The Egyptian Journal of Hospital Medicine (October 2017) Vol. 69 (6), Page 2601-2606

A Single Large Dose of Tranexamic Acid before Vaginal Delivery: Is It Beneficial?

Ahmed Abd Elhamid, Ashraf Hamdy, Sileem Ahmed Sileem
Department of Obstetrics and Gynaecology, Faculty of Medicine,Al-Azhar University, Asuit , Egypt
***Corresponding author: Ahmed Abd Elhamid, E-mail: drahmedhamid1977@yahoo.com**

ABSTRACT

Background: many factors are attributed in the management of postpartum hemorrhage after vaginal delivery

Objective: to assess the efficacy and safety of a single large dose of intravenous tranexamic acid in reducing postpartum blood loss after vaginal delivery.

Subjects and Methods: this is a multicentric prospective randomized double blind placebo controlled trial. 240 pregnant women were randomized to receive either 60 mg/kg of TA (n=120) or placebo (n=120) intravenously in the second stage of labour. Postpartum blood loss was collected and measured accurately from placental delivery to 2 hours postpartum and adverse effects of were observed.

Results: the mean estimated postpartum blood loss was significantly lower in women treated with tranexamic acid compared to women in the placebo group (241.5 ± 82.7 versus 322.8 ± 127.4, respectively; $p < 0.001$), and the proportion of women in the tranexamic acid group who had an estimated blood loss ≥ 500 mL was significantly lower than in the placebo group (5 [4.2%] versus 18 [15%], relative risk [RR]=0.30; 95% confidence interval [CI] 0.11 to 0.78; P<0.05). Maternal and neonatal outcomes did not differ significantly between both groups.

Conclusion: A single large dose of tranexamic acid administrated intravenously before vaginal delivery significantly reduces the amount of postpartum blood loss and contributes to prevention of PPH. Adverse effects were only mild and transient. Thus, tranexamic acid can be used safely and effectively to reduce bleeding after vaginal delivery.

Keywords: tranexamic acid, postpartum hemorrhage, vaginal delivery.

INTRODUCTION

Postpartum haemorrhage (PPH) stills the most common cause of maternal mortality worldwide, accounting for about 300,000 deaths every year, and most of deaths occur in the immediate postpartum period. PPH causes morbidity related to anaemia, blood transfusion and haemorrhage related ischaemic complications. Haemostatic abnormalities have long been considered consequences of uncontrolled bleeding [1, 2] .

PPH also contributes to hospital morbidity because patients may require a blood transfusion, which can transmit blood borne viral infections. Approximately 1% of women with spontaneous vaginal deliveries receive a blood transfusion, but the rate increases to about 5% for women with instrumental deliveries or caesarean sections [3]. Direct causes of PPH are mainly uterine atony, trauma to the birth canal, coagulopathy and retained placenta [2, 4]. PPH is poorly predictable, underestimated when diagnosed clinically and not deserving of early specific treatment. Accordingly, detailed guidelines have been issued for optimal use of obstetric interventions and uterotonic drugs [5].

PPH is commonly defined as blood loss of ≥ 500 ml after vaginal delivery of a baby, or ≥ 1000 ml after caesarean section. However, these thresholds do not take into account pre-existing health status, and blood loss of as little as 200 mL can be life-threatening for a woman with severe anaemia or cardiac disease and the problem is more hazardous in the developing countries [6]. Therefore, measures aiming to reduce postpartum blood loss have positive effects in reducing bleeding related maternal morbidity and contributing the global commitment to the Millennium Development Goal (MDG) of reducing maternal deaths by three-quarters by the year 2015, a commitment that requires a reduction of the maternal mortality ratio by 5.5% each year. Several measures for minimizing bleeding as well as preventing PPH are available, but further advances in this field are important, especially the identification of safe, easy to use, and cost-effective regimes. Tranexamic acid (TA) merits evaluation to assess whether it meets these criteria. TA was chosen because it has been demonstrated to be a potent antifibrinolytic agent in elective surgical patients and because it is the most often used antifibrinolytic agent worldwide. TA has the

Received: 8 / 8 /2017
Accepted:17 /8 /2017
DOI : 10.12816/0042235

additional advantages of being inexpensive and easy to stock and handle [2].

TA is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of the 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 excessive or recurrent bleeding is reduced [7]. Intravenous administration of TA has been routinely used for many years to reduce hemorrhage during and after surgical procedures like coronary artery bypass, oral surgery, orthopedic surgery, liver transplantation and urinary tract surgery. TA has been shown to be very useful in reducing blood loss and incidence of blood transfusion in these surgeries [2,8]. Moreover, the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) study demonstrated that TA safely reduces the risk of death in bleeding trauma patients [9].

