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. Although maternal mortality has become a rare event in developed countries, it nonetheless remains a crucial indicator of the quality of obstetric care and the health status of mothers.2 3 Among high-resource countries, and especially in Europe, France is notable for the strong contribution of PPH to its maternal mortality:2–4 it is the leading cause of maternal death, responsible for 27% of direct maternal deaths in France for 2007–9, compared, for example, with 8% in the UK for 2006–8,6 7 despite their relatively similar overall maternal mortality rates.

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 deliveries11–14 and show that it is the main component of severe maternal morbidity.
The most common causes of postpartum haemorrhage are uterine atony, abnormal placenta 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 (AMTSL), 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 uterotonic drug—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 AMTSL, 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, 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 39% (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.
by a relative 38% [RR = 0.62 (95% CI 0.58 – 0.65)]; TXA’s preventive effect was also observed regardless of the type of surgery.59

Moreover, the CRASH-2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) demonstrated that the administration of TXA reduced mortality in bleeding trauma patients in high-, middle-, and low-income countries.60

Finally, significant reductions of 26–54% vs placebo or control in mean menstrual blood loss were reported in women with menorrhagia treated with TXA.61 This result is particularly significant since the efficacy of TXA in menorrhagia suggests that it can reduce uterine blood loss, even of low volume, and in a nonsurgical context. This provides further support for the hypothesis that TXA might be effective for the prevention of PPH after both caesarean and vaginal deliveries.

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.48 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.48 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).62 – 73 All were performed in low- or middle-income countries (China, India, Iran, Turkey, Pakistan, and Egypt). All but two of them72 73 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.48 74

TXA for preventing PPH after caesarean delivery

We found 10 published RCTs evaluating the efficacy of TXA in preventing PPH after caesarean delivery.62 – 71 Their characteristics are summarized in Table 1. In all studies except one,68 caesareans were elective. This 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.62 – 71 (Table 1). However, they all present several limitations. They were all single-centre trials, and some were quasi-randomized.63 64 Three studies had no placebo group,62 63 and only two clearly stated the primary outcome.55 70 As well, only those two studies provided a trial flow diagram.65 70 However, the main limitation in all the studies except one55 was the blood loss assessment; the method varied widely from study to study (Table 1). Moreover, the assessment depended strongly on the operator’s judgment, for it was based mainly on the weight of the material used (gauze, pads, sheets, etc.) and the suction container, although all authors clearly mentioned that their method did not take amniotic fluid quantity or blood loss before placental delivery into account. Another perhaps more major concern is that neonatal outcomes were not reported in any study. Neonatal safety requires careful assessment, especially since TXA was administered in all the studies at least 10 min before the caesarean incision and thus at least 10 min before the cord clamping.

