Review

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Tranexamic acid for the prevention and treatment of postpartum hemorrhage in resource-limited settings: a literature review

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Introduction: Postpartum haemorrhage is a major cause of maternal morbidity and mortality worldwide. Early recognition and appropriate treatment are crucial for managing postpartum haemorrhage.

Objectives: This literature review aimed to evaluate the efficacy of tranexamic acid in the prevention and treatment of postpartum haemorrhage in resource-limited settings.

Search methods: This literature review was conducted based on the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines. A computerized systematic search of the MEDLINE (PubMed), Google Scholar, and Cochrane databases using a combination of the following Medical Subject Headings (MeSH) terms for PubMed: [(obstetric haemorrhage OR postpartum haemorrhage OR massive obstetric haemorrhage) AND (tranexamic acid OR antifibrinolytic drugs) AND (prophylaxis OR prevention) AND (management OR treatment) AND (resource-limited settings OR resource-limited area OR developing countries)] to find articles published in English since 2010.

Selection criteria: Studies on the obstetric population who underwent vaginal or caesarean delivery, comparing the use of tranexamic acid versus placebo (or no treatment) for treatment (or prevention) of postpartum haemorrhage with the outcome of postpartum haemorrhage rate, blood transfusion requirements, uterotonics requirements, hysterectomy, or mortality were included.

Result: In total, 5315 articles were identified. Following the elimination of duplicates, the methodological quality of 15 studies was evaluated independently, with eligibility determined based on the inclusion and exclusion criteria, as well as outcome variables. Finally, eight articles were included in the review.

Conclusion: This review provides evidence that the administration of tranexamic acid has the potential to decrease the need for blood transfusion, incidence of postpartum haemorrhage, demand for supplementary uterotonics, and maternal morbidity and mortality with marginal adverse effects. Healthcare systems must develop and implement interventions that involve the use of tranexamic acid for the treatment of postpartum haemorrhage in resource-limited settings.

Keywords: blood transfusion, tranexamic acid, postpartum haemorrhage, resource-limited setting

Introduction

Obstetric haemorrhage is a major cause of maternal morbidity and mortality worldwide. Postpartum haemorrhage (PPH) accounts for 72% of all cases[1]. The global incidence of PPH (> 500 ml) and severe PPH (> 1000 ml) is reported to be ~ 6.6% and 1.86%, respectively. Notably, Africa has higher rates of PPH (10.45%) than other regions, with rural areas experiencing a higher incidence than urban areas[2]. Postpartum haemorrhage is responsible for 27.1% of all maternal deaths globally, with varying rates across regions. Low-income countries and those with limited resources report a higher proportion of maternal deaths resulting from PPH (36.9%) than high-income countries (16.3%)[1]. This discrepancy can be attributed to the higher prevalence of PPH and inadequate healthcare in regions with limited resources[1,2].

Prompt recognition of postpartum haemorrhage is crucial to improve patient outcomes, ensure timely intervention, and ensure

HIGHLIGHTS

- Postpartum haemorrhage is the leading causes of maternal morbidity-mortality in the world, especially in developing countries.
- Tranexamic acid is one of the most commonly used antifibrinolytic agents in various non-obstetric surgeries.
- Tranexamic acid offers a promising option for preventing and managing postpartum haemorrhage in resource-limited settings, potentially improving maternal outcomes.

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optimal teamwork. Various medical and surgical treatments are available for managing PPH, including resuscitation with blood products and circulatory support in the intensive care unit. However, in resource-limited settings, it is challenging to perform these interventions and establish a favourable environment for their implementation[3,4]. This is particularly true in cases of poverty, socioeconomic disadvantages in the community, weak healthcare systems, and geographical barriers that impede access to medical facilities[5,6]. Therefore, it is vital to establish safe, low-cost, and easily accessible techniques for preventing and treating significant PPH[7,8].

