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Tranexamic Acid in Obstetrics: A Clinical Review

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Abstract:

Blood loss and subsequent transfusions are associated with major morbidity and mortality. Obstetrics is a bloody business and caesarean section is associated with complications like haemorrhage and problems in subsequent pregnancies. The use of antifibrinolytics can reduce blood loss in surgeries including Obstetrics and Gynecology, and the need for blood transfusion. Tranexamic Acid (TXA), a synthetic lysine-analogue antifibrinolytic, was first patented in 1957 and its use has been increasing in contrast to aprotinin, a serine protease inhibitor antifibrinolytic. The clinical evidence available for TXA therapy in Obstetrics will navigate Obstetrician to develop a better understanding about its applications though still further trials are being conducted for its proper usage and safety. Till date TXA proved to be a promising drug in Obstetrics and other specialities for reducing blood loss in terms of its efficacy and safety profile. However questions regarding clinical effects of TXA, adverse effects and risks necessitate further clinical trials.

Keywords: ***transfusions, Obstetrics, caesarean section, haemorrhage, tranexamic acid.***

Introduction

Haemorrhage constitutes 35% of maternal deaths globally according to the World Health Organisation (WHO) from 1997-2007.[1] In the United States haemorrhage and hypertensive disorders contribute 12.5% and 12.3% of maternal deaths respectively.[2] Blood loss and subsequent transfusions are associated with major morbidity and mortality.[3] Caesarean section is associated with complications like haemorrhage, infection, and pulmonary embolism and problem in subsequent pregnancies. The risk of a mother requiring hysterectomy is 10 times greater following CS compared to vaginal delivery and the risk of mortality is increased up to several folds when compared to vaginal delivery.[4] One of the most common complications of CS is primary or secondary postpartum haemorrhage (20%), which leads to increased maternal mortality and morbidity.[5] The main purpose oftranexamic acid(TXA) is the reduction of perioperative bleeding and transfusion requirements in both cardiac and non-cardiac surgery.[3]

Mechanism of Action

Tranexamic acid (trans-4-aminomethylcyclohexane-1-carboxylic acid) is a synthetic derivative of the amino acid lysine. It exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules and inhibits endometrial plasminogen activator and thus prevents fibrinolysis and the breakdown of clot.[6]

Clinical pharmacology

Having molecular weight of 157.21 g/mol, TXA can cross the placental barrier. The concentration in cord blood after an intravenous injection of 10 mg per kg to pregnant women is about 30 mg per L, as high as in the maternal blood. Unlike other antifibrinolytic agents, TXA is proved to be a better drug under its class for various purposes, as well as proved to be the safest haemostatic with minimum side effects.[6] Its potency is approximately 10-fold greater than epsilon-aminocaproic acid (EACA).[7] The plasma protein binding of TXA is about 3% at therapeutic plasma levels, which is fully bound to plasminogen and not bound to serum albumin. The initial volume of distribution is 9 to 12 litres and the concentration of TXA remains in different tissues for about 17 hours and in serum, up to seven or eight hours. The overall renal clearance is equal to overall plasma clearance about 110 to 116 ml/min with 95% of the dose excreted in urine as the unchanged drug. TXA is typically administered at a loading dose of 15 mg/kg, followed by a continuous intravenous infusion of 1.5 mg/kg/hr. The initial elimination half-life of both TXA and EACA is approximately 1–1.5 hr.[6,7] Under normal conditions, fibrinolysis provides an important mechanism to limit propagation of intravascular thrombosis. Tissue plasminogen activator (t-PA), released from vascular endothelium, converts plasminogen to plasmin, the active mediator of fibrinolysis. Plasmin impairs the haemostatic process by a number of mechanisms including degradation of cofactors Va and VIIIa, proteolysis of platelet adhesive receptors, consumption of alpha 2-antiplasmin, and the degradation of fibrin and fibrinogen.[7]Along with TXA, other haemostatic drug like recombinant Factor VIIa has been considered in patients with major haemorrhage in Obstetrics and other specialties in an attempt to control massive haemorrhage.[8]

