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Effect of Intravenous Tranxenamic Acid On Incidence of Postpartum Haemorrhage Among Parturients in Ekiti State

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ABSTRACT: *Post-partum haemorrhage (PPH) contributes to approximately 25% of maternal death globally. Tranexamic acid (TXA) has been confirmed to be effective in reducing post-partum blood loss, thereby preventing PPH and its possible sequelae. This clinical controlled trial compared the efficacy of a single dose of 0.5g of intravenous TXA to a single dose of 1g of intravenous TXA in prevention of primary PPH among high-risk parturient women in a teaching hospital. A total of 308 women served as the study sample; 154 women were randomly selected to be administered with 0.5g of tranexamic acid (study group), while the remaining 154 respondents were administered with 1g of tranexamic acid (control group). Post-partum blood loss was*

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monitored immediately. All results were recorded in a proforma. Data were coded and entered into Statistical Package for the Social Sciences (SPSS) version 23. Continuous variables were presented as mean ± Standard deviation while categorical data such as frequency tables and percentages. Student's t-test was used as appropriate for statistical significance. Results were considered statistically significant when P< 0.05. The mean blood loss of 475.79ml was higher in the study group compared to the mean blood loss of 430.18ml in the control group, this was statistically significant, (t=2.401, p<0.05). In conclusion, the 1g of tranexamic acid is more effective in the prevention of PPH compared to the 0.5g of tranexamic acid. It was recommended that 0.5g of tranexamic can be administered in the face of challenges at obtaining the standard 1g doses of tranexamic acid. However, the 1g standard dose of tranexamic acid is still the recommended dose especially for high-risk patients

KEYWORDS: Tranexamic Acid (different doses), Post-partum Haemorrhage, High-Risk, Parturients

INTRODUCTION

Post-partum haemorrhage (PPH) is a global public health issue as it is said to be responsible for the death of over 300,000 women yearly. Obstetric haemorrhage contributes to approximately 25% of maternal deaths worldwide, with up to 99% of all maternal deaths happen in developing countries (Alkema, et al., 2016). PPH is defined as the blood loss per vaginum of 500ml or more following vaginal delivery or at least 1000 ml following caesarean section (CS) (Habitamu et al., 2019). Other definitions specified PPH as blood loss >15% of total blood volume or 10% decline in haemoglobin levels measured peripartum, or any amount of vaginal bleeding following delivery that causes vital sign derangement (Habitamu et al., 2019; Salem et al., 2016). Blood loss during the first 24 hours after delivery is known as primary PPH and most deaths resulting from PPH occur during this period (El-Refaey & Rodeck 2003).

The Four T's mnemonic can be used to identify and address the four most common causes of PPH (uterine atony [Tone]; laceration, hematoma, rupture [Trauma]; retained placenta tissue [Tissue]; and coagulopathy [Thrombin] (Evensen et al., 2017; Oyelese & Ananth 2020; Ajenifuja et al., 2021). By far the most common cause of PPH is the failure of adequate uterine contraction, referred to as uterine atony. It has been estimated that this is the cause of over 70% of cases of PPH. Uterine atony can frequently be anticipated in any patient with the following risk factors, uterine overdistension, such as that caused by polyhydramnios, multifetal gestations, or foetal macrosomia may lead to uterine atony, and consequently PPH (Evensen et al., 2017; Oyelese & Ananth 2020). Genital tract trauma may result from lacerations of the perineum, cervix, episiotomy, or uterine rupture. Retained placenta tissue from morbidly adherent placenta and poorly managed the third stage of labour. Coagulopathy can be from abruption placentae, intrauterine foetal death and

hypertensive disorders of pregnancy. Factors that predispose to any of these will increase the risk of PPH.
The global prevalence of PPH is 6 % while the highest-burden is experienced in low-income countries with the magnitude in sub-Saharan Africa as high at 10.5 % (Ononge et al., 2016). In Nigeria, the incidence of PPH varies from centre to centre. In Ilorin, Port Harcourt, and Kano, the incidences were 4.2%, 4.28% and 2.48% respectively (Adeniran et al., 2014; Green et al., 2015; Garba et al., 2019). The incidence of PPH in Ekiti State was 11.2% (Awoleke et al., 2020). PPH can also lead to significant morbidity associated with substantial blood loss, shock and end-organ dysfunction (Habimatu et al., 2019; El-Rafaey & Rodeck 2003; Henry & McFarland 2015).

