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FACULTY OF MEDICINE

The use of tranexamic acid in pregnant women in the prevention and management of postpartum bleeding

Sabine Thieren

Presented in fulfilment of the requirements for the degree of Master of Medicine

Promotor: Prof. Dr. Van de Velde Marc

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Sabine Thieren, Marc Van de Velde, MD, PhD, EDRA

Abstract

Background

Postpartum haemorrhage (PPH) is one of the most frequent complications after labour and giving birth and a major cause of maternal death. Major haemorrhage, an obstetric emergency, can be due to uterine atony, retained placenta, genital tract trauma or coagulopathy. Tranexamic acid (TA), an antifibrinolytic agent, can be useful in the treatment of postpartum bleeding. In this systematic review, the effectiveness and safety of TA was evaluated.

Methods

Fifteen randomized trials comparing TA and placebo in women undergoing vaginal or caesarean delivery were identified. Four trials were excluded and eleven trials were included in this review. The primary outcome variable is blood loss during and after delivery. The secondary outcomes are the need for transfusion, the incidence of PPH, the side effects and possible complications of TA.

Results

Eleven randomized trials involving a total of 2488 women were included. The effect and complications of the use of TA was evaluated as compared to placebo. All studies note a significant reduction of blood loss in the group which received TA. Only a few articles described the need for transfusion, but there was no significant difference. Five trials note side effects of TA, mostly nausea, diarrhoea and vomiting, but this didn't reach significance. Two large trials are still ongoing and the results are expected in 2017.

Conclusion

We conclude that blood loss is significantly lower when using TA as compared to placebo. The need for transfusion is rather inconclusive, just like the dose and mode of administration of TA. Most studies used 1 gram of TA. Complications due to the use of TA are rather mild and reversible. There was no increased risk of thrombotic events.

Key words: postpartum haemorrhage, tranexamic acid.

Introduction

Postpartum haemorrhage is a major cause of maternal death in both underdeveloped and developed countries. TA, an antifibrinolytic agent, is used in a variety of surgical procedures and can be useful in the treatment of postpartum bleeding. In this systematic review, we compared eleven randomized controlled trials comparing TA and placebo in the context of postpartum bleeding.

Background

Postpartum bleeding

Postpartum haemorrhage (PPH) is one of the most frequent complications after labour and delivery. It occurs in 3% to 5% of all vaginal deliveries. PPH can be due to uterine atony, retained placenta, genital tract trauma or coagulopathy (Table 1).

Table 1: Causes of postpartum haemorrhage

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

PPH is defined as a blood loss of more than 500 mL after delivery (1). The incidence of PPH is 5% in population-based studies. However, The Royal College of Obstetricians and Gynaecologists defined minor PPH as a blood loss of less than 1000 mL after delivery with an incidence of 2%. Moderate PPH is a blood loss of 1000 to 2000 mL, severe PPH is a blood loss of more than 2000 mL. Another definition of PPH is a blood loss of more than 500 mL after vaginal birth and a blood loss of more than 1000 mL after Caesarean delivery (2). Obstetric haemorrhage is still an important cause of maternal mortality in developing and developed countries. PPH represents 13% of maternal deaths in developed countries (3). PPH is usually a preventable cause of death when timely diagnosis and appropriate management is instituted correctly.

The risk of a massive bleeding after delivery is high because of a high uterine arterial blood flow. In late pregnancy the blood flow is 500 to 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 haemostatic factors and systemic coagulation factors such as platelets and clotting factors. When there is an imbalance of these mechanisms, PPH occurs. Causative factors are retained placenta, uterine atony and coagulopathy. Genital tract trauma due to delivery is another cause of PPH.

Retained placenta affects 1% of all vaginal deliveries and needs mostly manual exploration. Uterine atony is the most common cause of PPH. It can occur immediately after labour or several hours later. A dilated uterus collects a significant amount of blood, but is often responsive to uterotonic therapy, such as oxytocin and methylergonovine. Coagulopathy is both a cause and a result of PPH. Severe bleeding leads to the consumption of clotting factors whereby there are less clotting factors to stabilise the bleeding. Genital tract trauma can be the result of a laceration, uterine rupture or surgical incision.

The diagnosis of PPH is based on clinical signs (Table 2). The volume of blood loss is usually underestimated by obstetricians and midwifes. Differential diagnoses of PPH are neuraxial anesthesia and vasovagal reaction. Both can give vasodilation with syncope, tachycardia and hypotension, but these differential diagnoses are reversible and not life threatening.

Table 2: Symptoms related to blood loss with postpartum bleeding

Blood loss: percent (ml)	Blood pressure (mmHg)	Signs and symptoms
10 – 15 (500 – 1000)	Normal	Palpitations, lightheadedness, mild increase in hart rate
15 – 25 (1000 – 1500)	Slightly low	Weakness, sweating, tachycardia
25 – 35 (1500 - 2000)	70 – 80	Restlessness, confusion, pallor, oliguria, tachycardia
35 – 45 (2000 – 3000)	50 – 70	Lethargy, air hunger, anuria, collapse, tachycardia

Tranexamic acid

Tranexamic acid (TA) is a synthetic derivate of lysine (Fig. 1, Fig. 2) and discovered in the 1950s. It is an antifibrinolytic agent that binds to plasminogen and thereby inhibits its binding to fibrin (4).

