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Tranexamic acid for the prevention and treatment of postpartum hemorrhage : a review

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Abstract : *Background :* Postpartum hemorrhage (PPH) is a frequent complication and a major cause of maternal death. PPH can be due to retained placenta, uterine atony, genital tract trauma or coagulopathy. Tranexamic acid (TA), an anti-fibrinolytic agent, can be useful to prevent or treat PPH. In this review, the effectiveness and safety of TA was evaluated.
Methods : Randomized trials comparing TA and placebo in women undergoing vaginal or cesarean delivery were identified. The distinction between the use of TA as a prophylactic or a therapeutic agent was made. The primary outcome in most studies was estimated blood loss during and after delivery. The secondary outcomes were the need for blood transfusion, changes in hemoglobin concentration, the incidence of PPH, side effects and possible complications of TA.
Results : Nine randomized trials involving a total of 25,815 women were included. Most trials were small, except for the *TRAAP* and the *WOMAN* trial. As a prophylaxis, TA decreased blood loss during and after childbirth, but not the need for blood transfusion. Used for therapy of PPH, TA reduced death due to bleeding.
Side effects of TA, such as nausea and vomiting were mild and reversible. There was no difference in the incidence of thromboembolic events between TA and placebo.
Conclusion : TA has a place in the therapy of PPH when given as soon as possible. The effect as a prophylaxis of PPH is less clear. Additional trials are needed to determine the optimal dose and use of TA. However, TA is a cheap agent, complications are minor, and There is no increased incidence of thromboembolic events.

Key words : postpartum hemorrhage ; tranexamic acid.

Introduction

Postpartum hemorrhage (PPH) is a major cause of maternal death. Tranexamic acid (TA) is an anti-fibrinolytic agent and is used in a variety of surgical procedures. Its use in the prevention or treatment of PPH is less obvious. We reviewed the literature to examine the evidence for the use of TA in the prevention and treatment of PPH.

Postpartum hemorrhage

PPH is defined as a blood loss of more than 500 mL after vaginal delivery and more than 1000 mL after cesarean section (1). PPH is one of the most frequent and severe maternal complications. It occurs in 3 to 5% of all vaginal deliveries and is still an important cause of maternal mortality, especially in developing countries. The risk of a massive bleeding after delivery is high because of the high uterine arterial blood flow. In late pregnancy, the uterine blood flow is estimated to range between 500 and 700 mL/min, which is about 15 % of total cardiac output. At the time of delivery, blood loss is controlled by contraction of the myometrium, local decidual hemostatic factors, and systemic coagulation (platelets and clotting factors). When there is an imbalance between these mechanisms, PPH occurs. Causes of PPH are retained placenta, uterine atony, genital tract trauma and coagulopathy (Table 1).

Table 1

Causes of postpartum hemorrhage (the 4 T's)

Tissue	Retention of tissue from placenta
Tone	Atony of the uterus
Trauma	Injury of the uterus, cervix, vagina, or perineum
Thrombin	Coagulopathy, due to consumption of clotting factors and hemodilution

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Table 2

Treatment of postpartum haemorrhage (1)

Before delivery	Screen for risk factors Basic laboratory evaluation Ensure IV access
At delivery	Plasma expansion by crystalloids (target systolic pressure > 90 mmHg) Oxygen therapy if necessary Bair hugger (protection against hypothermia) Oxytocin IM or IV (slow bolus 5-10 IU, infusion 5-10 IU/h with max 40 IU)

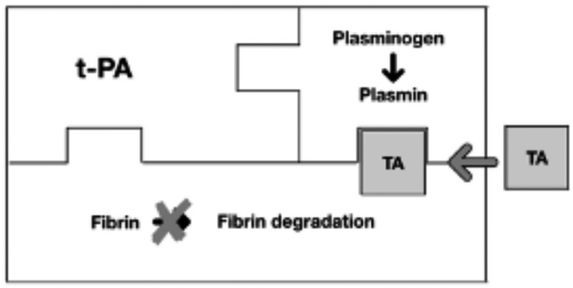

Fig. 1. — Anti-fibrinolytic action of tranexamic acid.