Antepartum Use

In 12 women with vaginal bleeding in the second half of pregnancy, Walzman M and Bonnar J[9] investigated the treatment with TXA by giving 1g 8-hourly for 7 days. Plasma fibrinolytic activity, plasminogen, antiplasmin and platelet count significantly decreased during treatment, while antithrombin III and factor VIII related antigen significantlyincreased with plasma TXA levels ranging from

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5 mg/l to 17 mg/l. No adverse effects were detected in any of the mothers and all of them delivered live born infants.

Treatment with TXAhad proven useful to prolong pregnancy with maturation of the foetus in cases with partial separation of placenta and immature foetus, however, in most cases of abruptio placenta immediate delivery by caesarean section is necessary.[10] Svanberg L et al[11] analysed 73 consecutive cases of abruptio placentae, who were treated with TXA, of which 67 of them were immediately delivered by caesarean section while the remaining six patients were in early gestational age and were treated for a prolonged period. The perinatal mortality was only 8 per cent with no maternal mortality and complications like haemorrhagic diathesis or thrombosis was not recorded.[11]Haemostasis occurred more rapidly in women taking TXA than in the control group, when it was given for arresting bleeding and prolonging pregnancies in women with threatened abortion and miscarriage.[12]

Intrapartum and Postpartum Use

WHO care pathways for postpartum haemorrhage and retained placentarecommended the use of TXA for continued bleeding during uterine atony, uterine rupture and lower genital tract trauma supported by a study on 154 women randomised to receive large-dose TXA versus placebo after > 800 ml blood loss following vaginal delivery that showed significant reduction in blood loss in the TXA group statistically.[1]

TXA has been found to have good effect on placental bleeding, postpartum haemorrhage and conisation of the cervix along with menorrhagia.[13]The most frequently used drugs for the treatment ofpost-partum haemorrhage wereantifibrinolytics, such as TXA, which will help to reduce the magnitude of post-partum haemorrhage (Bonnet MP et al).[14] The use of viscoelastic haemostatic assays, fibrinogen, TXA and balanced transfusion therapy may prove to be potentially pivotal in the treatment of postpartum haemorrhage.[15] Prohaemostatic treatments based on high fresh frozen plasma and red blood cell (FFP:RBC) ratio transfusion and procoagulant agents (fibrinogen concentrates, recombinant activated factor VII, and TXA) are crucial aspects of management in obstetrical haemorrhage (Bonnet MP and Basso O).[16] Fibrinogen concentrate should be transfused if the fibrinogen plasma level remains below 1.0 g and perhaps even as soon as it falls below 1.5-2.0 g; the addition of TXA (1 g) is cheap, useful and appears safe (Mercier FJ and Bonnet MP).[17] Initial therapy of postpartum haemorrhage consists of uterotonic drugs and inspection of the uterine cavum, at the same time, optimization of the clotting potential should be initiated early and TXA may be considered as a first line choice, followed by fibrinogen if necessary (Gogarten W).[18]