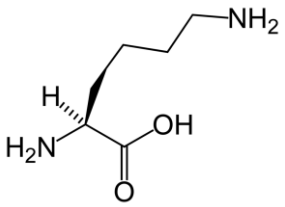


Fig. 1: Structural formula of Lysine

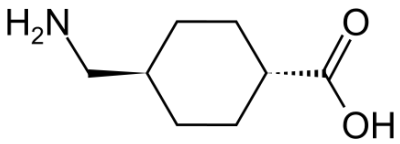


Fig. 2: Structural formula of Tranexamic Acid

Fibrin is a final product of the coagulation cascade after activation by different coagulation factors (Fig. 3). Fibrin is responsible for cessation of bleeding and maintains a haemostatic seal on the damaged vessel wall. Cross-linked fibrin also activates the fibrinolytic system to create a balance between the coagulation cascade and the fibrinolytic cascade. After binding fibrin with plasmin – which is first activated by tissue plasminogen

activator (t-PA) – fibrin is decomposed and fibrinolysis occurs. Plasmin binds to lysine residues on the surface of fibrin. Because TA is a synthetic derivate of lysine – it binds on the same place on plasmin as fibrin – so fibrin cannot bind to plasmin and the fibrin clot is stabilized (Fig. 4). This binding is reversible and TA is in competition with fibrin. TA binds with a high affinity to the lysine binding site and thereby almost completely blocks the binding site for fibrin. In addition TA blocks the binding of α_2-antiplasmin to plasmin and thereby inactivates plasmin.

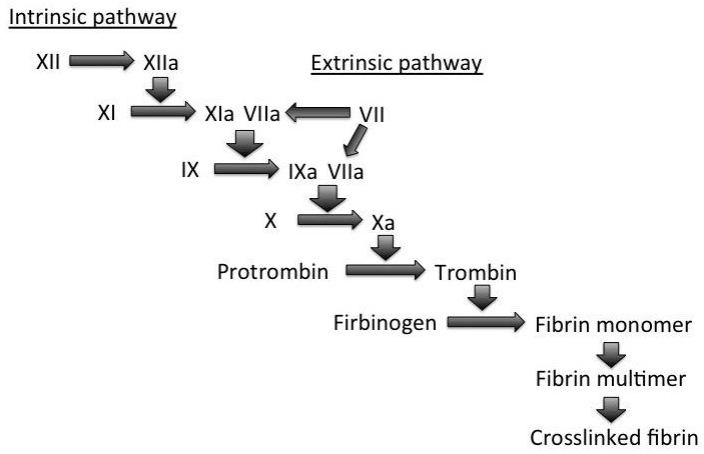


Fig. 3: Coagulation cascade with final product crosslinked fibrin

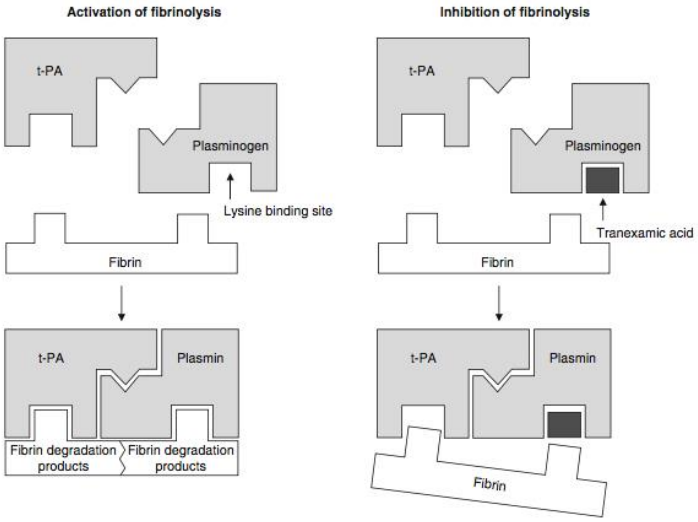


Fig. 4: Antifibrinolytic action of tranexamic acid (source: Dunn and Goa. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999; 57 (6): 1005-32.)

The optimal concentration of TA is still under discussion. *Harrow et al* proposed a dose of 10 mg/kg followed by 1 mg/kg/h for twelve hours as prophylaxis after cardiac surgery (5). This resulted in a significantly reduced blood loss. These investigators could not show an additional haemostatic benefit of larger doses. In contrast, *Karski et al* suggested using a higher dose. A better haemostatic control could be demonstrated

using a single dose of 100 mg/kg compared with 50 mg/kg (6). More recently *Sigaut et al* investigated the use of TA during cardiac surgery in a double-blinded, randomized study between 10 mg/kg bolus followed by 1 mg/kg/h compared with 30 mg/kg bolus followed by 16 mg/kg/h. The higher dose proved superior (7). It is still unclear which dose of TA gives the most optimal results.

TA can be given orally, intramuscularly and intravenously. There is good absorption after oral intake with a maximum plasma concentration after 2 to 3 hours. It is also rapidly absorbed following muscular injection with a maximum concentration 30 minutes after administration. Following intravenous administration the plasma concentration remains therapeutic for 5 to 6 hours.

The effect of TA can be noted from 10 mg/mL plasma concentration expressed as a prolonged protrombin time. A blood concentration of TA less than 10 mg/ml has no effect on the coagulation parameters. A maximal effect – seen as a reduction of plasmin activity – was dependant of tissue. A maximal reduction was seen in plasma after 30 minutes, in the liver after 90 minutes and in heart and muscle after 120 minutes.

Pharmacokinetics

TA is mainly distributed in liver, kidneys and lungs. A small percentage of TA, 3%, is bound to plasma proteins. The clearance of TA is mainly renal and has a half-life of 2 to 3 hours. Only a small amount of TA is metabolized and therefore negligible. Dosage adjustment is needed in patients with renal impairment, but isn't needed in patients with hepatic impairment because of the negligible amount of TA that is metabolized. The excretion of TA is mainly renal where there is no significant metabolisation.

