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Review

The role of tranexamic acid in obstetric hemorrhage: a narrative review

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Abstract

Abnormal postpartum hemorrhage is a common problem, complicating 3-5% of vaginal and operative deliveries. In a majority of cases (98%) uterine atony, retained placenta or genital tract lacerations are responsible for excessive blood loss. However, occasionally, serious coagulopathy may occur early after delivery or in specific circumstances such as with placental abruption. Also, when bleeding is caused by uterine atony, retained placenta or vaginal lacerations, a dilutional coagulopathy may develop. Hence correcting coagulation abnormalities is often required. Crucial to manage postpartum coagulopathy is the use of tranexamic acid to reduce hyperfibrinolysis. In the present narrative review, we will discuss the use of tranexamic acid for the prevention and management of major postpartum hemorrhage by reviewing the available literature.

Keywords: **Major postpartum haemorrhage, fibrinolysis, tranexamic acid, bleeding, pregnancy.**

Introduction

Postpartum hemorrhage (PPH) is commonly defined as blood loss of more than 500 mL within 24 hours after delivery[1]. Worldwide, hemorrhage is responsible for 25% of pregnancy-related deaths[2].In 2015, 34% of the 275.000 estimated global maternal deaths was caused by hemorrhage[3]. The majority of these deaths occurs in low-income countries; [2]however, obstetric hemorrhage is also witnessing an increasing trend in high-income countries[4,5]. In Europe, approximately 13% of obstetric patients will experience PPH (≥500 mL) and about 3% severe PPH (≥1000 mL)[6]. PPH is associated with significant morbidity such as anaemia, blood transfusion, coagulopathy, postpartum hypopituitarism, renal impairment and psychological morbidity such as depression and post-traumatic stress disorder[7-9]. Active management of the third stage of labour and treatment such as administration of uterotonic drugs are the most effective strategies to prevent PPH and subsequent maternal deaths[10,11].

Many patients with an obstetric hemorrhage will be presenting with coagulation abnormalities or will develop dilutional coagulopathy. Specifically, hypofibrinogenemia or hyperfibrinolysis are common. Causes of coagulopathy in massive bleeding include hyperfibrinolysis or dilutional coagulopathy as a result of resuscitation. Consumptive coagulopathy characterised by activation of the coagulation cascade and consequent consumption of coagulation factors and platelets is less common in PPH, but may contribute to severe cases of bleeding[12].

In the present narrative review, the authors will review the available literature on the use of tranexamic acid (TXA) to prevent and manage hyperfibrinolysis during obstetric hemorrhage. The authors will try to answer the questions: What is the role of TXA in the mamangement of postpartum hemorrhage and what is the role of TXA in the prevention of postpartum hemorrhage?

Search Strategy

The literature was searched using the following search terms: “tranexamic acid” AND “obstetric hemorrhage” OR “Cesarean section” OR “vaginal delivery” AND “postpartum” AND/OR “fibrinolysis”.

Coagulation during delivery

During pregnancy a hypercoagulopathic state develops1[3]. The haemostatic system is in a delicate

balance between clot formation and prevention of unwanted thrombosis. During pregnancy, it undergoes profound local and systemic changes resulting in a prothrombotic state associated with increased capacity to clot. Clotting factors are increased. At delivery this procoagulant state will result in very rapid formation of a fibrin clot by a combination of thrombin, fibrinogen and thrombocytes.

Fibrinogen levels are normally increased to 6 g/L at the end of pregnancy[14]. However, in some patients this increase is less pronounced. These patients are at increased risk of major hemorrhage.14 When hemorrhage occurs fibrinogen also rapidly is diluted whilst the other coagulation factors are maintained at normal levels much longer[15]. Hence, avoiding or treating (hyper)fibrinolysis may be extremely valuable to boost clot formation and to stop obstetric hemorrhage.

Additionally, to balance the pro-coagulant state the fibrinolytic system seems to be activated in the peri-delivery period[13]. Fibrinolysis is the process of dissolution of fibrin clots into fibrin degradation products which is initiated by plasmin and other fibrinolytic proteases. Hence, microcirculatory thrombosis can be prevented. Observational evidence suggests that maternal fibrinolysis is activated at the time of delivery[15-20]. Indeed, evidence shows increased plasma urokinase-plasminogen activator or tissue plasminogen activator and decreased plasminogen activator inhibitor 1 levels after placental delivery. However, this needs further study to assess the impact of fibrinolysis in a large cohort of parturients. Indeed, Arnolds and Scavone only noted evidence of hyperfibrinolysis in 15 out of 118 women with major hemorrhage when using visco-elastic testing[21].

Mechanism of action of tranexamic acid Mechanism of action of tranexamic acid

Fibrin, a protein generated from fibrinogen by thrombin cleavage, is the final product of the coagulation cascade: together with platelets, polymers of fibrin form a thrombus, thus achieving hemostasis in response to endothelial injury[22]. Upon healing of the endothelial damage, fibrinolysis is initiated: plasminogen is converted into plasmin, a proteolytic enzyme that catalyzes fibrin digestion, resulting in the removal of the blood clot[23]. Fibrinolysis is an important part of the coagulation process, maintaining patency of the vascular system. Fibrinolysis is regulated by a complex series of interactions and feedback mechanisms[22].

