Tranexamic acid for reducing blood loss following vaginal delivery: a double-blind randomized controlled trial.

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Abstract

Background: Postpartum haemorrhage (PPH) is a major cause of maternal morbidity and mortality worldwide with the highest incidence in the developing countries. Tranexamic acid (TXA) is a useful drug for prevention of PPH and merits evaluation in our environment. This study evaluates the efficacy of TXA in reducing blood loss following vaginal delivery.

Methods: This was a double-blind randomized placebo-controlled study on the efficacy and safety of intravenous TXA in reducing blood loss in women undergoing vaginal delivery in a tertiary hospital. Data analysis was conducted with IBM SPSS software (version 20, Chicago Il, USA). P-value <0.05 was considered statistically significant.

Results: The mean estimated blood loss was lower in TXA compared with the placebo group (174.87±119.84 ml versus 341.07±67.97 ml respectively; P<0.0001). PPH (blood loss >500ml) was 5.13% in the study arm compared to the control arm 7.14%- risk ratio (RR) 0.82; 95% [CI 0.38 – 1.79, p=0.5956]. Additional uterotonics was required more in the control group compared to the treatment group 14(16.67%) versus 3(3.85%) of the treatment group, p-value of 0.007. There were no major complications noticed in the treatment group.

Conclusion: This study demonstrated that intravenous administration of TXA acid following vaginal delivery reduced blood loss following vaginal delivery. It also reduced the need for additional uterotonics. However, blood loss greater than 500 was not significantly reduced.

Pan African Clinical Trial Registry: PACTR202010828881019

Background

Globally, about five hundred thousand women lose their lives yearly from complications of pregnancy and child birth.[1] Majority of these deaths occur within the immediate postpartum period and in most cases are due to postpartum haemorrhage.[2,3] Postpartum haemorrhage is the commonest cause of maternal death with the highest incidence in developing countries.[1,4] Postpartum haemorrhage (PPH) is the excessive loss of blood per vaginam after the delivery of the baby and up to six weeks postpartum.[1] It can either be primary or secondary.[5,6] Primary postpartum haemorrhage is the loss of more than half a litre of blood within the first twenty-four hours of delivery or loss of any amount that is enough to cause haemodynamic instability in the mother.[5,6] It has been reported that approximately 3% of vaginal deliveries are complicated by severe primary postpartum haemorrhage[7].

In many cases of PPH, the true blood loss is often underestimated due to the problem with visual blood estimation.[8,9,10] The risk of dying from postpartum haemorrhage depends not only on the amount and rate of blood loss but also on the clinical state of the woman[8] and blood loss of as little as 200 ml can be

catastrophic for a woman with severe anaemia or cardiac disease[11] making it necessary to reduce any amount of blood loss as much as possible.

The risk factors for excessive blood loss at delivery include previous PPH, primiparity, prolonged or augmented labour, multiple pregnancy, previous cesarean delivery, polyhydramnios, and macrosomia.[12]Nevertheless, most women with PPH have low-risk pregnancies and no identifiable risk factors. It is therefore important to prevent PPH in all women.[13]The interval between delivery and placental expulsion is a critical window for the prevention of PPH; early activation of fibrinolysis is recorded after childbirth and within one hour of giving birth, the serum concentration of tissue plasminogen activator doubles, possibly because of tissue trauma during childbirth.[14] Also, sequential physiologic and hemostatic changes occur and reduce bleeding, including strong myometrial contractions, increased platelet activity, and a massive release of coagulant factors; at the same time, however, fibrinolytic activity multiplies.[15] While oxytocin administration enhances the first mechanism, tranexamic acid (TXA) administration might be able to counter the latter and thus facilitate the hemostatic process. The close relation observed between reduced fibrinogen levels and outcome in cases of PPH[16] further suggests that TXA might be essential to preventing PPH.[17]

Various preventive interventions during this stage have been advanced.[12] Active management of the third stage of labour (AMTSL) as one of such interventions comprises a combination of interventions: preventive administration of uterotonic agents after delivery of the child, cord clamping and cutting as well as controlled cord traction (CCT).[18] The administration of uterotonics, and in particular oxytocin, after birth is a potent component of AMTSL used in averting PPH.[19,20,21] In addition to this enhancement of mechanical hemostasis, a supportive biochemical hemostatic effect might also be expected from the complementary use of prohemostatic drugs such as tranexamic acid in the prevention of PPH.[22]

