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Effect of Tranexamic Acid on Primary Postpartum Haemorrhage in at Risk Women at Abuth, Zaria: A Randomized Controlled Study

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Abstract

Background: *Postpartum haemorrhage is an obstetric nightmare. Although it may occur in women with no identified risk, women with certain risk profiles are at increased risk PPH. Tranexamic acid has been shown to be effective in low risk women.*

Aim: *To compare the effectiveness of Tranexamic acid to placebo in preventing PPH in at-risk women following vaginal delivery.*

Research Methods: *The study was a randomized controlled trial at ABUTH, Zaria, in which 334 women identified as being at risk for PPH, were sequentially randomized into Tranexamic and placebo groups of 167 each. The Tranexamic acid group received intravenous 1g Tranexamic acid made up to 20ml with 0.9% Normal saline, while the placebo group received 20ml 0.9% Normal saline at delivery. Both groups received I.M 10IU oxytocin as part of AMTSL protocol. Blood loss was collected objectively in a blood collection drape at delivery.*

Results: *The primary outcome, blood loss >500ml, was significantly lower in the study arm 12.9% versus 27.9% p-value =0.001, while the mean blood loss was also significantly lower in the Tranexamic acid arm, 260.61±183.74 versus 365.84±191.79; p-value <0.001. On the secondary outcomes, there was significant difference in mean haemoglobin fall with significant reduction on the need of additional uterotonic agent in the Tranexamic arm of the study, p-value 0.001. There was no significant difference on the need for blood transfusion, and side effect profile in both arms of study p-value 0.075 and 0.124 respectively.*

Conclusion: *Tranexamic acid is efficacious in reducing PPH in at-risk women during vaginal delivery.*

Keywords: *Postpartum haemorrhage, Tranexamic acid, at-risk, vaginal delivery.*

Introduction

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality in low income countries, and the primary cause of nearly one quarter of all maternal deaths globally.[1] Most deaths from PPH occur in the first 24 hours of birth. Majority of these could be avoided by the use of prophylactic uterotonics, during the third stage of labour and by timely and appropriate management.[2]

There are a number of drugs available for management of PPH, with the most recent being the anti-fibrinolytics and recombinant factor VIIa.[3]The World Health Organization (WHO), recommends oxytocin as the first line prophylactic management for PPH, [4] as part of the active management of third stage of labour protocol (AMSTL). Pro-haemostatic drugs such as Tranexamic acid (TXA), provide complementary

biochemical, haemostatic effects to the well proven uterotonics, especially oxytocin.[5]

Tranexamic acid is a potent anti-fibrinolytic agent, that exerts its effect by blocking lysine binding sites on plasminogen molecule and has the potential to enhance the effectiveness of the patient's own haemostatic mechanisms.[6] Anti-fibrinolytic agents reduce obstetric blood loss as the fibrinolytic system is known to get activated after placental delivery.[7] The plasma fibrinogen level decreases during the third stage of labour and after placental delivery and the level of fibrin degradation products in serum increases one hour after child birth and remains raised in the early puerperium.[8]

Although PPH may occur in women with no identifiable clinical or historical risk factors, women whose profiles include certain factors have been associated with tendencies to PPH.[9]A systematic review and meta-analysis to determine the safety and efficacy of Tranexamic acid concluded on the need for further studies on the use of Tranexamic acid in high-risk women.[10] Ahmadzia and fellow researchers also recommended the consideration of Tranexamic acid in the prevention of PPH both at vaginal and caesarean deliveries in high risk women[11]

Mirghafourvand et al,[12] recruited 120 women in a double blind randomized controlled trial on the effect of Tranexamic acid on blood loss at vaginal delivery and reported it reduced the amount of blood loss in women with low risk of PPH with mean loss of 519 ±320ml versus 659 ±402ml in the control group. Priyankur and colleagues ina randomized controlled study in India,[7] on the role of Tranexamic acid in reducing blood loss at vaginal delivery, founded that post-delivery haemoglobin and haematocrit were significantly reduced in the control group, compared to the study (Tranexamic acid) group.

