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TRANEXAMIC ACID FOR THE PREVENTION AND THE TREATMENT OF PRIMARY POSTPARTUM HAEMORRHAGE : SYSTEMATIC REVIEW

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ABSTRACT

Despite the fact that the majority of fatalities occur in the former two groups, postpartum hemorrhage remains a leading cause of maternal mortality in both high-income and low- and middle-income nations. Uterine atony, lacerations, retained placenta or clots, and a lack of clotting factors are the most prevalent causes of postpartum bleeding. The principal treatments for this disease are uterine massage, oxytocin, and methylergonovine, as well as blood transfusions and cardiovascular support. Tranexamic acid, sometimes known as TXA, is an antifibrinolytic medication that is commonly used in the treatment and prevention of bleeding. TXA is used to treat a wide range of disorders, including severe menstrual bleeding, trauma, postpartum hemorrhage, traumatic brain injury, and surgical site bleeding. Despite having been used for several decades and a large body of research, TXA is still viewed with suspicion in many therapeutic settings. The study found that the difference in postpartum hemorrhage, mortality, and adverse effects between those who got tranexamic acid and those who received a placebo was not statistically significant. Nonetheless, studies demonstrate that tranexamic acid can help reduce postpartum bleeding.

KEYWORD: *Bleeding; Mortality rate; Postpartum haemorrhage; Tranexamic acid*

INTRODUCTION

The World Health Organization (WHO) estimates that up to 830 mothers die every day around the world, with 38 mothers dying in Indonesia due to diseases/complications related to pregnancy and childbirth. The majority of these deaths could have been avoided and saved. The rising maternal mortality rate demonstrates that many mothers should not have died, but did so because they did not receive adequate prevention and treatment.[1] The most common cause of maternal death around the world is a condition called postpartum hemorrhage.[2]

It is estimated that hemorrhage was the cause of around 27 percent of all maternal deaths that occurred in the world.[2] The majority of deaths occur during the first 2-3 hours of giving birth, and almost all (99%) occur in low- and middle-income nations, with Sub-Saharan Africa accounting for the bulk.[3] This indicates that a woman dies from postpartum hemorrhage somewhere in the world every six minutes on average. Postpartum hemorrhage is a primary cause of maternal mortality in both high-income countries and low- and middle-income countries, despite the fact that the majority of deaths occur in the former two categories.[4]

The most common reasons for postpartum bleeding include uterine atony, lacerations, retained placenta or clots, and a deficit in clotting factors. The primary therapies for this condition are uterine massage, oxytocin, and methylergonovine, in addition to blood transfusions and support for the cardiovascular system.[5] Infusion rates of oxytocin can be increased, early administration of tranexamic acid can be given, directing transfusions with point-of-care diagnostics can be done, and cell salvage can be used. These treatments have all been shown to be successful. It is important to develop protocols and checklists within the framework of systems in order to foster good communication amongst teams.[6]

Biomarkers of fibrinolysis known as D-dimers are found in higher concentrations in the blood of women who have experienced postpartum hemorrhage.[7] Although postpartum bleeding can be treated using established medical and surgical procedures, tranexamic acid offers an alternative method to support haemostasis by suppressing the enzymatic action of plasmin on fibrin. This helps to support the body's natural ability to stop bleeding. Because tranexamic acid is able to lessen the amount of blood lost after surgery, it was obvious that this medication had the potential to improve the prognosis for patients suffering from postpartum hemorrhage.[8,9]

Tranexamic acid, often known as TXA, is an antifibrinolytic drug that is frequently employed in the treatment of bleeding as well as its prophylaxis. TXA is used to treat a wide variety of conditions, some of which are severe menstrual bleeding, trauma, postpartum hemorrhage, traumatic brain injury, and bleeding at the surgical site. TXA is still met with skepticism in many therapeutic settings, despite having been utilized for several decades and a sizable body of data.[9,10] This article investigate benefit of tranexamic acid for prevention and treatment of primary postpartum haemorrhage.