Several investigations have established a significant association between activation of the fibrinolytic pathway and the development of severe haemorrhage in various medical conditions, including trauma, heart disease, orthopaedic surgery, and obstetrics[9]. Therefore, the use of tranexamic acid, a synthetic lysine-analogue antifibrinolytic agent, is widely acknowledged and employed in non-obstetric surgical procedures. The mechanism of action of this medication involves competitive inhibition of plasminogen activation and non-competitive blocking of plasmin at high concentrations. Extensive literature has documented its potential to enhance patients' haemostatic mechanisms and their clinical effects in medical and surgical situations[9,10].

Several clinical trials have explored the efficacy of tranexamic acid in obstetric settings. It is noteworthy that this drug is safe to use during pregnancy and breastfeeding and can significantly reduce maternal morbidity and mortality[9,10]. It has been demonstrated to decrease the use of blood products, the requirement for uterotonic agents, the need for hysterectomy, and the risk of severe anaemia. Furthermore, reports indicate that TXA is likely to be cost-effective and available at a low cost. Nevertheless, the optimal and most effective doses, infusion rate, time of administration, and adverse events of prophylactic use of TXA vary in different studies[11–13].

Therefore, it is of utmost importance to carry out a comprehensive review of the literature regarding the efficacy of tranexamic acid therapy as a prophylaxis and treatment for postpartum haemorrhage; to demonstrate that the conclusions drawn may have a greater impact when applied to resource-limited settings. The main aim of this literature review was to enhance the quality of care provided to women and reduce maternal mortality due to postpartum haemorrhage. Our primary focus was to evaluate the effectiveness of tranexamic acid in the prevention and treatment of PPH, determine the optimal dosages, and evaluate potential adverse events.

Objectives

This literature review aimed to evaluate the efficacy of tranexamic acid in the prevention and treatment of postpartum haemorrhage in resource-limited settings.

Methods and materials

This literature review followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) 2020 statement (https://www.sciencedirect.com/science/article/pii/S1743919121000406?via%3Dihub)[14]. This review included randomized controlled trials and non-randomized studies on the effects of TXA in the prevention and treatment of postpartum haemorrhage.

Literature search strategies

A comprehensive and rigorous systematic investigation was performed using electronic databases, such as MEDLINE (PubMed), Google Scholar, and Cochrane, to identify studies published in English between 2010 and 2022. The search methodology was designed to explore all the available published and unpublished studies. A comprehensive exploration was carried out in PubMed/Medline utilizing a combination of Mesh Terms, such as [(obstetric haemorrhage OR postpartum haemorrhage OR massive obstetric haemorrhage) AND (tranexamic acid OR antifibrinolytic drugs) AND (prophylaxis OR prevention) AND (treatment OR management) AND (resource-limited settings OR resource-limited area OR developing countries)], to discover relevant information on the topic of interest.

Eligibility criteria

Population

Randomized controlled trials (RCTs) and non-randomized studies on obstetric patients who underwent vaginal or caesarean delivery were included. We excluded review articles, case reports, repeated publications, and articles with no available data.

Intervention

We considered interventions comparing the use of tranexamic acid with placebo (or no treatment) to treat (or prevent) postpartum haemorrhage. Studies that failed to mention the dose or time of intervention were excluded from our analysis.

Outcomes

The included studies had to use clinical outcomes that specifically related to the postpartum haemorrhage rate, blood transfusion requirements, uterotonics requirements, hysterectomy, or mortality. The selected studies were published in English from 2010 onwards. The primary outcome measure was the incidence of PPH, whereas the secondary outcomes included the need for blood transfusion, uterotonic agents, hysterectomy, mortality, and overall severe side effects related to TXA.

Data extraction

Data were extracted by two independent evaluators using an adjusted Excel spreadsheet. Any conflicting data were resolved through mutual agreement. The gathered information included patient age, country/study area, sample size, study design, year of publication, outcomes, complications, type of anaesthesia, and duration of surgery. If pertinent details were ambiguous, the authors of the reports were contacted for further clarification.

