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Use of tranexamic acid at the time of delivery

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ABSTRACT

Postpartum haemorrhage (PPH) is responsible for 25% of maternal deaths worldwide. Tranexamic acid (TXA) is a lysine analogue which acts as an antifibrinolytic via competitive inhibition of the binding of plasmin and plasminogen to fibrin. It has been studied extensively in non-pregnant adults. TXA is safe in pregnancy, being FDA category B. Evidence suggested that TXA is a safe and effective methods for prevention and treatment of PPH at the dose of 1 g IV.

INTRODUCTION

Postpartum haemorrhage (PPH) is defined as blood loss from the birth canal in excess of 500 mL or 1,000 mL during the first 24 hours after vaginal or caesarean delivery, respectively [1], and is responsible for 25% of maternal deaths worldwide [2].
Different techniques have been studied in prevention of PPH [3-11]. Active management of the third stage of labour should be used routinely to reduce its incidence [4]. It involves giving a prophylactic uterotonic, early cord clamping and controlled cord traction to deliver the placenta. Uterine massage as part of active management of the third stage of labour has also been studied, with low quality of evidence [10, 11].
Moreover, specific managements have been proposed for women at risk of severe PPH, including those with abnormally invasive placenta [12-14].
Appropriate management of PPH also includes prompt diagnosis and treatment. The four T's can be used to evaluate the four most common causes of PPH, including Tone (uterine atony); Trauma (laceration, inversion, uterine rupture, haematoma); Tissue (retained tissue or AIP); and Thrombin (coagulopathy) [3].

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Recently, compelling evidence on the use of tranexamic acid (TXA) for treatment and prevention of PPH have been published [15-18]. TXA, a synthetic derivative of the amino acid lysine, is an antifibrinolytic agent that acts by binding to plasminogen and blocking the interaction of plasmin(ogen) with fibrin, thereby preventing dissolution of the fibrin clot [19].
In large, randomized controlled trials, tranexamic acid generally significantly reduced perioperative blood loss compared with placebo in a variety of surgical procedures, including cardiac surgery with or without cardiopulmonary bypass, total hip and knee replacement and prostatectomy [19].

USE OF TRANEXAMIC ACID IN OBSTETRICS

In obstetrics, TXA have been proposed in four different conditions:
1. Prevention of PPH at the time of vaginal delivery.
2. Treatment of PPH at the time of vaginal delivery.
3. Prevention of PPH at the time of caesarean delivery.
4. Treatment of PPH at the time of caesarean delivery.

Prevention of PPH at the time of vaginal delivery

The largest trial on prevention of PPH in vaginal delivery using TXA was published in the 2018 by Sentilhes *et al.* [20]. The authors investigated whether the prophylactic administration of TXA in addition to prophylactic oxytocin in women with vaginal delivery would decreased the incidence of PPH in a multicentre, double-blind, randomized trial. The primary outcome was PPH and occurred in 156 of 1,921 women (8.1%) in the tranexamic acid group and in 188 of 1,918 (9.8%) in the placebo group (relative risk (RR]) 0.83; 95% confidence interval (CI) 0.68-1.01; p = 0.07) [20].
A meta-analysis of 4 RCTs [20-23], including 4,671, evaluated the effectiveness of TXA for the prevention of PPH after vaginal delivery. The trials evaluated TXA at the dose of 1 g intravenous (IV) within 10 min after vaginal delivery in addition to oxytocin, cord traction, and uterine massage, at term [15]. Pooled data showed that women who received prophylactic TXA had a significantly lower incidence of primary PPH (8.7 *versus* 11.4%; RR 0.61; 95%CI 0.41-0.91) and lower mean blood loss (mean difference (MD) -84.74 mL; 95%CI -109.76 to -59.72). The risk of thrombotic events was not increased in the TXA group (**Table 1**).