METHODS

Protocol

This review adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards. These items constituted the basis for the regulations.

Eligibility Criteria

This systematic review was developed to assess literature on “tranexamic acid” and “primary postpartum haemorrhage”. These are the subjects that were thoroughly covered in the study under consideration. The following conditions must be met in order for your work to be taken into consideration: 1) In order to be accepted, articles must be written in English about benefit of tranexamic acid for primary postpartum haemorrhage. 2) In order to be considered, the articles had to have been published after 2017, but before this systematic review was created. The following types of textual entries will not be considered for inclusion in the anthology: 1) Editorial letters, 2) submissions without a Digital Object Identifier (DOI), and 3) article reviews and submissions equivalent to those previously published in the journal.

Search Strategy

The search for studies to be included in the systematic review was carried out from December, 20nd 2022 using the PubMed and SagePub databases by inputting the words: “tranexamic acid” and “primary postpartum haemorrhage”. Where ("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields]) AND ("postpartum hemorrhage"[MeSH Terms] OR ("postpartum"[All Fields] AND "hemorrhage"[All Fields]) OR "postpartum hemorrhage"[All Fields] OR ("primary"[All Fields] AND "postpartum"[All Fields] AND "haemorrhage"[All Fields]) OR "primary postpartum haemorrhage"[All Fields]) is used as search keywords.

