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Research Article

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Efficacy of Intravenous Tranexamic Acid at Reducing Blood Loss During Caesarean Section in A Parturient at Increased Risk of Primary Postpartum Hemorrhage: A Randomized Placebo Controlled Trial

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Abstract

Background: *Caesarean section is the most frequently performed surgery worldwide and is a source of concern to obstetricians due to the attendant increased health risk. Its most common complication is increased risk of bleeding which occasionally may be life threatening. Tranexamic acid (TXA), an anti-fibrinolytic agent, has recently been investigated as a potentially useful drug for both prevention and treatment of excessive blood loss at caesarean section and its advantages need evaluation in our environment.*

Objective: *This study was designed to evaluate the efficacy of tranexamic acid at reducing the quantity of blood loss in women at increased risk of primary postpartum haemorrhage (PPH) undergoing caesarean section.*

Method: *This was a double-blind randomized placebo-controlled trial on the efficacy and safety of intravenous tranexamic acid at reducing blood loss in women at increased risk for PPH undergoing caesarean section at the Alex Ekwueme Federal University Teaching Hospital Abakaliki (AEFUTHA). Data analysis was done using statistical Package for Social Science (IBM SPSS) software (version 20, Chicago II, USA). Continuous variables were presented as mean and standard deviation (Mean ± 2SD), while categorical variables were presented as numbers and percentages. A difference with a P value <0.05 was considered statistically significant.*

Results: *The mean estimated blood loss was significantly lower in the tranexamic acid group compared with the placebo group (689.8±257.4mls versus 918.1±331.4mls, respectively; p<0.001). More so, blood loss > 1000mls was also significantly lower in the study group compared with the control group with 9(10.9%) versus 19(22.9%) respectively; Odd Ratio (OR) 0.42; 95% Confidence interval (CI) 0.17 to 0.98; p=0.0414. The mean change in haematocrit value was significantly less in the tranexamic acid group compared with the control group p=0.0012. Tranexamic acid significantly reduced the need for additional uterotonics 13(15.8%) versus 27(32.5%) OR 0.39 (0.18 – 0.82) p value equals 0.0122. However, there was no difference in the number of patients that had blood transfusion between the groups and the maternal side effect profiles were similar.*

Conclusion: *Intravenous tranexamic acid significantly reduced blood loss in women at increased risk of bleeding during caesarean section. It also reduced the risk of blood loss greater than 1000mls and the need for additional uterotonics without increasing maternal risks.*

Keywords: Tranexamic Acid, Blood Loss, Caesarean Section

Introduction

Caesarean delivery is the most frequently performed major surgical procedure worldwide [1, 2]. Women undergoing caesarean section are at increased risk of blood loss and are more likely to need blood transfusion when compared to women who had vaginal delivery [3, 4]. The global rise in caesarean section rate has led to increase in the primary complications especially blood loss associated with caesarean section [5, 6]. The risk of primary postpartum haemorrhage is further increased in the presence of risk factors such as multiple pregnancy, polyhydramnios, grandmultiparity, induction or augmention of labour, prolonged obstructed labour, severe preeclampsia/eclampsia, antepartum haemorrhage and anaemia [7]. Primary postpartum haemorrhage is a significant potentially life-threatening complication following delivery and it accounts for nearly 25% of maternal death worldwide and 24% of maternal death in Abakaliki Primary postpartum haemorrhage is defined as blood loss of 500mls or more from the genital tract after vaginal delivery or greater than 1000mls following Caesarean section or any amount of blood that is enough to compromise the patient's haemodynamic status within the first 24 hours after delivery or a 10% drop in the hematocrit after delivery that will require transfusion of blood products [8-11]. The incidence of PPH varies widely throughout the world. The proportions range from less than 10% in high income countries to nearly 60% in low income countries. The incidence of primary postpartum haemorrhage was 3.1% of all deliveries in Sagamu [12].

