Tranexamic acid for the prevention and treatment of postpartum haemorrhage

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Editor’s key points

- The authors considered the evidence regarding the effect of tranexamic acid in preventing and treating postpartum haemorrhage.
- They found promising effects, but concluded that there is, as yet, inadequate evidence (of efficacy and of safety) to support widespread uptake.

Introduction, the burden of postpartum haemorrhage

Primary postpartum haemorrhage (PPH) is classically defined as blood loss of ≥ 500 ml in the first 24 h after delivery.1 It is a major cause of maternal mortality and accounts for about one-quarter of all maternal deaths worldwide. Uterotonics after birth are the only intervention that has been shown to be effective for PPH prevention. Tranexamic acid (TXA), an antifibrinolytic agent, has therefore been investigated as a potentially useful complement to this for both prevention and treatment because its hypothesized mechanism of action in PPH supplements that of uterotonics and because it has been proved to reduce blood loss in elective surgery, bleeding in trauma patients, and menstrual blood loss. This review covers evidence from 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). It discusses its efficacy and side effects overall and in relation to the various doses studied for both indications. TXA appears to be a promising drug for the prevention and treatment of PPH after both vaginal and caesarean delivery. Nevertheless, the current level of evidence supporting its efficacy is insufficient, as are the data about its benefit:harm ratio. Large, adequately powered multicentre RCTs are required before its widespread use for preventing and treating PPH can be recommended.

Keywords: caesarean and vaginal deliveries; postpartum haemorrhage; prevention; tranexamic acid; treatment

Postpartum haemorrhage (PPH) is a major cause of maternal mortality, accounting for one-quarter of all maternal deaths worldwide. Uterotonics after birth are the only intervention that has been shown to be effective for PPH prevention. Tranexamic acid (TXA), an antifibrinolytic agent, has therefore been investigated as a potentially useful complement to this for both prevention and treatment because its hypothesized mechanism of action in PPH supplements that of uterotonics and because it has been proved to reduce blood loss in elective surgery, bleeding in trauma patients, and menstrual blood loss. This review covers evidence from 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). It discusses its efficacy and side effects overall and in relation to the various doses studied for both indications. TXA appears to be a promising drug for the prevention and treatment of PPH after both vaginal and caesarean delivery. Nevertheless, the current level of evidence supporting its efficacy is insufficient, as are the data about its benefit:harm ratio. Large, adequately powered multicentre RCTs are required before its widespread use for preventing and treating PPH can be recommended.

Keywords: caesarean and vaginal deliveries; postpartum haemorrhage; prevention; tranexamic acid; treatment

Prevalence estimates for PPH in the literature vary widely, from 3% to 15% of deliveries.8–16 This diversity is explained partly by the variety of criteria and methods used to define PPH: definitions are based on haematological indicators or on the volume of blood loss, which in turn can be estimated clinically or measured more objectively by, for example, a blood collection bag. About one in five of these haemorrhages progresses to a severe form that may endanger the mother’s life or at least her future fertility; expose her to the risks of transfusions, complications, and resuscitation; and cost families, governments, and insurance companies a great deal of money. Population-based studies conducted in high-resource countries report a prevalence of severe maternal morbidity due to PPH between 0.5% and 1.5% of deliveries13–19 and show that it is the main component of severe maternal morbidity.
Tranexamic acid for postpartum haemorrhage

The most common causes of postpartum haemorrhage are uterine atony, abnormal placental detachment including placental abruption, lower genital tract lacerations, retained placental tissue, coagulopathies, vessel malformation, and uterine rupture. Risk factors for PPH include previous PPH, primiparity, obesity, prolonged or augmented labour, multiple pregnancy, previous caesarean section, polyhydramnios, and macrosomia. Nevertheless, most women with PPH have low-risk pregnancies and no identifiable risk factors. It is therefore essential to prevent PPH in all women. This prevention is especially important since several reports from various high-resource countries describe recent increases in the incidence of PPH.

Because placental expulsion is a critical window for the prevention of PPH, various preventive interventions during this stage have been proposed. They can be schematically divided into two categories: those involving a mechanical mechanism and those involving prohaemostatic agents.

Active management of the third stage of labour (AMTLS), first described in the UK and in Ireland, consisted, as initially conceived, of a combination of the following interventions: preventive administration of uterotonic agents immediately after delivery of the child, early cord clamping and cutting, controlled cord traction (CCT), and, according to some authors, uterine massage. The underlying principle is to use a uterotonically drug—and oxytocin is the primary and most frequently evaluated uterotonic—and uterine massage to stimulate uterine contraction after birth and to use CCT to promote rapid placental expulsion, thereby rapidly obtaining the uterine retraction necessary for good local haemostasis through the use of mechanical tools.