More important is the distribution of TA in placenta, cerebrospinal fluid and joint fluid. TA crosses placenta and blood-brain barrier. Around 10% of the plasma concentration of TA is found in cerebrospinal fluid and aqueous humour concentrations. The excretion of TA in breast milk is about 1% of the plasma concentration (4). It is know that TA crosses the placenta, but there aren't well-controlled studies in pregnant women. Studies done in mice, rat and rabbits, show that TA had no adverse effect on the embryo-fetal development, neither on the viability, growth and development in the perinatal and postnatal period. (8)

Side effects of tranexamic acid

Generally, TA is well tolerated. Minor adverse effects, such as gastrointestinal side effects are described. Nausea and vomiting are more common in patients who used TA compared to controls (9). The mechanism of TA – inhibiting the breakdown of fibrin – might increase the risk of thrombo-embolic events. On the other hand there is no evidence of increased risk of thrombotic events (10,11).

TA may bind to $GABA_A$ receptors and provoke hyperexcitability in the Central Nervous System. *Slag et al* prove that the topical use of TA to the cortex can induce epileptic seizures in rats (12). This effect is dose related. *Garcha et al*, *Kaabachi et al* and *Mohseni et al* reported cases where accidentally TA was injected intrathecal in humans, which causes epileptic seizures and even death (13–15).

A positive side effect of TA is that TA would be a membrane stabilisator. This is described in a few cases where TA was used in the treatment of anaphylactic shock (16).

Use of tranexamic acid in surgery

TA is used in a variety of surgical procedures where there is a risk of intraoperative or postoperative bleeding (Table 3).

Table 3: Use of TA in surgery

	Study	Year	Type of surgery	Number of patients	Dosis
Cardiac Surgery	Myles et al	2016	Cardiac surgery	4631	50 mg/kg
	McHugh et al	2016	CABG	184	30 mg/kg + 15 mg/kg/h vs 15 mg/kg + 6 mg/kg/h
	Kimenai et al	2016	Pericard lavage	739	2g + 2g
Orthopaedic	Farrow et al (review)	2016	Hip fracture	770	
	Cankaya et al	2017	Knee arthroplasty	100	25 mg/kg, max 2g
	Colomina et al	2015	Spine surgery	95	10 mg/kg + 2 mg/kg/h
Traumatology	CRASH-2	2010	Trauma patients	20211	loading 1 g + 1 g over 8h
	McCaul et al (review)	2016	Trauma patients	20451	
Urology	Crescentie et al	2011	Prostatectomy	200	loading 500 mg + 250 mg/h
	Pourfakhr et al	2016	Prostatectomy	186	500 mg
Gynaecology	Topsoee et al	2016	Hysterectomy	322	1 g

Cardiac surgery

TA and epsilon aminocaproic acid, two antifibrinolytics have been used for a long time as prophylaxis to reduce bleeding in coronary artery bypass surgery. Recently, *Myles et al* compared in a randomized trial the use of TA and placebo in patients undergoing cardiac surgery (17). TA in a dose of 100mg/kg or 0,9% saline was given 30 minutes after induction. Several seizures were reported when given 100mg/kg and the dose of TA was halved to 50 mg/kg. The patients who received TA had less blood loss, with less need for blood transfusion, less major haemorrhage and less cardiac tamponade. The incidence of stroke, myocardial infarction, thrombotic complications and death were similar in both groups.

McHugh et al compared the use of a high-dose and low-dose TA for primary coronary artery bypass surgery (18). The use of TA reduces the use of allogeneic blood products and therefore reduces postoperative complications and mortality. However, the most optimal dose of TA remains unclear. *McHugh et al* prove that there is no difference between a high dose (30 mg/kg bolus followed by 15 mg/kg/h with 2 mg/kg priming dose in the bypass circuit) and a low dose (15 mg/kg bolus followed by 6 mg/kg/h with 1 mg/kg priming dose in the bypass circuit) TA. They suggested using the low-dose protocol, as it seems as effective as the high-dose protocol and might give fewer side effects.

Kimenai et al examined the effectiveness of the use of TA during pericardial lavage in cardiac surgery patients (19). There was no significant difference in het twelve hours post-operative blood loss between patients who received TA or placebo.

Orthopaedic surgery

Orthopaedic surgeons are often confronted with intraoperative and postoperative blood loss. Different placebo controlled, randomized trials suggest the efficacy of TA in reducing blood loss associated with total knee arthroplasty, total hip arthroplasty en hip fracture surgery. However some of these results are not significant (4). *Farrow et al* concluded that there was a lower need of blood transfusion in patients who received TA during hip surgery after a hip fracture (10). *Cankaya et al* compared the use of TA during knee arthroplasty, showing a significant difference between haemoglobin and haematocrit levels post-operative (20). *Colomina et al* also concluded that there is a significant difference in perioperative blood loss in patients undergoing major spine surgery. However, there was no statistically significant reduction of transfusion requirements (21).

Traumatology

Antifibrinolytics are used to reduce blood loss and mortality in trauma patients. The *Crash-2 trial* proves a benefit in mortality when using TA early after trauma (22). TA reduces also the risk of myocardial infarction and has no adverse effects on the vascular system (such as thrombosis, stroke or embolism). It is most effective when given within three hours after injury and becomes less so when given later (23,24).

Urology

Bleeding is a known intraoperative and postoperative complication of prostatectomy for which in some cases blood transfusion is needed. Topical and intravenous TA can be used, but the systematic use of TA is more effective. The intraoperative use of TA significantly reduces the need for blood transfusion during and after prostatectomy. *Crecentie et al* and *Pourfakhr et al* concluded that TA reduces the post-operative blood loss and need for blood transfusion after prostatectomy surgery (11,25).

Gynaecology

TA is also used in gynaecology surgery. *Topsoee et al* proved that TA reduces the total blood loss, incidence of substantial blood loss and the need for reoperations when 1 gram TA was given to patients who undergo a hysterectomy. TA was given at the start of the operation (26).