In a double-blind randomised controlled trial (Mirghafourvand M et al) on 120 women with a singleton pregnancy, the prophylactic use of 1 gram TXA on blood loss after vaginal delivery in women at low risk for postpartum haemorrhage was compared with placebo control group. The total blood loss (519 (320) vs 659 (402) ml, P = 0.036) and measured blood loss from placental delivery to 2 hours postpartum (69 (39) vs 108 (53) ml, P < 0.001) was significantly lower in the TXA group compared to the control group. The blood loss > 1000 ml was also lower in the TXA group (7% vs 18%, P = 0.048).[19] In a systematic review and meta-analysis ofseven trials with a low risk of bias comparing TXA vs. placebo with a total of 1760 parturients, the blood loss was significantly lower after TXA use (WMD -140.29 ml, 95% CI -189.64 to -90.93 ml; P<0.00001) and also reduced the risk for blood transfusions (RR 0.34, 95% CI 0.20-0.60, P=0.0001). Additional uterotonics were required in the placebo groups (Heesen M et al).[20] Peitsidis P and Kadir RA[21] performed a systematic search on the use of TXA during pregnancy and puerperium and yielded 34 articles, dating from 1976 to 2010 with five randomised controlled trials (RCTs), seven observational studies, and twenty-two case reports,where half of the RCTs were multicentre studies. These studies assessed doses of TXA that ranged from 500mg to 6g, treatment duration ranging from over five minutes to 64 days. Treatment administering from five weeks to 40 weeks gestations was reported whereTXA had shown to reduce the amount of blood loss during caesarean sections and vaginal deliveries and reduced the need for blood transfusion.In 400 primiparas of term singleton pregnancy, vertex presentation with spontaneous delivery, the average blood loss at 2 hours postpartum was 129.7 ml, 133.9 ml with I.V. TXA 1 gm and 0.5 gm respectively.Whereas the blood loss was 168.5 ml and 178.2 ml with aminomethylbenzoic acid 0.5 g I.V. and no treatment respectively.TXA was efficient and safe in reducing postpartum blood loss with 1.0 g TXA having the best efficacy, followed by 0.5 g TXA (Yang H et al).[22]

In a randomized, case controlled, prospective study on 100 women undergoing LSCS, TXA significantly reduced the quantity of blood loss from placental delivery to 2 hours post-partum: 372.71 ml in the study group, versus 469.70 ml in the control group (P=0.003), without any side effect or complication like thrombosis (Mayur G et al).[23] A systemic review on anti-fibrinolytic agents in postpartum haemorrhage involving 461 participants on three randomized controlled trials (Gai 2004, Gohel 2007 & Yang 2001), TXA reduced the blood loss by 92 millilitres, with the most frequently reported adverse effect being nausea (Ferrer P et al).[24]

A study conducted ontwo RCTs, with one RCT involving 273 women who had vaginal birth and a second RCT of 180 women who underwent caesarean section compared TXA (1 g intravenously given 10 minutes before incision) with placebo. Blood loss greater than 400 ml was less common in women who received TXA during vaginal birth or caesarean section in the dosage of 1 g or 0.5 g intravenously with the mean blood loss being lower and no serious side effects in women who received TXA in the included studies (Novikova N and Hofmeyr GJ).[25] High-dose TXA (4 g infusion over 1 h followed by 1 g/ hr for 6 hrs) in women (n=144) during vaginal delivery with blood loss greater than 800 ml, reduced the blood loss significantly in the TXA group than in control group (173 ml vs. 221 ml) (P = 0.041). The bleeding duration was shorter and progression to severe PPH and PRBC transfusion was less frequent in the TXA

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group as well (P < 0.03) (Ducloy-Bouthors et al).[26] Movafegh A et al[27] demonstrated that 10 mg/kg of TXA, administered intravenously 20 minutes before abdominal incision when compared to placebo reduced the mean blood loss forboth intraoperative bleeding (262.5±39.6 vs 404.7±94.4 mL) and postoperative bleeding (67.1±6.5 vs 141.0±33.9 mL; P=0.001), respectively during LSCS.

Shahid A and Khan A[28] in a randomized double-blind placebo controlled study demonstrated that TXA significantly reduced the quantity of blood loss from placental delivery to the end of LSCS when compared to the placebo group (356.44 ± 143.2 ml vs. 710.22 ± 216.72 ml) (p < 0.001) and the blood loss from the end of LSCS to 2 hours postpartum (35.68 ± 23.29 vs. 43.63 ± 28.04 ml) (p = 0.188), was not significant.A prospective randomized trial on 124 pregnanciesat term for elective LSCS showed that TXA 10 mg/kgi.v.5 min before skin incision reduced the total blood loss by 206 ml when compared to the control group (391 ml vs. 597 ml) with decreased in the risk of postpartum blood loss by 30% (Ahmed MR et al).[29] Sentilhes L et al[30] reviewed on randomized controlled trials (RCTs) for PPH prevention after caesarean (n=10) and vaginal (n=2) deliveries and for PPH treatment after vaginal delivery (n=1) showed that TXA appeared to be a promising drug for the prevention and treatment of PPH after both vaginal and caesarean delivery.