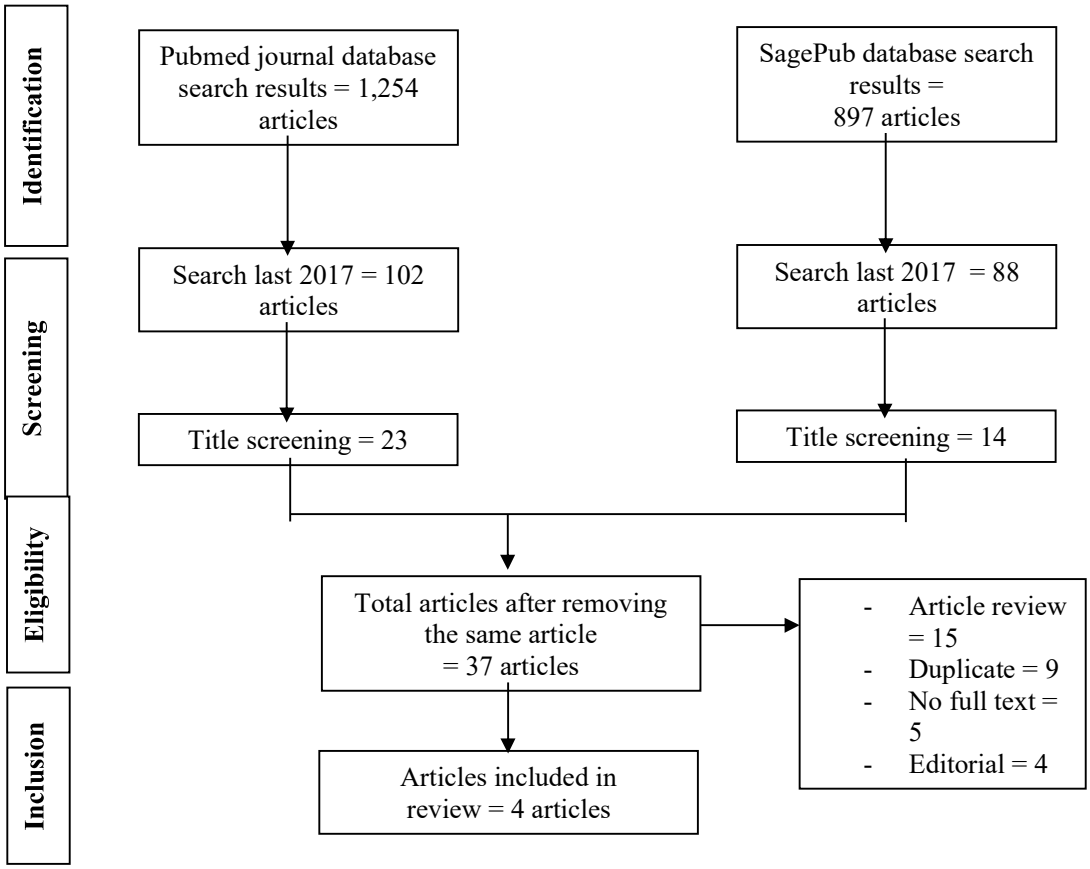

Figure 1. Article search flowchart

Data retrieval

After doing a literature analysis and examining titles and abstracts of previously published research, the author of the study revised the inclusion and exclusion criteria. The amended criteria can be found in the study's supplementary materials. This was done to limit the problem's scope and determine which areas required additional examination. The author reached this result after evaluating previously conducted and published studies with similar findings. During the process of creating the systematic review, it was concluded that only studies that met all inclusion criteria should be included.

This meant that only research proposals that met all of the standards would be considered. This was done so that the evaluation could be as comprehensive as possible. The objective was to collect information about each study, including its title, author, publication date, study site of origin, research study design, and research parameters. This type of information is obtainable. The following are examples of possible sources of information: This information can be presented to you in a number of different ways, depending on the desired presentation style.

Quality Assessment and Data Synthesis

To determine which publications should be reviewed, the writers conducted independent assessments of a subset of the research presented in the titles and abstracts of the articles. Then, the full texts of the papers that meet the systematic review's inclusion criteria will be assessed to determine which publications will be included in the review. This is done in response to the question, "Which studies are eligible for inclusion in the review?"

RESULT

Hemorrhaging that occurs during pregnancy is the leading cause of death among mothers all over the world. The use of pharmacological agents (such as tranexamic acid) and clotting factor concentrates (such as fibrinogen concentrates and prothrombin complex concentrates), in addition to adequate surgical control and the judicious transfusion of blood products, results in improved hemostasis and decreased bleeding-associated mortality. This is the case even when these

interventions are combined. It is possible that in the not-too-distant future, standard of care will call for guidance in the administration of these agents through the utilization of viscoelastic testing.[11]

Tranexamic acid, often known as TXA, is a fibrinolytic antagonist. It prevents plasmin activation by binding to lysine residues in plasminogen and plasmin, which are found in both proteins. TXA has a short half-life of only two hours and is removed by the kidneys; hence, it should not be used in patients who have renal failure.[11] WOMAC trial showed death due to bleeding was significantly reduced in women given tranexamic acid (155 [1,5%] of 10 036 patients vs 191 [1,9%] of 9985 in the placebo group, risk ratio [RR] 0,81, 95% CI = 0,65-1,00; p = 0,045), especially in women given treatment within 3 h of giving birth (89 [1,2%] in the tranexamic acid group vs 127 [1,7%] in the placebo group, RR 0,69, 95% CI = 0,52-0,91; p = 0,008). All other causes of death did not differ significantly across groups.[12]

Tranexamic acid did not reduce hysterectomy (358 [36%] tranexamic acid patients versus 351 [35%] placebo patients, RR 102, 95% confidence interval [CI] = 0,88-1,07; p = 084). Tranexamic acid had no impact on the composite primary endpoint of death from any cause or hysterectomy (534 deaths or hysterectomies in the tranexamic acid group versus 546 fatalities or hysterectomies in the placebo group, RR 097, 95% CI 087-109; p=065). The tranexamic acid and placebo groups did not have significantly different adverse effects (including thromboembolic events).[12]

Shakur-Still *et al* (2018)[13] study showed mean (SD) D-dimer concentration in TXA-treated women was 7.1 (7.0) mg/l and 9.6 (8.6) mg/l in placebo-treated women (p=0.09). After correcting for baseline, the D-dimer concentration in TXA-treated women was 2.16 mg/l lower (-2.16, 95% CI = -4.31 to 0.00, p=0.05). There was no statistically significant change in ML between TXA- and placebo-treated women (12.3% (18.4) and 10.7% (12.6), respectively; p=0.52), and no difference after controlling for baseline maximum clot lysis (ML) (1.02, 95% CI = -3.72 to 5.77, p=0.67). TXA had no significant influence on any other metrics.