Critical appraisal

The appraisal of possible bias was performed using the Cochrane risk-of-bias assessment tool for randomized controlled trials (RCTs) and the ROBIN tool for assessing the risk of bias in non-randomized studies[15,16]. The methodological quality of each RCT was evaluated using the Risk-of-Bias (ROB) tool, which consists of several components, such as selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete

outcome data), reporting bias (selective reporting), and other biases (any other bias, ideally pre-specified). Each study included in the analysis was independently evaluated by two reviewers using a standardized tool. The reviewers recorded judgments of bias risk for each domain (low, high, and some concerns) along with supporting information and justifications. Disagreements in judgment or justification were resolved through discussion with a third reviewer, who acted as an arbiter when necessary. For each specific outcome, a comprehensive 'Risk of Bias' judgment was derived, which categorized it as low, with some concerns, or high. The overall RoB level for each study was based on the highest RoB level found in any of the evaluated domains. A summary of these assessments is provided in (Table 1). According to the AMSTAR 2 criteria[24], the quality of our systematic review is moderate.

Result

This comprehensive search strategy facilitated identification of 5315 articles from different electronic databases. After rigorous screening, 5295 duplicate and unrelated records were identified and excluded. After a thorough examination of the abstracts and titles, we excluded five articles based on our pre-established criteria, leaving 15 articles for an in-depth review. Using EndNote, we analyzed the complete texts and eliminated five more articles, while two were insufficient in terms of data and were excluded. Finally, eight articles were included in the literature review. A PRISMA flowchart (Fig. 1) graphically depicts this process. A summary of the studies included in this review is presented in (Table 2).

Discussion

Postpartum haemorrhage and the consequent requirement for blood transfusions have a profound impact on morbidity and mortality rates worldwide, particularly in developing nations. To minimize this impact, it is vital to conduct a targeted risk assessment prior to delivery, utilize preventive strategies, and promptly provide treatment in settings with limited resources. Available evidence suggests that immediate administration of tranexamic acid after the onset of postpartum haemorrhage is advantageous[11,25–27].

Effectiveness of Tranexamic Acid for PPH Prevention

A review determined that the administration of intravenous TXA during either caesarean section or vaginal delivery reduces blood loss and the need for blood transfusions, thereby reducing the occurrence of PPH and severe PPH. The use of TXA has been demonstrated to significantly decrease total blood loss by 80.1 and 71.5 ml for CS and VD, respectively, as shown in two trials conducted by Cochrane. However, it is worth noting that these trials may have been affected by selection, performance, and detection biases[28].

The TRAAP study, a multicenter, double-blind trial, was conducted to evaluate the efficacy of Tranexamic Acid in preventing postpartum haemorrhage in women who underwent planned vaginal delivery and were at a risk of PPH. The trial involved 3891 participants, and the results indicated that prophylactic administration of TXA 1 g reduced the incidence of PPH by 32% and decreased the need for uterotonics compared

Table 1

The table displays for each included study the risk-of-bias judgment for each of six domains of bias, and for the overall risk of bias.

	Selection bias							
References	Random sequence generation bias	Allocation Concealment bias	Performance bias (blinding of participants and personnel)	Detection bias (blinding of outcomes)	Attrition bias (incomplete outcome)	Reporting bias (selective reporting)	Other bias	Overall ROB
Sentilhes *et al.*[17]	0	0	0	0	0	0	0	0
Fahmy *et al.*[18]	0	0	0	0	0	0	0	0
Sentilhes *et al.*[19]	0	0	0	0	0	0	0	0
Naghavi-Behzad *et al.*[20]	0	0	0	0	0	0	0	0
Ducloy-Bouthors *et al.*[21]	0	0	0	0	0	0	0	0
Shakur *et al.*[10]	0	0	0	0	0	0	0	0
Li *et al.*[22]	1	1	0	0	0	0		1
Ducloy-Bouthors *et al.*[23]	0	0	0	0	0	1	0	0

ROB, Risk of Bias; (0, low risk; 2, high risk; 1, some concerns; U, uncertain).