The third stage of labour is essential in preventing PPH because placental expulsion is a critical window for the prevention of PPH, and various preventive measures during this stage have been proposed. The interventions can be divided into two categories; those involving a mechanical intervention and the use of pro-haemostatic agents (Sentihes et al., 2015). Active management of the third stage of labour (AMTSL) consists of a combination of mechanical interventions involving the administration of uterotonics, particularly oxytocin, immediately after the delivery of the baby, controlled cord traction and finally uterine message. However, AMTSL may only prevent about 60% of postpartum haemorrhages. However, in addition to this enhancement of mechanical haemostasis, a complementary biochemical haemostatic effect might be expected from the complementary use of pro-haemostatic drugs such as tranexamic acid (Sentilhes et al., 2015). Tranexamic acid (TXA) is a potent antifibrinolytic agent that exerts its effect by blocking lysine binding sites on plasminogen molecules and has the potential to enhance the effectiveness of the patient's haemostatic mechanisms. Consequently, clot breakdown (fibrinolysis) is inhibited and bleeding is reduced (Fischer et al., 2020). TXA is a promising agent, easy to administer, readily available, and can be added to the other routine management in hospital deliveries (Abd El-Gaber et al., 2018). A recently published WOMAN trial, which was a randomized, placebo-controlled, multicentred large study involving more than 20,000 women in 193 hospitals in 21 countries reported that TXA reduced bleeding deaths by almost one third (Shakur, et al., 2017).

This study considered the efficacy of a lower dose (500mg) among women in Nigeria where cost may be a hindrance to the use of the standard 1g dose. Also, the higher dose of 1g and above has been associated with the occurrence of disturbing side effects including epigastric pain, nausea, vomiting and increased possibility of thromboembolic phenomenon which was what spur the researcher to embark on this study. This trial, therefore, is designed to investigate the efficacy and safety of 0.5g of intravenous TXA as compared to 1g in the prevention of primary postpartum haemorrhage following vaginal births among parturient women with risk factors such as the previous history of PPH, multiple gestations, fibroid coexisting with pregnancy, polyhydramnios, augmentation of labour, anaemic parturient, multiparity and women with foetal macrosomia.
The overall aim of this study is to compare the efficacy of prophylactic intravenous 0.5g with 1.0g Tranexamic acid in the prevention of postpartum haemorrhage in parturient with risk factors. It specifically examined;

1. the efficacy of 0.5g with 1.0g prophylactic Intravenous Tranexamic Acid in the Prevention of postpartum haemorrhage; and
2. compare the incidence of side effects of Tranexamic acid between the two groups.

METHODOLOGY

The study is a randomized double blind controlled trial. The study population comprised all parturient with a risk factor for primary PPH in the third stage of labour after vaginal delivery at term. The study was carried out over nine months. Sample size was determined using data from the previous study (Yang, Zheng & Shi, 2001). The formula for sample size calculation for comparison between two groups for non-inferiority designed randomized controlled trial (RCT) was used (Zhomg, 2009)

$N = 2 \times \left(\frac{Z_{1-\alpha}+Z_{1-\beta}}{\delta_0}\right)^2 \times p \times (1- p)$

$Z_{1-\alpha} = 1.96$ at type 1 error of 5%

$Z_{1-\beta} = 0.84$ at 95% power

P = Pooled prevalence = [prevalence in case group (P_1) + prevalence in control group (P_2)] / 2

Pooled prevalence = (6.4 + 13.3) / 2 = 9.85

δ_o = clinically acceptable margin = 0.1 (small design effect)

$$N = 2 \times \frac{(1.96+0.84)^2}{0.1^2} \times 0.0985\ (1 - 0.0985)$$

$$N = \frac{2\ (7.8400)\ (0.0888)}{0.01}$$

$$N = \frac{1.3924}{0.01}$$

N = 139.2

To make provision for attrition, 10% of the sample size was added. Thus, the total sample size was 154 in each arm of the study.