The specific and independent efficacy of preventive oxytocin has been shown with a high level of evidence. The meta-analysis of these trials concluded that oxytocin administration for the third stage of labour reduces the risk of blood loss >500 ml by 50% and the risk of blood loss >1000 ml by 40%. The situation is very different for CCT. Two large randomized controlled trials (RCTs) recently showed that CCT for the management of placenta expulsion had no significant effect on the incidence of PPH in women receiving systematic preventive oxytocin, in either high- or low-resource settings. Moreover, in view of evidence suggesting that delayed clamping benefits the child, early cord clamping is generally no longer included in AMTLS, although its risks and benefits for the mother have not yet been assessed. Finally, it has been shown that, in women giving birth vaginally who received prophylactic oxytocin, transabdominal uterine massage after placental delivery does not reduce blood loss compared with oxytocin alone.

In conclusion, the administration of uterotonic drugs, and in particular oxytocin, after birth is the only intervention that has been shown to be effective in preventing PPH. However, in addition to this enhancement of mechanical haemostasis, a complementary biochemical haemostatic effect might be expected from the use of prohaemostatic drugs.

Tranexamic acid for the prevention of PPH

Rationale

Biochemical action

In the haemostatic process, coagulation occurs rapidly at the site of a damaged vessel by the build-up of a tight net of fibrin; at the same time, the fibrinolytic system removes the fibrin deposits that might cause permanent vascular occlusion once vascular repair has taken place. The coagulation and fibrinolytic systems are believed to be in a state of dynamic balance that maintains an intact vascular system. Tranexamic acid (TXA) is a potent antifibrinolytic agent that exerts its effects by blocking lysine binding sites on plasminogen molecules and has the potential to enhance the effectiveness of the patient’s own haemostatic mechanisms. Consequently, clot breakdown (fibrinolysis) is inhibited and bleeding is reduced. During delivery, when the placenta separates from the uterine wall, physiologic and haemostatic changes occur sequentially to reduce bleeding: strong myometrial contractions, increased platelet activity, massive release of coagulation factors and consequently a parallel increase in fibrinolytic activity. While oxytocin administration enhances the first mechanism, TXA administration might be able to counter the latter and thus facilitate the haemostatic process. Finally, the association between the extent of the initial decrease in plasma fibrinogen and the subsequent severity of blood loss reported in women with early PPH suggests that both the coagulation and fibrinolysis processes are implicated in the control of postpartum blood loss and further supports the hypothesis that TXA might be effective in PPH prevention. Accordingly, there is a clear theoretical rationale for the use of antifibrinolytic agents to reduce postpartum blood loss.

Evidence from clinical studies in other medical contexts

Systemic antifibrinolytic agents are widely used in planned surgery to prevent clot breakdown (fibrinolysis) and reduce perioperative blood loss. A systematic review of RCTs assessing the impact of antifibrinolytic agents in patients undergoing elective surgery identified 211 RCTs including 20 781 randomized participants. The results showed that TXA reduced the risk of blood transfusion by a relative risk (RR) = 0.61 [95% confidence interval (CI) 0.54–0.69] and the mean transfused volume by 1.1 units (95% CI 0.64–1.59). TXA may also reduce the need for reoperation due to bleeding, although the difference did not reach statistical significance (RR = 0.67 [95% CI 0.41–1.09]). There was no evidence of an increased risk of thrombotic events. This positive effect of TXA was observed regardless of the type of surgery (including cardiac, orthopaedic, hepatic, urological, and vascular). A more recent meta-analysis of RCTs specifically evaluating the impact of preventive TXA administration in elective surgery identified 129 RCTs including 10 488 randomized participants and concluded that TXA reduces the risk of blood transfusion.
Efficacy of TXA for preventing PPH: evidence from clinical studies

A Cochrane systematic review published in 2011 identified five RCTs evaluating the use of TXA to prevent PPH; two of these were included in the meta-analysis, which covered a total of 453 women. The authors concluded that the available evidence, although it suggested that TXA decreases postpartum blood loss, was of unclear quality and that further investigation was needed. Since then, several additional trials have been published.

Using a Medline search through March 1, 2014, we identified 12 RCTs that have assessed this issue (Tables 1 and 2). All were performed in low- or middle-income countries (China, India, Iran, Turkey, Pakistan, and Egypt). All but two of them included only women with caesarean deliveries. Overall, the quality of these trials was poor. Selection, performance, and detection bias may have influenced their results; in particular, the primary outcome was rarely the incidence of either PPH or severe PPH, but other indicators of blood loss that may not be clinically relevant. The method used to measure the primary outcome based on estimated blood loss was often imprecise and subject to both performance and detection bias. This warrants a cautious interpretation of their results.

