% CI -2.00 to 0.25;  $p=0.13$ ;  $I^2=93\%$ ). In the research conducted by Safran in 2023, the removal of drains in the topical TXA group occurred 1.4 days earlier (with a range of 0 to 4 days) compared to the control group.<sup>16</sup>

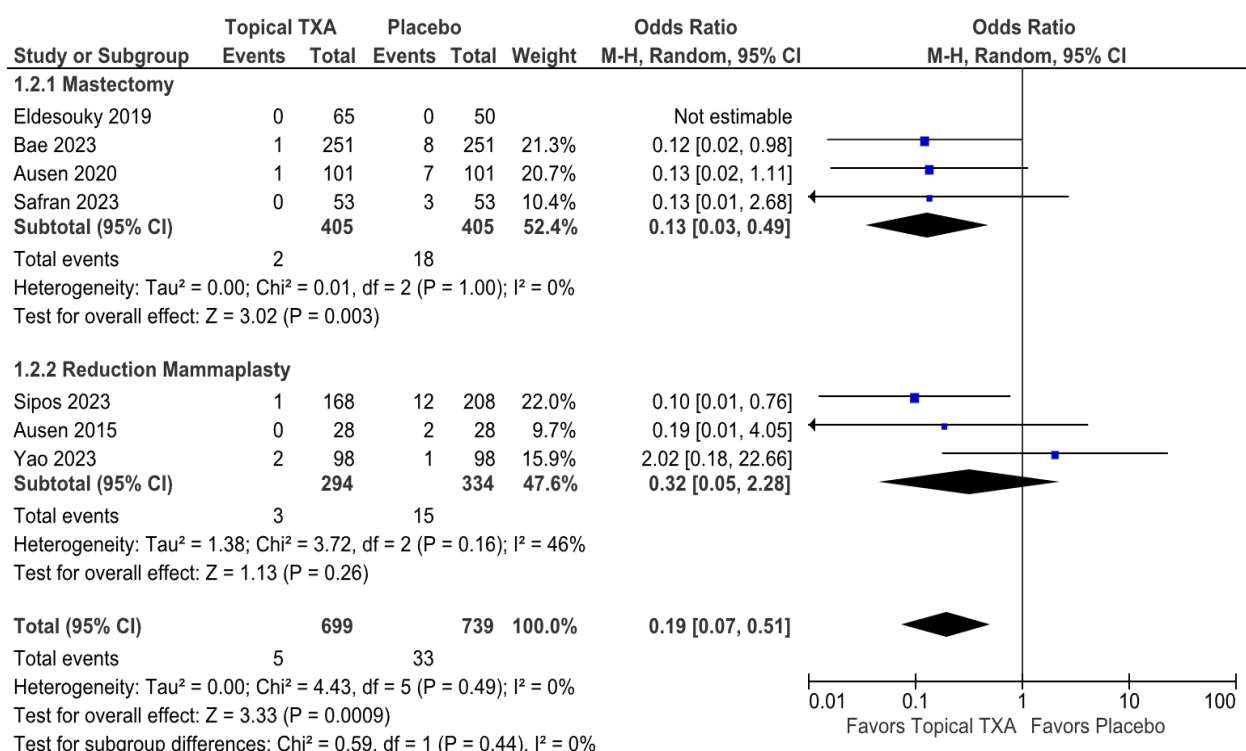
### Other secondary outcomes

Two investigations involving 398 breasts documented postoperative thromboembolic occurrences. No thromboembolic events were observed in either the topical TXA or control groups. Safran's investigation in 2023 disclosed a diminished incidence of capsular contracture in the topical TXA cohort (1.9%) in contrast to the control cohort (13.2%). Nevertheless, these findings did not attain statistical significance ( $P=0.06$ ). The occurrence of skin flap necrosis, as documented in studies by Safran (2023) and Eldesouky (2019), showed no recorded events in either the topical TXA or control groups.<sup>16,17</sup>

### Subgroup Analysis

#### The effect of operation type on haematoma formation (mastectomy versus reduction mammoplasty).

Three investigations were conducted to assess the occurrence of hematoma following mastectomy, revealing a notable decrease in the incidence among patients treated with topical TXA compared to the control group (0.5% (2/405)