Retained placenta occurs in 1% after vaginal delivery. Uterine atony is the most common cause of PPH. It can occur immediately after labor or several hours later. A dilated uterus can collect a significant amount of blood (2). Genital tract trauma can be the result of a laceration, uterine rupture or surgical incision. Coagulopathy is both a cause and a result of PPH. Severe bleeding leads to the consumption of clotting factors and, as a consequence, less efficient clotting to stop bleeding.

The diagnosis of PPH is based on clinical signs (3). The volume of blood loss is usually underestimated by obstetricians, anesthesiologists, and midwifes. To avoid underestimation, the French College of Gynecologists and Obstetricians recommends the use of collect bags for vaginal delivery (1).

PPH is usually a preventable cause of death when diagnosis and management is instituted correctly in time. Preventive administration of uterotonics is effective in reducing the incidence of PPH (Table 2) (1).

Tranexamic acid

TA is an anti-fibrinolytic agent and a synthetic derivative of lysine. It was discovered in the 1950s (4). Tissue plasminogen activator (t-PA) converts plasminogen into plasmin. Trauma and childbirth trigger the release of t-PA, thus promoting fibrinolysis and bleeding. TA binds to plasminogen and plasmin, and inhibits binding of plasminogen at the lysine residues of fibrinogen. As a consequence, fibrin cannot be broken down (Fig. 1).

It is still unclear which dose of TA is optimal (5,6). Recommended doses in the literature vary largely, ranging from 1 mg/kg/h to 16 mg/kg/h, with or without a loading dose (6,7). In the *CRASH-2* study in trauma patients, a loading dose of 1 g was given over 10 minutes followed by an infusion of 1 g over 8 hours (8).

TA can be given orally, intramuscularly, and intravenously. There is good absorption after oral intake, with a maximum plasma concentration after two or three hours. It is also rapidly absorbed following intramuscular injection, with a maximum plasma concentration after 30 minutes.

TA is mainly distributed in the liver, kidneys and lungs. Three percent of TA is bound to plasma proteins. The clearance of TA is mainly renal, and its elimination half-life ranges between two to three hours. Dosage adjustment is needed in patients with renal impairment. TA crosses the blood-brain barrier. The concentration of TA in breast milk is about 1% of the plasma concentration (4). TA also crosses the placenta, but there are no well controlled studies in pregnant women. Studies done in mice, rat and rabbits, show that TA has no adverse effect on the embryo-fetal development, neither on the viability, growth and development in the perinatal and postnatal period (9).

Generally, TA is well tolerated. Nausea and vomiting are the most frequent gastrointestinal side effects (10). Other minor side effects are headache, abdominal discomfort, back pain and dizziness (4). The mechanism of TA – inhibiting the breakdown of fibrin – might increase the risk of thromboembolic events. However currently, there is no evidence of an increased risk of thromboembolic events after TA intake (11,12). Rapid administration of intravenous TA can cause hypotension (4). TA binds to $GABA_A$ receptors and can provoke hyperexcitability of the central nervous system. Topical use of TA to the cortex induces epileptic seizures in rats (13). This effect is dose-dependent. The accidental intrathecal injection of TA in humans has been reported to cause epileptic seizures and even death (14-16). In a retrospective multivariate analysis in almost 12,000 cardiac surgery patients, 0.9% developed postoperative convulsive seizures and TA was the only modifiable factor. There was an increased risk of seizures when the dose of TA exceeded 80 (17).