TXA for preventing PPH after caesarean delivery

We found 10 published RCTs evaluating the efficacy of TXA in preventing PPH after caesarean delivery. Their characteristics are summarized in Table 1. In all studies except one, caesareans were elective. These 10 RCTs all reported that women who had received TXA had significantly less blood loss without any effect on their primary vital signs (blood pressure, heart rate, and respiratory rate) or thrombosis. TXA significantly reduced bleeding during caesarean delivery [mean 499.9 (SD 206.4) ml vs 600.7 (215.7), P < 0.001], the percentage of patients with blood loss > 1000 ml [2.1% vs 5.8%; RR = 2.7 (95% CI 1.1 – 6.3), P < 0.03], and the need for additional uterine tonic agents [8.5% vs 14.5%; RR = 1.7 (95% CI 1.1 – 2.6), P = 0.02]. Despite some concerns regarding the reliability of the reported data (enrolment of 88% of eligible patients, no patients lost to follow-up), these results suggest TXA may be useful in reducing both postpartum blood loss and haemorrhage (Table 1).

Abdel-Aleem and colleagues recently published another large open RCT including 740 women. They found a statistically significant reduction in the mean blood loss in the experimental group [241.6 (SD 7.7) ml], which received TXA, compared with the control group [510.6 (SE 7.7) ml; weighted mean difference (WMD) – 269.0 (95% CI – 288.6 to – 249.5)]. Moreover, when measured 24 h after the procedure, both haemoglobin [0.48 (SD 0.87) g dl⁻¹ vs 1.42 (1.16), P = 0.001] and haematocrit [0.1.7% (2.93) vs 4.30% (3.64), P = 0.001] values had dropped significantly less in the experimental than in the control group. However, no placebo was used and the trial was not blinded (Table 1).

In conclusion, the 10 published RCTs that have assessed the effects of TXA in preventing PPH during caesarean deliveries showed a significant reduction in blood loss by patients who received TXA and no reported increase in the incidence of adverse events. Nevertheless, it is important to emphasize that most of these RCTs have various methodological flaws and included small samples with inadequate power to assess the risk of adverse effects. The quality of the available evidence remains unclear and the results should be interpreted cautiously.

TXA for preventing PPH after vaginal delivery

We found only two trials evaluating the efficacy of TXA for the prevention of PPH after vaginal delivery. In 2001, Yang and colleagues reported an RCT comparing four groups. One group (n = 94) received a single dose of 1 g TXA by intravenous (IV) infusion, another group (n = 92) received a single dose of...
Table 1 Characteristics of the randomized controlled trials that have assessed tranexamic acid for the prevention of postpartum haemorrhage after caesarean deliveries. CS, caesarean section; EBV, estimated blood volume [i.e. the woman’s weight (kg) × 85]; IV, intravenous; preop, preoperative; postop, postoperative; TXA, tranexamic acid. *The authors did not mention the mode of anaesthesia for the caesarean.