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 own hemostatic mechanisms. Consequently, clot breakdown (fibrinolysis) is arrested, and bleeding is decreased.[22] Results from previous trials have shown that TXA in planned surgery reduces the risk of blood transfusion, mean transfused volume, and need for re-operation due to bleeding, without enhancing thrombotic events.[23, 24] Tranexamic acid is associated with a good safety profile. However, some side effects (nausea, vomiting and diarrhoea, dizziness and hypotension) have been reported.[23]

Considerable decrease in mean menstrual blood loss have been reported in women with menorrhagia treated with TXA, in contrast to control or placebo-treated women.[25,26] This result is especially important since the efficacy of TXA in menorrhagia suggests that it can decrease uterine blood loss, even of low volume, and in a nonsurgical circumstances.[27] A randomized controlled trial (RCT) which assessed the effect of prophylactic intravenous TXA on blood loss after vaginal delivery revealed the preventive action of TXA on PPH.[28] However, this study was limited by the small sample size as stated by the authors.

Hence, the need for more studies (with increased sample size) to evaluate the efficacy and safety of this drug in preventing PPH following vaginal deliveries.

AIM OF THE STUDY

To determine the efficacy of TXA in reducing blood loss following vaginal delivery

SPECIFIC OBJECTIVES

This will seek to determine;

1. The effects of TXA on haematocrit value following vaginal delivery.
2. If addition of TXA following initial administration of oxytocin reduces the need for additional uterotonics following vaginal delivery.
3. If administration of TXA reduces the need for blood transfusion following vaginal delivery.

The effects of TXA in reducing the quantity of blood loss following vaginal delivery

Methods

Study design

This was a double-blind randomized placebo-controlled study on the efficacy and safety of intravenous TXA at reducing blood loss in women undergoing vaginal delivery at a tertiary centre southeastern Nigeria who met the inclusion criteria after obtaining an informed consent. The study lasted between June 2019-December 2019. The study was approved by was approved by the Human Research and Ethics Committee (HREC) of Alex-Ekwueme Federal Teaching Hospital, Abakaliki (FETHA/REC/VOL1/2017/541) and registered with Pan African Clinical Trial Registry: (PACTR202010828881019).

Study setting

The Federal Teaching Hospital Abakaliki (FETHA) was established in December 2011 following the merger between the defunct Federal Medical Centre and the then Ebonyi State University Teaching Hospital. FETHA has eleven clinical departments including Obstetrics and Gynaecology. The department of Obstetrics and Gynaecology of the hospital runs antenatal clinics managed by consultants and resident doctors with trained Nurses and Midwives. Antenatal clients are booked daily; Monday through Friday and patients are assigned to consultants according to the units/teams running antenatal clinic each day. The department has five units (each divided into two teams). Each team is manned by at least two consultant staff. The department manages both low and high risk pregnant women using standardized protocols.

Participants

The participants for this study were from the population of women within the reproductive age group admitted to undergo vaginal delivery at the Alex-Ekwueme Federal University Teaching Hospital, Abakaliki who met the inclusion criteria after obtaining an informed consent.

The inclusion criteria include spontaneous labour in booked patients, planned vaginal delivery, term pregnancy, singleton pregnancy and cephalic presentation, parturient who has no contraindication to the use of tranexamic acid and informed consent form signed.

Women with prior history of thromboembolism/autoimmune/ sickle cell disease, bleeding disorders, renal disease, liver pathology, known cardiovascular disease, multiple pregnancy/intra-utero fetal death/previous uterine surgeries, patients with chronic hypertension, preeclampsia/eclampsia/HELLP syndrome, antepartum haemorrhage, ruptured uterus, varicose veins at increased risk of deep vein thrombosis, history of epilepsy/seizure and those that had episiotomy were excluded.