**Fig. 5.** Forest plot illustrating the rates of hematoma formation in patients underwent mastectomy and reduction mammoplasty in receipt of topical TXA versus those who received placebo.

|       |              | Risk of bias domains |    |    |    |    |         |
|-------|--------------|----------------------|----|----|----|----|---------|
|       |              | D1                   | D2 | D3 | D4 | D5 | Overall |
| Study | Ausen K 2015 | +                    | +  | +  | +  | +  | +       |
|       | Ausen K 2020 | +                    | -  | +  | +  | +  | -       |
|       | Safran 2023  | +                    | -  | +  | +  | +  | -       |
|       | Yao Amy 2023 | +                    | +  | +  | +  | +  | -       |

Domains:  
 D1: Bias arising from the randomization process.  
 D2: Bias due to deviations from intended intervention.  
 D3: Bias due to missing outcome data.  
 D4: Bias in measurement of the outcome.  
 D5: Bias in selection of the reported result.

Judgement  
 - Some concerns  
 + Low

Fig. 6A. A. Risk of Bias Assessment (ROB-2)

|       |                  | Risk of bias domains |    |    |    |    |    |    |         |
|-------|------------------|----------------------|----|----|----|----|----|----|---------|
|       |                  | D1                   | D2 | D3 | D4 | D5 | D6 | D7 | Overall |
| Study | Bae Juyoung 2023 | -                    | +  | +  | +  | +  | +  | +  | -       |
|       | Sipos 2023       | X                    | +  | +  | +  | +  | +  | +  | X       |
|       | Eldesouky 2019   | X                    | +  | +  | +  | +  | +  | +  | X       |

Domains:  
 D1: Bias due to confounding.  
 D2: Bias due to selection of participants.  
 D3: Bias in classification of interventions.  
 D4: Bias due to deviations from intended interventions.  
 D5: Bias due to missing data.  
 D6: Bias in measurement of outcomes.  
 D7: Bias in selection of the reported result.

Judgement  
 X Serious  
 - Moderate  
 + Low

Fig. 6B. A. Risk of Bias Assessment (ROBINS-I)

vs. 4.4% (18/405), OR 0.13, 95% CI 0.03 to 0.49; p=0.003; I<sup>2</sup>=0%). Similarly, two studies investigating individuals undergoing reduction mammoplasty assessed hematoma development rates. No statistically significant difference was observed between the topical TXA (1%, 3/294) and control groups (4.5% 15/334) (OR 0.32, 95% CI 0.05 to 2.28; p=0.26; I<sup>2</sup>=46%). However, it is noteworthy that the disparity in hematoma formation between mastectomy and reduction mammoplasty did not achieve statistical significance (P=0.44) (Fig. 5).

*The effect of operation type on seroma formation (mastectomy versus reduction mammoplasty)*

Three investigations explored the incidence of seroma formation in mastectomy patients, revealing no statistically significant distinction between the topical TXA group and the control group (29.7% (116/391) vs. 28.4% (110/388), OR 1.10, 95% CI 0.65 to 1.87; p=0.72; I<sup>2</sup>=34%). Only one of the studies, which encompassed patients undergoing reduction mammoplasty, assessed the rates of seroma development. Similarly, no notable distinction was observed between the topical TXA (1.8% 3/168) and control groups

(2.4% 5/208) in these investigations (OR 0.74, 95% CI 0.17 to 3.13;  $p=0.68$ ;  $I^2$ =not applicable).

*The effect of operation type on surgical site infection (mastectomy vs reduction mammoplasty)*

The occurrence of surgical-site infection was evaluated in three trials that included mastectomy patients. In comparison to the control group, the topical TXA group demonstrated no significant reduction (1.9% (7/369) vs. 2% (7/354), OR 0.99, 95% CI 0.27 to 3.66;  $p=0.98$ ;  $I^2=16\%$ ). Similarly, in a trial involving patients undergoing reduction mammoplasty, there was no noteworthy distinction between the topical TXA group (2.8%, 15/537) and the control group (4.6%, 26/562) (OR 0.65, 95% CI 0.30 to 1.39;  $p=0.27$ ;  $I^2=7\%$ ).

