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A REVIEW ON TRANEXAMIC ACID

Obstetrics & Gynaecology

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ABSTRACT

The objective is to study the effectiveness of hemostatic therapy with tranexamic acid in pregnant women with miscarriage that started. Tranexamic acid works by slowing the breakdown of blood clots, which helps to prevent prolonged bleeding. It belongs to a class of drugs known as antifibrinolytics. Tranexamic acid is a synthetic derivative of the amino acid lysine and binds the 5 lysine binding sites on plasminogen. This inhibits plasmin formation and displaces plasminogen from the fibrin surface. It may also directly inhibit plasmin and partially inhibit fibrinogenolysis at higher concentrations. The investigators hypothesize that tranexamic acid as an adjunct to misoprostol will be more effective than misoprostol alone in stopping postpartum bleeding without recourse to further treatment in significantly more women. The use of tranexamic acid, as hemostatic therapy in pregnant women with a miscarriage, significantly reduces the duration of bleeding, promotes the accelerating the organization and resorption of intrauterine hematomas, reduces the duration of inpatient treatment. The first trimester is associated with the highest risk for miscarriage. Most miscarriages occur in the first trimester before the 12th week of pregnancy. A miscarriage in the second trimester (between 13 and 19 weeks) happens in 1% to 5% of pregnancies. Tranexamic acid appeared safe and effective for the prevention and management of bleeding during pregnancy.

KEYWORDS

Tranexamic acid, miscarriage, postpartum bleeding.

INTRODUCTION:

This tranexamic acid is used to treat heavy bleeding during your menstrual period. Tranexamic acid works by slowing the breakdown of blood clots, which helps to prevent prolonged bleeding. It belongs to a class of drugs known as antifibrinolytics.

Antifibrinolytic agents including tranexamic acid (TXA) have been shown to be effective at preventing bleeding complications in a variety of hemostatic challenges and reduce mortality with minimal adverse effects in some settings.1'2

Chemical Name:

Tranexamic acid is a *trans*-stereoisomer of 4-(aminomethyl) cyclohexane-carboxylic acid) and has a molecular weight of 157.21

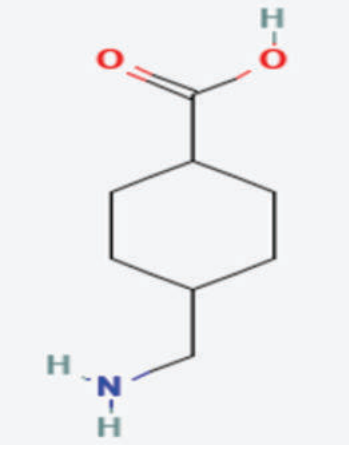

Fig. no.1: Chemical structure of tranexamic acid

Mechanism Of Action Of Tranexamic Acid:

Tranexamic acid competitively and reversibly inhibits the activation of plasminogen via binding at several distinct sites, including four or five low-affinity sites and one high-affinity site, the latter of which is involved in its binding to fibrin. The binding of plasminogen to fibrin induces fibrinolysis – by occupying the necessary binding sites tranexamic acid prevents this dissolution of fibrin, thereby stabilizing the clot and preventing hemorrhage.[3]

Tranexamic acid is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin.3 At much higher concentrations it behaves as a noncompetitive inhibitor of plasmin similar to aminocaproic acid, a similar antifibrinolytic which is 10-fold less potent. Tranexamic acid binds more strongly than aminocaproic acid to both the strong and weak receptor sites of the plasminogen molecule in a ratio corresponding to the difference in potency between the compounds. In patients with hereditary angioedema, inhibition of the formation and activity of plasmin by tranexamic acid may prevent attacks of angioedema by decreasing plasmin-induced activation of the first complement protein (C1).4

Off-target antagonism of GABA(A) receptors may be associated with the development of convulsions and hyperexcitability following tranexamic acid administration1– the risk appears higher with improper administration or administration during cardiovascular surgery. Consider EEG monitoring of patients with a history of seizure.[3]

Tranexamic acid is also thought to exert an anti-inflammatory effect (by inhibiting plasmin-mediated activation of complement, monocytes, and neutrophils) and may improve platelet function in certain circumstances (Fig. 2).