Sample size

The minimum sample size was determined using the formula for comparison between two groups when the end point is a quantitative data[29]

$$\text{Sample size} = \frac{2SD^2\ (Z_{\alpha/2} + Z_{\beta})^2}{d^2}$$

Where:

SD: standard deviation in blood loss from treatment group 39[28]= 0.39

$Z_{\alpha/2}$: Standard normal deviate at 5% type 1 error= 1.96

Z_{β} : To increase accuracy of the study 90% power was used = 1.282

d: Standardized effect size 21% reduction in blood loss[28]= 0.21

Sample size per group = $2\ (0.39)^2 \times (1.96 + 1.282)^2 / (0.21)^2$

Twenty percent (20%) of the minimum sample size per group (20/100×73/1≈15) was added to correct for any attrition hence the final sample size was 88 for each arm.

Randomization And Concealment

The participants were randomized by means of a computer-generated random number using the software Research Randomizer®. Eighty-eight (88) numbers were randomly generated from a pool of one hundred

and seventy-six (1-176) and these numbers were assigned to group A (tranexamic acid group), while the remaining eighty-eight were automatically assigned to group B (the placebo group).

Group A received 1g tranexamic acid (Exacyl®; Sanofi Aventis Paris France) slowly (over 30-60 seconds) intravenously, within 2 minutes after birth and prophylactic oxytocin administration once the cord had been clamped.

Group B received 10mls of water for injection (Biofem®; Juhel Anambra Nigeria) slowly (over 30-60 seconds), within 2 minutes after birth and prophylactic oxytocin administration, once the cord had been clamped. These drugs were sourced from their drug representatives.

Concealment was done in sequentially numbered opaque sealed envelopes (SNOSE).[32] These numbers (1-176) were inscribed on brown envelopes and a piece of paper with the inscription 'tranexamic acid' or 'placebo' was placed with the respective drug or placebo accordingly inside these envelopes and sealed. The randomization was done by a statistician and me, while the concealment was done by a hospital pharmacist without revealing the results to the researcher. All the envelopes were kept in a locker that was made accessible to all the members of the research team.

Participants that met the inclusion criteria having signed the informed consent form were given sequential study number and the corresponding numbered opaque sealed envelope was allocated to the patient.

Study Procedure

Women were selected for vaginal delivery in the facility and admitted into the labour ward. They were counseled on the study and those who signed the informed consent form were recruited. The antenatal card was retrieved, and highlights reviewed. History was taken and clinical examination was done to confirm the stage of labour while ancillary investigations; haematocrit, haemoglobin and urinalysis were done and patients were transferred into the labour ward in active phase of labour. The labour was managed actively with the partograph, and augmentation was done as indicated.

The researcher or any of the research assistants took the allotted sealed envelope to the labour ward and handed same over to the labour ward officer who administered the drug or the placebo over 30 to 60 seconds within 2 minutes of delivery of the baby. The envelope with its used content (resealed) was returned to the investigators who kept all the used envelope/packs in a separate locker until the end of the study when un-blinding was done.

AMTSL was carried out for all recruited patients according to departmental protocol (cord clamping, use of oxytocin and controlled cord traction).[28] Other oxytocics and surgical interventions required to control excessive bleeding were given or done and patients who needed blood transfusion received same.

These interventions were noted. Immediately after the delivery of the baby, when all the liquor were drained, a blood drape (an improvised BRASS-V, a disposable conical, graduated plastic collection bag)

was inserted under the patient.[28,32] This was locally manufactured. The blood collected in the blood drape was transferred into a transparent plastic measuring cylinder with a capacity of 500ml, corrected to 2ml and manufactured by Measure Masters®. The blood in the measuring cylinder was read off and documented by the researcher or the assistants. Then, the patient was given pre-weighed pads, which were re-weighed 2 hours post-partum.[28] For uniformity, the regular labour ward sanitary pad with negligible dry weight was used. EBSA-20 electronic weighing scale, which operates at room temperature with readability of 20kg/5g for maximum and minimum weights respectively and manufactured by the Zhongshan Jimli Electronic Weighing Equipment Co. Ltd was used.