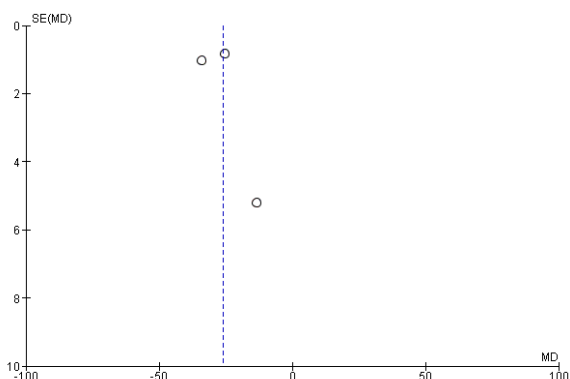
**Quality assessment**

The evaluations of individual RCTs can be found in Supplementary Table 1. Two non-randomized studies matched intervention and

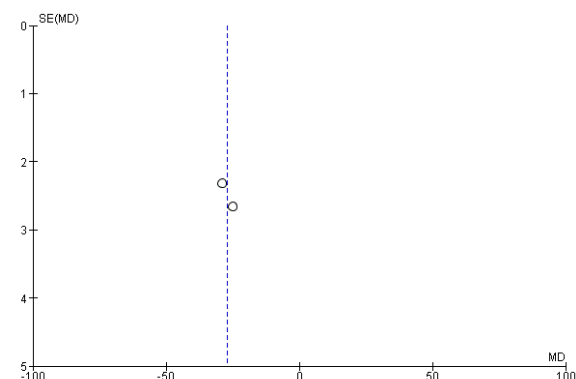
control participants based on baseline characteristics. Supplementary Figure 6.A.,B. illustrates a moderate level of publication bias in four studies, with one study indicating a serious bias due to confounding. The funnel plot in Fig 7. A., B., D. displays a symmetrical distribution of studies, while the distribution of hematoma outcomes in Fig 7.C. appears asymmetrical. This asymmetry may be attributed to small study effects, as suggested by Yao (2023), where smaller studies with more extreme results could influence the outcome.<sup>18</sup>

**DISCUSSION**

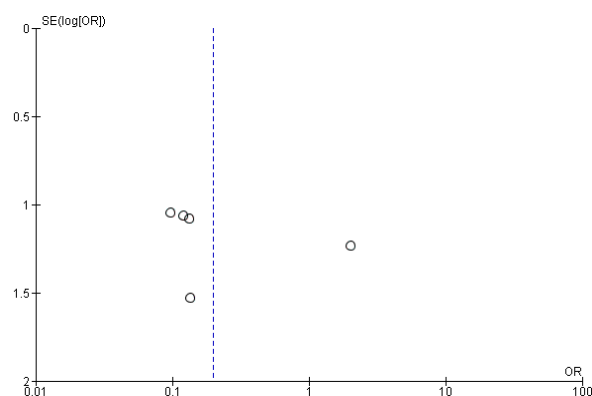
This comprehensive examination, involving seven studies encompassing four RCTs, two retrospective cohort studies, and one prospective cohort study, investigated the impact of intraoperative application of topical TXA in breast surgery. The results of the present study indicate that the intraoperative use of topical TXA is associated with a significant decrease in



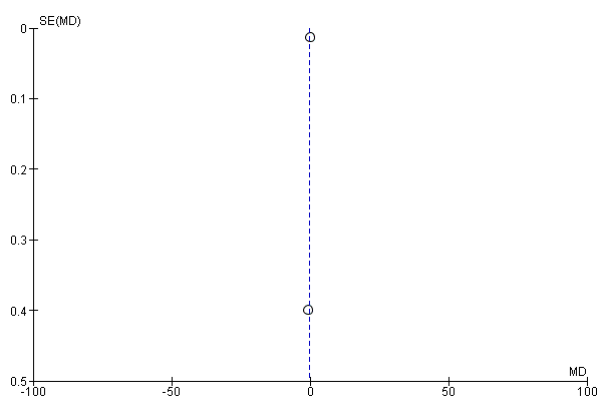
**Fig. 7A.** Funnel Plot of Drain Output 24 hours Postoperative



