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THE ROLE OF TRANEXAMIC ACID IN THE MANAGEMENT OF POSTPARTUM HEMORRHAGE

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Abstract:

Introduction: *The reduction of postpartum hemorrhage (PPH) fatalities through early tranexamic acid treatment has significant global implications for obstetrical care. Further research is necessary to determine the relative benefits and risks of tranexamic acid in the prevention of postpartum hemorrhage. The majority of postpartum hemorrhage deaths occur in low- and middle-income nations, where access to tranexamic acid treatment is frequently limited. Tranexamic acid, or TXA, has become a vital tool for managing blood loss during pregnancy in the last few decades. Currently, prophylaxis is being researched in high-risk groups, including women who have placenta previa or prepartum anemia. TXA effectively lowers morbidity and mortality associated with postpartum hemorrhage (PHH) during active PPH due to blood loss.*

Aim of the study: *The aim of the present study is to understand the role of tranexamic acid in the management of postpartum hemorrhage*

Methodology: *The study is a comprehensive research of PUBMED since the year 1983 to 2019.*

Conclusion: *Tranexamic acid is a molecular analog of lysine that prevents bleeding by decreasing the binding of plasminogen and tPA to fibrin, which inhibits fibrinolysis, the enzymatic breakdown of fibrin blood clots. Postpartum hemorrhage can be safely and effectively treated with tranexamic acid. Tranexamic acid reduces bleeding-related deaths by one-third when administered early. Since tranexamic acid is most effective when administered within three hours of childbirth and shows no discernible benefit after that, prompt treatment is essential for women suffering from post-partum hemorrhage, who often bleed to death.*

Keywords: *postpartum hemorrhage, Tranexamic acid, maternal health*

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INTRODUCTION:

PPH is linked to almost 25% of all maternal deaths worldwide, and it is the primary cause of maternal mortality in the majority of low-income nations. In 72% of cases, some amount of postpartum hemorrhage (PPH) occurs. Global PPH (>500 ml) and severe PPH (>1000 ml) incidences are estimated to be approximately 6.6% and 1.86%, respectively. Africa is notably the region with the highest PPH rates (10.45%), with rural areas having a higher incidence than urban areas. With varied rates across regions, postpartum hemorrhage accounts for 27.1% of all maternal deaths worldwide.[1]

The percentage of maternal deaths due to PPH that occur in low-income and resource-constrained countries is higher (36.9%) than in high-income countries (16.3%). The Prophylactic use of uterotonics during the third stage of labor and prompt, appropriate PPH management could prevent most PPH-associated deaths. The use of TXA to prevent severe bleeding has increased since it is known to improve outcomes when treating PPH. The effectiveness of tranexamic acid in obstetric settings has been investigated in a number of clinical trials. Notably, this medication can significantly lower maternal morbidity and mortality and is safe to use during pregnancy and lactation. It has been shown to reduce the risk of severe anemia, the need for uterotonic agents, the need for a hysterectomy, and the use of blood products.[2,3]

Complications of Postpartum hemorrhage

After giving birth, every woman bleeds. During pregnancy, the mother's blood becomes more and more prothrombotic, as if she is expecting this inevitable outcome. Higher levels of inhibitors cause the activity of clot-dissolving (fibrinolytic) proteins to decrease, while levels of clot-forming proteins, such as fibrinogen and coagulation factor VII, increase. Strong fibrinolysis inhibitors (plasminogen activator inhibitor [PAI]-1 and PAI-2) are released by the placenta itself. Blood levels reach their peak right after birth and quickly decline after placental separation.[4,5]

Even with a prothrombotic inclination, postpartum hemorrhage can be severe and occasionally lethal. Pregnant women are more susceptible to venous and arterial thrombosis due to the clotting nature of blood and the pressure exerted by their growing womb. Pregnant women have a five-fold increased risk of thromboembolism compared to non-pregnant women, which increases to a 20-fold increase in the postpartum period. [6]

Mechanism of Tranexamic acid and Fibrinolysis

Tranexamic acid stops bleeding by preventing fibrin blood clots from being broken down by enzymes. The breakdown of fibrin begins when tissue plasminogen activator (tPA) transforms the glycoprotein pro-enzyme plasminogen, which is produced by the liver, into the fibrinolytic enzyme plasmin. The plasminogen protein is folded into several finger-like molecular loops known as kringles. The lysine-binding sites at the tips of these "fingers" are where plasminogen binds to fibrin. Plasminogen binding is inhibited if the lysine residues on fibrin are eliminated.[7,8]

In reaction to tissue damage, ischemia, and the presence of thrombin, the vascular endothelium releases tPA. By means of the lysine-binding sites, tPA binds to fibrin as well. Plasminogen and tPA are bound by fibrin, which localizes plasmin formation. Inhibitors of plasmin are ineffective against plasmin bound to fibrin. The fibrin blood clot is divided into fibrin degradation products (FDPs) by plurisomin. Through increased exposure of lysine residues, more plasminogen is bound, speeding up fibrinolysis in a positive feedback loop. A molecular analogue of lysine, tranexamic acid decreases the binding of plasminogen and tPA to fibrin, thereby inhibiting fibrinolysis.[9]