Methods

Electronic searches were performed on PubMed, MEDLINE, ClinicalTrials.gov databases started on October 10th till March 10th 2017. Randomized controlled trials comparing TA and controls were used. The MeSH terms were: tranexamic acid, postpartum, postpartum bleeding, vaginal delivery, caesarean section.

Randomized controlled trials comparing TA and placebo in women undergoing a vaginal or caesarean delivery were identified. Trials were excluded when a full text was not available in English. The primary outcome is estimated blood loss during and after delivery. The secondary outcomes are the need for blood product transfusion, the incidence of PPH, the side effects and possible complications of TA (such as nausea, vomiting, diarrhea, deep venous thrombosis and renal failure). For each trial, the Jadad score was calculated (Table 4).

Table 4: Jadad score

Study	Year		Number of participants	Number of patients who received TA	JADAD
Gungorduk et al	2011	Vaginal delivery	439	220	4
Ducloy-Bouthors et al	2011	Vaginal delivery	144	72	4
Mirghafourvand et al	2015	Vaginal delivery	120	60	4
Gai et al	2003	Caesarean section	180	91	4
Gungorduk et al	2011	Caesarean section	660	330	5
Movafegh et al	2011	Caesarean section	100	50	5
Poonia et al	2012	Caesarean section	100	50	2
Senturk et al	2013	Caesarean section	223	101	3
Xu et al	2013	Caesarean section	262	174	4
Singh et al	2014	Caesarean section	200	100	2
Sujata et al	2015	Caesarean section	60	30	5

Results

Fifteen trials were identified. Four were excluded because they were not in English. Eleven randomized controlled trials were used in our systematic review, involving a total of 2488 women (Table 5). All trials were published between 2003 and 2015. The median sample size is 226 women. Studies are geographically spread over the Middle East, Asia and France. Beside these studies, two large trials are still ongoing and the results are expected in 2017.

Table 5: Overview of the randomized controlled trials comparing tranexamic acid with placebo

Study	Year	Country	Type of delivery	Controls	Number of patients who received TA	Dose	Mode of administration	Conclusion
Gungorduk et al	2011	Turkey	Vaginal delivery	219	220	1g IV	TA in third stage of labor	The use of TA in the third stage of labor reduces postpartum blood loss Frequency of PPH is lower in the group who received TA The group who received TA needed less additional uterotonics No increased risk of thrombosis Minor adverse events (nausea, diarrhea) are uncommon
Ducloy-Bouthors et al	2011	France	Vaginal delivery	72	72	4g/1h IV + 1g/h for 6 hours	Bolus of 4g in 1 hour, followed by 1g/hour for 6 hours	Blood loss was significant lower in TA group than in the control group Bleeding duration was shorter and less progression to severe PPH Transfusion was less frequent than in controls
Mirghafourvand et al	2015	Iran	Vaginal delivery	60	60	2*500mg IV	TA after delivery of the anterior shoulder	Mean haematocrit decline is greater in placebo group and statistically significant No significant difference of mean blood loss from delivery of the fetus to placental delivery Less blood loss from placental delivery to 2h postpartum (significant) Frequency of calculated PPH is lower in TA group
Gai et al	2003	China	Caesarean section	89	91	1g IV	5 min before incision	The total quantity of blood from placental delivery to 2h postpartum was significantly reduced There was no statistical difference of blood loss from the time of placental delivery to the end of CS There was no statistical difference in the incidence of PPH from the end of CS to 2h postpartum between the two groups
Gungorduk et al	2011	Turkey	Caesarean section	330	330	1g IV	TA at least 10 minutes before skin incision	Blood loss is significant lower in TA group No difference between both groups in the requirement for blood transfusion No significant difference in vital signs More additional uterotonics needed in placebo group

Study	Year	Country	Type of delivery	Controls	Number of patients who received TA	Dose	Mode of administration	Conclusion
Movafegh et al	2011	Iran	Caesarean section	50	50	10 mg/kg IV	Infused over 10 min, 20 min before spinal anesthesia	Reduction of blood loss in group who received TA, intra-operative and postoperative Decline of hemoglobin was significantly decreased, but no difference in platelet count Amount of oxytocin used after CS was significantly reduced in TA group
Poonia et al	2012	India	Caesarean section	50	50	1g IV	5 min before incision	Reducing blood loss Safe to mothor as well as baby
Senturk et al	2013	Turkey	Caesarean section	122	101	1g IV	5 min before anesthesia and 10 min before incision	Significant difference in blood loss between both groups Significant difference in pre- and postoperation Hb between both groups TA can be effective in reducing obstetric bleeding
Xu et al	2013	China	Caesarean section	88	174	10mg/kg IV	immediately before CS	Total of blood loss two hours postpartum was significant decreased
Singh et al	2014	India	Caesarean section	100	100	1g IV	20 minutes before skin incision	Reduction of blood loss in group who received TA Can be safely used as a prophylactic agent
Sujata et al	2015	India	Caesarean section	30	30	10mg/kg IV	10 min before incision	TA before skin incision reduces the requirement for additional uterotonics Estimated blood loss at 48h was lower in TA group compared with controls No significant difference between both groups for blood transfusion TA is safe for the fetus no increased risk for trombogenetic episodes in the mother

Effect of tranexamic acid and dosage

Firstly, we compared randomized controlled trials, which looked at the use of TA in vaginal deliveries. *Gungorduk et al* compared the prophylactic use of TA (1g) with the use of a placebo (glucose 5%) in addition to prophylactic injection of oxytocin in the third stage of labour. The use of TA when administered in the third stage of labour reduces postpartum blood loss (27). *Mirghafourvand et al* showed that TA (2*500mg), when given after delivery of the anterior shoulder, reduces postpartum blood loss (28). The drop of haematocrit was significant lower in comparison with the control group. There is also no significant difference of mean blood loss from delivery of the baby to placental delivery, but there is a significant reduction of blood loss from placental delivery to 2 hours postpartum. In contrast to the previous studies, *Ducloy-Bouthors et al* studied the effect of a high-dose of TA, similar to the doses used in cardiac surgery, on blood loss in postpartum haemorrhage (29). The effect of TA is a significant reduction in blood loss and duration of the bleeding with less progression to severe PPH. More mild and reversible side effects were noted in the group which received the high-dose of TA. Two thromboembolic events were observed in the group of TA, possibly due to the high dose of TA.