Sentilhes et al,[13] in a multicenter, randomized, double blind, placebo controlled trial on tranexamic acid for prevention of PPH after vaginal delivery. The primary outcome, blood loss >500ml, occurred in 156 women (8.1%) in the Tranexamic acid group and in 188 women (9.8%) in the placebo group. Gungorduk and fellow workers in Turkey,[14] in a study to estimate the effects of adding intravenous Tranexamic acid to the standard active management of third stage of labour, found significantly lower estimated blood loss in the Tranexamic acid group. Anuchat and other workers in their study randomized 150 women to either receive Tranexamic acid or placebo with blood loss measured directly with a collection bag combined with gravimetry of gauzes and diapers during the first two hours postpartum.[15] Their result revealed mean blood loss was not significantly different from the placebo group (226.59± 114.66ml versus 234.05±142.41) adjusted mean difference was 4.61ml (95% CI:-48.25 to 39.02). Only one woman had a mild side effect of nausea and no episode of thrombosis occurred in women who had Tranexamic acid.

El-Gharhy and fellow workers[15] in a multicentric randomized trial in Egypt,randomized 200 women. Their result showed mean estimated postpartum blood loss was significantly lower in the Tranexamic acid compared to the placebo group (442.50±128.55 versus 555.75±191.88, respectively, $p<0.001$.

A study in Abuja, Nigeria, by Nggada et al,[17] on the efficacy of intravenous Tranexamic acid in reducing blood loss after vaginal delivery randomized 114 women to receive either Tranexamic acid (n=56) or placebo (n=58). They found the mean calculated estimated blood loss, at the end of third stage of labour to be significantly lower in the Tranexamic acid arm than in the placebo arm (309.21±131.4ml versus 424.14±297.9ml).

Aim

To compare the effectiveness of 1g intravenous Tranexamic acid to placebo in reducing blood loss in women at risk of PPH, following vaginal delivery.

Specific Objectives

1. To determine the volume of blood loss within 2 hours of delivery.
2. To determine the fall in haemoglobin concentration 24 hours after delivery.
3. To determine the need for additional uterotonic agent and blood transfusion in both arms of the study.
4. To document any adverse effects of the drug.

Hypothesis

Null hypothesis H_o = Prophylactic Tranexamic acid has no effect in reducing blood loss in women at risk of PPH at vaginal delivery.

Alternate hypothesis H_o = Prophylactic Tranexamic acid is effective in reducing blood loss in women at risk of PPH at vaginal delivery.

Methodology

Study Design

The study was a randomized, double blind controlled trial.

Study Setting

This study was conducted at the Ahmadu Bello University Teaching Hospital (ABUTH) Zaria.

Study Participants

High risk women who presented to the delivery suite in labour having been earlier identified during the antenatal care period and sensitized and meet the inclusion and exclusion criteria.

Inclusion Criteria

Women with singleton pregnancy at gestational age: 37weeks 1day to 41weeks 6 days with any of the following risk factors:

Previous history of PPH
Nullipara
Grand multipara
Induced, augmented or prolonged labour
Hypertensive disorders
Obesity
Anaemia (Hb<10g/dl)
Bleeding disorders.

Exclusion Criteria

Non consenting women
Diabetes mellitus in pregnancy
Heart disease, Renal disease, Liver disease
Past history of deep venous thrombosis
Placenta praevia
Severe abruption placentae
Allergy to Tranexamic acid

Intervention

Group A (Study group): Intravenous 1g TXA diluted up to 20ml (with 0.9% Normal saline)

Group B (Placebo group): Intravenous 20ml of 0.9% Normal saline

Study Outcomes

Primary outcome

Proportion of women with blood loss > 500ml (PPH) in both arms of the study.

Secondary Outcomes:

1. Percentage fall in haemoglobin 24 hours after delivery in both arms of the study.
2. Proportion of women in both arms who require additional uterotonics or maneuvers.
3. Proportion of women in both arms who need blood transfusion
4. Any adverse effect of drug in the study group.

Sample Size Determination

Sample size was calculated using the formula: [18]

$$\text{Sample size (n)} = \frac{[(Z_{\alpha/2} + Z_{\beta})^2 \times \{2(\sigma)^2\}]}{(\mu_1 - \mu_2)^2}$$

σ = Standard deviation from previous study

$Z_{\alpha/2} = Z_{0.05/2} = Z_{0.025} = 1.96$ (from Z table at type 1 error of 5%)

$Z_{\beta} = Z_{0.90} = 1.28$ (from Z table) at 90% power

$\mu_1 - \mu_2$= effect size = difference between mean values

The study on prophylactic tranexamic acid at vaginal delivery in low risk women by Nggada et al, found mean blood loss of 309.21 ml in the study group and 424.14 ml in the control group. The power of this study was set at 90%- and two-sided confidence interval at 95%.