In a meta-analysis TA has been shown to decrease bleeding and to reduce blood transfusion by a third in surgical patients (18). In the *CRASH-2* study, TA reduced all-cause mortality and the risk

Table 3

Overview of the randomized-controlled trials comparing tranexamic acid with placebo

	Population	Methods	Conclusion	Side effects
Vaginal delivery		**TA vs placebo**		
TRAAP	3891	1 g TA IV over 30-60 seconds at delivery of the anterior shoulder after prophylactic oxytocin IV	1. = PPH 2. = blood loss: 220 mL vs 237 mL = drop in hemoglobin	↑ vomiting or nausea: 7% vs 3% ↑ mean liver aminotransferase levels = PT, aPTT, fibrinogen level = in thromboembolic events
Gungorduk et al.	439	1 g TA IV over 5 min at delivery of the anterior shoulder	1. ↓ blood loss: 262 mL vs 350 mL 2. ↓ PPH: 2% vs 7% = blood trans-fusion: 0.5% vs 0.4%	no major complication ↑ nausea: 15% vs 5% ↑ vomiting: 14% vs 6% = PT, aPTT, liver/renal blood tests
Mirghafourvand et al.	120	1 g TA IV over 10 min at delivery of the anterior shoulder	1. ↓ blood loss: 519 mL vs 659 mL 2. = drop in hemoglobin = PPH: 15% vs 25%	= minor side effects
Cesarean section				
Gungorduk et al.	660	1 g TA IV over 5 min > 10 min prior skin incision	1. ↓ blood loss: 500 mL vs 601 mL 2. ↓ PPH: 2% vs 6% = blood transfusion: 0.6% vs 2.2% ↓ additional uterotonics: 9% vs 15%	= PT, aPTT, liver or renal functional tests = in birth weight, Apgar score = in thromboembolic events
Movafegh et al.	100	10 mg/kg TA IV over 10 min 20 min before spinal anesthesia	1. ↓ blood loss: intraoperative: 263 mL vs 405 mL postoperative: 67 mL vs 141 mL 2. ↓ drop in hemoglobin : 1.0 g/dL vs 1.8 g/dL ↓ amount of oxytocin: 39 vs 43 units	= in blood test = complications
Senturk et al.	223	1 g TA IV over 5 min 10 min before incision	1. ↓ blood loss: 272 mL vs 347 mL 2. ↓ drop in hemoglobin: 1.1% vs 1.3%	no gastrointestinal side effects no venous thromboembolism
Xu et al.	262	10 mg/kg TA IV 10-20 min before spinal anesthesia	1. ↓ blood loss: 379 mL vs 442 mL 2. ↓ drop in hemoglobin: 1.1 g/dL vs 1.6 g/dL	= PT, aPTT, platelet count no renal failure, seizure, maternal death = mild transient adverse effects
Sujata et al.	60	10 mg/kg TA IV 10 min before skin incision	1. ↓ additional uterotonic drugs: 23% vs 83% 2. ↓ blood loss: 432 mL vs 819 mL = postoperative hematocrit: 31% vs 29% = blood transfusion: 3 vs 10 patients	
Therapeutic				
WOMEN	20060	1 g TA IV at 100 mg/min A second dose could be given when necessary	1. = death from all causes or hysterectomy 2. ↓ deaths due to bleeding: 1.5% vs 1.9% ↓ laparotomy to control bleeding: 0.8% vs 1.3%	= incidence of thromboembolic events: 0.3% vs 0.3% = incidence of renal, cardiac or respiratory failure

= No significant difference between groups (TA vs control; $p > 0.05$) ; ↑ **:** Difference between groups (TA vs control) is higher ($p < 0.05$) ; ↓ **:** Difference between groups (TA vs control) is lower ($p < 0.05$) ; 1. : Primary outcome ; 2. : Secondary outcomes.

of death due to bleeding in trauma patients (8). The beneficial effect of TA on the risk of death in trauma patients varied with the delay between injury and TA administration : the earlier TA was given, the greater the effect on the risk of death. Treatment given after 3 hours seemed to be associated with an increased risk of death (19). The use of TA in obstetrics is less obvious.