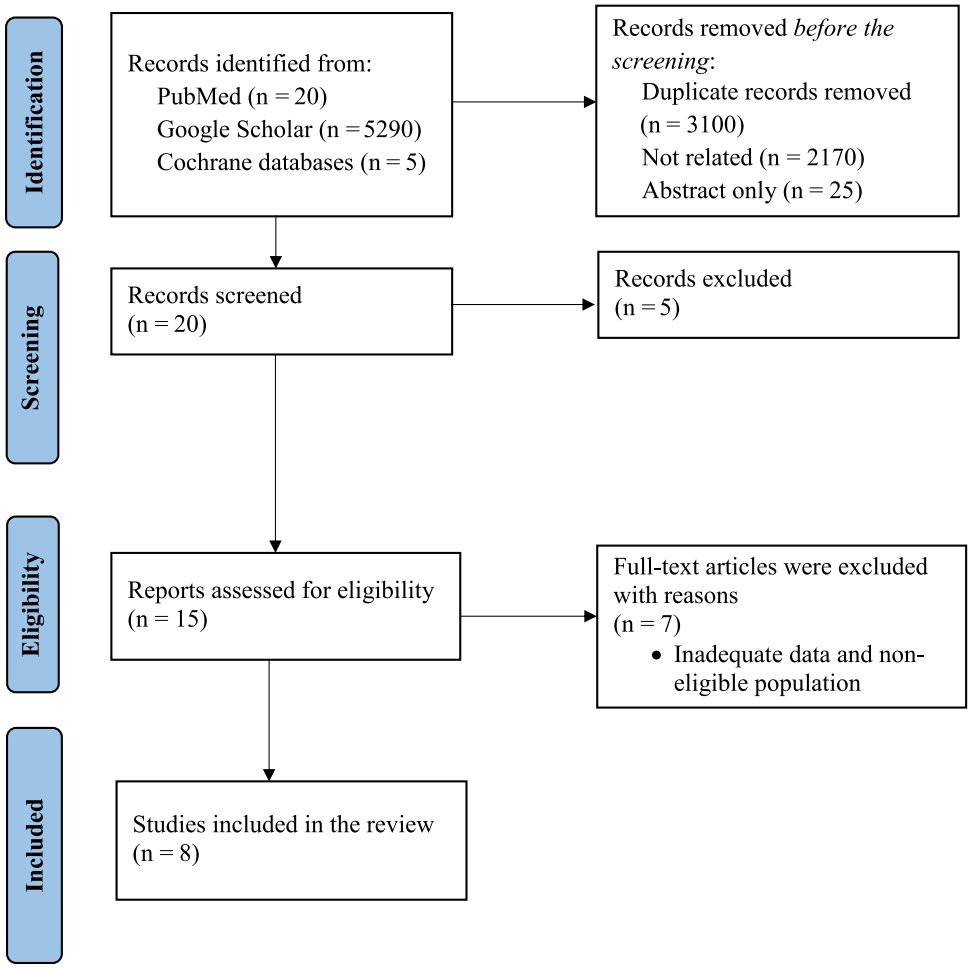

Figure 1. Flowchart for selection of studies by PRISMA flow diagram. Sources: adapted from[38].

with placebo. However, no significant difference was observed in the degree of postpartum haemorrhage (> 500 ml). Notably, this study included a substantial population with risk factors for PPH. Nevertheless, the haemoglobin level and haematocrit results obtained from routine prenatal care may pose potential concerns as the timing of sample collection was not standardized[17].

A further randomized controlled trial was conducted to investigate the efficacy of prophylactic tranexamic acid in reducing blood loss, both during and after lower-segment CS. These findings are comparable to those of the TRAAP trial[17]. Results indicated that there was a significant reduction in blood loss among those who were administered with TXA (416.12 ± 89.95 vs. 688.68 ± 134.77) in comparison to the control group. The amount of blood loss was estimated by utilizing preoperative and 24-hour postoperative haematocrit values, thus minimizing the possibility of either overestimation or underestimation. The study group was administered a fixed-dose strategy of 2 g TXA, regardless of body weight. However, it is important to note that the study did not evaluate the incidence of severe PPH (exceeding 1000 ml of blood) or significant complications such as severe thromboembolic events, seizures, and the need for blood transfusion[18].