TA significantly reduces uterine blood loss in women with menorrhagia and is recommended for consideration "as a treatment in intractable postpartum haemorrhage [2]. In the field of obstetrics, four randomized controlled trials have shown that TA reduces postpartum bleeding following cesarean delivery[10,13]. but only one randomized trial is available evaluating the effect of TA use to prevent bleeding in the postpartum period following spontaneous vaginal delivery[14]. However, quality of these trials was poor. None had adequate allocation concealment and trials were too small to assess the effect of TA and none used a large dose of intravenous TA. Many non obstetric trials have been proved the safety of high doses of TA[8,9,15]. Freeman et al. [16] reported that doubling daily dose of TA is associated with a significant reduction of blood loss among women with heavy menstrual bleeding without increase in adverse effects of TA. **Ducloy-Bouthors *et al.*** [2] were the first to study the high dose of intravenous TA in obstetric field and reported that it can reduce blood loss and maternal morbidity in women with established PPH and strongly supported the need for large study to investigate the potential of high dose of TA to reduce maternal morbidity worldwide.

This study aimed to quantify the effectiveness and safety of a prophylactic single large dose of intravenous tranexamic acid before vaginal delivery in reducing the postpartum blood loss and prevention of PPH.

SUBJECTS AND METHODS

Subjects: 240 patients were enrolled in this study in obstetric and gynecology department of al-azhar university -assiut

METHODS

This is a multicentric prospective randomized double blind placebo controlled study. The study was conducted from May 2015 to July 2016. Randomization was done by the rule of odds and even. 240 pregnant women were enrolled in the study. In 120 women, tranexamic acid (Cyklokapron ampoule [500 mg/5 ml] manufactured by Pfizer Ltd, UK) was given before vaginal delivery (TA group) compared with that in 120 others to whom saline solution (sodium chloride 0.9%) was given (control group). Full term pregnant women (gestational age ≥ 37 weeks) with singleton pregnancy being delivered vaginally were included in the study. Exclusion criteria were age <18 years, women delivered by caesarean section, presence of known haemostatic abnormalities, history of thrombosis or epilepsy, history of medical problems involving the heart, liver, kidney and brain. Women with known allergy to tranexamic acid, abnormal placentation, antepartum haemorrhage, uterine scar, severe preeclampsia, multiple pregnancy, macrosomia, polyhydromnios, women taking anticoagulant drugs and those requiring blood transfusion due to severe anemia were also excluded from the study. All women were given information about the study and written consent was taken from each of them.

In TA group, tranexamic acid in dose of 60 mg /kg was given slowly intravenously over 5 minutes/500mg (5ml). In control group, saline solution was given slowly intravenously by corresponding volume and duration according to maternal body weight. Intravenous TA administration was started in the second stage of labour in both groups. Immediately after delivery of the fetal shoulders, 10 units of oxytocin in 500 ml of dextrose 5% was given by intravenous drip over 30 minutes and 0.4mg methyl ergometrine was given intravenously and this was applied for all women in both groups. In each participating Centre, an under-buttocks plastic drape draining blood in graduated metal container used in delivery room and another under-buttocks plastic drape with a collection pouch was placed after each vaginal delivery in postnatal room to measure blood loss in the postpartum

period. Overestimation of blood loss because of the addition of antiseptic or saline solutions used for sterilization or washing during delivery was avoided. Midwives unaware of the group allocation measured the volume of blood in the metal container and collection pouches of drapes. Soaked mops, gauzes, pads, drapes and bed sheets were weighed by electronic scale (with 1 g deviation range) before and after blood soaking. Hemoglobin %, urine analysis, liver and renal function were noted before delivery and on the postnatal visits one week after delivery. Major side effects of TA (such as thrombotic events, renal failure or seizures) and minor side effects were reported during postnatal visits. With respect to venous thrombosis, clinical signs of superficial or deep thrombosis were collected, and ultrasonography was performed as soon as the signs were detected.

Outcome measures of interest were the amount of blood loss, number of women lost more than 500 ml of blood from placental delivery to 2 hours postpartum and adverse effect of TA therapy.

Results were expressed as means ± SD in cases of normal distribution and as medians and interquartile ranges otherwise. Comparisons between groups were performed using the X^2 test or Fisher's exact test for categorical variables. For numerical variables, we used Student's t-test in cases of normal distribution and the Mann-Whitney U test otherwise. All statistical analyses were performed using SAS software (SAS Institute, Cary, NC, USA). P value < 0.05 was considered statistically significant.