In amonocenter prospective case control double blind randomized study on 90 anaemic patients undergoing LSCS, with haemoglobin between 7-10 g percent, Goswami U et al[31] found that the reduction in blood loss withi.v. TXA 10mg/kg(n=30) and 15mg/kg (n=30) when compared to the control group (n=30) were 146.34±56.32ml and 262±31.51ml respectively. Difference in blood loss between the 2 doses was also significantly reduced (115.66±24.81ml; P<0.05).A randomized controlled trial on seven hundred and forty women at term with singleton pregnancy for elective caesarean section showed that the mean total blood loss with administration of 1 gm TXA was 241.6 ml and that without TXA was 510 ml (Abdel-Aleem H et al).[32] Sentürk MB et al[33] in a double-blind, placebo-controlled study found out that tranexamic acid reduced intraoperative and postoperative blood loss during LSCS in 223 patients with no complication such as venous thromboembolism, gastrointestinal problems or hypersensitivity.

In a systematic review with meta-analysis, prophylactic administration of tranexamic acid reduced blood loss and the incidence of severe post-partum haemorrhage (Faraoni D et al).[34] A randomized, double-blind, placebo-controlled study on 660 women showed that intravenous infusion of 1 gm TXA significantly reduced blood loss during CS when compared to the placebo control group (499.9 ± 206.4 ml versus 600.7 ± 215.7 ml, respectively; P < 0.001). The percentage of patients with blood loss >1000 ml, and the need for additional uterotonic agents were also reduced (Gungorduk K et al).[35] TXA significantly reduced the blood loss from the end of CS to 2 hours postpartum; 28.02 +/- 5.53 ml in the tranexamic group versus 37.12 +/- 8.97 ml in the control group (p = 0.000) in 90 primiparas (Sekhavat L et al).[36] In another prospective, randomized, case-controlled clinical trial,TXA significantly reduced the quantity of blood loss from the end of CS to 2 hours postpartum: 42.75 +/- 40.45 ml in the study group versus 73.98 +/- 77.09 ml in the control group (P=0.001) and also reduced the quantity of total blood loss from placental delivery to 2 hours postpartum: 351.57 +/- 148.20 ml in the study group versus 439.36 +/- 191.48 ml in the control group (P=0.002)(Gai MY et al).[37]A randomized, double-blind, case-controlled study by Xu J et al[38]on 174 primiparas, 10 mg/kg TXA reduced the quantity of total blood loss from placental delivery to 2 hours postpartum (p = 0.02) when compared to the control group (379.2 ± 160.1 vs. 441.7 ± 189.5).

Adverse effects

TXA has been well tolerated with nausea and diarrhoea being the most common adverse events with no increased risk of thrombosis (Dunn C J and Goa K L).[13] The side effects were usually mild and transient (Xu J et al).[38] Gastrointestinal adverse events were more common after TXA use and only few trials observed adverse events including thromboembolic complications and seizures (Heesen M et al).[20] Walzman M and Bonnar J[9] detected no adverse effect in any of the mothers and several studies did not detect any side effect or complication like thrombosis or thromboembolic events with TXA.[23,33,35,36.]

Conclusion

TXA is a better drug in terms of its safety with minimum side effects and about 10-fold greater in potency than epsilon-aminocaproic acid (EACA). Till date every study showed TXA to be very effective in reducing blood loss during antenatal period, following vaginal deliveries and caesarean sections with a good safety profile. It proves to be a promising drug for reducing blood loss in Obstetrics, however further studies/reviews should come up with certain guidelines for its use and clear off concerns regarding adverse effects. Currently, there are on-going researches to answer the concerns regarding the use of TXA.

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