A meta-analysis of high-quality studies with minimal bias and large populations of women undergoing caesarean section demonstrated that prophylactic administration of TXA significantly reduced postpartum haemorrhage, which is consistent with the results of previous trials[17,18]. The analysis revealed a relative risk of 0.40 (95% CI:0.24–0.65), including severe PPH, total blood loss, and transfusion requirements. However, the systematic review is constrained by certain limitations, such as heterogeneity across study designs, the variation among different definitions of PPH (blood loss > 400 or > 500 ml), and postpartum blood loss assessment (2 h, 24 h, or 48 h postpartum)[29].

A systematic review and meta-analysis, with congruent outcomes, demonstrated that the utilization of tranexamic acid leads to a reduction in intraoperative, postoperative, and overall blood loss by an average of 141.25 mm in patients undergoing CS or VD[9], which is comparable to the results obtained from clinical trials[17,18,28]. These findings are supported by another study that revealed that TXA reduced the requirement for additional uterotonic agents compared to the control group, with a rate of (4.2% vs. 7.3%)[30]. In contrast, Misoprostol does not demonstrate any specific preference for TXA[20].

The studies concluded that prophylactic administration of tranexamic acid during both CS and VD has been observed to have a positive impact on the reduction of blood loss and the need for blood transfusions. However, it is important to note that these findings are limited by heterogeneity across study designs and

Table 2

Summary of included studies in the review

S.N	Authors with citation	Publication year	Country	Sample size	Design	Intervention modality (prevention or treatment)	Main findings
1	Sentilhes *et al.*[17]	2018	France	4079	RCT	Prophylactic administration of (1 g tranexamic acid or placebo) for the Prevention of Blood Loss after Vaginal Delivery	Prophylactic use of tranexamic acid was a significantly lower rate of postpartum haemorrhage than the placebo.
2	Fahmy *et al.*[18]	2020	Egypt	100	RCT	Assessment of the role of tranexamic acid in the prevention of postpartum haemorrhage (TXA 2 g vs. control group)	Prophylactic administration of tranexamic acid reduces intraoperative and postoperative bleeding and the incidence of postpartum haemorrhage in caesarean section.
3	Sentilhes *et al.*[19]	2021	France	4551	RCT	Effect of Tranexamic Acid for the Prevention of Blood Loss after Caesarean Delivery (TXA (1 g) VS. placebo)	Tranexamic acid treatment resulted in a significantly lower incidence of calculated estimated blood loss greater than 1000 ml or red-cell transfusion.
4	Naghavi-Behzad *et al.*[20]	2014		200	RCT	Comparison effect of intravenous tranexamic acid and misoprostol for postpartum haemorrhage (TXA vs. Misoprostol)	No significant differences between the two groups in haemorrhage during labour.
5	Ducloy-Bouthors *et al.*[21]	2011	France	144	RCT	Effects of High-dose tranexamic acid on blood loss in postpartum haemorrhage (TXA (loading dose 4 g over 1 h, infusion of 1 g/h. over 6 hours) vs. control)	High-dose TXA reduces blood loss and maternal morbidity in women with PPH.
6	Shakur *et al.*[10]	2017	UK	20,060	RCT	Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with postpartum haemorrhage (TXA 1g vs. placebo)	TXA reduces death due to bleeding in women with PPH with no adverse effects.
7	Li *et al.*[22]	2021	USA	30	RCT	Population pharmacokinetics and pharmacodynamics of Tranexamic acid in women undergoing caesarean delivery (5, 10, or 15 mg/kg of TXA)	Suggests that a 650 mg dose provides adequate PPH prophylaxis for up to 1 hour, which is less than the currently used 1000 mg of TXA in pregnant women.
8	Ducloy-Bouthors *et al.*[23]	2022	France	45 each	RCT	Tranexamic acid dose-response relationship for antifibrinolytics in postpartum haemorrhage during Caesarean delivery (placebo vs. TXA 0.5 g vs. TXA 1 g)	Fibrinolytic activation was significantly inhibited by a dose of intravenous tranexamic acid 1 g but not 0.5 g.