Sample size (n) = $\frac{[(Z_{\alpha/2}+ Z_{\beta})^2 \times \{2(\sigma)^2\}]}{(\mu_1 - \mu_2)^2}$

σ= 309.21

$Z_{\alpha/2}$= 1.96, Z_{β} = 1.28

$\mu_1 - \mu_2$ = 424.14ml – 309.21ml = 114.93ml

$\mu_1 - \mu_2$ = 114.93ml

$n= \frac{[(1.96 + 1.28)^2 \times \{2(309.21)^2\}]}{(424.14ml - 309.21ml)^2}$

$n= \frac{[(3.24)^2 \times \{2(95610.8241)\}]}{114.93^2}$

$n= \frac{(10.4976) \times (191221.6482)}{13208.9049}$

$n= \frac{2007368.37414432}{13208.9049}$

n= 152

With calculation of 10% drop-out rate, 167 patients were recruited in each group with a total of 334 eligible women.

Study Protocol

Patient Enrolment

As parturient presented to the delivery suite in spontaneous labour or for induction of labour, at-risk women who had been identified and sensitized on the study at the antenatal clinic were identified from their antenatal card and admitted. Parturient who consent were given the study information and consent form to sign. Pre-delivery haemoglobin were estimated and the events of labour monitored on a partogram.

Randomization Technique

This was done using the basic steps in a randomization process.

Sequence Generation: A computer generated chart of 334 random numbers was prepared by a research assistant who was not involved in the study. A print out of the randomization chart was pasted at a secure site in the delivery suite. This depicted the random numbers in each group either A or B**.**

Allocation Concealment: Three hundred and thirty-four (334) sealed opaque envelopes each containing a piece of paper, with a random number from 001-334 (from the above computer generated chart), was prepared by a research assistant. The envelope being opaque prevented its contents, from being seen by the patient or the investigator, thus preventing selection bias. The sealed envelopes were put in a box, kept secured and inaccessible from the principal investigator and others in the delivery suite.

Allocation: The numbers 001-334 were allocated to the two groups. Group A (167 numbers) were for 1g intravenous tranexamic acid and group B (167 numbers) were for placebo (0.9% Normal saline solution).

Implementation

Following counseling and informed consent, the patients were asked by a research assistant to pick a sealed opaque envelope. The assistant opened the envelope to retrieve the piece inside it and checked the number on it. At the second stage of labour, this number was handed over to a research assistant in charge of the drug administration and randomization chart, who checked the group a parturient belonged on the chart: A or B. For tranexamic acid group, 1g tranexamic acid (10ml) was made up to 20ml with 0.9% normal saline, while in placebo group, 20ml of 0.9% normal saline was withdrawn. At delivery, the dedicated research assistant administered the drug, immediately, after administration of intramuscular 10IU of oxytocin. The outcome at the time of delivery, up to two hours after delivery, was determined primarily by the principal investigator or a research assistant, who will filled the proforma and handed it back to the research assistant who randomized, who then took it to research assistant in charge of drug administration to identify and tick the study group to which a parturient belonged, without the knowledge of the patient and principal investigator. The latter was in custody of the filled proformas until the end of the study.

Study Blinding and Drug Administration

The contents of the study sample were blinded to the patients and the principal investigator. Procurement of the drug was done in collaboration

with the clinical pharmacy department of ABUTH to obtain certified, approved and NAFDAC licensed tranexamic acid preparations. At delivery of the fetus, the umbilical cord was doubly clamped and cut by the accoucheur, who quickly inserted the sterile under-buttock blood collection drape under the parturient buttocks to ensure that blood is collected in the plastic pouch of the drape. Intramuscular 10IU of Oxytocin was administered within 1 minute of delivery. Additionally, patients in group A received 1g TXA diluted up to 20ml (with 0.9% Normal saline), as an intravenous solution slowly over 5 minutes while women in group B (the control group), received 20ml of placebo (0.9% Normal saline) slowly over 5 minutes. The drugs were administered by a research assistant.