Other study showed primary outcome happened in 556 out of 2086 women (26.7%) in the group that was given tranexamic acid, and it occurred in 653 out of 2067 women (31.6%) in the group that was given a placebo (adjusted risk ratio [RR] = 0.84; 95% CI = 0.75-0.94; P = 0.003). There were no significant differences between the groups when it came to mean estimated blood loss, additional uterotonic agents or postpartum blood transfusions, or amount of clinically significant postpartum hemorrhage that was assessed by the provider. In the three months following delivery, thromboembolic events occurred in 0.4% who were given tranexamic acid, compared to 0.1% who were given a placebo (adjusted risk ratio, 4.01; 95% CI = 0.85-18.92; P = 0.08).[14]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Dose	Result
WOMAC Trial collaboration, 2017[12]	Multinational (21 counties)	Randomised, double-blind, placebo-controlled trial	20,060 woman	1 gr	Death due to bleeding was significantly reduced in women given tranexamic acid (155 [1,5%] of 10 036 patients vs 191 [1,9%] of 9985 in the placebo group, risk ratio [RR] 0,81, 95% CI = 0,65-1,00; p = 0,045), especially in women given treatment within 3 h of giving birth (89 [1,2%] in the tranexamic acid group vs 127 [1,7%] in the placebo group, RR 0,69, 95% CI = 0,52-0,91; p = 0,008). All other causes of mortality were not statistically different across groups. Tranexamic acid did not reduce hysterectomy (358 [36%] patients in the tranexamic acid group versus 351 [35%] in the placebo group, RR 102, 95% CI = 0,88-1,07; p = 084). Tranexamic acid had no effect on the composite primary endpoint of death from any cause or hysterectomy (534 [53%] fatalities or hysterectomies in the tranexamic acid group versus 546 [55%] in the placebo group, RR 097, 95% CI 087-109; p=065). Adverse events (including thromboembolic events) were not substantially different between the tranexamic acid and placebo groups.
Shakur-Still, 2018[13]	Multinational (UK, Nigeria, Albania, Germany)	Randomised, double-blind, placebo-controlled trial	167 woman	1 gr	The mean (SD) level of D-dimer in women who took TXA was 7.1 mg/l, while the level in women who took a placebo was 9.6 mg/l (p=0.09). After adjusting for baseline, the D-dimer concentration was 2.16 mg/l lower in women who were given TXA (-2.16, 95% CI = -4.31 to 0.00, p=0.05). There was no significant difference in ML between women who were given TXA or a placebo (12.3% (18.4) and 10.7% (12.6), respectively; p=0.52), and there was no difference after adjusting for ML at the start (1.02, 95% CI = -3.72 to 5.77, p=0.67). TXA didn't have any big effects on any of the other parameters.
Sentilhes, 2021[14]	French	Double-blind, randomized, controlled trial	4,551	1 gr	Adjusted risk ratio (RR) = 0.84; 95% CI = 0.75 to 0.94; P = 0.003; 556/2086 women in the tranexamic acid group experienced the main outcome compared to 653/2067 women in the placebo group. The percentage of women who experienced clinically severe postpartum hemorrhage, the need of further uterotonic medications, or postpartum blood transfusion, as well as the mean gravimetrically determined blood loss, were all comparable across the two groups. In the three months following delivery, 0.4% (8 of 2049) of women who took tranexamic acid and 0.1% (2 of 2056) of women who received placebo experienced thromboembolic events (adjusted RR = 4.01; 95% CI = 0.85-18.92; P = 0.08).
Sentilhes, 2018[15]	French	Double-blind, randomized, controlled trial	4,075	1 gr	Primary outcome occurred in 8.1% woman in the TXA group and 9.8% in placebo group (RR = 0.83; 95% CI = 0.68-1.01; P = 0.07). Women in TXA acid group had a lower rate of provider-assessed clinically significant PPH than those in the placebo group (7.8% vs. 10.4%; RR = 0.74; 95% CI = 0.61-0.91; P = 0.004; P=0.04 after adjustment for multiple comparisons post hoc) and also received additional uterotonic agents less often (7.2% vs. 9.7%; RR = 0.75; 95% CI = 0.61-0.92; P = 0.006; adjusted P=0.04). The incidence of thromboembolic events in 3 months after delivery did not differ significantly between TXA and placebo group (0.1% and 0.2%, respectively; RR = 0.25; 95% CI = 0.03-2.24).