The study population was recruited using the simple random sampling method, for patients that meet the inclusion criteria, the study population was then divided into the study and control groups using simple random sampling method. A total number of 154 numbers was generated randomly from a pool of 308 numbers using Software Research randomizer, The 154 generated numbers were assigned as the study group, while the remaining 154 numbers were allotted to the control group. A sealed envelope with the inscription “1-308” was inscribed on a sealed envelope containing a piece of paper with the inscription “TXA 0.5” and “TXA 1.0” respectively to match the corresponding randomized group number on the envelope. The envelope was arranged sequentially and kept in a box from which each eligible participant was serially pick from as they are recruited. Each selected envelope was opened individually and the patient was allotted to the corresponding treatment group they contained.

The blinding was done by involving the pharmacists at the pharmacy department within the maternity complex, they were the custodians of the drugs and also helped in withdrawing the required dosage to be given to the patient depending on the number picked by the patient. Both the patient and the house office in the managing team were not aware of the group the patient belongs to, the same type and volume (10ml) of syringe were used for both patient in the control and study groups. The same colour code was used to identify the respondents. Finally, the assessor of the quantity of blood loss was also unaware of the group the patient belonged to. The Likelihood of Loss to follow-up was at the barest minimum because the study started at the third stage of labour and ends 24-hours after the delivery, which is the routine time for patients' discharge following delivery in the department.

For blood loss evaluation, immediately after the delivery of the baby when the umbilical cord has been doubly clamped and cut in between the clamps, the absorbent sheet underneath the buttock and all the perineal pads used were discarded and replaced with a pre-weighed absorbent sheet which were placed underneath the buttock, also two pre-weighed perineal pads were applied to the perineum after placental delivery and all the perineal pad that were used for episiotomy and laceration repair were pre-weighed. The perineal pads used for episiorhaphy and laceration repair where indicated were reweighed after the repair. The perineal pads and the absorbent sheath were removed after the first hour and reweighed. New perineal pads and an absorbent sheet of known weight were replaced and removed every four hours as the usual practice in this facility till the first 24hours after the delivery. These perineal pads used were reweighed immediately after removal.

The blood loss was calculated by the difference in weight between the dry and soaked perineal pads and absorbent sheets used based on the fact that 1gram difference is equal to 1ml of blood loss (Atunkunda et.al., 2016). The difference in the weight before and after use of the pads and the absorbent sheet were noted and added together 24hours after the delivery. Any patient with blood loss of 500mls or more (as the definition for PPH for this study) were classified to be having primary postpartum haemorrhage (Salem, Mohamed, Salem, & Abbas, 2016). The pads and absorbent sheets were weighed using MB130 Detecto digital weighing scale (MB130 Detecto digital weighing scale is highly accurate, sensitive, very portable, simple to use, easy to clean, low power consumption from the chargeable 9-volt Alkaline battery. It is manufactured in China, total capacity is 20KG and being digital, it can measure any material as small as 5gm) which are used in the labour ward.

The following parameters were recorded on the study proforma for every participant: baseline data including her age, parity, estimated gestational age, risk factors for PPH, admission haematocrit, and estimated postpartum blood loss. Data obtained were coded and entered into Statistical Package for the social sciences (SPSS) version 23. Student's t-test was used as appropriate for statistical significance. Results were considered statistically significant when $P< 0.05$.

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RESULTS

A total of 308 women were recruited for the study and 154 were randomly selected to be administered with 0.5g of tranexamic acid (study group) while the remaining 154 respondents were administered with 1g of tranexamic acid (control group).