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<th>Study</th>
<th>Country</th>
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<th>Study groups</th>
<th>Prophylactic uterotonics</th>
<th>Intervention</th>
<th>TXA dosage/ route/ duration</th>
<th>Primary outcome/ calculated sample size/ flow chart</th>
<th>Method for assessing estimated blood loss</th>
<th>Result</th>
<th>P-value</th>
<th>Adverse effects</th>
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</thead>
<tbody>
<tr>
<td>Gohel and colleagues (2004)†</td>
<td>India</td>
<td>Prospective, single-centre, randomized, controlled</td>
<td>N = 180, primiparas and multiparas, elective CS under spinal anaesthesia</td>
<td>N = 91 (experimental) N = 89 (no placebo)</td>
<td>10 IU oxytocin IV simultaneously with 20 IU oxytocin into the uterine wall</td>
<td>Infusion of TXA 10 min before CS</td>
<td>1 g IV for 5 min</td>
<td>Postpartum blood loss not clearly mentioned Not reported Not reported</td>
<td>(weight of materials used + weight of all materials before surgery)/1.05 + volume included in the suction container from placental delivery to 2 h postpartum</td>
<td>359.3 vs 439.3 ml</td>
<td>0.002</td>
<td>No thromboembolic or other side effects reported</td>
</tr>
<tr>
<td>Gohel and colleagues (2007)†</td>
<td>India</td>
<td>Prospective, single-centre, randomized, controlled</td>
<td>N = 100, primiparas and multiparas, elective CS under spinal anaesthesia</td>
<td>N = 50 (experimental) N = 50 (no placebo)</td>
<td>10 IU oxytocin IV for 30 min with 0.4 mg methylergometrine IV</td>
<td>Infusion of TXA 20 min before CS</td>
<td>1 g IV for 5 min</td>
<td>Postpartum blood loss not clearly mentioned Not reported Not reported</td>
<td>(weight of materials used – weight of material before use) + volume included in the suction container from placental delivery to 2 h postpartum</td>
<td>374.9 vs 472.8 ml</td>
<td>0.003</td>
<td>No thromboembolic or other side effects reported</td>
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<tr>
<td>Sekhavat and colleagues (2009)†</td>
<td>Iran</td>
<td>Prospective, single-centre, randomized, controlled</td>
<td>N = 90, primiparas and multiparas, elective CS under general anaesthesia</td>
<td>N = 45 (experimental) N = 45 (placebo)</td>
<td>10 IU oxytocin IV for 30 min</td>
<td>Infusion of TXA 10 min before CS</td>
<td>1 g IV for 5 min</td>
<td>Postpartum blood loss not clearly mentioned Not reported Not reported</td>
<td>(weight of materials used – weight of material before use)/1.05 from the end of CS to 2 h postpartum</td>
<td>28.0 vs 37.1 ml</td>
<td>0.001</td>
<td>No thromboembolic or other side effects reported</td>
</tr>
<tr>
<td>Gungorduk and colleagues (2011)†</td>
<td>Turkey</td>
<td>Prospective, single-centre, randomized, controlled</td>
<td>N = 666, primiparas and multiparas, elective CS*</td>
<td>N = 330 (experimental) N = 330 (placebo)</td>
<td>5 IU IV bolus oxytocin, then 30 IU oxytocin in 500 ml solution at a rate of 125 ml h⁻¹</td>
<td>Infusion of TXA 10 min before CS</td>
<td>1 g IV for 5 min</td>
<td>Estimated blood loss during CS. Yes, 327 per group Yes</td>
<td>Estimated blood loss = EBV × [(preop haematocrit – postop haematocrit)/preop haematocrit]</td>
<td>600.7 vs 499.9 ml</td>
<td>&lt;0.001</td>
<td>Gastrointestinal side effects (16.3%) in the experimental group Gastrointestinal side effects not mentioned for the placebo group No thromboembolic events</td>
</tr>
<tr>
<td>Movafegh and colleagues (2011)†</td>
<td>Iran</td>
<td>Prospective, single-centre, double-blinded, randomized controlled study</td>
<td>N = 100, primiparas and multiparas, elective CS under spinal anaesthesia</td>
<td>N = 50 (experimental) N = 50 (placebo)</td>
<td>10 IU oxytocin IV over 20 min, then 30 IU oxytocin over 8 h</td>
<td>Infusion of TXA 20 min before CS</td>
<td>10 mg kg⁻¹ IV for 10 min</td>
<td>Postpartum blood loss not clearly mentioned Yes, 50 per group Not reported Method of Gai and colleagues*</td>
<td>Method of Gai and colleagues*</td>
<td>262.5 vs 404.7 ml</td>
<td>&lt;0.001</td>
<td>No thromboembolic events</td>
</tr>
<tr>
<td>Xu and colleagues (2013)†</td>
<td>China</td>
<td>Randomized, single-centre, double-blinded, controlled study</td>
<td>N = 174, primiparas, elective CS under spinal anaesthesia</td>
<td>N = 88 (experimental) N = 86 (placebo)</td>
<td>10 IU oxytocin IV for 30 min with 0.4 mg methylergometrine IV</td>
<td>Infusion of TXA 10 min before CS</td>
<td>10 mg kg⁻¹ IV for 5 min</td>
<td>Postpartum blood loss not clearly mentioned Yes, 76 per group Not reported Method of Gai and colleagues*</td>
<td>Method of Gai and colleagues*</td>
<td>379 vs 441 ml</td>
<td>0.02</td>
<td>2 thromboses occurred in each group Gastrointestinal side effects occurred in 10 TA patients vs 1 placebo patient</td>
</tr>
</tbody>
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### Table 1 Continued