Secondly, we looked at randomized controlled trials in which TA was used in Caesarean deliveries. *Gai et al* were the first to compare TA to a control group who didn't received TA. 91 women undergoing Caesarean section received 1g TA 5 minutes before incision. The total blood loss from placental delivery to two hours postpartum was significantly reduced in the group who received TA (30). *Gungorduk et al.* compared the use of TA (1g) and placebo (5% glucose) in women undergoing Caesarean section. Blood loss during Caesarean section was significant lower in women who received TA 10 minutes before skin incision. They also needed less additional uterotonics (31). *Movafegh et al* used 10 mg/kg infused over 10 minutes given 20 minutes before spinal anaesthesia. The blood loss was significantly reduced, less additional oxytocin was needed and there were no complications – neither for the mother, nor for the neonate – in the group who received TA (32). *Poonia et al* used the same dose as *Gungorduk*, 1 gram TA and TA was given five minutes before Caesarean section. A reduction of blood loss was noted in the TA group. *Poonia et al* suggest that TA can be used safely in pregnant mothers and babies (33). *Senturk et al* note a significant difference in pre- and postoperative haemoglobin between the group who received TA (1g) and a placebo group (5% glucose). The drop of haemoglobin in women who received TA was less compared to the placebo group (34). *Xu et al* used 10 mg/kg TA that was given immediately before Caesarean section. This was compared with a placebo group and demonstrated a reduction in blood loss after Caesarean section. Mild side effects were reported in the group who received TA (35). *Singh et al* prove a reduction of blood loss during and after Caesarean

section when TA (1g) was given prophylactic. *Singh et al* suggest that TA can be used as a prophylactic agent to prevent postpartum blood loss (36). *Sujata et al* compared the use of TA (10 mg/kg) with the use of a placebo (saline 0,9%) in women having at least one risk factor for developing PPH. Women who received TA needed less additional uterotonics after operative delivery (37). The eleven studies showed us that the blood loss was significantly lower when using TA (Table 6). We calculated the weighted average in both groups. The weighted average of the bloodloss in the group who received TA was 343,75 mL comparing 454,32 mL in the group who received placebo.

Table 6: Total blood loss

Study	Dose	Blood loss TA (ml)	Blood loss control (ml)	p-value
Gungorduk et al	1g IV	261,5 ± 146,8	349,98 ± 188,85	0,001
Ducloy-Bouthors et al	4g/1h IV + 1g/h for 6 hours	Mean:170	Mean: 221	0,041
Mirghafourvand et al	2*500mg IV	Mean: 519[1] Mean: 69	Mean: 659 Mean: 108	0,036 0,001
Gai et al	1g IV	359,29 ± 152,02	439,36 ± 191,48	0,002
Gungorduk et al	1g IV	499,9 ± 206,4	600,7 ± 215,7	0,001
Movafegh et al	10 mg/kg IV	262,5 ± 39,6[2] 61,1 ± 6,5	404,7 ± 94,4 141 ± 33,9	0,001 0,001
Poonia et al	1g IV	166,5 ± 24,72	378,48 ± 23,75	0,001
Senturk et al	1g IV	272,05 ± 143,23	346,87 ± 189,49	0,001
Xu et al	10mg/kg IV	379,2 ± 160,1	441,7 ± 189,5	0,02
Singh et al	1g IV	270 ± 30,88	510,45 ± 30,34	0,001
Sujata et al	10mg/kg IV	Mean: 432	Mean 819	0,001

[1] calculated total blood loss versus blood loss during placenta delivery to 2h postpartum
[2] intraoperative blood loss versus postoperative blood loss

Two large trials are still ongoing (Table 7). The first is the *WOMAN* trial. It can be seen as the successor of the *CRASH2* trial. In the *CRASH2* trial, patients received 1 gram TA in ten minutes followed by infuses of 120 mg/h during eight hours. Their conclusion was that TA reduces the risk of death in bleeding trauma patients and therefore that TA should be used in patients with bleeding trauma (22). As discussed above, there are several smaller studies about TA and its effect on blood loss in postpartum bleeding. But all these studies are rather small and less conclusive. The *WOMAN* trial is the first large randomized, double blind, placebo-controlled trial examining the effect and side effects on TA used in pregnant women. The trial started in 2010 in 22 countries, mostly in Africa, and recruitment of the planned 20,000 patients is finished (Table 8). When a postpartum bleeding is diagnosed – currently defined as a blood loss of 500 mL after a vaginal delivery, a blood loss of 1000 mL after a Caesarean section or any blood loss compromising the haemodynamic status of the patient – the woman received 1 gram TA at a rate of 1 mL/min or a placebo

(0,9% NaCl). When the bleeding persists after 30 minutes, a second gram TA is given at a rate of 1 mL/min (or placebo) (38). The primary outcomes are the incidence of death and the need for a hysterectomy.

The secondary outcomes are: blood transfusion, effect on quality of life, thromboembolic events, other medical events (such as renal failure, acute respiratory distress syndrome, hypertension), length of stay in hospital, status of the baby and a cost-effectiveness analysis. Results are expected mid 2017.