We summarize here the details for the two most reliable studies. Gundokurk and colleagues65 reported the first large double-blinded RCT with an intention-to-treat analysis. This study is methodologically the most robust, as it used a primary outcome that did not depend on visual estimation of blood loss (Table 1).65 These authors found that TXA significantly reduced bleeding during caesarean delivery [mean 499.9 (se 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 agents [8.5% vs 14.5%; RR = 1.7 (95% CI 1.1 – 2.6), P = 0.02].65 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 colleagues70 recently published another large open RCT including 740 women. They found a statistically significant reduction in the mean blood loss in the experimental group [241.61 (se 6.77) ml], which received TXA, compared with the control group [510.66 (se 7.72) 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) vs −1.42 (1.16) g dl−1, P = 0.001] and haematocrit [−1.82% (sd 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.62 – 71 (Table 1). 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.72 73 In 2001, Yang and colleagues71 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>
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<tr>
<td>Gai and colleagues (2004)$^{52}$</td>
<td>China</td>
<td>Prospective, single-centre, randomized, controlled</td>
<td>N = 180, primiparas, elective CS under epidural analgesia</td>
<td>N = 91 (experimental) N = 89 (no placebo)</td>
<td>10 IU oxytocin IV simultaneously with 20 IU oxytocin into the intrauterine 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</td>
<td>Not reported</td>
<td>Not reported</td>
<td>(weight of materials used + materials not 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>
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<td>Gohel and colleagues (2007)$^{63}$</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</td>
<td>Not reported</td>
<td>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>
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<td>Sekhavat and colleagues (2009)$^{53}$</td>
<td>Iran</td>
<td>Prospective, single-centre, randomized, controlled</td>
<td>N = 90, primiparas, 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</td>
<td>Not reported</td>
<td>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>
</tr>
<tr>
<td>Gungorduk and colleagues (2011)$^{55}$</td>
<td>Turkey</td>
<td>Prospective, single-centre, double-blinded, 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</td>
<td>Yes</td>
<td>Not reported</td>
<td>Estimated blood loss = EBV × (preop haematocrit – postop haematocrit)/preop haematocrit</td>
<td>600.7 vs 499.9 ml</td>
</tr>
<tr>
<td>Movafegh and colleagues (2011)$^{66}$</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</td>
<td>Yes, 50 per group</td>
<td>Not reported</td>
<td>Method of Gai and colleagues$^{51}$</td>
<td>262.5 vs 404.7 ml</td>
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<tr>
<td>Xu and colleagues (2013)$^{67}$</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</td>
<td>Yes, 76 per group</td>
<td>Not reported</td>
<td>Method of Gai and colleagues$^{51}$</td>
<td>379 vs 441 ml</td>
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<tr>
<th>Study</th>
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<td>Sentürk and colleagues (2013)</td>
<td>Turkey</td>
<td>Randomized, single-centre, double-blinded, controlled study</td>
<td>N=223, primiparas and multiparas, elective and emergency CS under spinal anaesthesia</td>
<td>N=101 (experimental) N=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</td>
<td>Not reported</td>
<td>Not reported</td>
<td>272 vs 347 ml</td>
<td>0.001</td>
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<tr>
<td>Shahid and colleagues (2013)</td>
<td>Pakistan</td>
<td>Randomized, single-centre, double-blinded, placebo-controlled study</td>
<td>N=74, primiparas and multiparas, elective CS under spinal anaesthesia</td>
<td>N=38 (experimental) N=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</td>
<td>Not reported</td>
<td>Not reported</td>
<td>356 vs 710 ml</td>
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<tr>
<td>Abdel-Aleem and colleagues (2013)</td>
<td>Egypt</td>
<td>Randomized, single-centre, open, controlled study</td>
<td>N=740, primiparas and multiparas, elective CS under spinal anaesthesia</td>
<td>N=373 (experimental) N=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</td>
<td>Yes, 350 per arm</td>
<td>Yes</td>
<td></td>
<td>241.6 vs 510.6 ml</td>
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<tr>
<td>Goswami and colleagues (2013)</td>
<td>India</td>
<td>Randomized, single-centre, double-blinded, placebo controlled study</td>
<td>N=90, primiparas and multiparas, elective CS under spinal anaesthesia</td>
<td>N=30 (experimental 1) N=30 (experimental 2) N=30 (placebo)</td>
<td>20 IU oxytocin in 500 ml at the rate of 8 mlU min⁻¹ IV</td>
<td>Infusion of TXA 20 min before CS</td>
<td>Experimental 1: 10 mg kg⁻¹</td>
<td>Postpartum blood loss not clearly mentioned</td>
<td>Not reported</td>
<td>Not reported</td>
<td>376.8 vs 527.2 ml</td>
<td>Not reported</td>
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<td>Yang and colleagues (2001)</td>
<td>China</td>
<td>Multicentre, comparative, randomized controlled</td>
<td>N=400, primiparas</td>
<td>N=94 (experimental 1)</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</td>
<td>NA</td>
<td>1 g IV</td>
<td>0.5 g IV</td>
<td>0.5 g IV placebo</td>
<td>243.3 vs 242.9 vs 308.1 vs 314.8 ml</td>
</tr>
<tr>
<td>Gungorduk and colleagues (2013)</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</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</td>
<td>261.5 vs 350.0 ml</td>
<td>&lt;0.001</td>
<td>Gastrointestinal side effects significantly higher in the experimental group</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, Gundorkuk 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 1.27–11.15), 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 uterotonics 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 EXADELI 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 intratable 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). Nevertheless, this interesting study presents several limitations: the absence of placebo and blinding is a major limitation, particularly when the primary (estimated blood loss) and secondary (need for transfusion, invasive procedures) measures are dependent on the judgment and decision of the clinicians. Moreover, the low absolute difference in blood loss (primary outcome) between the two groups may not be clinically relevant. Finally, this study was not adequately powered to address safety for severe and rare adverse events.

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).
### Table 3

Characteristics of the randomized controlled trials that assessed tranexamic acid for the treatment of postpartum haemorrhage. IV, intravenous; NR, not reported; TXA, tranexamic acid.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size</th>
<th>Study groups</th>
<th>Sample size/flow chart</th>
<th>Interventions</th>
<th>Dosage/route/duration</th>
<th>Proportion of women who died in the study</th>
<th>Result</th>
<th>p-value</th>
<th>Adverse effects</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ducloy-Bouthors &amp; colleagues (2010)</td>
<td>France</td>
<td>Randomized, controlled, multicentre, open-label</td>
<td>N=144 primiparas and N=150 multiparas</td>
<td>N=72 (study), N=72 (placebo)</td>
<td>Proportion of women who died in the study 77 per arm Yes, 7500 per arm</td>
<td>Infusion of TXA 4 g IV, 1 g h⁻¹ if bleeding continues after 30 min (1 ml min⁻¹)</td>
<td>Yes, 77 per arm (P=0.40), 3% (P=0.11)</td>
<td>Ongoing study</td>
<td>No nausea/vomiting, 15% vs. 2% (P=0.002), Thrombosis: 2 (3%) vs. 1 (1%) (P=0.40), Thrombosis: 2 (3%) vs. 1 (1%) (P=0.11)</td>
<td>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].</td>
<td></td>
<td></td>
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<tr>
<td>EXADEL trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infusion of TXA 221 ml over 6 h IV</td>
<td>Yes, 7/77 per arm (P=0.40), 2%</td>
<td>Ongoing study</td>
<td>No nausea/vomiting, 15% vs. 2% (P=0.002), Thrombosis: 2 (3%) vs. 1 (1%) (P=0.40), Thrombosis: 2 (3%) vs. 1 (1%) (P=0.11)</td>
<td>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].</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shakur and colleagues</td>
<td>International</td>
<td>Randomized, controlled, double-blind, placebo-controlled</td>
<td>N=15,000 (expected sample size)</td>
<td>N=7500 per arm</td>
<td></td>
<td>Infusion of TXA 1 g h⁻¹ IV</td>
<td>Yes, 7500 per arm (P=0.40), 2%</td>
<td>Ongoing study</td>
<td>No nausea/vomiting, 15% vs. 2% (P=0.002), Thrombosis: 2 (3%) vs. 1 (1%) (P=0.40), Thrombosis: 2 (3%) vs. 1 (1%) (P=0.11)</td>
<td>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].</td>
<td></td>
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</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...
hypercoagulable 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 γ-aminobutyric acid A (GABA\textsubscript{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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