Statistical Analysis

Data from 301 parturient which completed the study were analyzed using IBM statistics data editor, SPSS version 21. Categorical data were expressed as frequencies and percentages. Means and standard deviations were calculated for maternal age, gestation age and amount of blood loss. Unpaired t-test was used to find the significant differences between the two groups with regards to continuous variables. Chi test was used to find significant difference blood loss and the percentage fall in hemoglobin in both groups. Probability value of $p \leq 0.05$ was the level of significance.

Ethical Considerations

Approval to conduct the study was obtained from the ABUTH Research Ethics Committee: **ABUTHZ/HREC/CL/05/954524802**. The study was also registered at the Pan African clinical trial registry: **PACTR 202004568331645**. Consent forms were translated to Hausa language.

Results

This study was conducted over a Sixteen-month period, from June 2019 to October 2020. Three hundred and Thirty-Four patients were recruited for the study and Three hundred and one completed the study and were analyzed.

Figure 1. Study Flow Diagram

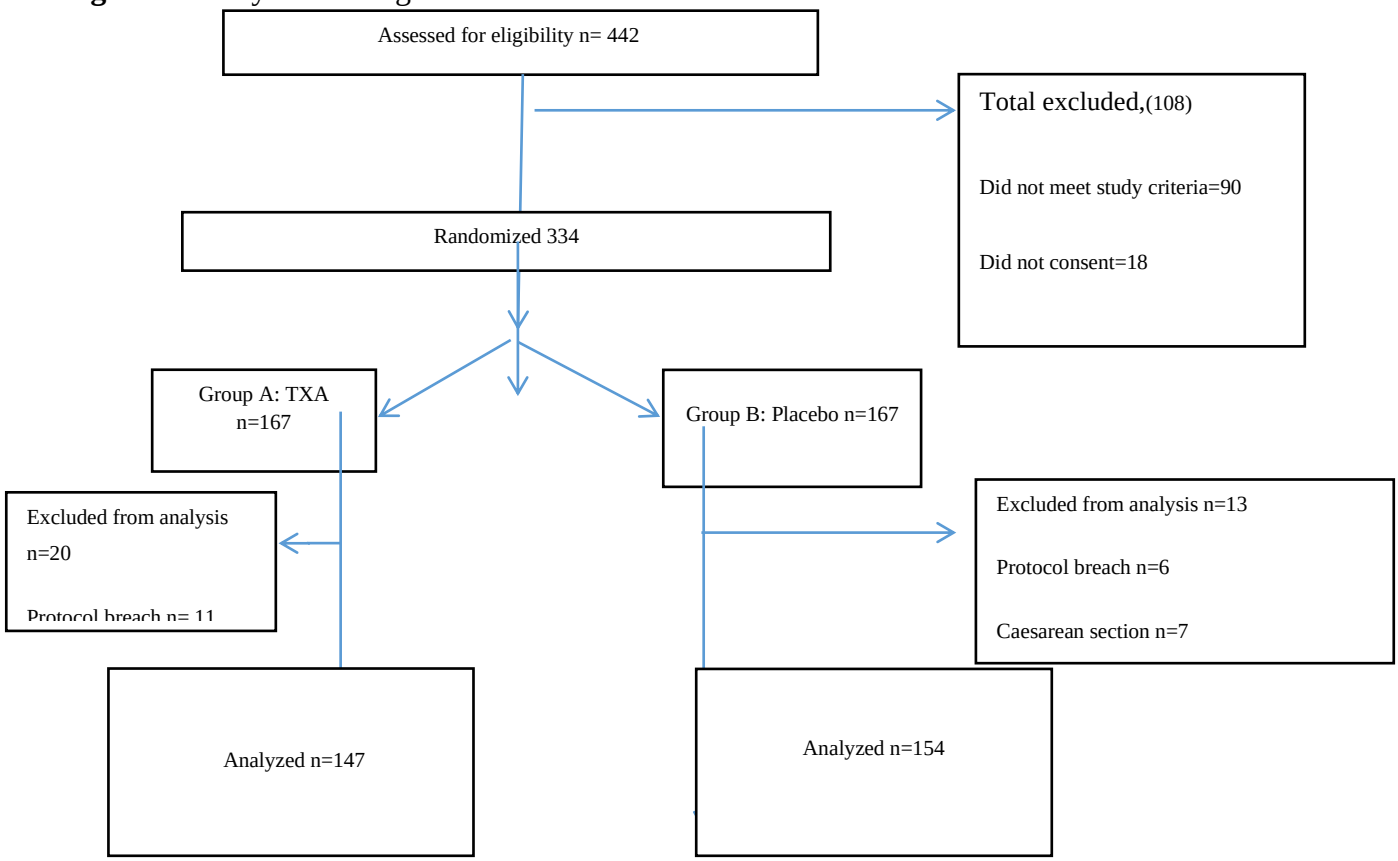

Table 1: Baseline characteristics

	Group A (n=147)	Group B (n=154)	p -value
Mean Age (years)	28.70 ± 6.29	27.64 ± 6.57	0.155
Parity	3.94 ± 2.83	4.10 ± 2.91	0.615
Gestational Age (weeks)	39.09 ± 1.33	38.74 ± 3.12	0.215

Table 1. There was no significant difference in the baseline characteristics of the women.

Table 2: Volume of Blood loss in both groups

Blood loss	Group A	Group B	x^2	p -value
≤ 500mls n(%)	127 (87.1%)	111(72.1%)	10.342	0.001
≥500ml n(%)	20 (12.9%)	43 (27.9%)		
Total	147 (100.0%)	154(100.0%)		

Table 2 reveal there was significant difference in the primary outcome of the study, with the proportion of women with blood loss >500ml (incidence of PPH), significantly lower in the study arm 12.9% versus 27.9% p-value =0.001. **Table 3**, shows the mean blood loss in the tranexamic acid arm of the study is significantly lower than the placebo arm p-value <0.001.