<table>
<thead>
<tr>
<th>Study</th>
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</thead>
<tbody>
<tr>
<td>Sentürk and colleagues (2013)</td>
<td>Turkey</td>
<td>Randomized, single-centre, double-blinded, controlled study</td>
<td>223</td>
<td>101 (experimental) 122 (placebo)</td>
<td>20 IU IV bolus oxytocin</td>
<td>Infusion of TXA 10 min before CS</td>
<td>10 mg kg⁻¹ IV for 5 min</td>
<td>Postpartum blood loss not clearly mentioned Not reported Not reported</td>
<td>(weight of wet – dry pads or tampon) / 1.05</td>
<td>272 vs 347 ml</td>
<td>0.001</td>
<td>No thromboembolic or gastrointestinal side effects</td>
</tr>
<tr>
<td>Shahid and colleagues (2013)</td>
<td>Pakistan</td>
<td>Randomized, single-centre, double-blinded, placebo-controlled study</td>
<td>74</td>
<td>38 (experimental) 36 (placebo)</td>
<td>5 IU oxytocin and 0.4 mg methylergometrine IV bolus then 30 IU oxytocin over 6 h</td>
<td>Infusion of TXA 10 min before CS</td>
<td>Measurement of blood loss from the time of placental delivery to end of CS</td>
<td>1 g IV</td>
<td>Postpartum blood loss not clearly mentioned Not reported Not reported</td>
<td>(weight of materials used - weight of material before use) + volume included in the suction container from the placental delivery to the end of CS</td>
<td>356 vs 710 ml</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdel-Aleem and colleagues (2013)</td>
<td>Egypt</td>
<td>Randomized, single-centre, open, controlled study</td>
<td>740</td>
<td>373 (experimental) 367 (no placebo)</td>
<td>5 IU IV bolus and 20 IU IV infusion of oxytocin</td>
<td>Infusion of TXA 10 min before CS</td>
<td>1 g IV for 10 min</td>
<td>Blood loss 2 h after delivery Yes, 350 per arm Yes</td>
<td>(weight of all towels used - weight of dry towels) + 0.9 x volume included in the suction container from the placental delivery to 2 h postpartum</td>
<td>241.6 vs 510.6 ml</td>
<td>&lt;0.001</td>
<td>Gastrointestinal side effects (74.3% vs 53.1%; P=0.0001) No thromboembolic side effects</td>
</tr>
<tr>
<td>Goswami and colleagues (2013)</td>
<td>India</td>
<td>Randomized, single-centre, double-blinded, placebo controlled study</td>
<td>90</td>
<td>30 (experimental 1) 30 (placebo)</td>
<td>20 IU oxytocin in 500 ml at the rate of 8 ml min⁻¹ IV</td>
<td>Infusion of TXA 20 min before CS</td>
<td>Experimental 1: 10 mg kg⁻¹ Experimental 2: 15 mg kg⁻¹</td>
<td>Postpartum blood loss not clearly mentioned Not reported Not reported</td>
<td>(weight of all towels used - weight of dry towels) + 0.9 x volume included in the suction container from the placental delivery to 2 h postpartum</td>
<td>376.8 vs 527.2 ml</td>
<td>Not reported</td>
<td>No thromboembolic side effects</td>
</tr>
</tbody>
</table>

**Legend:**
- **TXA**: Tranexamic Acid
- **CS**: Cesarean Section
- **IV**: Intravenous
Table 2  Characteristics of the randomized controlled trials that have assessed tranexamic acid for prevention of postpartum haemorrhage following vaginal deliveries. AMBA, aminomethylbenzoic acid; AMTSL, active management of the third stage of labour (which included prophylactic injection of 10 IU oxytocin within 2 min of birth, early umbilical cord clamping, and controlled cord traction); IV, intravenous; NA, not available; TXA, tranexamic acid.

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<tr>
<th>Study</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Yang and colleagues</td>
<td>China</td>
<td>Multicentre, comparative, randomized controlled</td>
<td>N=400, primiparas</td>
<td>N=94 (experimental 1) N=92 (experimental 2) N=92 (experimental 3) N=87 (no placebo)</td>
<td>10 IU oxytocin after delivery of the foetal shoulders</td>
<td>Infusion of TXA after delivery of the foetal shoulders in the first 2 groups and infusion of AMBA in the third</td>
<td>Measurement of blood loss 2 h after delivery NA Not reported</td>
<td>NA</td>
<td>1 g IV 0.5 g IV 0.5 g IV placebo</td>
<td>243.3 vs 242.9 vs 308.1 vs 314.8 ml</td>
<td>&lt;0.01</td>
<td>No major adverse effects</td>
</tr>
<tr>
<td>Gungorduk and colleagues</td>
<td>Turkey</td>
<td>Prospective, single-centre, double-blinded, randomized controlled</td>
<td>N=439, primiparas and multiparas</td>
<td>N=220 (study) N=219 (placebo)</td>
<td>AMTSL</td>
<td>Infusion of TXA at delivery of the anterior shoulder</td>
<td>Volume of blood loss during the third and fourth stages of labour Yes, 215 patients in each arm Yes</td>
<td>(weight of material used – weight of materials before use)/1.05 from the end of delivery to 2 h postpartum</td>
<td>1 g IV for 5 min 350.0 ml</td>
<td>&lt;0.001</td>
<td>Gastrointestinal side effects significantly higher in the experimental group No thromboembolic event</td>
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</table>
0.5 g TXA, also intravenously, the third group (n=92) received a single IV dose of 0.5 g aminomethylbenzoic acid, and the fourth group (n=87) served as the control group. They reported a lower incidence of postpartum haemorrhage (defined by the authors as blood loss ≥400 ml) in women receiving the larger TXA dose (6/94) than the control group (22/87) (Table 2). The pooled RR of PPH was thus 0.44 (95% CI 0.31–0.64). The main limitation of this study is the absence of placebo and blinding, as well as the limited number of patients in each of the four groups. Moreover, the randomization method was not described.