The study was approved by the Ethics Board of Al-Azhar University.

RESULTS

There were no statistical significant differences between TA group (n=120) and control group (n=120) regarding maternal and obstetric characteristics including maternal age, weight, height, gestational age, parity, duration of the second stage of labour and instrumental delivery (P > 0.05, table 1).

The median volume of postpartum blood loss from placental delivery to 2 hours postpartum, were significantly lower in the TA group than control group (241.5 ± 82.7 versus 322.8 ± 127.4, P< 0.001; table 2).

According to World Health Organization (WHO) definition of postpartum haemorrhage (PPH) as a loss of ≥ 500 ml of blood after placental delivery [17], there was significant reduction in incidence of PPH in TA group compared to control group (5 [4.2%] versus 18 [15%]%, relative risk [RR]= 0.30; 95% confidence interval [CI] 0.11 to 0.78; P<0.05; table 2).

As regard side effects of treatment, there were no significant differences between both groups regarding severe or non severe complications of TA. There were no fetal or maternal deaths. There were no significant differences in either Apgar scores at 1 and 5 minutes or neonatal intensive care admission between both groups (P>0.05, table 3).

Table 1. Maternal and obstetric characteristics in both groups.

Characteristic	TA group Mean ± SD	Control group Mean ± SD	P value
Number of patients	**120**	**120**	
Maternal age (years)	**29.3 ± 4.2**	**28.8 ± 4.5**	**NS**
Weight (kg)	**68.8 ± 12.9**	**69.5 ± 14.4**	**NS**
Height (cm)	**163.7 ± 6.1**	**164.3 ± 5.7**	**NS**
Gestational age (weeks)	**38.8 ± 1.3**	**38.5 ± 1.2**	**NS**
Parity, n (%)			
Primipara	**28 (23.3%)**	**25 (20.8%)**	**NS**
Multipara	**92 (76.7%)**	**95 (79.2%)**	**NS**
Duration of second stage of Labour (min)	**51.5 ± 10.8**	**49.7 ± 9.6**	**NS**
Instrumental delivery, n (%)	**5 (4.1%)**	**7 (5.8%)**	**NS**
Forceps delivery	**2 (1.6%)**	**3 (2.5%)**	**NS**
Ventouse extraction	**3 (2.5%)**	**4 (3.3%)**	**NS**

NS=non significant

Table 2. Postpartum blood loss in both groups.

	TA group (n=120)	control group (n=120)	P value
Duration of bleeding from placental delivery to 2 hours PP (ml, Mean± SD)	**241.5 ± 82.7**	**322.8 ± 127.4**	**<0.001**
Incidence of PPH			
< 500 ml (n, %)	**115 (95.8%)**	**112 (93.3%)**	**NS**
≥ 500 ml (n, %)	**5 (4.2%)**	**18 (15%)**	**<0.01**

PP=postpartum PPH=postpartum haemorrhge

Table 3. Side effects of treatment.

Side effect	TA group n, (%)	control group n, (%)	P value
Non severe side effects			
Nausea/vomiting	**8 (6.6%)**	**6 (5%)**	**NS**
Headache	**7 (5.8%)**	**4 (3.3%)**	**NS**
Dizziness	**6 (5%)**	**5 (4.1%)**	**NS**
Allergic reactions	**0 (0)**	**0 (0)**	**NS**
Severe side effects			
DVT	**0 (0)**	**0 (0)**	**NS**
Renal impairment	**0 (0)**	**0 (0)**	**NS**
Liver impairment	**0 (0)**	**0 (0)**	**NS**
Seizures	**0 (0)**	**0 (0)**	**NS**
Maternal death	**0 (0)**	**0 (0)**	**NS**
Neonatal death	**0 (0)**	**0 (0)**	**NS**
Neonatal intensive care admission	**4 (3.3%)**	**5 (4.1%)**	**NS**

DVT=deep venous thrombosis, Renal and liver impairment= abnormal renal and liver functions

DISCUSSION

During delivery, when the placenta separates from the uterine wall, a sequence of physiologic and haemostatic changes occurs to reduce bleeding including strong myometrial contractions, increased platelet activity, a massive release of clotting factors with a parallel increase in the fibrinolytic activity[18]. As a result, fibrinogen and fibrin are rapidly degraded, whereas plasminogen activators and fibrin degradation products (FDP) increase due to activation of the fibrinolytic system. This activation can last up to 6-10 hours postpartum and tends to reduce the potential of blood to clot causing more bleeding[10]. Accordingly, there is a theoretical rationale for the use of a potent antifibrinolytic agent such as TA in the prevention of postpartum haemorrhage [19].