RCT, randomized controlled trials; ROB, risk of bias; TXA, tranexamic acid.

variations between different definitions of PPH and postpartum blood loss assessments[9,17,18,28–30]. Based on the findings, we suggest the prophylactic use of TXA during both CS and VD for women who are at a heightened risk of PPH, particularly in settings with limited resources.

Effectiveness of Tranexamic Acid for PPH Treatment

Tranexamic acid has demonstrated efficacy in reducing bleeding-related mortality in PPH treatment. This effect was more pronounced when the medication was promptly administered after delivery. An open-label, multicenter RCT (EXADELI) involving 144 women who utilized high-dose TXA (4 g administered within the first hour and maintained at 1 g/h over the subsequent 6 h) revealed a significant reduction in blood loss with TXA treatment. Additionally, treatment led to a shorter duration of bleeding and decreased the progression of severe PPH. However, this study was not sufficiently powered to adequately address safety concerns[21].

Similarly, the WOMAN trial study, which involved a significantly large sample size, also reported a significant reduction in mortality rates resulting from bleeding in females who received TXA treatment, particularly among those treated within three hours post-delivery (1.2% vs. 1.7%)[10]. Consistent with the aforementioned trial, both the CRASH-2 and WOMAN trials demonstrated that immediate administration of TXA was associated with a survival benefit exceeding 70% (OR = 1.72). Nonetheless, the treatment advantage declines by 10% with every additional 15-minute delay in treatment, emphasizing that no treatment gain is noticeable when TXA is administered more than three hours after delivery[25]. Moreover, Shakur's systematic review concluded that the primary PPH mortality rate can be reduced by 19% through immediate administration of intravenous TXA following the onset of bleeding[31].

The available studies concluded that the administration of TXA within three hours of delivery results in a significant reduction in both blood loss and mortality rates. Delayed treatment, on the other hand, reduces treatment gains and no noticeable benefit is observed after 3 h[10,21,25,31]. Therefore, we suggest using TXA as an early intervention for the management of postpartum haemorrhage in resource-limited settings, along with other medical and surgical treatments. However, there are concerns about the feasibility and acceptability of this approach.

Effective dose of Tranexamic Acid

The dose of TXA used for the prophylaxis and treatment of PPH varies in different clinical trials. Li *et al*. conducted a clinical trial to assess the efficacy of TXA by targeting a plasma concentration of 10 mg/l, which resulted in a reduction of maximal fibrinolysis from 100% to 17%. However, this study has certain limitations. Notably, the trial failed to consider the effect of the high variability of fibrinolytic activation on PPH. A target plasma TXA concentration of 10 mg/l was established based on an in vitro model that did not account for body weight as a co-variable; the 15 mg/kg dose was limited to a maximum total dose of 1 g, and urine samples were not collected, thereby impeding validation of excreted concentrations[22].

In the TRACES biomarker investigation carried out by Ducloy-Bouthors and colleagues, 151 patients who underwent haemorrhagic CS were randomly assigned to one of three groups: receiving placebo (0.5 g) or 1 g of TXA. The primary outcome of the study was the difference in plasma D-dimer level increase over the baseline during the 120 min following the initiation of infusion compared to the placebo group. The study findings revealed that the dose of TXA 1 g was associated with lesser increases over baseline (D-dimer:38%; $P < 0.003$) compared to placebo. Additionally, the dose of 0.5 g was observed to be less potent, with non-significant reductions (D-dimer:58%; $P = 0.06$) compared to placebo[23].

The investigation provides evidence to advocate for the administration of a 1 g dosage of TXA, with repeated dosages as necessary in cases of severe haemorrhage and excessive fibrinolysis. It has been proposed that this amount is the minimum required to impede the hyperfibrinolysis triggered by PPH. Despite the quality of the study design, there were limitations. Specifically, the sample size of 175 patients was deemed insufficient to establish the clinical effectiveness of TXA[23].

The EXADELI study, a multicenter open-label randomized controlled trial, demonstrated that administering a high dose of TXA 4 g at the onset of PPH was clinically effective[21]. Conversely, in patients with trauma-induced hemodynamic decompensation, the administration of a repeated dose of TXA at 3 g within an hour has been found to significantly reduce 30-day mortality compared with placebo. However, the use of 4 g TXA has been associated with a potential risk of seizures, venous thrombotic events, and suspected kidney injury. Prehospital administration of TXA at 1 or 2 g was not effective[32].