TXA is an antifibrinolytic agent synthetized from the amino acid lysine and it is widely used for the prevention and treatment of hemorrhage. It was first described in the 1960's[24,25]. TXA acts by inhibiting the interaction of fibrin with plasminogen, hindering fibrinolysis and preserving blood clots from degradatio[26]. TXA binds the 5 binding sites on plasminogen and in thus inhibits plasmin formation and displaces plasminogen from the fibrin surface. In higher concentrations it might also directly inhibit plasmin and partially fibrinolysis.

Side-effects of tranexamic acid and use in surgery and trauma

TXA is widely used as a hemostatic[28]. The benefits during off-pump coronary artery bypass graft surgery and during cardiac surgery on cardiopulmonary bypass have been clearly demonstrated[29-31]. TXA has been shown useful in trauma care, both prehospital and during trauma surgery[32,33]. The most convincing multicenter RCT in trauma to date is the comparison of TXA vs placebo in over 20,000 patients in the CRASH-2 trial[34]. This study showed that early administration of TXA safely reduces the risk of death in bleeding trauma patients and is highly cost-effective. They emphasize the importance of early treatment and state that TXA treatment beyond 3 hours of injury is unlikely to be effective.

The biggest concerns with TXA administration relate to the potential for thrombotic events and seizures[35]. The risk of thromboembolic phenomena associated with tranexamic acid use has traditionally led to caution in its use, particularly in those with other risk factors. There is currently no evidence that the use of TXA increases the risk of thromboembolic events such as myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism[36]. However it is recommended to take precautions in case of previous thrombotic events or with concomitant use of other prothrombotic drugs.

Seizure activity after TXA has also been described[37]. TXA can cross the blood–brain barrier and might increase seizures by antagonizing inhibitory gamma-aminobutyric acid receptor type A (GABAA) in brain, although the mechanism for this is yet to be confirmed[37]. Most TXA-associated seizures occur in patients who have undergone cardiac procedures[38,39]. However, several case reports indicate that TXA-associated seizures also occur in nonsurgical patients.

Overall, the cumulative evidence shows that TXA is a well-tolerated drug when delivered orally, intravenously and/or topically. Other minor, well tolerated side-effects include gastrointestinal disturbance, allergic skin reaction and visual disturbance[40].

Use of tranexamic acid for treatment in postpartum hemorrhage (Table I)

Duclos-Bouthors et al. were the first to study TXA for the treatment of established PPH[41]. In a cohort of 144 patients with proven PPH of > 800 mL following vaginal delivery, either TXA (dose of 4g IV followed by 1g over 6 hours in infusion) or no TXA were administered[41]. In the treatment arm, less blood loss, reduced duration of blood loss, less transfusion requirements and less progression to severe PPH were note[41]. Only mild side-effects were noted with TXA.

In the WOMAN-trial the use of TXA 1g, repeated once if bleeding continued after 30 minutes or re-started, was studied in women with established PPH[42]. Over 20,000 women were included in this multicenter RCT involving almost 200 centers. Death due to bleeding was significantly reduced in women given tranexamic acid: 155 [1.5%] of 10,036 patients vs 191 [1.9%] of 9,985 in the placebo group (risk ratio 0.81, 95% CI 0.65 - 1.00; p = 0.045). This effect was especially present in women given treatment within 3 hours of delivery (1.2% in the tranexamic acid group vs 1.7% in the placebo group, risk ratio of 0.69, 95% CI 0.52 – 0.91; p = 0.008). Complications and side-effects were similar between TXA and placebo. Overall mortality was similar between the groups[42].

Diop et al. recently investigated the effect of oral TXA in a dose of 1950 mg as adjunct to misoprostol in 256 women with established PPH of an estimated volume of >700 mL[43]. These authors could not identify any differences in bleeding outcomes.

Two very similar meta-analysis pooled the data of the WOMAN trial with the data from Duclos-Bouthors et al. and not surprisingly concluded that "TXA when administered intravenously reduces mortality due to bleeding in women with primary PPH, irrespective of mode of birth, and without increasing the risk of thromboembolic events"[44,45].

Clearly, the use of TXA is increasing and more and more guidelines recommend TXA early in the treatment of established PPH. However, in some recent editorials or opinion papers, the value of TXA in PPH especially in the developed world is questioned and discussed[46,47]. This was reinforced by Gilissen et al. who, in a Dutch retrospective cohort study which included 1250 patients, could not identify any benefit related to blood loss or need for transfusion when TXA was administered[48]. Despite the reservations made by many authors, currently the evidence supports the use of TXA 1g IV repeated once when abnormal blood loss is noted. Preferably, TXA is given early after delivery and the onset of PPH.