Table 3: Mean Blood loss

Blood loss (mls)	Mean ± SD	t- value	p–value
Group A	260.612±183.74	4.897	<0.001
Group B	365.844± 191.79		

While **table 4** shows, there was no difference in haemoglobin concentration in the Pre and Post-delivery baselines between the groups, **table 5 and 6** reveals a significant reduction in the Hb concentration and percentage fall in Hb concentration in the placebo group p-value 0.024 and 0.011 respectively.

Table 4: Haemoglobin concentration in the groups Pre and Post-delivery

Hb Concentration.		Mean ± SD	p -value
Hb. before Delivery			0.392
	Group A	11.68±1.40	
	Group B	11.52±1.71	
Hb. after Delivery			0.087
	Group A	10.89±1.44	
	Group B	10.59±1.63	

Table 5: Mean difference in Haemoglobin concentration

Mean Hb Difference	Mean ± SD	p –value
Group A	0.82 ± 0.755	0.024
Group B	1.03± 0.867	

Table 6: Mean percentage Haemoglobin fall

	%Hb fall	t	P –value
Group A	6.755	2.540	0.011
Group B	8.647		

For other secondary outcomes, there was significant reduction in the need of additional uterotonic agent in the Tranexamic arm of the study compared to the placebo arm, p-value 0.001 (**table 7**), however, while

8.8% required blood transfusion in the study group versus 15.6% in the placebo arm, this was not statistically significant p-value 0.075 (**table 8**).

Table 7: Additional Uterotonics in both groups

Uterotonics	Group A	Group B	x^2	p-value	OR
Needed n(%)	18 (12.2%)	42 (27.3%)	10.642	0.001	0.372
No need n(%)	129(87.8%)	112(72.7%)			
Total	147(100%)	154(100%)			

Table 8: Blood transfusion both groups

Blood Transfusion n(%)	Group A	Group B	X^2	p- value	OR
Transfused	13 (8.8%)	24 (15.6%)	3.170	0.075	0.53
Not Transfused	134(91.2%)	130(84.4%)			
Total	147(100.0%)	154(100.0%)			

There was no significant reduction in the side effect profile in both arms of study (p value = 0.124 **Table 9**) and there was no significant difference in maternal vital signs except the pulse rate 24hours postpartum p-value 0.030 (**Table 10**). There was no thromboembolism reported and no maternal death.