Table 7: Current trials

Study	Country	Type of delivery	Number of participants	Dose	Complications	Conclusion
WOMAN trial	22 countries	Vaginal delivery of caesarean section	> 20,000	1g IV (+ 1g)	Collect data on adverse events: thromboembolic events and secondary outcomes	Outcome: Primary: death or hysterectomy Secondary: death, surgical intervention: hysterectomy, blood transfusion, QoL (EQ-5D), thromboembolic events, renal failure/ARDS/hypertensive, length of stay in hospital, status of baby, cost-effectiveness analysis
TRAAP trial	France	Vaginal delivery	4000	1g IV	Follow-up during 3 months	Outcome: Primary: incidence of PPH Secondary: postpartum blood loss, proportion of women who needed additional uterotonic agents, arterial embolization, need for emergency surgery for PPH, mean peripartum change in haemoglobin and haematocrit

Table 8: List of countries who participate in the WOMEN trial

Europe	***Number of centers***
UK	7
Albania	4
Africa	
Burkina Faso	3
Cameroon	10
Cote d'Ivoire	1
Democratic Republic of Congo	10
Egypt	2
Ethiopia	3
Ghana	2
Kenya	9
Nigeria	53
Sudan	10

	Number of centers
Tanzania	6
Uganda	13
Zambia	6
Asia	
Bangladesh	5
Nepal	4
Pakistan	46
Americas	
Columbia	1
Ecuador	2
Jamaica	1
Oceania	
Papua New Guinea	1

Another trial which is still running is the *TRAAP* trial – Tranexamic acid for preventing postpartum haemorrhage after vaginal delivery – in which *Sentilhes et al* examine the effect of a low dose of TA after vaginal delivery in the prevention of a postpartum haemorrhage (39). The trial started in February 2015 and will end in May 2017. Patients receive 1g TA in two minutes or a placebo (0,9% NaCl) and both groups

receive prophylactic oxytocin. The inclusion criteria are: older than 18 years old, > 35 weeks of gestation and a planned vaginal delivery. The primary outcome is the incidence of PPH, which is defined as a blood loss of more than 500 mL after vaginal delivery. The secondary outcomes are: postpartum blood loss, proportion of women who needed additional uterotonic agents, arterial embolization, need for emergency surgery, mean peripartum change in haemoglobin and haematocrit. There will be a follow up of three months to monitor the potential side effects of TA, such as the hemodynamic parameters, gastrointestinal -, renal -, hepatic side effects, coagulation and venous or arterial thrombosis.

Complications

Five of the previous eleven discussed trails report possible complications due to the use of TA compared to placebo. Mostly, these complications were rather mild and reversible (Table 9).

Table 9: Complications due to the use of TA comparing placebo

	Nausea			Vomiting			Diarrhea		
	TA	Placebo	p-value	TA	Placebo	p-value	TA	Placebo	p-value
Gungorduk et al	15,00%	5,50%	0,001	13,60%	6,40%	0,010	7,30%	1,80%	0,01
Ducloy-Bouthors et al	6,00%	4,00%	0,280	15,00%	2,00%	0,002	-	-	-
Mirghafourvand et al	3,00%	0,00%	0,490	-	-	-	-	-	-
Gungorduk et al	-	-	-	-	-	-	-	-	-
Xu et al	2,87%	2,27%	0,440	5,75%	1,14%	0,010	-	-	-

	Deep vein thrombosis			Renal failure		
	TA	Placebo	p-value	TA	Placebo	p-value
Gungorduk et al	-	-	-	-	-	-
Ducloy-Bouthors et al	3,00%	1,00%	0,370	0,00%	0,00%	-
Mirghafourvand et al	-	-	-	-	-	-
Gungorduk et al	0,00%	0,00%	-	0,00%	0,00%	-
Xu et al	1,15%	2,27%	0,380	0,00%	0,00%	-

Most patients experienced gastrointestinal side effects, such as nausea, vomiting and diarrhea. *Gungorduk et al* describes minor side effects with the use of TA. Patients who received TA had more gastrointestinal side effects. There was a significant increase in patients who suffer from nausea, vomiting and diarrhea. Other side effects, such as tachycardia, headaches and shivering were not significantly increased. No major complications such as thromboembolic events were reported (27). *Ducloy-Bouthors et al* reported milder, reversible side effects in the group who received TA. The increase of vomiting was significant, but there was no significant increase of nausea. Other mild side effects were not reported. These investigators however also describe two deep vein thromboses in the group of TA and one DVT in the placebo group. Major

complications are rare and there was no significant increase in the group who received TA (29). The study of *Mirghafourvand et al* did not evaluate the safety of TA and side effects were marked as secondary outcomes. The only side effect was nausea, which was not significantly increased (28). In the study of *Gungorduk et al* where they compared TA and placebo in women who received a Caesarean section, minor side effects weren't evaluated. Thromboembolic events – divided in DVT, myocardial infarction, stroke, renal failure and pulmonary embolism – were evaluated but none of these major side effects were reported in the study (31). The study of *Movafegh et al* could not evaluate side effects since sample size was too small (32). Similar to the previous study, *Poonia et al* only reported nausea and vomiting in ten women who received TA and in two women in the placebo group (33). *Senturk et al* describes no drug allergies due to TA, neither gastrointestinal side effects, nor thromboembolic events (34). *Xu et al* describes more vomiting (significant) and dizziness (not significant) in the group who received TA. Two thromboembolic events were reported in the TA group and two events in the placebo group, so there was no increased risk of thromboembolic events in the group who received TA. Other major complications such as renal failure, seizures or maternal death were not reported (35). *Gai et al, Singh et al* and *Sujata et al* did not report any side effect or complication (30,36,37).