The administration of TXA for PPH prophylaxis should be performed within 10–20 min before skin incision or spinal anesthesia. An alternative to this approach could be administration at the time of the umbilical cord clamp, thereby avoiding placental transfer of medication[33]. The inefficacy of TXA administration 3 hours after PPH was revealed in the WOMAN trial[10]. ALT-IT Trial Collaborators elaborated on the optimal time frame characterized by the absence of TXA's effect on delayed plasminogen activation attributed to the urokinase-plasminogen activator as well as the competitive mode of action of TXA on alpha-2 plasmin inhibitors. This mechanism further underscores the ineffectiveness of low-dose TXA[34]. International recommendations recommend the use of TXA at a predetermined quantity of 1 g in 10 ml IV within 3 h of PPH onset. Additionally, if bleeding continues for 30 min or recurs within 24 h of the first dose, a second dose of 1 g IV should be administered[35]. Nevertheless, no published data are available on the measured serum levels in the pregnant population after intravenous administration of TXA.

Adverse events associated with Tranexamic Acid

This review also addressed the deleterious effects of TXA. Pregnancy is a state of hypercoagulability and, as such, inherently carries the risk of thromboembolism. The use of TXA to prevent PPH can theoretically increase the risk of thromboembolism. However, the earliest in vitro studies of TXA and its impact on clot formation using thromboelastometry demonstrated that the addition of TXA at therapeutic levels greater than ten-fold in blood from pregnant women before delivery does not increase the hypercoagulable profile[36]. Furthermore, recent studies assessing TXA for prophylaxis and treatment of haemorrhage suggest that there is no association between the use of TXA and an increased risk of venous thromboembolism[9,10,17]. Nonetheless, a recent RCT study found higher rates of thromboembolic events in the

three months following delivery among women who received tranexamic acid than among those who received placebo (0.4% vs. 0.1%; adjusted risk ratio = 4.01; $P = 0.08$). This finding may be attributable to higher doses and longer duration of therapy; therefore, caution should be to exercised[19].

The most frequently reported adverse effects are nausea and vomiting. Adverse gastrointestinal effects and seizures have been reported at escalated doses. According to a meta-analysis, the frequency of nausea and/or vomiting was greater in the TXA group (RR, 2.17) than in the control group, although no significant difference in the incidence of dizziness and photopia was observed[37]. Another study indicated that nausea and vomiting were more prevalent in the TXA group than in the placebo group (7.0% vs. 3.2%)[17].

Strengths and limitations

This review included high-quality randomized controlled trials with a substantial number of participants, predominantly published in recent years. This review highlights the strengths of this study. However, certain limitations, such as the constraints imposed on the publication year and language, the methodology employed for assessing blood loss differences across studies, dissimilarities in the study population, surgical experience, patient costs, and implementation of the study, were not elucidated. Despite the review's objective of demonstrating the efficacy of the intervention in areas with limited resources, the majority of the available studies originated from high-income countries. Moreover, our review revealed inadequate information on the safety, feasibility, acceptability, and effectiveness of TXA at lower and often resource-limited levels of care.

Conclusion

This review concluded that the use of tranexamic acid has the potential to reduce the need for blood product transfusion, lower the incidence of postpartum haemorrhage, decrease the requirement for supplementary uterotonics, and lower rates of maternal morbidity and mortality. In resource-limited settings, this cost-effective and easily accessible tool holds substantial promise for achieving positive outcomes. It is important to note that gastrointestinal complications and seizures are the most commonly reported adverse effects. Therefore, caution must be exercised when considering higher doses and prolonged therapy, particularly because of the heightened risk of venous thromboembolism. In addition, healthcare systems must plan and implement interventions involving tranexamic acid for the management of postpartum haemorrhage in resource-limited settings.

Ethical approval

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Consent

None.

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Author contribution

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Data availability

Up on request from the corresponding author.

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