This study showed that tranexamic acid significantly reduces blood loss from time of placental delivery to 2 hours postpartum after vaginal delivery (P<0.001). This study also showed a significant decrease in the incidence of ≥ 500 mL blood loss in TA group compared to control group (P< 0.01). Results of our study have been corroborated by the four trials those investigated the effect of TA injection before caesarean deliveries [10,13]. and the only one trial carried out by **Yang *et al.*** [14]. that investigated the efficacy of TA in reducing postpartum bleeding after spontaneous vaginal delivery. However, the incidence of PPH in TA group compared to control group was lower in our study (RR = 0.30) than reported by other trials. A pooled relative risk for 3 of these trials was 0.44[3]. and RR reported by **Gungorduk *et al.*** [13]. was 0.37. This could be mostly explained by using a higher dose of TA in our trial than doses used in those trials.

Yang et al [14] reported no significant differences between women injected by 0.5 gm TA and those injected by 1 gm TA before vaginal delivery regarding postpartum blood loss and incidence of PPH. However, Yang et al compared two relatively small fixed doses of TA (0.5 gm and 1gm) irrespective to maternal body weight that might expose the trial to risk of bias. They also used 400 ml instead of 500 ml as a threshold of blood loss in diagnosis of PPH, studied lower samples (less than 100 women in each group), excluded instrumental deliveries, multigravidas and adopted inadequate allocation concealment. No other studies compared the different doses of TA in obstetrics. However, Ducloy-Bouthors et al. [2] reported that high-dose of TA (loading dose 4 g over 1 hour, then infusion of 1 g/hour over 6 hours) can reduce blood loss and maternal morbidity in women with PPH. Given the lack of previous obstetric studies on the efficacy of higher doses of TA, we chosed TA (60 mg/kg) in our study as the best clinically effective dose used to reduce haemorrhage in high-risk cardiac surgery patients [15,20].

No single patient developed severe side effects such as thrombosis, allergic reaction, seizures, renal or hepatic impairment and incidences of non severe side effects like nausea, vomiting and diarrhea as well as neonatal morbidity were not statistically significant by difference in the two groups. These have been corroborated by other non obstetric studies that investigated adverse effects of high TA doses[9,15,21]. **Ducloy-Bouthors *et al.*** [2]. reported 3 cases of deep venous thrombosis (DVT) but without significant differences between both groups (2cases in TA group [2.5%] and 1 case in control group [1.3%]; P=0.4).

Because thromboembolic events are relatively rare, this trial lacks statistical power to detect the risk of thrombosis related to TA use in puerperium. As the risk of thromboembolism increased in pregnancy and the risk shows more increase in postpartum period, some increased risk of thromboembolic events with TA as a potent antifibrinolytic might be expected on theoretical grounds[22]. Although, recent evidence from the CRASH-2 trial [9]. of TA in bleeding trauma patients showed a statistically significant reduction in mortality with no increase in thromboembolic effects, a need for a large pragmatic clinical trial of the effect of routine use of high dose TA on puerperal thromboembolic morbidity is warranted because a modest increase in the risk of thromboembolic morbidity could outweigh the benefits of reduced blood loss. A second limitation is that the design of this study was not powered to show decreases in maternal death. However, we demonstrated a trend toward a decrease in the rate of PPH. From this perspective, we urge investigators involved in all ongoing trials of TA to collect data on thromboembolic events and mortality for inclusion in a prospective meta-analysis until these uncertainties are resolved. A third limitation of this study is that the duration of follow up was short and adverse events may have occurred after the study period ended. TA is not completely eliminated from the blood until 9–18 hours after administration[3]. However, because the half-life of TA is two hours, levels in the blood would be reduced after the study period and any late adverse event would be discovered in postnatal visits.

Our results propose to future studies concerning to using intravenous injection of high dose TA in routine practice of active management of the third Stage of labour.

CONCLUSIONS

A single large dose of tranexamic acid administrated intravenously before vaginal delivery significantly reduces the amount of postpartum blood loss and contributes to prevention of PPH. Adverse effects were only mild and transient. Consequently, tranexamic acid can be used safely and effectively to reduce bleeding after vaginal delivery.

REFERENCES

1. Hogan MC, Foreman KJ, Naghavi M, Ahn SY, Wang M, Makela SM, bLopez AD, Lozano R, Murray CJ (2010): Maternal mortality for 181 countries, 1980-2008: a systematic analysis of progress towards Millenium Development Goal 5. Lancet, 375:1609-1623.