Uterine blood flow reaches up to 750mls/minute at term [13]. As the placenta separates from the uterine wall during delivery, strong myometrial contractions occur along with increased platelet activity and a release of coagulant factors. Fibrinolytic activity also increases during placental delivery and can continue for a variable period of time after delivery [14]. At the same time, it was recognized that other tissue injury that is encountered during caesarian section can shift the haemostatic equilibrium toward fibrinolysis contributing to more coagulopathy and bleeding [15]. Hence, placental expulsion is a critical window for the prevention of PPH, and various preventive interventions during this stage have been proposed. Active management of the third stage of labour (AMTSL) had been shown to be effective in reducing postpartum haemorrhage [16]. Evidence had shown that the administration of uterotonics, and in particular oxytocin, after birth is the major component of AMTSL that is effective in preventing PPH [17]. In addition, a complementary biochemical haemostatic effect might be expected from the complementary use of pro-haemostatic drugs such as tranexamic acid and may go a long way in potentiating the effect of oxytocin in the prevention of primary postpartum haemorrhage [18].

Tranexamic acid (TXA), a synthetic derivative of the amino acid lysine, exerts its anti-fibrinolytic effect through the reversible blockade of the lysine binding sites on the plasminogen molecules [19-21]. Intravenous administration of the tranexamic acid has been shown to reduce the need for transfusion and risk of death in trauma patients [22]. Its efficacy in the treatment of postpartum hemorrhage was the subject of a large global multicenter randomized control trial [23]. Compared with placebo, some randomized controlled trials have shown that it is effective in reducing blood loss at caesarean section however, a systematic review has recommended that further trials are required to confirm its efficacy and safety [24-29]. Tranexamic acid is associated with a good safety profile however, some adverse effects (nausea, vomiting and diarrhea, dizziness and hypotension) have been reported; the most dreaded being venous thromboembolism.

Methods of Estimating Blood Loss

Methods used to estimate blood loss at delivery may include clinical method, quantitative methods (visual, gravimetric, using containers and special drapes and estimation of change in hematocrit) and other laboratory methods [30]. Estimating blood loss at caesarean section enables the Obstetrician to decide on the need for blood transfusion. Overestimation of blood loss can increase the risk of unnecessary cross matching of blood, which wastes valuable time and resources. Blood is a precious resource and over transfusion of patients can result in morbidity as well as unnecessary exposure to the known risks of blood products [31].

The Clinical Method: The intraoperative estimation of blood loss using clinical method is done by monitoring the patient's vital signs and it remains a primary means to diagnose the extent of bleeding and to direct interventional therapy. It is the most commonly used method by the Anaesthetist and is considered to be accurate due to the fact that it is dependent on physiological response [32]. However, it varies from individual to individual due to different levels of haemodynamic states and haemoglobin levels at the time of surgery. In anaemic patients the expected changes in haemodynamic status, reflected by changes in vital signs occur at a much earlier stage, thus over estimating blood loss.

At caesarean section, this method may not be feasible to the Obstetrician who would be engaged in the surgery and may not be involved in monitoring the patient's vital signs.

The Visual Inspection of Blood Loss: This is the most common method employed in most operation suites and involves estimation of blood loss as observed by the Obstetrician. Visual estimation of blood loss is relatively straightforward and cheap. Despite its inaccuracy and variation from one surgeon to another, Obstetricians correlate it with clinical signs. The major advantage of this method is that it is a real time assessment and enables the Obstetrician to correlate findings, on an individualized basis, with the clinical presentation. This method is associated with lots of inconsistences, when losses are large, they are most often underestimated, and smaller losses tend to be overestimated [33].

As swab count is a universal method for estimating blood loss at caesarean section, Bose P and colleagues developed a standardized measure of visual estimation of blood loss.

Guidelines for Visual Estimation of Blood Loss.

Small, 10-x10-cm 32 ply swab (maximum saturated capacity)	60 ml
Medium, 30- x 30-cm 12 ply swab (maximum saturated capacity)	140 ml
Large, 45- x 45-cm 12 ply swab (maximum saturated capacity)	350 ml
1-kg soaked swabs	1000 ml
50-cm diameter floor spill	500 ml
75-cm diameter floor spill	1000 ml
100-cm diameter floor spill	1500 ml
Vaginal PPH limited to bed only Unlikely to exceed	1000 ml
Vaginal PPH spilling over from bed to floor Likely to exceed	1000 ml

Gravimetric Method: This method involves weighing sponges before and after use. The difference in weight provides a rough estimate of blood loss. The gravimetric method requires the weighing of materials such as soaked pads on a scale and subtracting the known weights of these materials to determine the blood loss [34]. Inaccuracies can arise at several steps in this procedure. These include lack of international standardization of size and weight of gauze, sponges and pads. There is also an increased risk of contamination with amniotic fluid which could lead to over estimation of the blood loss at caesarean section. However, this method of blood loss estimation does not depend on personal bias. This method of assessment of blood loss at caesarean section was used in some studies.