More recently, Gundukurk and colleagues recruited 439 patients with vaginal deliveries in a double-blinded RCT. Women in the intervention group received a single IV dose of 1.0 g TXA at delivery of the anterior shoulder and those in the control group received a placebo. The primary outcome was the mean estimated blood loss during the third and fourth stages of labour. It was significantly lower in the TXA group than in the placebo group [261.5 (so 146.8) vs 349.98 (188.85) ml, P<0.001]. The incidence of PPH >500 ml was also lower in the TXA group (n=4, 1.8%) than in the control group (n=15, 6.8%) [RR 3.76 (95% CI 1.27–1.15), P=0.01]. Moreover, the rate of total blood loss of at least 1000 ml was higher among women who received placebo (2.3%) than among women given TXA (0.5%), but the difference was not statistically significant [RR 5.02 (CI 0.59–42.64), P=0.12]. Significantly more women in the placebo group (8.7%) than in the TXA group (2.7%) required additional uterotonic agents [RR 3.18 (95% CI 1.29–7.81), P=0.007]. The groups did not differ significantly in their requirements for blood transfusion. Predelivery haemoglobin and haematocrit levels were the same in both groups, but the day after delivery, both haemoglobin [9.9 (so 1.4) g dl⁻¹ and 9.3 (so 0.9) g dl⁻¹, P<0.001] and haematocrit [30.2% (so 1.2) and 29.0% (so 1.3), P<0.001] levels were higher in the TXA than the placebo group. Finally, no episodes of thrombosis occurred in the women who received TXA. The results of this single-centre trial suggest that TXA is a promising drug for the prevention of PPH after vaginal delivery and possibly for the reduction of maternal morbidity related to PPH. Nevertheless, there are again some concerns about the validity of these data because (1) the period from the end of the study to the submission of the manuscript was extremely short, (2) there was no loss to follow-up among either women or children at the short- and midterm clinical check-up (3 weeks after delivery), (3) only women who received TXA appear to have been advised about the signs and symptoms of thromboembolic events, although the authors stated that the study was a double-blinded placebo-controlled randomized trial until the conclusion of the study, and (4) all patients in both groups had all three components of AMTSL. This trial was also underpowered to assess severe adverse events.

Nevertheless, these two trials suggest that TXA administration may decrease blood loss after vaginal delivery.

**TXA in the treatment of PPH**

There is currently very little reliable evidence on the effectiveness of TXA in the treatment of PPH. We found only one published RCT testing whether a high dose of TXA reduces blood loss in women with PPH: the EXADELLI trial, a multicentre open-label trial conducted in France (Table 3). Women with PPH>800 ml following vaginal delivery were randomly assigned to receive a high dose of TXA (loading dose 4 g over 1 h, then infusion of 1 g h⁻¹ for 6 h) or not. In both groups, packed red blood cells (PRBCs) and colloids could be used according to French guidelines. The use of additional procoagulant treatments was permitted only in cases of intractable bleeding. A total of 144 women fully completed the protocol (72 in each group). Blood loss, measured with a collector bag, between enrolment and 6 h later (primary outcome) was significantly lower in the TXA group than in the control group (173 vs 221 ml, P=0.041) (Table 3). Compared with controls, the TXA group also had a shorter duration of bleeding and less frequent progression to severe PPH (defined by one or more of the following criteria: haemoglobin decrease >4 g dl⁻¹, transfusion of at least 4 units of PRBCs, invasive haemostatic intervention, or death) or need for PRBC transfusion (28 vs 62 PRBC units, P<0.001). Mild, transient adverse manifestations occurred more often in the TXA group (Table 3).

In response to the sparseness of evidence, the recently updated World Health Organization (WHO) guidelines for PPH treatment state that TXA may be used if other measures fail, but point out that the evidence base is poor and that further clinical trials of TXA in PPH are needed. Similarly, TXA is ‘recommended for consideration’ as a treatment in intractable PPH in the UK.

The WOMAN trial, coordinated by the London School of Hygiene & Tropical Medicine (University of London), has been launched to clarify this clinical uncertainty. WOMAN is a pragmatic, randomized, double-blinded, placebo-controlled trial in women with a clinical diagnosis of postpartum haemorrhage and is intended to determine reliably the effect of the early administration of TXA on death, hysterectomy, and other morbidity (surgical intervention, blood transfusion and risk of nonfatal vascular events). This trial is currently recruiting eligible women in hospitals in Africa and Europe, aiming to reach the target sample size of 15,000 women (http://www.thewomantrial.lshtm.ac.uk) (Table 3). It will therefore have the power to assess severe objective maternal morbidity (the primary outcome is the proportion of women who die or undergo hysterectomy) as well as such severe adverse events as thromboembolic events. Nonetheless, selection bias may occur at recruitment because women with PPH are eligible only if the clinician is uncertain as to whether or not to use TXA, and exclusion criteria include women for whom the clinician considers there is a clear indication for TXA (pragmatic trial).
The characteristics of the randomized controlled trials that assessed tranexamic acid for the treatment of postpartum haemorrhage are presented in Table 3. IV, intravenous; NR, not reported; TXA, tranexamic acid.