WHO's 2012 recommendations for the prevention and treatment of PPH included a conditional recommendation to use TXA for the treatment of PPH when uterotonics fail to control the bleeding or the bleeding is suspected to be related to trauma. This recommendation was based on evidence for the benefit of TXA in improving trauma care outcomes.[10]

The World Maternal Antifibrinolytic Trial, a large-scale randomized controlled trial, published its results in 2017. It demonstrated that the administration of IV TXA as soon as possible after the onset of bleeding and within three hours of delivery reduces the risk of bleeding-related death in PPH women, regardless of the cause, and has no negative effects on the mother. The World Health Organisation (WHO) updated its 2012 PPH treatment recommendations to include the use of TXA for PPH treatment in response to this new evidence, as well as evidence from the upcoming Cochrane systematic review on the efficacy of TXA for PPH and an individual participant data meta-analysis of 40,138 bleeding patients. The 2012 WHO recommendations for the prevention and treatment of PPH are superseded by this recommendation regarding TXA.[11-13]

<u>WHO recommendation on tranexamic acid for the treatment of PPH (2017):</u>

For women with clinically diagnosed PPH after vaginal delivery or cesarean section, early use of IV TXA is advised in addition to standard care (as early as possible after clinical diagnosis of PPH, and only within 3 hours of birth). Following are the recommendation criteria [13-15]

1. Blood loss estimated to be more than 500 mL following a vaginal delivery or 1,000 mL following cesarean section, or any blood loss significant enough to jeopardize hemodynamic stability, is referred to as postpartum hemorrhage (PPH).
2. In all PPH cases, tranexamic acid (TXA) should be administered, irrespective of the cause of the bleeding—genital tract trauma or other factors.
3. TXA ought to be viewed as a component of the typical all-inclusive PPH treatment regimen, which also includes nonsurgical, surgical, and medicinal (uterotonics) interventions in compliance with WHO guidelines or locally customized PPH treatment protocols.
4. In delivery and postpartum areas of facilities offering emergency obstetric care, TXA should always be easily accessible.
5. In delivery and postpartum areas of facilities offering emergency obstetric care, TXA should always be easily accessible.
6. TXA is generally inexpensive, simple to use, and frequently accessible in healthcare settings because it is used in surgery and trauma cases. It also has a three-year shelf life and can be kept in many locations at room temperature (15–30 C).
7. The time of birth serves as the reference point for the beginning of the three-hour window during which TXA administration can begin.
8. The most accurate estimate of the time of birth should be used as the benchmark if it is unknown.
9. There seems to be less benefit when TXA is used after treatment. After three hours, there is no longer any benefit, and it seems to decline by 10% for every fifteen minutes of delay.
10. Although not statistically significant for women with PPH, the point estimates of the effect of TXA use beyond three hours on death for trauma and PPH were both in the direction of harm. The World Health Organisation advises against using TXA more than three hours after delivery in light of this data.
11. TXA should be given intravenously (IV) at a fixed dose of 1 g in 10 mL (100 mg/mL) at 1 mL per minute (i.e., over 10 minutes). If bleeding persists after 30 minutes or if it recurs within 24 hours of the initial dose, another 1 g IV dose should be given.
12. Due to the possibility of a brief drop in blood pressure with a bolus injection, TXA should be given slowly over ten minutes as an IV injection.
13. TXA for injection can be given via the same IV cannula that is used for IV hydration or uterotonic administration. It can be combined with the majority of infusion solutions, including electrolyte, carbohydrate, amino acid, and dextran solutions. TXA shouldn't be combined with mannitol, penicillin-containing solutions, or blood intended for transfusion.
14. Women who have a clear contraindication to antifibrinolytic therapy, including TXA (such as a history of coagulopathy, active intravascular clotting, or a known thromboembolic event during pregnancy), should not use TXA.

Comparison of WHO recommendation on TXA for PPH (2012 and 2017):[10,14,15]

	Indication	Timing	Dosing
WHO 2012 recommendation	If oxytocin and other uterotonics are ineffective in stopping the bleeding or if there is a possibility that trauma may be a contributing factor in the bleeding, TXA should be used to treat PPH.	If oxytocin and other uterotonics are unable to stop the bleeding in an atonic uterus, use TXA.	IV: 1 g (slowly) If bleeding persists, repeat in 30 minutes.
WHO 2017 recommendation	Regardless of whether the bleeding is the result of genital tract trauma or other causes, TXA should be used in all PPH cases.	As soon as PPH starts, and no later than three hours later, start using TXA. Unless TXA is being used for bleeding that resumes within 24 hours of finishing the first dose, do not start TXA more than 3 hours after birth (see dosing).	IV at 1 mL per minute for a fixed dose of 1 g in 10 mL (100 mg/mL) (i.e., administered over 10 minutes) If the bleeding doesn't stop after 30 minutes or if it starts again within 24 hours of finishing the first dose, administer a second dose of 1 g IV.

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