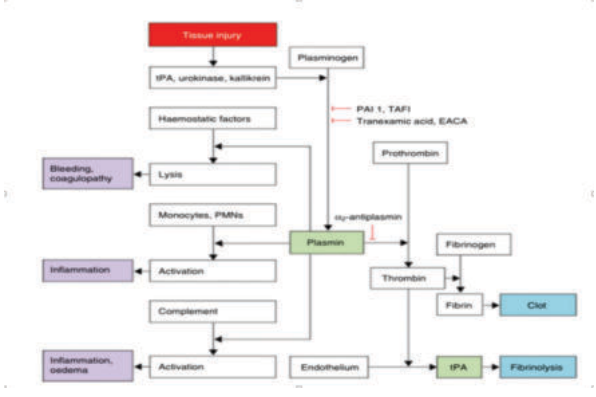

Fig 2: Tranexamic acid and its relationship with tissue injury, fibrinolysis, and inflammation. Reproduced from The Lancet, Levy (2010)[14]

Uses Of Tranexamic Acid:

Abnormal Uterine Bleeding:

Abnormal uterine bleeding (AUB) is a common complaint accounting for one-third of all gynecologic evaluations. In addition to standard of care which involve treatment of the underling etiologies of the AUB, prospective trials have shown that TXA when used as a supplemental therapy reduces menstrual blood loss by 54% (mean blood loss 164 mL before treatment, 75 mL during treatment).[5] Limited data suggest TXA may be as effective as oral contraceptives in the prevention of heavy menstrual bleeding (HMB) in adolescents.[6] A dose of 1300 mg by mouth 3 times daily for up to 5 days during menses is approved for this

indication by the US Food and Drug Administration (FDA).[7,8,9]

Postpartum Haemorrhage (PPH):

Postpartum haemorrhage (PPH) heaving bleeding within the first 24 hours after giving birth , is one of the main causes of death of women after childbirth. Antifibrinolytics, primarily tranexamic acid (TXA), have been shown to reduce bleeding in surgery and safely reduces mortality in trauma patients with bleeding without increasing the risk of adverse events.[10]

In general, TXA is used when estimated blood loss exceeds 500 mL after vaginal birth or 1000 mL after cesarean section, or with any blood loss sufficient to compromise hemodynamic stability.[5] A loading dose of 1 g (100 mg/mL) of TXA intravenously at a rate of 1 mL/min is the standard. If bleeding continues after 30 minutes, or recurs within 24 hours of the first dose, a second dose of 1 g of TXA can be given.[5]

Early Pregnancy Spotting:

First trimester bleeding is a matter of great concern to a large group of the obstetric population. One-quarter of pregnant woman will experience vaginal bleeding during the first trimester. About half of these will end in miscarriage within 20 weeks of gestation and those women who remain pregnant have an increased risk of developing other complications later in pregnancy.

Bleeding can be in the form of spotting, light, or heavy bleeding. Spotting is bleeding reported by the patient as scant or traces of blood or visualized by clinician as scant or no blood in the vagina and at the cervix. It is considered a spotting when a woman notices a few drops of blood occasionally in her underwear, or if a woman wipes herself with tissue and sees a little blood on the paper. Light bleeding is reported by the patient as like a "menses". It is visualized by the clinician as a small amount of blood in the vagina or at the cervix. Heavy bleeding is reported by the patient as more than a "menses". It is visualized as a moderate to heavy amount of blood in the vagina or at the cervix.[11]

It is not always possible to make a diagnosis at the first presentation. In some cases, the need for follow-up investigations or referral to a Hospital Center is required.

Causes of first-trimester vaginal bleeding includes obstetric and non-obstetric etiologies. The most frequent etilogies are miscarriage and ectopic pregnancy. Rarer causes include cervical and vaginal lesions (e.g., malignancy, cervical ectropion, polyps, infection) and uterine infection. Gestational trophoblastic disease (GTD) should always be considered, particularly in the setting of an abnormally raised serum human chorionic gonadotropin (hCG) or suggestive ultrasound findings. Establishing the site of the pregnancy is a crucial step, as failure to correctly diagnose an ectopic pregnancy can have potentially life-threatening consequences.

The early weeks of (4–12 weeks) pregnancy is the period of organogenesis. Various factors may disturb the pregnancy during this period, which has a subsequent effect on obstetric outcome. First-trimester vaginal bleeding is an independent risk factor for adverse obstetric outcome that is directly proportional to the amount of bleeding. Heavy vaginal bleeding subjects are more likely to have intrauterine growth restriction, preterm delivery, preterm premature rupture of membranes, and placental abruption.