2. Ducloy-Bouthors A, Jude B, Duhamel A (2011): High dose tranexamic acid reduces blood loss in postpartum haemorrhge. Critical Care, 15:R117.

3. Ian R, Emma S, K, Haleema S(2009): Anti-fibrinolytic agents in postpartum haemorrhage: a systematic review. *BMC Pregnancy and Childbirthm,* doi: 10.1186/1471-2393-9-29.

4. Dupont C, Touzet S, Colin C, Deneux-Tharaux C, Rabilloud M, Clement HJ, Lansac J, Colle MH, Rudigoz RC (2009): Incidence and management of postpartum haemorrhage following the dissemination of guidelines in a network of 16 maternity units in France. Int J Obstet Anesth., 18:320-327.

5. Department of Reproductive Health and Research, World Health Organization(2009): WHO Guidelines for the Management of Postpartum Haemorrhage and Retained Placenta. Geneva: WHO Library Cataloguingin- Publication Data NLM classification: WQ 330. whqlibdoc.who.int/publications/2009/9789241598514

6. Lalonde A (2006): Postpartum hemorrhage today: ICM/FIGO initiative 2004-2006. *Int J Gynaecol Obstet*., 94(3):243-53.

7. Caglar GS, Tasci Y, Kayikcioglu F, Haberal A(2008): Intravenous tranexamic acid use in myomectomy: a prospective randomized double-blind placebo controlled study. Eur J Obstet Gynecol Reprod Biol.,137(2):227-31. Epub 2007 May 11.

8. Elwatidy S, Jamjoom Z, Elgamal E, Zakaria A, Turkistani A, El-Dawlatly A (20018): Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: a prospective, randomized, double-blind, placebo-controlled study. Spine (Phila Pa 1976),33(24):2577-80.

9. Shakur H, Roberts I, Bautista R, Caballero J*et al.* (2010): Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet, 376:23-32.

10. Gohel M, Patel P, Ashoo G, Desai P(2007): Efficacy of tranexamic acid in decreasing blood loss during and after cesarean section**:** A randomised case controlled prospective study. *Journal of Obstetrics and Gynecology of India*, 57(3):227-230.

11. Movafegh A, Eslamian L, Dorabadi A(2011): Effect of intravenous tranexamic acid administration on blood loss during and after cesarean delivery. nt J Gynaecol Obstet. Dec.,115(3):224-6.

12. Sekhavat L, Tabatabaii A, Dalili M, Farajkhoda T, Tafti AD(2009): Efficacy of tranexamic acid in reducing blood loss after caesarean section. J Matern Fetal Neonatal Med. , 22(1):72-5.

13. Gungorduk K, Yıldırım G, Asıcıoğlu O, Gungorduk O, Sudolmus S, Ark C(2011): Efficacy of Intravenous Tranexamic Acid in Reducing Blood Loss after Elective Cesarean Section: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. Amer J Perinatol.,28(3): 233-240.

14. Yang H, Zheng S, Shi C (2001): Clinical study on the efficacy of tranexamic acid in reducing postpartum blood lose: a randomized, comparative, multicenter trial Chin J Obstet gynecol.,6:590-2**.**

15. Karski JM, Dowd NP, Joiner R, Carroll J, Peniston C, Bailey K, Glynn MF, Teasdale SJ, Cheng DC(1998): The effect of three different doses of tranexamic acid on blood loss after cardiac surgery with mild systemic hypothermia (32 degrees C). J Cardiothorac Vasc Anesth., 12:642-646.

16. Freeman EW, Lukes A, VanDrie D, Mabey RG, Gersten J, Adomako TL. A (2011): dose-response study of a novel, oral tranexamic formulation for heavy menstrual bleeding. Am J Obstet Gynecol.,205(4):319.e1-7.

17. World Health Organisation (2007): www.biomedcentral.com/imedia/1028787481283747

18. Hellgren M(2003): Hemostasis during normal pregnancy and puerperium. *Semin Thromb Hemost*., 29(2):125-30.

19. Bolte AC, Bouma L, van Geijn HP(2005): Medical therapies for primary postpartum hemorrhage. *International Congress Series. Gynaecology, Obstetrics, and Reproductive Medicine in Daily Practice*, 1279:364-368.

20. Karski JM, Teasdale SJ, Norman PH, Carroll JA, Weisel RD, Glynn MF(1993): Prevention of postbypass bleeding with tranexamic acid and ε- aminocaproic acid. J Cardiothorac Vasc Anesth., 7:431-435.

21. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W(2009): Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. Thromb Res., 123:687-696.

22. Heit JA (2005): Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med., 143(10):697-706.