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TRANEXAMIC ACID IN CAESAREAN DELIVERY: PROPHYLACTIC USE VERSUS USE AS DEFINITIVE TREATMENT FOR POSTPARTUM HAEMORRHAGE

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Abstract

Background: Postpartum haemorrhage (PPH) remains an important cause of maternal morbidity and mortality. Tranexamic acid (TXA), an antifibrinolytic agent, has been studied both to reduce blood loss around caesarean delivery and as treatment after clinically diagnosed PPH. These applications address different clinical questions and should not be considered interchangeable. Objective: To synthesize evidence available up to 31 December 2020 regarding prophylactic TXA in caesarean delivery and TXA for established PPH, with emphasis on blood loss, transfusion, major morbidity and safety. Methods: A structured systematic-review framework was developed using PubMed/MEDLINE, Cochrane and reference-list searching concepts. Randomized trials and systematic reviews available before 2021 were considered. Because prophylaxis and treatment involve different populations, comparators and outcomes, the evidence was synthesized in separate domains rather than combined into a single pooled estimate. Results: Pre-2021 evidence from caesarean-delivery trials and meta-analyses consistently suggested reductions in measured blood loss and some bleeding-related outcomes with prophylactic TXA, although trials were heterogeneous and often small. For established PPH, the large WOMAN randomized trial demonstrated a reduction in death due to bleeding, particularly when treatment occurred early, without a significant difference in hysterectomy or overall mortality. Conclusion: By the end of 2020, the evidence supported a clear distinction between TXA as a preventive intervention studied during caesarean delivery and TXA as treatment for established PPH. The treatment evidence was anchored by a large, clinically important randomized trial, whereas prophylactic caesarean evidence remained more heterogeneous and uncertain regarding patient-important outcomes and routine universal use.

Keywords

Tranexamic acid; caesarean delivery; postpartum haemorrhage; prophylaxis; haemorrhage treatment; maternal morbidity; systematic review.

1. Introduction

Postpartum haemorrhage is a major contributor to maternal morbidity and mortality worldwide and remains particularly important in settings where access to blood products, surgery and critical care is limited. Caesarean delivery itself is associated with greater expected blood loss than uncomplicated vaginal birth, creating interest in pharmacological strategies that might reduce perioperative bleeding. Tranexamic acid is an antifibrinolytic drug that stabilizes fibrin clots by inhibiting plasminogen activation and plasmin activity. Early trials in obstetric surgery suggested that prophylactic administration could reduce measured blood loss, but the studies varied substantially in design, timing, outcome definitions and baseline risk. [1-4]

Before 2021, several systematic reviews and meta-analyses reported reductions in blood loss, haemoglobin decline and some transfusion-related outcomes among women undergoing caesarean delivery who received prophylactic TXA. A 2016 meta-analysis including nine randomized trials and 2,365 women reported lower

postpartum blood loss and lower frequencies of several bleeding outcomes, while noting uncertainty around mortality and thromboembolic events. [1] A 2018 updated meta-analysis identified 18 randomized trials involving more than 3,500 women and reported reductions in postpartum haemorrhage thresholds and red-cell transfusion, without identifying a specific safety signal in the included trials. [2]

The question of treatment is fundamentally different. Once clinically diagnosed PPH has occurred, TXA is not being evaluated as prevention of an event that may never occur; rather, it is evaluated as an adjunct to standard haemorrhage management with patient-important outcomes such as death due to bleeding. The WOMAN trial, published in 2017, randomized 20,060 women with clinically diagnosed PPH after vaginal or caesarean birth and found that death due to bleeding was reduced, particularly among women treated early. [5] These findings informed the 2017 World Health Organization recommendation supporting early TXA as part of treatment for clinically diagnosed PPH. [6]

However, prophylactic use at caesarean delivery and treatment of established PPH should not be treated as two versions of the same intervention. They differ in indication, baseline risk, outcome importance and certainty of evidence. The purpose of this review was therefore to examine these two evidence domains separately and then compare the strength and clinical relevance of their findings. The review was restricted to evidence available before 1 January 2021 so that later trials and meta-analyses would not influence the historical evidence synthesis.

2. Review Question

Among women undergoing caesarean delivery or women who develop clinically diagnosed postpartum haemorrhage after childbirth, what was the evidence available before 2021 regarding TXA for prevention versus treatment, particularly for blood loss, transfusion, major maternal morbidity, mortality and adverse events?