Other study by Sentilhes, *et al* (2018)[15] showed primary outcome occurred in 8.1% woman in the TXA group and 9.8% in placebo group (RR = 0.83; 95% CI = 0.68-1.01; P = 0.07). Women in TXA acid group had a lower rate of provider-assessed clinically significant PPH than those in the placebo group (7.8% vs. 10.4%; RR = 0.74; 95% CI = 0.61-0.91; P = 0.004; P=0.04 after adjustment for multiple comparisons post hoc) and also received additional uterotonic agents less often (7.2% vs. 9.7%; RR = 0.75; 95% CI = 0.61-0.92; P = 0.006; adjusted P=0.04). The incidence of thromboembolic events in 3 months after delivery did not differ significantly between TXA and placebo group (0.1% and 0.2%, respectively; RR = 0.25; 95% CI = 0.03-2.24).

DISCUSSION

Tranexamic acid is able to stop bleeding because it blocks the enzymes that are responsible for breaking down fibrin blood clots. When the glycoprotein pro-enzyme plasminogen, which is produced by the liver, is transformed into the fibrinolytic enzyme plasmin by tissue plasminogen activator, the breakdown of fibrin can begin (tPA). The protein known as plasminogen is folded into a multitude of molecular loops known as kringles, which jut out like fingers. Plasminogen attaches itself to fibrin via lysine-binding sites located at the very tips of these so-called "fingers".[17–19]

It is possible to prevent plasminogen from binding to fibrin by removing the lysine residues that are present on fibrin. In reaction to tissue injury, ischaemia, and the presence of thrombin, tPA is secreted from the vascular endothelium. Additionally, tPA can attach to fibrin by way of the lysine-binding sites in fibrin. Because fibrin binds to both plasminogen and tPA, it is able to localize the synthesis of plasmin. When coupled to fibrin, plasmin is shielded from the effects of plasmin inhibitors.[17–19]

Plasmin is responsible for the disintegration of the blood clot into the various fibrin degradation products (FDPs). A positive feedback loop is created when this process exposes additional lysine residues, which then bind additional plasminogen and speed up the fibrinolysis process. An analogue of lysine at the molecular level, tranexamic acid inhibits fibrinolysis by decreasing the binding of plasminogen and tissue plasminogen activator (tPA) to fibrin.[17–19]
With tranexamic acid, there was a statistically significant decrease in death owing to bleeding, with no significant increase or decrease in any other cause of death. Because more than a quarter of fatalities were not caused by bleeding, tranexamic acid's reduction in all-cause mortality, calculated as a weighted average of its effect on bleeding and non-bleeding deaths, was not statistically significant.[12,20]