Treatment of PPH at the time of vaginal delivery

A meta-analysis [16] of two trials [24, 25], including 14,363 women with established primary PPH after vaginal delivery has been published. The authors found that women who received tranexamic acid soon after the diagnosis of PPH had a significant-

Table 1. *Outcomes of tranexamic acid for prevention of postpartum haemorrhage in vaginal delivery.*

	Yang 2001 [21]	Gungorduk 2013 [22]	Mirghafourvand 2015 [23]	Sentilhes 2018 [20]	Total	RR or MD (95% CI)
PPH	18/186 (9.7%) *vs* 22/87 (25.2%)	4/220 (1.8%) *vs* 15/219 (6.8%)	27/60 (45.0%) *vs* 34/60 (56.7%)	156/1,902 (8.1%) *vs* 188/1,902 (9.9%)	205/2,368 (8.7%) *vs* 259/2,268 (11.4%)	**0.61 (0.41 to 0.91)**
Mean blood loss (mL)	243.1+140.4 *vs* 314.8 ± 180.9	261.5 ± 146.8 *vs* 350 ± 188.8	518.9 ± 319.6 *vs* 659.3 ± 402.5	Not reported	-	**-84.74 mL (-109.76 to -59.72)**
Thromboembolic events	0/186 *vs* 0/87	0/220 *vs* 0/219	0/60 *vs* 0/60	1/1,902 (0.1%) *vs* 4/1,902 (0.2%)	1/2,368 (0.1%) *vs* 4/2,268 (0.2%)	0.25 (0.03 to 2.24)
Nausea	Not reported	33/220 (15%) *vs* 12/219 (5.5%)	2/60 (3.3%) *vs* 0/60 (0%)	133/1,902 (7%) *vs* 61/1,902 (3.2%)	168/2,182 (7.7%) *vs* 73/2,181 (3.3%)	**2.29 (1.75 to 2.99)**
Vomiting	Not reported	30/220 (13.6%) *vs* 14/219 (6.4%)	Not reported	133/1,902 (7%) *vs* 61/1,902 (3.2%)	163/2,122 (7.7%) *vs* 75/2,121 (3.5%)	**2.17 (1.66 to 2.83)**

RR: relative risk; MD: mean difference; CI: confidence interval; PPH: postpartum haemorrhage; data are presented as number in the intervention *vs* number in the control group or as mean ± standard deviation; boldface data: statistically significant.

ly lower incidence of hysterectomy (0.5% *vs* 0.8%; RR 0.63, 95%CI 0.42-0.94), compared to those who did not. The risk of thrombotic events was not increased in the tranexamic acid group (**Table 2**).
In the largest trial [24], enrolled participants received 1 g intravenous tranexamic acid or matching placebo in addition to usual care. If bleeding continued after 30 minutes or stopped and restarted within 24h of the first dose, a second dose of 1 g of tranexamic acid or placebo were given [24].

Prevention of PPH at the time of caesarean delivery

A meta-analysis [18] of 9 trials [26-34] with 2,365 evaluated the use of TXA 1 g IV 10-20 minutes before skin incision or spinal anaesthesia as prophylactic intervention in women undergoing caesarean delivery. Pooled data showed that women who received TXA had a statistically significant lower postpartum blood loss (MD -160.27 mL; 95%CI -224.63 to -95.92) (**Table 3**).
Data were confirmed also in two subsequent randomized controlled trials [35, 36].

Treatment of PPH at the time of caesarean delivery

Few data have been published in women with severe bleeding at the time of caesarean delivery. However, evidence can be extrapolated from level-1 data on emergency and urgent surgery in non-pregnant women, where TXA showed to reduce mortality significantly [37].

DISCUSSION

Obstetric haemorrhage is the world's leading cause of maternal mortality, responsible for an estimated 127,000 deaths annually.
PPH is the most common type of obstetric haemorrhage and accounts for the majority of the 14 million cases that occur each year.
Several risk factors are associated with PPH, including maternal demographics, mode of delivery and birth weight [38-41]. TXA is a lysine analogue which acts as an antifibrinolytic via competitive

Table 2. *Outcomes of tranexamic acid for treatment of postpartum haemorrhage in vaginal delivery.*

	Ducloy-Bouthors 2011 [25]	WOMAN trial 2017 [24]	Total	RR (95%CI)
Hysterectomy	0/72 *vs* 2/72 (2.8%)	37/7,080 (0.5%) *vs* 58/7,108 (0.8%)	37/7,152 (0.5%) *vs* 60/7,180 (0.8%)	**0.63 (0.42 to 0.94)**
Maternal death (due to bleeding)	0/72 *vs* 0/72	110/7,083 *vs* 135/7,108	110/7,155 (1.5%) *vs* 135/7,180 (1.9%)	0.82 (0.64 to 1.05)
Maternal death (all causes)	0/72 *vs* 0/72	148/7,083 *vs* 172/7,108	148/7,155 (2.1%) *vs* 172/7,180 (2.4%)	0.86 (0.69 to 1.07)
Surgical intervention*	4/72 (5.6%) *vs* 5/72 (6.9%)	1,375/7,080 (19.4%) *vs* 1,448/7,108 (20.4%)	1,379/7,152 (19.3%) *vs* 1,453/7180 (20.2%)	0.95 (0.89 to 1.02)