3. Objectives

- To summarize randomized and systematic-review evidence for prophylactic TXA in caesarean delivery.
- To summarize evidence for TXA used after established PPH, with particular attention to the WOMAN trial.
- To compare the certainty, population, outcomes and limitations of prophylactic and therapeutic evidence.
- To identify important evidence gaps relevant to future research.

4. Methods

4.1 Reporting framework

This review is structured in accordance with the principles of PRISMA reporting. PRISMA 2020 was published in March 2021, after the present evidence cut-off; it is therefore used here as a reporting framework rather than as an eligibility criterion. The evidence window was closed at 31 December 2020. [7]

4.2 Eligibility criteria

Domain	Eligibility
Population	Women undergoing caesarean delivery for prophylaxis studies; women with clinically diagnosed PPH for treatment studies.
Intervention	TXA administered with the intention of preventing peri-caesarean bleeding or treating established PPH.
Comparator	Placebo, no TXA, or usual care as reported in eligible studies.
Outcomes	Blood loss, PPH, severe PPH, transfusion, additional interventions, hysterectomy, maternal death, death due to bleeding and adverse events.

Study designs	Randomized controlled trials and systematic reviews/meta-analyses used for contextual synthesis.
Publication window	Evidence available from database inception through 31 December 2020.
Exclusions	Studies published from 1 January 2021 onward; non-obstetric populations; laboratory-only studies; editorials without primary evidence.

4.3 Search strategy

A reproducible search concept should combine controlled vocabulary and free-text terms for tranexamic acid, caesarean/cesarean delivery and postpartum haemorrhage. Representative PubMed concepts are: (tranexamic acid OR tranexamic) AND (cesarean OR caesarean) AND (postpartum haemorrhage OR postpartum hemorrhage OR obstetric haemorrhage). For treatment evidence, the PPH terms should be retained without requiring caesarean delivery, because the major treatment trial included both vaginal and caesarean births. Reference lists of eligible systematic reviews and major trials should be screened manually.

4.4 Study selection and data extraction

Records should be screened independently by two reviewers where possible, with disagreements resolved by consensus or a third reviewer. Extracted variables should include publication year, setting, sample size, caesarean characteristics, intervention/comparator, baseline risk, outcome definitions, effect estimates, adverse events and risk-of-bias judgments. For this manuscript, prophylaxis and treatment were deliberately separated because pooling them would create major clinical and methodological heterogeneity.

4.5 Risk of bias and certainty

Randomized trials should be assessed using a contemporary randomized-trial risk-of-bias framework, considering randomization, allocation concealment, deviations from assigned intervention, missing outcome data, outcome measurement and selective reporting. Where systematic-review certainty is reported, GRADE judgments should be presented as reported by the original review. The pre-2021 prophylactic literature was characterized by substantial variation in study size, definitions and methodology, limiting confidence in routine universal prophylaxis despite generally favorable estimates.

5. Results

5.1 Evidence identified

The pre-2021 literature contained multiple randomized trials of prophylactic TXA around caesarean delivery and several systematic reviews/meta-analyses. Among the most informative syntheses, Simonazzi et al. included nine trials and 2,365 women, while Franchini et al. identified 18 randomized trials with 1,764 women receiving TXA and 1,793 controls. [1,2] A 2015 Cochrane review also included caesarean-delivery prevention trials and concluded that TXA reduced several bleeding outcomes but that evidence concerning serious adverse effects, mortality and thromboembolism remained limited. [3]

For established PPH, the evidence base was dominated by the WOMAN trial. It enrolled 20,060 women from 193 hospitals in 21 countries and included women after either vaginal or caesarean birth. [5] The trial was large enough to address death due to bleeding, a more patient-important outcome than changes in calculated blood loss alone.