Discussion

Eleven studies were compared and a positive effect of TA in obstetric patients was suggested by most of these trials. The blood loss was always significantly lower when using TA, the bleeding duration was shorter and there was less need to use additional uterotonic agents. The time of measurement of the blood loss varies from trial to trial, but the total blood loss is significantly reduced in the group who received TA (Table 6). The weighted average of the bloodloss in the group who received TA was 343,75 mL comparing 454,32 mL in the group who received placebo. The total blood loss is significantly reduced and the difference is 110,57 mL, which is a reduction by a quarter (- 24,34%). The clinical relevance of this reduction is low in young women without risk factors for postpartum bleeding.

The need for blood transfusion was rather inconclusive. *Ducloy-Bouthors et al* suggest that there is less need for blood transfusion when using TA, but there isn't any data in their article. However, *Gungorduk et al* prove no significant difference in the need for blood transfusions.

Most studies used a dose of 1 gram TA, while others use a dose of 10 mg/kg. No definite conclusion can be drawn on which of these doses or any other dose is superior. *Ducloy-Bouthors et al* use a high dose of TA

(a bolus of 4 g, followed by an infuse of 6 g), which didn't have more benefit. However, more minor gastrointestinal side effect and deep venous thrombosis were reported.

Several studies discussed the possible complications of using TA. Mostly, the complications were mild and reversible. Patients had gastrointestinal side effects, such as nausea and vomiting. Depending on the study, there was – whether or not significant – an increased risk of gastrointestinal side effects when using TA. This is probably dose dependent. Major complications were rather rare and there was no increased risk on major complications in the group who received TA. But TA is an antifibrinolytic agent and we should foresee the possibility of a thrombotic event. In addition pregnant women and postpartum women are at greater risk to develop a postpartum thrombotic complication due to there hypercoagulable state associated with pregnancy. Most studies indicate that there is no additional risk of thrombosis due to the use of TA, however they are not powered to evaluate complications (31,35). *Ducloy-Bouthors et al* describe two events of DVT, not significantly increased, but possibly due to the use of high-dose TA. The *WOMAN trial* also evaluates the side effects and thromboembolic risk of TA.

TA is known to cause hypersensitivity reactions, but this is rather rare. None of the previous studies mention an allergic reaction due to TA. *Imbesi et al* describe a wide and various spectrums of allergic reactions after using TA (40). These reactions can be immunologic or non-immunologic. The underlying cause is that TA is a synthetic derivate of lysine and lysine is involved in IgE mediated reactions of several allergens. Although a hypersensitivity reaction is rather rare, we have to be aware of it.

Additional, *Gungorduk et* al mention that TA crosses the placenta and passes into breast milk. However, the concentrations are too low to have a side effect or antifibrinolytic effect in the neonates (31).

Which women might benefit from TA, is still unclear. All trials, except the trial of *Ducloy-Bouthors et al* and *Sujata et al,* included healthy women. We can say that TA was given as prophylaxis to all these women. *Ducloy-Bouthors et al* gave TA only to women with the diagnosis of PPH. *Sujata et al* included women with at least one risk factor for PPH. The *WOMEN* trial uses TA only when a postpartum bleeding is diagnosed. The *TRAAP* trial uses a low dose of TA as a prophylactic agent after vaginal delivery.

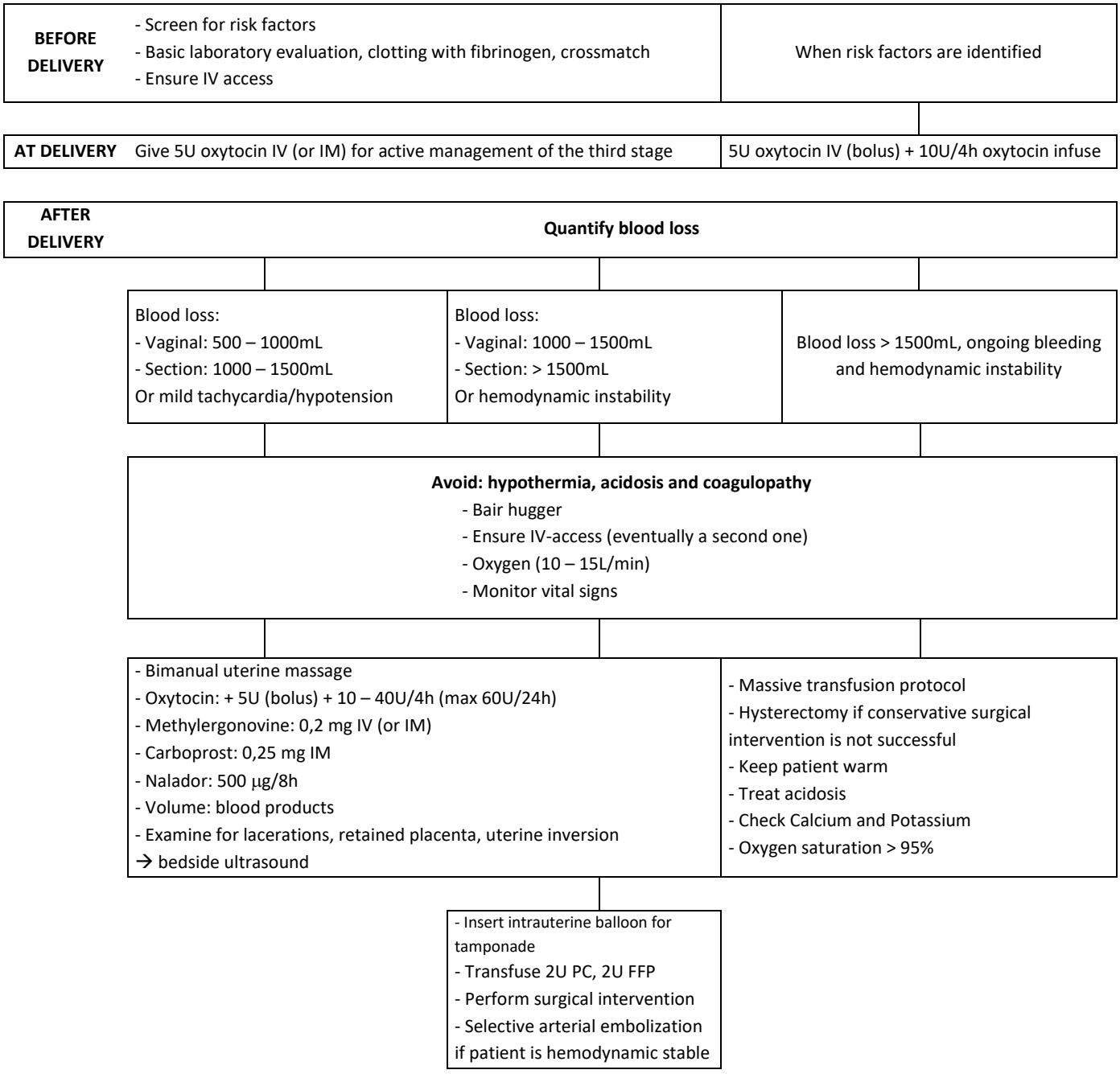
TA is additional to the standard protocol of caesarean and vaginal deliveries. Uterotonic agents, such as oxytocin are still needed to prevent uterine atony and complications due to the bleeding. TA can be used as an antifibrinolytic and its effect has been proven in several studies. The effect of TA is less blood loss after both vaginal delivery and caesarean section and there is less need for additional uterotonic agents. Thereby, confirming that TA it is a good additional agent to reduce postpartum haemorrhage and its complications.