Table 3: Characteristics of the randomized controlled trials that assessed tranexamic acid for the treatment of postpartum haemorrhage.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size</th>
<th>Study size</th>
<th>Primary outcome/characteristic of interest</th>
<th>Intervention</th>
<th>Dosage/route/duration</th>
<th>Flow chart</th>
<th>Method for assessing estimated blood loss</th>
<th>Result</th>
<th>p-value</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ducloy-Bouthors et al. (2010)</td>
<td>France</td>
<td>Randomized, controlled, multicentre, open-label</td>
<td>N=144, primiparas and N=72, multiparas</td>
<td>72 randomly assigned primiparas and 72 multiparas</td>
<td>Pregnancy-related postpartum haemorrhage (PPH) &gt;800 ml</td>
<td>Infusion of TXA 1 g over 6 h IV</td>
<td>NR</td>
<td>Graduated collection bag placed immediately after delivery</td>
<td>Yes</td>
<td>0.041</td>
<td>Nausea/vomiting: 15% vs 2% (p=0.001)</td>
<td>Thrombosis: 2% (p=0.54)</td>
</tr>
<tr>
<td>Shakur and colleagues (2010)</td>
<td>International</td>
<td>Pragmatic, randomized, double-blind, placebo-controlled</td>
<td>N=15,000 (expected sample size)</td>
<td>Ongoing study</td>
<td>Pregnancy-related postpartum haemorrhage (PPH) &gt;800 ml</td>
<td>Infusion of TXA 1 g/l/min over 6 h IV</td>
<td>1 g/l/min</td>
<td>Infusion of TXA 1 g/l/min over 6 h IV</td>
<td>Yes</td>
<td>0.041</td>
<td>Nausea/vomiting: 7% vs 1.6% (p=0.04)</td>
<td>Thrombosis: 3% (p=0.56)</td>
</tr>
</tbody>
</table>

In conclusion, TXA appears to be a promising drug for the treatment of PPH, but the results currently available are too limited to justify its widespread use in PPH. We can reasonably hope that this important issue will be informed by the results of the WOMAN trial.74

Adverse events related to TXA

TXA inhibits fibrinolysis and therefore carries a potential risk of thrombosis, especially in patients with a previous history of thrombosis and in pregnant women.

Maternal adverse events

Severe maternal adverse events related to TXA: evidence from clinical studies

The systematic review of RCTs of elective surgical patients cited above (129 RCTs including 10 488 randomized participants, 5484 of them allocated to TXA) assessed severe adverse events.59 No significant increases were observed for the risks of myocardial infarction [RR=0.68 (95% CI 0.43–1.09), P=0.11], stroke [RR=1.14 (95% CI 0.65–2.00), P=0.65], deep vein thrombosis [0.86 (95% CI 0.53–1.39), P=0.54], or pulmonary embolism [0.61 (95% CI 0.25–1.47), P=0.27]. Nevertheless, as the authors cautiously stated, this meta-analysis does not resolve the uncertainties about thromboembolic events. These events are relatively rare and most of these trials lacked the statistical power to detect clinically important increases in risk.

Although an increased risk of thrombotic events might be expected on theoretical grounds, recent evidence from the CRASH-2 trial of TXA in bleeding trauma patients (10 096 patients allocated to TXA and 10 115 to placebo) showed a statistically significant reduction in global mortality with no increase in thromboembolic events. Indeed, there was a statistically significant reduction in the risk of myocardial infarction in trauma patients who received TXA.60

Finally, it has been suggested that TXA administration may cause acute renal failure due to thrombosis-induced cortical necrosis. We found five published case reports of such acute renal failure.79–83 In these cases it was reported that intraglomerular capillary and arteriolar fibrin thrombosis with infarcts developed after TXA administration.79–83 Four of these five patients had risk factors for ischemic renal damage and acute renal cortical necrosis: hypotension,82 advanced age,83 haemophilia A80 and acute promyelocytic leukemia.81