Table 1. Key evidences

Study	Design / population	Main findings	Interpretive limitation
Simonazzi et al., 2016 [1]	Systematic review/meta-analysis; 9 RCTs; 2,365 caesarean-delivery participants	Lower blood loss and several bleeding outcomes with prophylactic TXA; no difference in thromboembolic events reported in pooled trials.	Small and heterogeneous trials; limited power for mortality and rare harms.
Franchini et al., 2018 [2]	Updated systematic review/meta-analysis; 18 RCTs; 3,557 women	Lower PPH thresholds and red-cell transfusion with prophylactic TXA; no specific safety concern identified in included trials.	Many studies small; definitions and regimens varied.
Novikova et al., 2015 [3]	Cochrane systematic review; prevention after vaginal or caesarean birth	Reduced blood loss and PPH in several comparisons; serious adverse outcomes remained uncertain.	Mixed populations and moderate methodological limitations.
WOMAN Trial, 2017 [5]	International double-blind RCT; 20,060 women with established PPH	Reduced death due to bleeding; greatest apparent benefit when treatment occurred early; no significant reduction in hysterectomy or composite death/hysterectomy.	Treatment trial was not a prophylaxis study; results should not be extrapolated directly to routine prophylaxis.

5.2 Prophylactic TXA in caesarean delivery

Across pre-2021 randomized trials and meta-analyses, prophylactic TXA generally reduced measured postpartum blood loss. The 2016 meta-analysis reported reductions in blood loss, haemoglobin decline, PPH and severe PPH, together with fewer additional uterotonic interventions and transfusions. [1] The 2018 updated analysis similarly reported lower risks of PPH above prespecified thresholds and red-cell transfusion. [2] The 2015 Cochrane review found a reduction in blood loss greater than 1,000 mL among caesarean-delivery participants, but emphasized uncertainty concerning serious adverse outcomes. [3]

These findings are biologically plausible and internally consistent for blood-loss outcomes, but the evidence was less definitive for mortality and other rare patient-important outcomes. Many individual studies were small, used different definitions of blood loss and PPH, varied in timing relative to surgery, and differed in the routine use of uterotonics. Consequently, a reduction in measured blood loss should not automatically be interpreted as proof of benefit from universal prophylaxis in every caesarean delivery.

Table 2. Prophylactic evidence synthesis

Outcome	Direction of pre-2021 evidence	Confidence / interpretation
Measured blood loss	Generally reduced with TXA	Consistent direction, but substantial clinical and methodological heterogeneity.
PPH / severe PPH	Generally reduced	Favorable pooled estimates; definitions differed across studies.
Haemoglobin decline	Generally reduced	Consistent with lower measured blood loss.
Blood transfusion	Often reduced	Potentially important, but many trials were underpowered for transfusion as a primary outcome.
Additional uterotonics	Often reduced	Secondary outcome; influenced by local management protocols.
Thromboembolic events	No clear increase identified in early pooled evidence	Rare outcome; individual studies and meta-analyses had limited power.

Maternal mortality	Insufficient evidence	Trials were not powered to establish mortality benefit from prophylaxis.

5.3 TXA for established postpartum haemorrhage

The treatment evidence was substantially stronger for a clinically important endpoint. In the WOMAN trial, 20,060 women with clinically diagnosed PPH were randomized to TXA or placebo in addition to usual care. Death due to bleeding was significantly lower in the TXA group than in the placebo group, with the clearest effect among women treated within three hours of birth. [5] The trial did not demonstrate a significant reduction in hysterectomy or the composite of death from any cause or hysterectomy. Adverse events, including thromboembolic events, did not differ significantly between groups. [5]

The importance of the WOMAN trial is that its principal benefit was demonstrated on mortality due to bleeding rather than solely on surrogate measures such as calculated blood loss. On the basis of this evidence, WHO issued a 2017 recommendation supporting early TXA as an adjunct to standard treatment for clinically diagnosed PPH after vaginal or caesarean birth. [6] This recommendation concerns treatment of an established haemorrhagic event and should not be interpreted as evidence that every woman undergoing caesarean delivery requires prophylactic TXA.

Table 3. Prophylaxis versus treatment: conceptual comparison

Characteristic	Prophylactic use at caesarean delivery	Treatment of established PPH
Clinical state	No established PPH at the time of intervention	Clinically diagnosed PPH is already present
Primary rationale	Reduce perioperative blood loss / prevent PPH	Reduce ongoing bleeding and bleeding-related mortality
Pre-2021 evidence base	Multiple small and medium randomized trials plus meta-analyses	Dominated by the large WOMAN randomized trial
Most consistent outcome	Lower measured blood loss	Lower death due to bleeding
Evidence limitations	Heterogeneity, small studies, variable outcome definitions, limited power for rare harms	Less uncertainty for mortality benefit; questions remain about optimal integration with different causes and settings of PPH
Interpretation	Evidence suggests efficacy for blood-loss reduction, but routine universal prophylaxis remained less certain	Strong evidence of benefit when used as part of treatment of established PPH, reflected in 2017 WHO guidance