RR: relative risk; CI: confidence interval; PE: pulmonary embolism; data are presented as number in the intervention *vs* number in the control group; boldface data: statistically significant; *surgical interventions done after randomization to control bleeding and achieve haemostasis excluding hysterectomy.

Table 3. *Outcomes of tranexamic acid for prevention of postpartum hemorrhage in caesarean delivery.*

	PPH	Severe PPH	Blood transfusion
Gai 2004 [26]	22/91 (24.2%) *vs* 35/89 (39.3%)	N/R	N/R
Gungorduk 2011 [27]	N/R	7/330 (2.1%) *vs* 19/330 (5.8%)	2/330 (0.6%) *vs* 7/330 (2.1%)
Movafegh 2011 [28]	N/R	N/R	0/50 *vs* 0/50
Abdel-Aleem 2013 [28]	11/373 (2.9%) *vs* 179/367 (48.8%)	2/373 (0.5%) *vs* 2/367 (0.5%)	N/R
Xu 2013 [30]	19/88 (7.9%) *vs* 28/86 (12.8%)	N/R	8/88 (9.1%) *vs* 19/86 (22.1%)
Shahid 2013 [31]	N/R	N/R	3/38 (7.9%) *vs* 12/36 (33.3%)
Senturk 2013 [32]	N/R	N/R	1/101 (1.0%) *vs* 1/122 (0.8%)
Goswami 2013 [34]	N/R	0/60 *vs* 0/30	0/60 *vs* 2/30 (6.7%)
Ahmed 2014 [33]	N/R	N/R	0/62 *vs* 0/62
Total	52/552 (9.4%) *vs* 242/542 (44.5%)	9/763 (1.2%) *vs* 21/727 (2.9%)	14/729 (1.9%) *vs* 41/716 (5.7%)
RR (95% CI)	**0.21 (0.16 to 0.28)**	**0.42 (0.19 to 0.92)**	**0.33 (0.19 to 0.58)**

RR: relative risk; CI: confidence interval; PPH, postpartum haemorrhage; PPH: blood loss more than 500 ml; Severe PPH: blood loss more than 1,000 ml; Hb: haemoglobin; data are presented as number of intervention *vs* number of control (percentage); boldface data: statistically significant.

inhibition of the binding of plasmin and plasminogen to fibrin. Peak plasma TXA concentration is obtained immediately after intravenous administration, then concentration decreases until the 6th hour. Its half-life is about 2 hours [42].
It has been studied extensively in non-pregnant adults [37, 43, 44], including trauma patients. TXA is safe in pregnancy, being FDA category B. One concern regarding use of TXA in pregnancy is the potential for thromboembolic events in a population at already high baseline risk of thrombosis [45].
Future studies should focus also on new biomarker for prevention and treatment of PPH. Indeed, the real challenge in the era of molecular medicine is to find a biomarker, or even better a panel of biomarkers, for early diagnosis of complications [46, 47].

CONCLUSIONS

Tranexamic acid is a safe, effective and affordable treatment for postpartum haemorrhage.
When given early, tranexamic acid reduces deaths due to bleeding by one-third. Urgent treatment is critical because women with postpartum haemorrhage bleed to death quickly, and tranexamic acid is most effective when given within 3h of childbirth, with no apparent benefit thereafter [48].
Following the results of the WOMAN trial, we recommend that women with clinically diagnosed postpartum haemorrhage receive 1 g of tranexamic acid intravenously as soon as possible and no more than 3h after childbirth, followed by a second dose if bleeding continues after 30 min or restarts within 24h of the first dose [49].
Research priorities include alternative routes of administration, tranexamic acid use for the prevention of postpartum haemorrhage and risk factors of morbidity after postpartum haemorrhage. The current research agenda must now address the need for interventions to prevent postpartum haemorrhage, particularly in high-risk groups.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

All authors contributed equally to this work.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

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N/A.

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N/A.

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