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NARRATIVE REVIEW

Use of tranexamic acid at the time of delivery

Running title: tranexamic acid and postpartum blood loss

Gabriele **Saccone**, Giovanni **Nazzaro**, Marilena **Miranda**, Elisabetta **Gragnano** *, Mariavittoria **Locci**

Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy.

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***Corresponding author:** Elisabetta **Gragnano**, M.D. Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

Email: elisabettagragnano@gmail.com

ABSTRACT

Postpartum hemorrhage (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.

Key words

Tranexamic acid; cesarean delivery; postpartum hemorrhage

INTRODUCTION

Postpartum hemorrhage (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 cesarean 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 labor 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 labor 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, hematoma); Tissue (retained tissue or AIP); and Thrombin (coagulopathy) (3).

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 cesarean delivery
- 4) Treatment of PPH at the time of cesarean 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 multicenter, double-blind, randomized trial. The primary outcome was PPH and occurred in 156 of 1921 women (8.1%) in the tranexamic acid group and in 188 of 1918 (9.8%) in the placebo group (relative risk [RR], 0.83; 95% confidence interval [CI], 0.68 to 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 to 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 significantly lower incidence of hysterectomy (0.5% vs 0.8%; RR 0.63, 95% CI 0.42 to 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 24 h 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 cesarean 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 anesthesia as prophylactic intervention in women undergoing cesarean 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 cesarean delivery

Few data have been published in women with severe bleeding at the time of cesarean 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 hemorrhage 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 hemorrhage 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 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). This study

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 biomaker, 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 post-partum haemorrhage. When given early, tranexamic acid reduces deaths due to bleeding by one-third. Urgent treatment is critical because women with post-partum haemorrhage bleed to death quickly, and tranexamic acid is most effective when given within 3 h of childbirth, with no apparent benefit thereafter (48). Following the results of the WOMAN trial, we recommend that women with clinically diagnosed post-partum haemorrhage receive 1 g of tranexamic acid intravenously as soon as possible and no more than 3 h after childbirth, followed by a second dose if bleeding continues after 30 min or restarts within 24 h of the first dose (49).

Research priorities include alternative routes of administration, tranexamic acid use for the prevention of post-partum haemorrhage and risk factors of morbidity after post-partum haemorrhage.

The current research agenda must now address the need for interventions to prevent post-partum haemorrhage, particularly in high-risk groups.

Conflict of interests

None.

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Table 1. Outcomes of tranexamic acid for prevention of postpartum hemorrhage 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	133/1902 (7%) vs 61/1902 (3.2%)	163/2122 (7.7%) vs 75/2121 (3.5%)	2.17 (1.66 to 2.83)

RR, relative risk; MD, mean difference; CI, confidence interval; PPH, postpartum hemorrhage

Data are presented as number in the intervention vs number in the control group or as mean ± standard deviation. Boldface data, statistically significant

Table 2. Outcomes of tranexamic acid for treatment of postpartum hemorrhage 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 1,453/7,180 (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 hemostasis excluding hysterectomy

Table 3. Outcomes of tranexamic acid for prevention of postpartum hemorrhage in cesarean 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 ²⁹	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)

Data are presented as number of intervention vs number of control (percentage)

RR: relative risk; CI: confidence interval; PPH, post partum hemorrhage

PPH: blood loss more than 500 ml; Severe PPH: blood loss more than 1000 ml; Hb: hemoglobin

Boldface data: statistically significant