**Fig. 7B.** Funnel Plot of Cumulative Drain Output



**Fig. 7C.** Funnel Plot of Hematoma Formation



**Fig. 7D.** Funnel Plot of Time to Drain Removal

drainage output within the initial 24 hours post-surgery, cumulative drainage output, and the occurrence of hematomas. Notably, this intervention does not demonstrate any discernible influence on the incidence of seroma, infection, thromboembolic events, or the duration until drainage removal.

### Comparison to Previous Literature

No meta-analyses have been conducted on investigations comparing the application of topical TXA with a control group in breast surgery. A systematic review and meta-analysis conducted by Montroy in 2018 explored the effectiveness and safety of topical TXA across various surgical procedures, revealing a significant reduction in blood loss, particularly in orthopedic and cardiac surgery. However, the review only included one study on reduction mammoplasty, conducted by Ausen in 2015. Another study by Hyunh in 2023 indicated that TXA reduces hematoma formation; however, there is an overlap in results between topical and intravenous administration.<sup>4</sup>

Calpin 2023 reported the superiority of topical TXA over intravenous administration in reducing hematoma formation, but only three studies utilized topical TXA in the meta-analysis.<sup>21</sup> The outcomes from two randomized controlled trials conducted by Safran (2023) and Yao (2023) were omitted from the meta-analysis. Notably, the latter trial, which investigated the effectiveness of topical TXA in breast surgery, was the most recent among the studies considered. As per Yao's findings in 2023, it was determined that the topical administration of TXA does not seem to reduce the occurrence of hematoma subsequent to breast reduction mammoplasty.<sup>18</sup> The meta-analysis omitted analyses of post-operative drainage within the first 24 hours, cumulative drain output, and the duration until drain removal due to limited data availability, hindering a conclusive determination.

### Interpretation of Results

This meta-analysis underscores a pivotal finding related to the efficacy of topical TXA in mitigating postoperative drainage. Our investigation demonstrates a substantial decrease in drain output during the first 24 hours when topical TXA is administered intraoperatively (MD -59.72;  $p < 0.00001$ ). However, it is essential to

recognize that the investigation carried out by Bae in 2023 is a retrospective cohort study, which is prone to inherent challenges like selection bias, ascertainment bias, and confounding bias. Consequently, we performed an autonomous analysis, excluding the mentioned study. The results persisted in revealing statistical significance (MD -24.38,  $p = 0.02$ ).

Evaluating cumulative drainage output until extraction offers valuable insights into the patient's recovery trajectory, allowing observation of trends and changes over time, aiding in a comprehensive understanding of fluid dynamics and detecting potential later complications.<sup>22,23</sup> When the data were combined, a noteworthy decline in cumulative drain output until removal was observed in the topical TXA group as opposed to the placebo group (MD -59.72;  $p < 0.00001$ ).

The contentious aspect of drain output volume revolves around the debate over whether the prolonged presence of elevated quantities could extend the duration of drainage and potentially elevate the risk of infection. In a 2022 study by Chua, sustained elevation in drain output, leading to delayed removal, emerged as an early indicator of impending complications. This implies that the link between delayed drain removal and complications is predictive rather than causative.<sup>23</sup> According to the statement, we performed statistical analyses of complications including the rate of hematoma, seroma and infection. Upon consolidating data from all participants in the six studies examining hematoma formation, topical TXA application revealed a significantly diminished incidence compared to the control group ( $p = 0.0009$ ). Two RCTs by Ausen demonstrated reduced 24-hour drain output and lower hematoma rates, consistent with the earlier statement. However, a thorough investigation is needed to establish the significance of the relationship between drainage output volume and hematoma formation rates.