Use of tranexamic acid for prevention of postpartum hemorrhage (Table II)

Yang and co-workers studied the administration of TXA in a dose of 1g or 0.5g and compared it to 2 control groups[49]. The study was a randomized trial involving 400 parturients who underwent vaginal delivery. All patients received oxytocin. At delivery of the baby TXA 1g, 0.5g, 0.5g aminomethyl-benzoic acid or placebo were administered[49]. With 1g of TXA PPH (defined as blood loss of more than 400 mL) was 6% versus >20% in the control groups. Gai et al. studied prophylactic TXA 1g or placebo during cesarean section in 180 patients[50]. Blood loss was significantly reduced with TXA.

The TRAAP trial is a multi-center RCT which randomized 4079 women who were planned to have a vaginal delivery at term[51]. Immediately after delivery, patients received either 1g of TXA or placebo. The primary outcome was the incidence of PPH defined as a blood loss greater then 500 mL. All women also received oxytocin at delivery. The

Table I. — Overview of trials of tranexamic acid (TXA) administered after postpartum hemorrhage was established.

Reference	Study methodology	Number of patients	Outcome
Duclos-Bouthors et al. (41)	TXA 4g vs no TXA in proven hemorrhage (>800 mL)	144 women	Less blood loss Less transfusion Less severe PPH
WOMAN trial (42)	TXA 1g versus placebo	20,000 women	Death due to bleeding reduced if TXA given within 3 hours after onset of bleeding
Diop et al. (43)	TCX 1950 mg versus placebo	256 women	No difference in outcomes
Shakur et al. (44)	Meta-analysis		Reduced mortality No increased risk of complications
Della Corte et al. (45)	Meta-analysis		Reduced mortality No increased risk of complications
Gilissen et al. (48)	Retrospective study	1250 women	No benefit of TXA

Table II. — Overview of trials of prophylactic administration of tranexamic acid (TXA) in the prevention of postpartum hemorrhage.

Reference	Study methodology	Number of patients	Outcome
Yang et al. (49)	TXA 0.5 or TXA 1 or placebo or 0.5 g aminomethyl-benzoic acid at delivery of baby	400 women	Less blood loss Lower incidence of PPH
Gai et al. (50)	TXA 1g versus placebo	180 women	Less blood loss
TRAAP trial (51)	TCX 1g versus placebo	4079 women	No difference in PPH incidence; higher incidence of clinically significant blood loss in placebo group; no difference in side-effects.
TRAAP 2 (52)	TCX 1g versus placebo, both groups with uterotonic agent	4551 women	Reduced incidence of postpartum hemorrhage of > 1000 mL in the TXA group.

incidence of PPH was 8.1% in the TXA-group and 9.8% in the placebo group (Relative risk of 0.83, p = 0.07). This difference did not reach statistical significance. According to the assessment of the obstetrician performing the delivery, clinically significant blood loss was more frequent in the placebo group as compared to the TXA-group: 10.4% versus 7.8%. In the TXA group also less rescue uterotonic agents were required and there were less patients with a blood loss of more than 500 mL. Mean blood loss and postpartum hemoglobin levels were similar between the groups. Side-effects were similar between groups, except for more nausea and vomiting in the TXA group.

In the TRAAP2 trial, 4551 women, undergoing cesarean section, were randomized to receive 1g TXA or placebo, always combined with a uterotonic agent.52 The composite endpoint of blood loss greater than 1000 mL or the need for blood transfusion within two days after delivery occurred in 27% in the TXA group and in 32% of cases in the placebo group. All other outcome variables were similar between the groups.

The results of these initial trials and the two TRAAP trials were confirmed in many other smaller studies[53-63] and in several meta-analyses[64-71]. Blood loss was reduced, the incidence of PPH was reduced and the need for blood transfusion was diminished. However, Ker et al. questioned the validity of these results because they identified many flaws in some of the RCT's. Flaws were related to randomization, group allocation and blinding[72].

TXA is safe in women of reproductive age. When given slowly, the risk of seizures is low. Thrombo-embolic complications occur extremely infrequently and in a similar incidence in the control groups.

Recently, Bamber and Ali in an excellent editorial discussed the available evidence and concluded that certainly in assisted vaginal delivery and cesarean section we should consider to administer prophylactic TXA immediately after delivery[46]. Also, after normal vaginal delivery they suggest using TXA in a prophylactic manner. Recommended doses are 1g TXA, potentially repeated once.

Conclusions (Box 1)

GMore and more guidelines support the use of early administration of TXA when PPH occurs. One gram, repeated if insufficient effect, should be given within 3 hours after onset of PPH. Prophylactic administration is heavily debated. For some high risk cases routine prophylaxis should be offered to patients because blood loss is reduced whilst very few complications occur. For others routine administration is currently not recommended because of the limited positive effects especially in the developed world.

Box 1: Recommendations for TXA use in obstetrics
Established PPH: Give TXA 1g as soon as possible, repeat if effect is limited or bleeding re-occurs.
Prophylaxis in patients at high risk for PPH: Recommended, TXA 1g.
Prophylaxis in patients with a low risk for PPH: Currently not recommended.

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