Conclusion

Postpartum haemorrhage is one of the most frequent complications after labour and giving birth. Several studies were compared. The studies concluded that TA reduces significantly the blood loss and need for transfusions. Eleven randomized controlled trails were included, but most trials are too small to be conclusive. Most of the trials used 1 gram TA. A higher dose of TA – like *Ducloy-Bouthers et al* did – does not give a significant benefit and the risk of complications rises. We are looking forward to the results of the WOMAN trial and the TRAAP trial. Unfortunately, these results are still not published.

The complications due to the use of TA are mild and reversible, major complications are rare. There was no increased risk of thrombotic events when using 1 gram TA. The WOMEN trial also evaluates the presence of thrombotic events.

TA reduces the blood loss, but the dose and mode of administration is still unclear. We can say that TA has its place in the treatment of postpartum bleeding, next to uterotonics. Most of the studies we included used TA as a prophylactic agent. Conversely, the WOMAN trial uses TA only when a postpartum bleeding is diagnosed. To young women without risk factors, we propose not to give TA as a prophylactic agent because there is less clinical relevance. In our protocol, we use TA as a secondary treatment – next to oxytocin – when a blood loss of more than 1000 mL is diagnosed. Following the above review, we suggest the following protocol – which is based on the postpartum haemorrhage protocol used at UZ Leuven, Belgium – which includes the use of TA. We give 1 gram TA (and 1 gram additional if bleeding persists) to women who lose more than 1000 mL. When women lose more than 1500 mL or when women are hemodynamic unstable, we give 1 gram TA followed by an infuse of 15 mg/kg/h. See protocol below.



Use of tranexamic acid in postpartum haemorrhage

- Blood loss: vaginal > 1000mL, section > 1500mL: 1 gram TA + 1 gram TA if bleeding persists
- Blood loss > 1500mL: 1 gram TA + infuse 15 mg/kg/h TA

Samenvatting

Postpartum bloeding (PPH) is één van de meest voorkomende oorzaken van maternale sterfte, zowel in ontwikkelingslanden als in ontwikkelde landen. Een atone uterus, achtergebleven weefsel van de placenta, een genitaal trauma of coagulopathie kan de oorzaak zijn van deze obstetrische urgentie. Tranexaminezuur (TA) kan worden gebruikt om deze postpartum bloeding te behandelen.

In deze literatuurstudie gaan we de effectiviteit en mogelijke complicaties na bij het gebruik van TA. In de meeste studies werd TA gegeven als profylaxe. Deze studies tonen aan dat TA voor een significante vermindering van bloedverlies zorgt. Er was ook minder nood aan bloedtransfusie, maar dit was niet statistisch significant. Momenteel zijn er nog twee grote studies lopende die het gebruik van TA onderzoeken. In de WOMAN trial wordt TA toegediend wanneer de diagnose van PPH gesteld werd. In de TRAAP studie wordt TA als profylaxe bij een vaginale bevalling gegeven. De resultaten van beide studies worden in de loop van 2017 verwacht. Verschillende studies bestudeerden de nevenwerkingen van TA. Er werden voornamelijk mineure en reversibele complicaties zoals nausea en braken gerapporteerd. Er was geen significante toename van diepe veneuze trombosen.

We kunnen stellen dat TA zorgt voor een significante vermindering van PPH. Bij jonge vrouwen zonder bijkomende risicofactoren voor PPH is deze echter klinisch weinig relevant. We stellen voor om TA te gebruiken als secundaire behandeling naast de klassieke uterotonica zoals oxytocine. In ons protocol stellen we voor om 1 gram TA toe te dienen aan vrouwen die meer dan 1000 mL bloed verloren hebben en bijkomend 1 gram toe te dienen wanneer het bloedverlies blijft aanhouden. Wanneer vrouwen hemodynamisch instabiel worden of meer dan 1500 mL bloedverlies hebben geleden, geven we 1 gram TA gevolgd door een continu infuus van 15 mg/kg/u.

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