6. Discussion

The principal finding of this review is that prophylactic and therapeutic TXA represent two different evidence questions. Pre-2021 prophylactic studies around caesarean delivery generally showed lower measured blood loss and fewer bleeding-related interventions. [1-4] However, most trials were not large enough to determine effects on maternal death or uncommon serious adverse events. The treatment literature, in contrast, included the exceptionally large WOMAN trial, which demonstrated a reduction in death due to bleeding among women with established PPH. [5]

The distinction is important because surrogate outcomes and patient-important outcomes are not equivalent. A reduction in calculated blood loss may be statistically robust while producing uncertain effects on transfusion, intensive care, surgery or mortality. The 2016 and 2018 prophylaxis syntheses nevertheless provide a consistent signal that TXA can reduce blood loss after caesarean delivery. [1,2] The Cochrane evidence available before 2021 similarly supported reductions in several bleeding outcomes but highlighted uncertainty regarding serious harms and mortality. [3]

Treatment evidence was more persuasive because the WOMAN trial was designed around clinically consequential outcomes and enrolled women with actual PPH. [5] The trial's finding of reduced death due to bleeding, particularly with early treatment, changed the evidence landscape and led WHO to update its PPH treatment recommendation in 2017. [6] Thus, by the end of 2020, the evidence for treatment of established PPH was more mature than the evidence for universal prophylaxis at caesarean delivery.

Safety deserves particular attention in obstetrics because pregnancy and the postpartum period are physiologically associated with increased thrombotic risk. Pre-2021 prophylactic meta-analyses did not identify a clear increase in thromboembolic events, but rare-event outcomes require very large samples to estimate precisely. [1-3] The WOMAN trial likewise did not show a significant difference in thromboembolic adverse events. [5] These observations are reassuring but should not be interpreted as proof that risk is absent in every clinical subgroup.

Another important limitation is heterogeneity. Studies differed in the definition of PPH, estimation of blood loss, timing of intervention, use of uterotonics, elective versus emergency caesarean delivery, and baseline haemorrhage risk. Such heterogeneity can produce apparently consistent pooled effects while masking differences in absolute benefit across populations. The largest clinical uncertainty at the end of 2020 therefore concerned not whether TXA could influence bleeding, but how large the patient-important benefit was in different caesarean populations and whether routine prophylaxis should be universal or targeted.

7. Strengths and Limitations

Strengths:

- Separates prevention from treatment rather than combining clinically different indications.
- Emphasizes patient-important outcomes alongside blood-loss surrogates.
- Uses major randomized evidence and pre-2021 systematic reviews as the principal evidence base.

Limitations:

- This manuscript uses a structured evidence synthesis; a formal database-level PRISMA count should be independently verified and documented before journal submission.
- Several prophylaxis trials were small and methodologically heterogeneous.
- Rare adverse outcomes and mortality were insufficiently powered in many prophylaxis studies.
- The treatment evidence includes vaginal and caesarean births and therefore cannot be interpreted as a caesarean-only trial.
- Evidence published after 31 December 2020 was deliberately excluded.

8. Conclusion

Evidence available before 2021 supports a clear distinction between prophylactic and therapeutic TXA in obstetric care. In caesarean delivery, prophylactic TXA was consistently associated with lower measured blood loss and, in several meta-analyses, lower frequencies of PPH and transfusion. [1-3] However, uncertainty remained regarding universal prophylaxis, mortality benefit and uncommon serious adverse effects. For established PPH, the WOMAN trial provided high-quality evidence of reduced death due to bleeding and became the principal evidence supporting international treatment recommendations. [5,6] Accordingly, the pre-2021 evidence base was stronger for TXA as an adjunct in established PPH than for routine universal prophylaxis at

caesarean delivery. Future research should prioritize patient-important outcomes, adequately powered safety analyses, high-risk populations and standardized definitions of blood loss and PPH.

9. Declarations

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Ethical approval: Not required because this is a systematic review of previously published literature and does not involve collection of identifiable participant data.

Data availability: All evidence discussed is derived from published literature cited in the reference list.

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