The side effects of the drug were noted. The patients were transferred to the post-natal ward for further observation. The patients' post-delivery pulse rate and blood pressure were noted and recorded.[32]

Blood Loss Estimation

The estimated blood loss ascertained by measuring the blood collected in the drape and complimented by measuring the weights of the sanitary pads before and after 2hrs of delivery. Immediate post-partum blood loss was calculated thus.[32]

Total blood loss (ml) = Blood in the measuring cylinder (ml) +[Pad weight after 2 hours (gm)-Pad weight prior to use (gm)]- converted to ml; taking that 1 gram difference in pad weight equals 1 ml of blood.[33]

Blood loss greater than >500ml was be regarded as excessive bleeding.Investigating Maternal Mortality in a Public Teaching Hospital, Abakaliki, Ebonyi State, Nigeria

Follow up

Patients were expected to stay for 48 hours on admission in the hospital before discharge except otherwise indicated. The duration of stay was dependent on the patient's clinical state. The participants were followed up until discharge from the facility. They were instructed to present to the hospital or reach the researcher or any of the research assistants by phone if they have any unforeseen adverse reaction which was to be reported.

Outcome measures

Primary outcome measure was estimated blood loss following vaginal delivery (total blood loss following vaginal delivery= estimated blood from cylinder+ difference in the weight of pad)[32]. Secondary Outcome Measures include primary PPH following vaginal delivery defined as blood loss > 500ml, need for additional uterotonics to control bleeding, need for blood transfusion (volume and amount) after vaginal delivery, mild maternal side effects (nausea, vomiting, headache, skin rash), major maternal side effects (thromboembolism, maternal death).[31]

Statistical analysis

Data was collated, tabulated, and statistically analyzed with the Statistical Package for Social Science (IBM SPSS) software (version 20, Chicago II, USA). Continuous variables as the maternal vital signs were presented as means and standard deviations (Mean ± 2SD), while categorical variables like minor and major side effects were presented as numbers and percentages. Chi-square test (X^2) was used for comparison between groups for qualitative variables while T-test was used for comparison between groups for quantitative variables. A difference with a p-value <0.05 was considered statistically significant.

Results

Over the study period of 6 months, 190 patients were assessed for randomization into the study; 14 were excluded while 176 were allocated to receive either TXA or placebo. Only 78 in the study group and 84 in the control (placebo) group were available for the final analysis.

The demographic characteristics of women in the two groups were matched and there were no significant differences in some of the maternal characteristics: maternal age, parity, gestational age and height as well as the fetal birth weight (p-value > 0.05). Also, the maternal weight difference between the two groups was not statistically significant (p-value > 0.05). Table 1

Table 1
Demographic characteristics of the patients.

Variables	Study group (mean ± SD)	Placebo group (mean ± SD)	P-value
Maternal age (years)	27.95 ± 5.10	29.95 ± 3.60	0.9958
Gestational age (weeks)	39.01 ± 1.38	39.01 ± 1.33	0.9966
Height (metres)	1.59 ± 0.05	1.59 ± 0.06	0.0993
Weight (kg)	78.68 ± 9.90	80.75 ± 12.01	0.2465
Fetal birth weight (kg)	3.26 ± 0.39	3.25 ± 0.45	0.9530
Parity	N = 78	N = 84	0.904
0	17	20	
1–4	61	64	
≥5	5	5	

The mean systolic blood pressure (BP) at presentation, 1 hour and 2 hours post- delivery were not significantly different. Also, the diastolic BPs at presentation, 1 hour and 2 hours post-partum as well as the pulse rates between the two groups were not significantly different at these times. Table 2

Table 2
Maternal vital signs at different times before and after delivery.

Maternal vital signs	Study group	Placebo	P-value
On Admission			
Pulse rate (beats per minute)	87.27 ± 5.96	86.33 ± 5.47	0.2968
Systolic BP (mmHg)	112.76 ± 9.76	113.40 ± 10.42	0.6838
Diastolic BP (mmHg)	77.26 ± 8.49	79.05 ± 7.86	0.1654
1 hour after delivery			
Pulse rate (beats per minute)	86.18 ± 6.13	87.07 ± 5.08	0.3145
Systolic BP (mmHg)	112.63 ± 8.60	112.83 ± 9.72	0.8874
Diastolic BP (mmHg)	75.64 ± 7.83	76.21 ± 7.14	0.6286
2 hours after delivery			
Pulse rate (beats per minute)	85.58 ± 5.73	84.74 ± 4.54	0.3009
Systolic BP (mmHg)	111.513 ± 7.82	111.31 ± 8.14	0.8716
Diastolic BP (mmHg)	74.52 ± 6.74	74.14 ± 6.64	0.7183