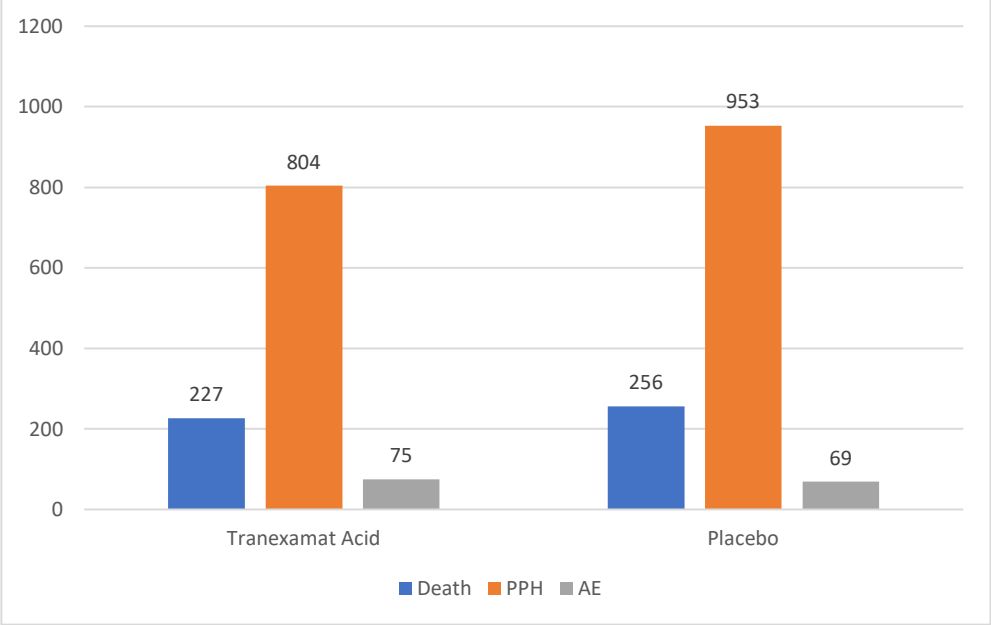

Figure 2. Comparison PPH, death, and AE in patient with TXA and placebo

Study has been demonstrated that a plasma concentration of 5–10 micrograms/mL of tranexamic acid is effective in causing considerable inhibition of systemic fibrinolysis in adults, with near maximum inhibition occurring between 10 and 15 micrograms/mL of tranexamic acid. It has been demonstrated that the amount of time required for clot lysis to occur increases from six minutes to sixteen minutes when tranexamic acid is present at a minimum concentration of five micrograms per milliliter. Following the oral administration of 2 grams of tranexamic acid, we discovered that postpartum women could acquire concentrations that were considered to be pharmacologically efficacious within one hour.[21]

Tranexamic acid did not prevent hysterectomy, it did significantly lower the number of laparotomies performed to manage bleeding. While in high-income countries, hysterectomy is commonly used as a last option to stop bleeding, in Africa and Asia, where many women are anemic and blood supplies are few, hysterectomy is frequently used as an early intervention to avoid death from exsanguination. Furthermore, there would have been a delay between randomization and administration of the trial treatment, so that even if the decision to randomize preceded the decision to perform a hysterectomy, the trial treatment would not have been received when the hysterectomy decision was made in some cases.[22,23]

Laparotomies, on the other hand, which frequently need re-operation to stop bleeding after a caesarean section, are more typically performed after other therapies, including the trial therapy, have been administered. This may have given tranexamic acid enough time to reduce the danger of laparotomy. Randomized trials in elective surgery reveal that tranexamic acid significantly reduces the need for re-operation to manage bleeding.[24]

The use of TXA was shown to be related with lower levels of D-dimer, but it did not appear to have any influence on ROTEM parameters or coagulation assays. The impact of TXA on D-dimer levels in this study is comparable to that seen in a nearly identical WOMAN trial sub-study that attempted to analyze the effects of TXA on platelet function. The purpose of the WOMAN trial sub-study was to examine the relationship between TXA and platelet function (ETAPLAT-study).[13,25] In women who have PPH, an increased fibrinolysis is a common finding.[26] Study showed this rise can be stopped by administering TXA. More extensive research is necessary to investigate the effects of TXA on fibrinolysis and coagulation in female patients with PPH or at risk for the condition.[13]

CONCLUSION

The study showed that the comparison between postpartum hemorrhage, death and side effects between those who received tranexamic acid and placebo was not significantly different. Even so, research shows that tranexamic acid provides benefits in reducing cases of postpartum hemorrhage.

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