Methods

Up to November 6th, 2018, we searched PubMed, MEDLINE and ClinicalTrials.gov databases using the following MeSH terms : tranexamic acid, postpartum hemorrhage, vaginal delivery and cesarean section. References of these articles were checked for additional studies. This search led to the retrieval of 31 studies. Out of them, only randomized, double-blind, placebo-controlled studies reported in English were retained. After this selection, nine studies were further analyzed.

In the analysis, the distinction between prophylactic and therapeutic use of TA was made, as well as between vaginal delivery and cesarean section. The primary outcome in most studies was the estimated blood loss during and after delivery, except in three studies. The primary outcome of the *TRAAP* trial was the incidence of PPH (20).

The composite primary endpoint of the *WOMAN* trial was death from all-causes or hysterectomy (21). *Sujata et* al investigated the requirement of additional uterotonics as primary outcome (22). The secondary outcomes were the need for blood transfusion, changes in hemoglobin concentration, the incidence of PPH, and side effects and possible complications of TA.

Results

Prophylactic use of TA

Eight studies used TA as an agent to prevent PPH : three during vaginal delivery and five during cesarean section.

Vaginal delivery

In the *TRAAP* trial, 3,891 women at maternity units in France received 1g of TA or placebo after the vaginal delivery of the anterior shoulder in addition to IV oxytocin (20). There was no significant difference in the incidence of PPH (8.1% in TA groups and 9.8% in the placebo group ; p = 0.07). The incidence of provider-assessed clinically significant PPH and the use of additional uterotonic agents for bleeding was lower in the TA group. The authors had anticipated that TA might reduce the incidence of PPH more among women in whom vaginal delivery required interventions (episiotomy or operative vaginal delivery) than among those in whom delivery was straightforward. However, the trial was not powered to perform subgroup analysis.

The other two trials were smaller : 439 and 120 women respectively. Both found a decrease in postpartum blood loss in the TA group (23,24). However, there was no difference in the need for blood transfusion or drop in hemoglobin concentration between groups (23).

Cesarean section

Five trials compared the use of TA and placebo in women undergoing cesarean section. All studies found a significant reduction in blood loss during cesarean section in the group that received TA (25-28, 22). In some studies the drop in hemoglobin was lower (26, 27, 22) in the TA group, in another study there was no difference (28). The incidence of blood transfusion was not different (25). The use of uterotonics was less in women that received TA (26, 22).

Therapeutic use of TA

The *WOMEN trial,* published in May 2017 and including more than 20,000 women, is the only randomized, double blind, placebo-controlled study examining the role of TA in the treatment of PPH after vaginal delivery or cesarean section (21). The *WOMAN* trial can be seen as the successor of the *CRASH-2* trial. The study started in 2010 in 21 countries, mostly in Africa. Most women received prophylactic uterotonics. When PPH was diagnosed (defined as a blood loss of more than 500 mL after a vaginal delivery, a blood loss of 1000 mL after a cesarean section or any blood loss compromising the hemodynamic status), the women received 1 g TA over 10 min or placebo (0.9% NaCl). When the bleeding persisted after 30 minutes or stopped and restarted within 24 hours of the first dose, a second dose of 1 g TA or placebo was given. The composite primary endpoint was death from all-causes or hysterectomy within 42 days of giving birth. The composite primary endpoint was not different between groups for two reasons. First, more than one quarter of deaths were not due to bleeding (pulmonary embolism, organ failure, sepsis), which were not different between groups. Second, there was no significant difference in the incidence of hysterectomy between groups, probably because hysterectomy is an early intervention to prevent death from exsanguination in developing countries. However, death due to bleeding was reduced in women given TA (1.5% vs 1.9% ; p = 0.045), especially when TA was administered within 3 hours of giving birth (1.2% vs 1.7% ; p = 0.008). After 3 hours of giving birth, TA did not reduce death due to bleeding. The number of laparotomies to control bleeding was lower in the TA group (0.8% vs 1.3% ; p = 0.002).