The mean estimated blood loss was significantly lower in the TXA group compared with the placebo group (174.87 ± 119.83 ml versus 341.07 ± 67.97 ml respectively; $P < 0.001$). There was no significant statistical difference between the mean haematocrit of the treatment group versus the control group at presentation (33.99 ± 3.00 versus 34.01 ± 2.92, $p = 0.9658$), however, the mean haematocrit between the two groups 48hrs postpartum was statistically different (32.54 ± 3.36 versus 31.33 ± 2.88, $p = 0.0147$). The mean change in haematocrit between the groups 48hours after delivery was also significantly different (3.14 ± 0.94 versus 4.11 ± 1.1, $p = 0.0018$). The haemoglobin concentration at presentation between the two groups was not significantly different (11.66 ± 1.00 versus 11.84 ± 0.90 for treatment and control groups respectively, $p = 0.2297$). However, the haemoglobin concentration 48hours after delivery was significantly different (11.14 ± 1.07 versus 10.45 ± 0.96 for treatment and control groups respectively, $p = < 0.0001$). There was no significant difference in the platelets and the risk of bleeding between both groups at presentation. Table 3

Table 3
Pre delivery and post-delivery Haemoglobin/Haematocrit levels in the study and in the control group

Variables	Study group (mean ± SD)	Placebo group (Mean ± SD)	P-value
Blood loss at delivery (ml)	174.87 ± 119.83	341.07 ± 67.97	< 0.0001
Maternal Haematocrit (%)			
Pre-delivery	33.99 ± 3.0	34.01 ± 2.92	0.9658
48 Hours Postpartum	32.54 ± 3.36	31.33 ± 2.88	0.0147
Mean Change in Haematocrit	3.14 ± 0.94	4.11 ± 1.1	0.0018
Maternal Haemoglobin (g/dl)			
Pre-delivery	11.66 ± 1.00	11.84 ± 0.90	0.2297
48 hours postpartum	11.14 ± 1.07	10.45 ± 0.96	< 0.0001
Difference in Haemoglobin after 48 hours	0.94 ± 0.43	1.21 ± 0.63	0.0019
Platelets	198.7 ± 36.5	203.1 ± 43.7	0.4895
Clothing Time	4.5 ± 0.9	4.7 ± 1.1	0.2092

Blood loss > 500ml was not significantly higher in the study group compared to the control group with 4(5.13%) versus 6(7.14%) respectively giving a Risk ratio (RR) 0.82; 95% confidence interval (CI) 0.38–1.79, p = 0.5956. Table 4.

Table 4
Pre-delivery and post-delivery variables in the study and control groups

Variable	Study group N (%)	Placebo group N (%)	RR (95%CI)	P-value
Blood loss > 500 (ml)	4(5.13%)	6(7.14%)	0.82(0.38–1.79)	0.5956
Additional interventions	1(1.28%)	3(3.57%)	0.51(0.09–2.82)	0.3496
Blood transfusion	3(3.85%)	14(16.67%)	0.34(0.12–0.96)	0.007
Uterotonics				
Patients with side effects	1(1.15%)	0(0%)	2.09(0.99–2.46)	0.481
Minor side effects				
Diarrhea				

There was no significant difference in the blood transfusion received by both groups 1(1.28%) versus 3(3.57%), risk ratio 0.51; 95% CI 0.09–2.82), p = 0.3496. Additional uterotonics was required more in the control group compared to the treatment group 14(16.67%) versus 3(3.85%), risk ratio 0.34; 95% 0.12–0.96, p = 0.007. Table 4

There were no major complications noticed in the treatment group. However, diarrhoea was noticed only in one patient in that group. Table 4

Discussion

In this study, administration of 1g intravenous TXA prior to placenta delivery after delivery of the baby was associated with a 48.7% (166.2 ml) reduction in blood loss at vaginal delivery compared to placebo. This reduction was higher than the 25.3% ($p < 0.001$) reported by Gungorduk and colleagues[31], 22.3% ($p < 0.01$) and 21.3% ($p < 0.03$) reported by Yang and co-workers[30] and Mirghafourvand and colleagues[28] respectively. These difference in blood loss may be as a result of the different time intervals for administration of TXA. In the present study, TXA was administered within 2 minutes of delivery of the baby. Gungorduk and colleagues[31] documented TXA administration of 5minutes while Mirghafourvand and colleagues documented 10minutes after delivery of the anterior shoulder.[28] The WOMAN trial had recommended early administration of tranexamic acid in the management of severe bleeding following delivery. It may also be due to the time interval of assessing the blood loss and the different methods used in the estimation of blood loss for the various studies. While some used graduated bags[26,28], others calculated the mean blood loss volume by measuring sheets of pads from the end of delivery to 2hrs after birth.[31] This study also incorporated the change in haematocrit after 48 hours of delivery.