Table 9: Adverse Effects in the Groups

Adverse Effects	Group A n (%)	Group B n (%)	x^2	p-value
None	134 (91.2%)	140 (90.9%)	5.757	0.124
Nausea	8 (5.4%)	6 (3.9%)		
Vomiting	5 (3.4%)	3 (1.9%)		
Others	0 (0.0%)	5 (3.2%)		
Total	147(100.0%)	154(100.0%)		

Table 10: Maternal vital signs

	Group A	Group B	p-value
PULSE RATE			
1hr Postpartum	83.87±11.94	87.67±14.47	0.118
2hr Postpartum	86.60±14.21	92.77±9.92	0.101
12hr Postpartum	82.91±17.64	89.64±8.64	0.183
24hr Postpartum	86.28±5.34	96.53±10.83	0.030
SYSTOLIC BP			
1hr Postpartum	120.12±17.34	120.57±16.65	0.861
2hr Postpartum	116.08±23.71	113.33±13.86	0.606
12hr Postpartum	122.46±13.97	111.76±8.82	0.869
24hr Postpartum	127.14±16.03	118.66±15.05	0.242
DIASTOLIC BP			
1hr Postpartum	77.09±11.54	80.58±10.13	0.126
2hr Postpartum	73.27±13.71	74.50±12.81	0.750
12hr Postpartum	76.35±10.05	70.00±7.90	0.058
24hr Postpartum	77.50±8.86	78.12±11.67	0.895

Discussion

The primary outcome in the study was the proportion of women with blood loss >500ml (PPH), in both arms of the study. We found the incidence of blood loss >500ml in at-risk women was significantly lower in the Tranexamic acid arm of the study, 12.9% versus 27.9% in the placebo arm, p-value 0.001. This finding is in agreement with the findings by Gongorduk et al,[14] Elgarhy and colleagues[16] and Sentilhes and co-workers,[13] however, it differs with the findings of Anuchat et al[15] and Ngadda and fellow researchers,[17] which found no significant difference in the incidence of PPH between the

Tranexamic acid arm and the placebo arm. The difference in outcome may not be unconnected to the method of blood loss estimation between the studies.

Our study also found there was significant difference in the mean blood loss between the study (Tranexamic acid) and placebo arms, with mean blood loss 260.612±183.74ml in the Tranexamic acid arm versus 365.844±191.79ml in the placebo arm, p-value <0.001. This finding is consistent with the findings by Mirghafourvand et al,[12] Pryankur et al,[7] Elgarhy et al,[16] Gongorduk et al [14] and Ngadda et al.[17] However, at odds with the finding by Anuchat et al,[15] which found no difference between the Tranexamic and placebo arms of their study with mean blood loss of 226.59±114.66ml versus 234.05±142.41ml p-value 0.73.

On the secondary outcomes, there was significant difference in the mean haemoglobin fall and percentage fall, p-value 0.024 and 0.011 respectively. This is in consonance with the findings by Priyankur et al,[7] but not in agreement with the findings by Anuchat et al.[15] Our study also found significant difference in the need for additional uterotonic agent between the groups, with significant reduction in the Tranexamic acid arm, 12.2% versus 27.3%, p-value 0.001; OR 0.372 (95CI: 0.203-0.683). This finding is in keeping with the findings by Pryankur et al,[7] Gongorduk et al[14] and Ngadda et al,[17] however at variance with findings by Anuchat et al.[15]

This study also revealed no statistically significant difference on the need for blood transfusion in both arms of the study p-value 0.075, OR 0.525 (95CI: 0.257 -1.076), despite 8.8% versus 15.6% need for blood transfusion in the Tranexamic acid and placebo arm of the study respectively. This finding is in agreement with the report by Pryankur et al[7] and Gongorduk et al,[14] however at variance with the findings of by Sentilhes et al.[30]

There was no significant difference in the side effect profile between the groups, p-value 0.131. This findings are in consonance with the findings of Anuchat et al[15] and Elgarhy et al.[16] There was also no significant difference in the maternal vital signs except for the pulse rate 24 hours postpartum which agrees with the findings of Pryankur et al,[7] which found increased pulse rate with decreased blood pressure in the control arm of their study. There was no episode of Thrombosis. This is in keeping with earlier studies, including Elgarhy et al,[16] Gongorduk et al,[14] Anuchat et al[15] and Ngadda et al.[17]

Conclusion

This study demonstrated intravenous Tranexamic acid is efficacious in reducing the incidence of postpartum haemorrhage in at risk women during vaginal delivery.

Conflict Of Interest

The authors had no conflict of interest or financial support

Dedication

This work is dedicated to the memory of one of the authors, Late **Prof Marliyya S Zayyan**, a mother, an obstetrician and gynaecologist per excellence, who is no longer with us to see the publication.

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