Complications

Six of the nine studies examined the complications due to the use of TA. Noteworthy, in seven of the nine trials, women with contraindications to TA (hemostatic abnormalities, history of thrombosis, epilepsy) or risk factors for PPH (abnormal placenta, hypertensive disorders such as preeclampsia or HELLP, and personal or family history of PPH) were excluded, except for the study of *Sujata et a*l., who included women with at least one risk factor for PPH (pregnancy hypertension, placenta abnormalities, …) (22). The *WOMAN* trial did not have exclusion criteria (except lack of an informed consent) (21).

Most complications were mild and reversible. Gastrointestinal side effects, such as nausea, vomiting and diarrhea were the most frequent. Nausea or vomiting was at least doubled in the group that received TA, but was severe in none of the cases (20, 23). Other trials described an increased incidence of these minor side effects, but their results were not significant (24, 28). None of the trials described an increased incidence of thromboembolic events. In the *WOMAN* trial, there was no difference between groups in the incidence of thromboembolic events or organ failure (21). The study of *Movafegh et al.* did not find any complication – neither for mother or neonate – in the group that received TA (26).

Discussion

It is difficult to give a general advice about the effectiveness and safety of TA after delivery. Based on the literature, the evidence to use TA is stronger for treatment than for prevention of PPH.

Used as a prophylactic agent, TA did not reduce the incidence of PPH in the *TRAAP* trial (20). Only markers of PPH (provider-assessed clinically significant PPH and the use of additional uterotonic agents for bleeding) were reduced. In the other studies where TA was used as a prophylactic agent, blood loss was significantly lower (25-28, 22). However, the clinical relevance of this finding is questionable, because the drop in hemoglobin (26-28), the need for transfusion (25) or additional uterotonics was not consistently increased (25, 26).

Used as a therapeutic agent, TA did reduce death due to bleeding and the need for laparotomy to control bleeding in the *WOMEN* trial, but only when TA was administered within 3 hours after giving birth (21). The authors concluded that TA should be given as soon as possible after the onset of bleeding. The *WOMAN* trial was performed in low- and middle-income countries, where the treatment of PPH is limited, and where a cheap agent like TA can offer a benefit. The World Health Organization (WHO) recommends that TA should be administered early when PPH is diagnosed, as a first-line agent together with uterotonics (29). The benefits of using TA in high-income countries is less clear (29,30). The American College of Obstetricians and Gynecologists (ACOG) recommends TA to be used as a second-line agent in the treatment of PPH when uterotonics have insufficient effect (29). The guideline of ACOG is in contradiction with the advice of the WHO. However, since every 15 minutes delay in the administration of TA is associated with, approximately, a 10% reduction in the benefit against bleeding-related deaths (20, 31), it is reasonable to add TA early in the protocols of PPH.

Complications were mild and reversible. Most studies found a doubling of the incidence of nausea and vomiting in the group that received TA. There was no increased incidence in thromboembolic events, although the risk to develop a postpartum thromboembolic event is increased in pregnancy due to the hyper-coagulable state.

Our review has some limitations. First, only two large trials were retreived, the *WOMAN* and the *TRAAP* trial (20,21). The vast majority of the studies reported were small. Second, in almost all studies, women with contraindications for the use of TA or risk factors for PPH were excluded. However, in the largest study, the *WOMEN* trial, there were no exclusion criteria and there was no increase in thromboembolic events (21).

Conclusion

TA has a place in the therapy of PPH when given as soon as possible. The effect as a prophylaxis of PPH is less clear. However, there is a thin line between the use of TA as a prophylactic or as a therapeutic agent. With active bleeding, it seems logical to give TA as quickly as possible instead of waiting for a formal diagnosis of PPH. Additional trials are needed to determine the optimal dose of TA. TA is a cheap agent, complications are minor, and, in the largest trial, there was no increased incidence in thromboembolic events.

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