Local hemostatic factors in the uterus during implantation, decidualization, and early pregnancy, for example, tissue factor expressed in cytotrophoblasts and systemic factors in the women during the ongoing pregnancy seem to play distinct roles in a successful pregnancy. Dysfunction of any of these factors could lead to an adverse outcome.

It is hypothesized that first-trimester bleeding may indicate an underlying placental development dysfunction, which manifest later in pregnancy causing adverse pregnancy outcome.[12,13]

Tooth Extractions In Patients With Hemophilia:

Two Cochrane reviews showed limited data in patients with hemophilia undergoing tooth extractions; however, TXA may reduce blood loss, postoperative bleeding, and additional need of clotting factors if given with clotting factor replacements of the known hemophilia type.[15,16]

Total Knee Arthroplasty:

In a double-blind prospective trial, patients were either given TXA or normal saline to investigate if TXA decreased the need for blood transfusions. In fact, the TXA group reduced both bleeding and the need for blood transfusion.They also noted no significant thromboembolic events.[17]

Cardiac Surgery:

A trial with a 2-by-2 factorial design was performed, assigning patients undergoing coronary artery surgery into an aspirin versus placebo group or a TXA versus the placebo group. Their results revealed that tranexamic acid was associated with a lower risk of bleeding than the placebo, without a higher risk of death or thrombotic complications within 30 days after surgery.[18]

Hereditary Angioedema (HAE):

A systematic review of four medications given prophylactically to reduce HAE attacks. All four drugs, one being TXA, reduced the frequency of HAE attacks compared to a placebo.[19]

Dose Of Tranexamic Acid

IV USES:

- Intravenous TXA for hemorrhagic shock, including postpartum hemorrhage and trauma patients.
- Adult dose: one gram bolus in 100 mL of normal saline over 10 minutes (slow intravenous push). Rapid infusion may cause hypotension. May repeat a 1 gram dose over the next 8 hours, but do not exceed a total of 2 grams.
- Pediatric dose: Weight-based, an initial dose of 20 mg/kg intravenous bolus over 10 minutes. May repeat a 10 mL/kg/hr over the next eight hours.
- Elective cesarean section: Intravenous (IV) TXA 1 g over 5 minutes at least 10 minutes before skin incision.
- Hip fracture surgery: IV TXA 15 mg/kg at the time of skin incision, followed by a similar second dose three hours later.
- Non-traumatic SAH: IV TXA 1 g at diagnosis of SAH then 1 g every 6 hours until the aneurysm is occluded.
- Unilateral and bilateral knee arthroplasty: IV TXA 10 or 15 mg/kg over 10 minutes before deflation of the first tourniquet, 3 hours after the first dose.
- Bleeding associated with cervical conization 1 g IV during the procedure followed by 1 g oral three times a day for 14 days, or 1.5 g every 8 hours the evening after the procedure for 12 days.
- Cardiac surgery: IV 50 mg/kg administered > thirty minutes after anesthesia.
- Spinal surgery: IV 2 g over 20 minutes before incision followed by 100 mg/hour during surgery and continued 5 hours postoperatively.
- Dental extraction in patients with hemophilia (with factor replacement therapy): IV 10 mg/kg immediately before surgery, then oral 10 mg/kg 3 to 4 times daily.[11]

ORAL USES:

- Oral TXA for cyclic heavy menstrual bleeding: 1300 mg TID for up to 5 days during menstruation.
- Oral TXA for HAE for long-term prophylaxis: oral 1g to 1.5 g 2 to 3 times daily. May reduce to 500 mg/dose once or twice a day when attacks reduce in frequency.
- Oral TXA rinse: Dental procedure in patients on oral anticoagulants. Oral rinse of 4.8% solution. Rinse 10 mL in the mouth for 2 minutes, then spit. May repeat 4 times. Avoid eating or drinking for 1 hour after administration.[11]

Summary:

There are many historical uses for tranexamic acid; however, there is a lack of research and therefore evidence to support these uses. Increasingly, concerns over the potential risk of thrombus formation have led to guidelines 'not recommending the use of tranaexamic acid.' Recent interest in the use of tranexamic acid in bleeding trauma patients has identified a mortality benefit without an apparent increased risk of thromboembolic events. It has been speculated that this survival benefit may be attributable to an anti-inflammatory rather than an antifibrinolytic effect.

It is the author's view that in the presence of bleeding prompting transfusion, tranexamic acid should be used. Its use as a prophylaxis to prevent potential bleeding is more controversial; however, in the absence of strong risk factors for thromboembolic disease, its use should be considered.

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