The evidence available for assessing the safety of TXA use in parturients for the treatment and prevention of PPH is even more limited than for non-pregnant patients, given the total number of such women enrolled and the expected incidence of these adverse events. Caution is necessary before recommending the use of this drug in routine practice for prevention or treatment of PPH, in view of the number of eligible women in both cases and the potential for an increase in venous and arterial thrombotic events following administration. It must be borne in mind that plasma concentrations of clotting factors increase not only during pregnancy but also after delivery, as does platelet activity; postpartum women are in a...
hypercogulable state.\textsuperscript{49, 84} Besides the changes in platelet activity, there are indications that an inflammatory response develops in the placental bed after placental delivery\textsuperscript{85} and promotes thrombi formation. It is thus well known that the risk of venous thromboembolism is increased during normal pregnancy (to slightly more than 1/1000 pregnant women), and especially during the first 6 weeks postpartum, when a woman’s risk of venous thromboembolism is 21.5–84 times greater than the risk found in non-pregnant, non-postpartum women.\textsuperscript{86} However, it is important to note that no significant increase in the incidence of thrombotic events related to TXA has been observed in any trials of TXA among pregnant women \((n=2228),\) including RCTs, observational non-randomized studies and case series.\textsuperscript{56}

In addition, adverse effects may differ between low-dose TXA (1 g, as used in PPH prevention trials) and high-dose TXA (e.g. a loading dose of 4 g over 1 h, then infusion of 1 g h\textsuperscript{-1} over 6 h, as used in the EXADELI trial). In the latter trial, no impairment of renal function was observed, and there were two cases of thrombosis in the TXA group and one in the control group \((P=0.4)\) after complicated delivery (Table 3).\textsuperscript{52} However, after this protocol was implemented in the district where the main reference maternity unit was the lead centre for EXADELI, those investigators issued a national Periodic Safety Update Report (PSUR) alerting healthcare providers to an abnormally high number of cases of unexplained and abnormally severe renal failure following PPH treated by, among other drugs, TXA (http://spiral.univ-lyon1.fr/files_m/M11263/files/897436_1562.pdf). They recommended reducing the TXA dosage to 1 g, with an additional 1 g if bleeding continues. At the time this article was written, no additional information was available and the role of TXA in these cases of renal failure has not, to our knowledge, been established. However, caution is required in the interpretation of these results, given that acute renal failure and renal cortical necrosis have been described following severe PPH without any TXA treatment.\textsuperscript{87} Nevertheless, one study reported that high-dose TXA (100 mg kg\textsuperscript{-1}) may be associated with an increased incidence of postoperative generalized seizures in patients undergoing aortic valve replacement.\textsuperscript{88} One possible explanation is that TXA acts as an antagonist at \(\gamma\)-aminobutyric acid A \((GABA_A)\) receptors and thereby reduces the seizure threshold.\textsuperscript{89}

Taking these relevant data into account, it seems reasonable to advise against high doses of TXA in acute bleeding, in particular in severe PPH, until further evidence about both efficacy and safety is available. It is crucial that the RCTs to come, which will assess the efficacy of TXA in pregnant women, have sufficient power to detect even a moderate increase in the incidence of thrombotic events compared with placebo. The WOMAN trial is planned to have such power.\textsuperscript{75}

Mild maternal adverse events related to TXA

None of the many trials (RCTs, observational non-randomized studies, or case series) including pregnant women that have assessed the impact of TXA on primary vital signs (blood pressure, heart rate, and respiratory rate) have observed any impact on these outcomes\textsuperscript{56} (Tables 1–3). Nevertheless, mild transient adverse effects, including such gastrointestinal signs as nausea and vomiting, may be associated with the use of TXA.\textsuperscript{65, 73, 90, 91}

Neonatal adverse events

We have no idea of the potential adverse neonatal effects that may occur when 1 g TXA is administered intravenously 10 or 20 min before a caesarean delivery as PPH prophylaxis, because these trials have never evaluated this essential outcome and have been underpowered to assess it adequately.\textsuperscript{62–71} However, we would like to emphasize that rare but severe adverse neonatal effects may occur when TXA is administered before the cord clamping since TXA is known to cross the placenta.\textsuperscript{92}

Conclusions

Both theoretical arguments and results from RCTs conducted in other clinical contexts indicate that TXA has promise in the prevention and treatment of PPH. Nevertheless, the available evidence from RCTs, which have focused mostly on PPH prevention after caesarean deliveries, is of insufficient quality to reach any definitive conclusion, although it does suggest that TXA administration reduces postpartum blood loss. Moreover, those trials lacked the statistical power to assess adverse effects.

Given the current uncertainty regarding both its efficacy and its adverse effects in parturient women and their babies, large, adequately powered, multicentre, randomized placebo-controlled trials are required before TXA can be recommended to prevent PPH during the third stage of labour.

Similarly, the only available evidence about TXA for treating PPH comes from one open-label RCT. The most reasonable course thus appears to be to await the results of the WOMAN trial, a large, multicentre, double-blinded RCT that should provide a solid basis for reaching a conclusion about this issue.

Authors’ contributions

L.S. and C.D.T. wrote the first draft of the article. All authors revised it critically for important intellectual content, gave final approval of the version to be published, and are accountable for all aspects of the work.

Declaration of interest

L.S. was a board member, lecturer, and carried out consultancy work for Ferring; the other authors declared no conflict of interest.

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