Surgery type, intraoperative topical TXA administration details, including timing and dosage, varied significantly in the studies. All included research clearly outlined specific surgical procedures, with four concentrating on mastectomy and three on reduction mammoplasty. This detailed categorization ensures a comprehensive analysis of diverse surgical interventions related to our study's objectives. Within the subgroup analysis, we observed a reduced occurrence of hematoma formation in the groups administered with

topical TXA following mastectomy procedures. (OR 0.03,  $p=0.003$ ). Oppositely, topical TXA failed to significantly show a potential reduction of hematoma rates in reduction mammoplasty procedure ( $p=0.26$ ), however the statistical result proved that there was no significant difference between this variable ( $p=0.44$ ). Oertli et al. proposed that the use of intravenous TXA could potentially decrease the occurrence of seroma formation post-surgery. However, our examination revealed that the application of topical TXA does not significantly influence the rates of seroma formation (OR 1.04;  $p=0.85$ ).<sup>25</sup>

Concerning additional recorded secondary outcomes, infection represents a significant complication associated with various surgical procedures, including breast surgery. As highlighted in a study by Palubicka in 2019, surgical site infection persists as a noteworthy concern demanding increased attention, particularly in terms of preventive measures.<sup>26</sup> In the prior meta-analysis conducted by Hyunh in 2023, only two studies were incorporated, documenting infection rates. Consequently, the limited data availability may yield insufficient statistical power for detecting significant outcomes. In order to add more accuracy, we added two newest study that were also recorded the comparison in rates of infection between groups. result in a study by Lohani 2019, stated that there are nonsignificant lower rates of infection in TXA group compared to placebo, however this was with intravenous administration.<sup>27</sup> In contrast, the analysis result in this study was not reflecting the significance of topical TXA in reducing the infection rates ( $p=0.27$ ).

This study found no significant effect of topical TXA in reducing thromboembolic event, capsular contracture and flap necrosis. The findings in this research align with a study that showed no increased occurrence of thromboembolic events linked to the application of topical TXA.<sup>28,29</sup> However, more study recording the rate of capsular contracture and flap necrosis are needed to draw more accurate conclusions. This study found no significant associations with age, BMI, or tissue resection weight. Variability in topical TXA dosages, timing, drain placement, surgeon experience, axillary clearance performance, and wound surface area may have influenced the meta-analysis outcomes. Additional research is needed to establish a consensus on the optimal concentration of topical TXA and the most

efficacious timing for its administration in medical practice.

### Limitations

This study has several limitations warrant consideration. It is crucial to acknowledge and address these constraints to enhance the overall understanding and interpretation of the research findings. There was considerable variability in the baseline characteristics and the combined analysis of secondary outcomes, which diminished its overall significance for research findings. The observed outcome might be attributed to potential residual confounding arising from unmeasured baseline characteristics that remain a factor beyond exclusion.

Secondly, certain research investigations have incorporated interventions that influence the observed outcomes of topical administration of TXA. These interventions include the use of tumescent solution, epinephrine, triple antibiotic irrigation, postoperative thromboprophylaxis, and a compression protocol following surgical procedures.<sup>3,15,16,19</sup> Furthermore, the outcomes are significantly influenced by various factors, including the dosage of topical TXA, the specific timing of TXA administration, the placement of drainage systems and the skill level of the surgeon. These elements collectively play crucial roles in shaping the overall impact on the results.

Thirdly, our data synthesis reliability is constrained by varying study quality, assessed with the ROBINS-I and ROB2 tools, showing a range of risks from moderate to serious and low to some concern, respectively. Despite identified bias, these preliminary findings can generate hypotheses, prompting further research that mirrors real-world heterogeneity. Emphasizing the need for standardized reporting and advocating for additional research, this study contributes to existing literature, highlighting the importance of unraveling specific factors impacting outcomes in the studied context.

### CONCLUSION

This meta-analysis reveals that using topical TXA during breast surgery is associated with decreased postoperative drainage and a significant reduction in hematoma occurrence compared to controls. This highlights its potential as an effective intervention for minimizing postoperative complications. The demonstrated benefits of lower drain output and reduced

hematoma rates with topical TXA suggest a promising approach to enhance patient outcomes. Further research, supported by well-designed randomized controlled trials, should explore the broader applicability of topical TXA in various breast surgical procedures, with the aim of establishing standardized guidelines for improved postoperative care.

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