Blood loss of > 500ml was not significantly reduced in the study group when compared to the control group. This finding is similar to the finding made by Mirghafourvand and colleagues[28] ($p = 0.14$) but contradicted the finding noted by Gungorduk and co- workers[31] in which the reduction of blood > 500ml was statistically significant ($p < 0.01$). This could have been because Gungorduk et al incorporated high risk parturient who were likely to bleed more into their study which was not the case in this study[31].This study showed that prophylactic administration of TXA after the delivery of the baby and before the delivery of the placenta reduced the need for additional uterotonics following vaginal delivery. This is consistent with the findings in most studies that compared the efficacy of TXA to placebo in reducing blood loss after vaginal delivery.[26,28, 30–31,32] Although a patient needed blood transfusion in the treatment group due to primary PPH following retained placenta, but this could also have happened to either group. A similar finding was documented by Gungorduk et al.[31] However, Sentilhes et al[26] and Roy et al[32] observed that the use of TXA reduced the need for blood transfusion.

There was a statistically significant difference in the mean haematocrit and haemoglobin 48hours after delivery between the two groups. This was consistent in the findings of other studies.[26,28,31,32,34] There was no significant difference in the vital signs of the patients on admission, one hour and two hours

postpartum between the placebo and the study groups. However, the use of TXA was associated with a small increase in the risk of minor side effects (majorly diarrhoea) in this study but this was not statistically significant. Other studies also reported minor maternal gastrointestinal side effects and were not documented as significant.[28,30,31,34] There were no major maternal side effects or maternal death recorded in the present study. This was also the finding by similar studies[26,28,30,31] and suggests that TXA did not have any adverse maternal outcome.

In conclusion, this study demonstrated that intravenous administration of TXA acid following the delivery of the baby and before delivery of the placenta reduced blood loss following vaginal delivery. It reduced the need for additional uterotonics to control blood loss. However, the incidence of primary postpartum haemorrhage and the need for blood transfusion was not significantly reduced between the two groups. Minor side effects as diarrhoea were noted but this was not statistically significant between the groups. There were no major maternal side effects, and no maternal death was recorded. From the findings of this study, the null hypothesis is hereby rejected. We therefore conclude that this result lays credence to the fact that intravenous TXA used to prevent primary PPH is safe and effectively reduced blood loss following vaginal delivery without increasing maternal risks and should be made available for women selected for vaginal delivery as no woman is immune to postpartum haemorrhage. Furthermore, that there is need to evaluate these findings on a larger scale for prophylactic purposes.

The limitations are that the study was a single centre randomized controlled study, it did not evaluate the efficacy of intravenous TXA in high-risk patients and liquor and lochia contamination of the measured blood may not have been completed avoided.

The cost-effectiveness, generalizability to and reliability are the strength of this study.

Further research is needed to evaluate the efficacy and safety of TXA in women at risk of excessive blood loss and anaemic patients in our setting.

Abbreviations

TXA: Tranexamic acid. PPH: Postpartum heamorrhage. FETHA: Alex-Ekwueme Federal Teaching Hospital Abakaliki. RCT: Randomized controlled trial. AMTSL: Active management of third stage of labour. HREC: Human research and ethics committee.

Declarations

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Authors' contributions: FNI, LOL and VOO contributed to the study design. The analysis was made by FNI and VOO with the assistance of LOL. FNI and VOO drafted the manuscript. LOL and BID revised the

manuscript. All authors read and approved the final manuscript.