Table 1: Comparing the incidence of PPH among parturient given in relation to dosage of TXA

Group	PPH Yes N (%)	No N (%)	TOTAL N (%)	OR	95% C.I.	p-VALUE
IV TXA 0.5g	19 (12.3)	135 (87.7)	154 (50.0)	1.830	0.251 – 1.191	0.124
IV TXA 1.0g	11 (7.1)	143 (92.9)	154 (50.0)			
Total	30 (9.7)	278 (90.3)	308 (100.0)			

Table 1 shows that 19 women in study group had PPH, while 11 women in control group had PPH, this implies that the risk of developing primary PPH when 0.5g TXA is used is about twice the risk when 1.0g TXA is used (95% C.I. 0.25 – 1.19).

Table 2: Comparing the incidence of Primary PPH by estimated blood loss in both groups.

Group	Mean blood loss	T-Test	95% Confidence Interval	P value
IV TXA 0.5g (n=154)	475.79 ± 175.58	2.401	434.29 – 471.61	**0.017**
IV TXA 1.0g (n=154)	430.13 ± 153.86			

Table 2 shows that the mean blood loss in the study group was higher than the mean blood loss was higher in respondents who had I.V. 0.5g compared to respondents who had I.V. TXA 1.0g (475.79mls versus 430.13ml) and this was statistically significant, (T-test =*2.401, p-value = 0.017).*

Table 3: Comparing the need for administration of additional uterotonics in both groups.

Group	Additional Uterotonics		Total (%)	$\chi 2$	p-VALUE
	Yes (%)	No (%)			
IV TXA 0.5g (n=154	20 (13.0)	`134 (87.7)	154 (50)	2.905	**0.088**
IV TXA 1.0g (n=154)	11 (7.1)	143 (92.9)	154 (50)		

Total	31 (10.1)	277 (89.9	308 (100)

Table 3 shows that majority of the respondents in both the study (87.0%) and control groups (92.9%) respectively did not require additional uterotonics, while only 13% and 7.1% of the respondents who belonged to the study and control groups respectively required additional uterotonics. However, there was no statistically significant difference ($\chi 2$ =2.905, p-value = 0.088).

DISCUSSION

The study revealed that incidence of PPH was 9.7%, this is similar to previous studies by Tiruneh B et al., (2022) where the incidence of primary postpartum haemorrhage in the hospitals was 8.8% (95% CI: 7.2, 10.6), In population-based studies, the incidence of PPH has been discovered to be about 5% of deliveries when blood loss is not precisely evaluated and around 10% when it is. (Deneux-Tharaux et al., 2014) Hence, justifying the reason for a prevalence of 9.7% in this study. The study also revealed that the incidence of PPH was higher in the study group than in the control group. This was although not statistically substantiated, the efficacy of tranexamic acid in the treatment of PPH has been studied and its role in PPH management has been confirmed (Shakur et al., 2017). The World Health Organization (WHO) updated their recommendations in 2017 to strongly recommend early use of 1gram of TXA within 3 hours of birth in all cases of PPH, used as part of standard PPH treatment irrespective of the cause of the PPH (Kachikis et al., 2018).

The study also revealed that the mean blood loss of 475.79ml was higher in respondents who had I.V. 0.5g compared to respondents who had I.V. TXA 1.0g and this was statistically significant, (T-test =2.401, p-value = 0.017) this is slightly different from the report of a similar study in a systemic review conducted by Sentilhes et al., (2015) one of the study reviewed compared four groups and 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 0.5 g TXA, also intravenously, the third group (n = 92) received a single I.V. 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). The pooled RR of PPH was thus 0.44 (95% CI 0.31–0.64). They also reported average blood loss of 243.3mls for respondents who had 1.0g TXA, 242.9mls for respondents who had 0.5g TXA, 308.1mls for respondents who had a single I.V. dose of 0.5 g aminomethylbenzoic acid, and 314.8 mls for respondents who had placebo. This implies that both doses reduce the volume of blood loss. This study did not however recruit respondents that were given placebo.

CONCLUSION

The study concluded that 1g of tranexamic acid is more effective in the prevention of PPH compared to the 0.5g of tranexamic acid.

Recommendation

Based on the findings in this study, it is worthy of note to recommend that 0.5g of tranexamic can be administered in the face of challenges at obtaining the standard 1g doses of tranexamic acid. However, the 1g standard dose of tranexamic acid is still the recommended dose especially for high-risk patients.

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