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Availability of data and materials: The data used or analyzed during the current study are included within the article. The datasets are not publicly available due to the hospital policy and personal privacy. However, the datasets are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: The study was approved by the Ethics Committee of the Human Research and Ethics Committee of the Alex-Ekwueme Federal Teaching Hospital Abakalik (FETHA/REC/VOL1/2017/541) . All participating patients were informed that their clinical data may be used for academic research in the future before entering into the study and signed written informed consents. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Consent for publication: Not applicable.

Conflict of interest: There was no conflict of interest in this study to declare.

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Figures

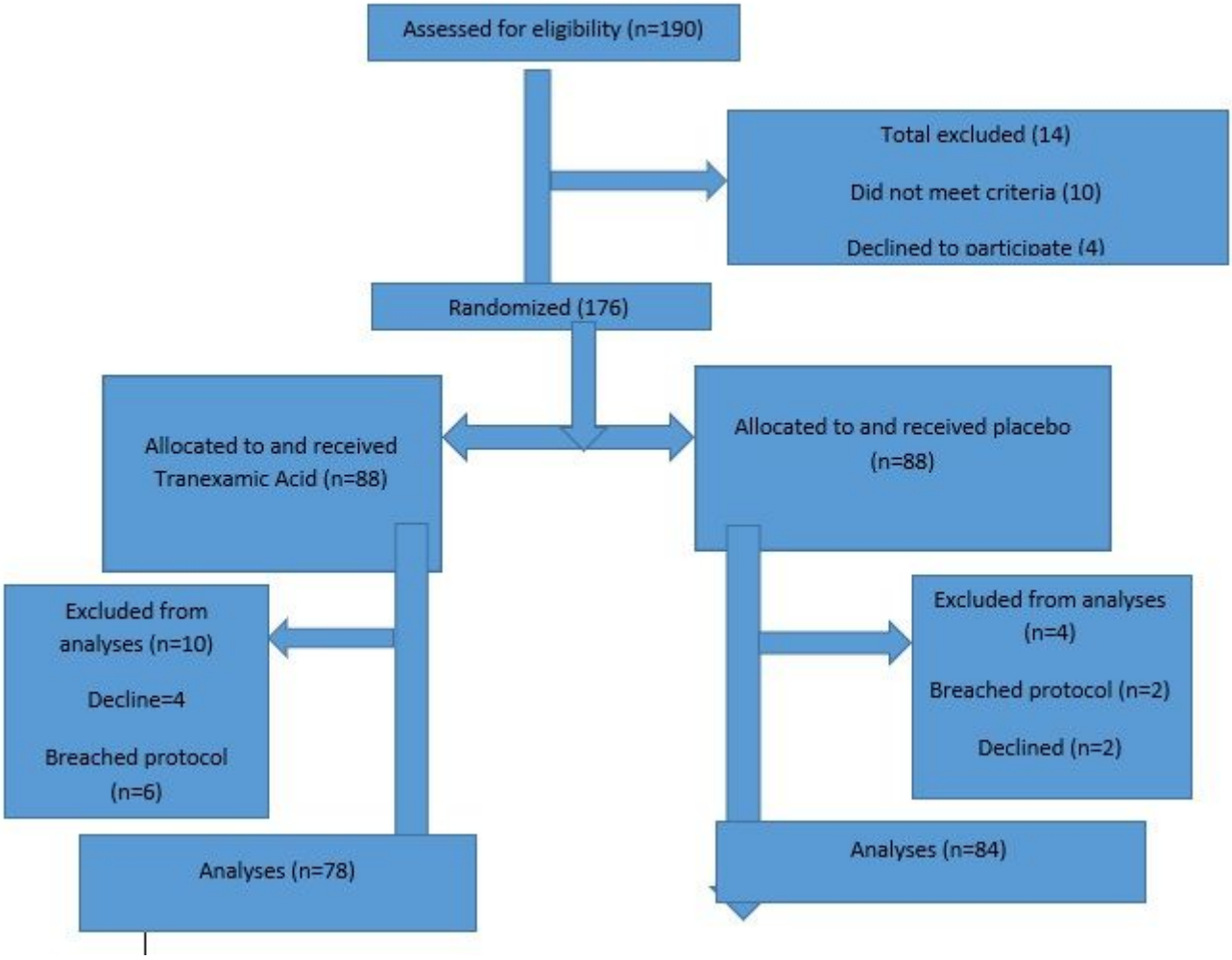

Figure 1

Flow of patients through the study.