Collection into Containers and Bags: Various calibrated containers and bags have been developed to aid estimation of blood loss. They are cheap and effective. They include pans and standardized measuring jar, Rubberized blood mat, Kelly's pad and Blood drape-BRASS-V drape. These containers and bags have been validated in some trials involving vaginal delivery but they are not feasible methods for estimating blood loss at caesarean section.

Laboratory Estimates

Change in Haematocrit: Changes in the haematocrit and haemoglobin values before and after delivery provide quantitative measurements of blood loss. The American College of Obstetricians and Gynecologists cites a 10% post-delivery decline in haematocrit compared with pre-delivery as a secondary definition of PPH [35]. Routine postpartum haematocrit may be unnecessary in clinically stable patients with an estimated blood loss of less than 500 mls. Following delivery that is associated with an average blood loss, the haematocrit drops moderately for 2–4 days, followed by an increase. The peak drop may be appreciated on day 2 or day 3 postpartum. Although this method involves estimation of blood volume using the maternal weight, it is very objective and not dependent on the personal experience of the surgeon. There is also no risk of liquour contributing to the blood loss estimation. This method of blood loss assessment had been used in several studies and had been shown to estimate blood loss appropriately. This method of blood loss estimation would be used in this study due to its objectivity. The formula used in some studies to evaluate blood loss at caesarean section is described below [36, 37].

- **EBL:** EBV x Pre-operative Hematocrit – Post-operative hematocrit Preoperative Hematocrit
- **Where EBL:** Estimated blood loss
- **EBV:** Estimated blood volume (maternal weight in Kg x 85ml)

Alkaline Haematin Method/ Acid Haematin Method: Another direct method of blood loss measurement is based on mixing collected blood with a standardized solution which converts haemoglobin to acid haematin or cyanmethemoglobin. This in turn can be measured by a spectrophotometer or colorimeter. This method is mainly used for research purposes and may not be readily available in resource poor settings like ours [38].

Justification

Uterotonics, specifically oxytocin, have been the only drugs shown to reduce blood loss at caesarean section. Excessive blood loss remains a major cause of maternal morbidity and mortality worldwide, there is an urgent need to evaluate additional preventive and therapeutic interventions especially in women at increased risk of primary postpartum haemorrhage. Tranexamic Acid (TXA), an anti-fibrinolytic agent, had recently been investigated, as a potentially useful drug for both prevention and treatment of PPH. It has also been widely used by surgeons (especially trauma and orthopaedic) and has been associated with significant reduction in blood loss and the need to transfuse patients following surgery. This significant finding in surgery had necessitated its use in obstetrics. No study had been done in Abakaliki, South East Nigeria to evaluate the efficacy of tranexamic acid at reducing blood loss during caesarean section in women at increased risk of primary postpartum haemorrhage, and to determine if it should be added to the protocol for the reduction of blood loss and the prevention of primary postpartum haemorrhage at caesarean section in our centre. The availability of such drug would lead to a reduction in the need for blood transfusion and its attendant consequences as well as reduction in maternal morbidity and mortality.

Economic evaluation has shown that giving tranexamic acid to reduce bleeding in elective surgery would be lifesaving in Sub-Saharan Africa where there is a shortage of blood, because more blood will be available for those who needs it. In addition, in places where there is no blood shortage, the administration of TXA decreases the risk of transfusion-transmitted viral infections. Systemic review and meta-analysis of randomized controlled trials have confirmed the use of tranexamic acid to reduce the risk of death and need for transfusion following surgery. In our environment where blood transfusion services are scarcely available, any measure/drug that would assist in preventing and

treating primary postpartum haemorrhage would be of great importance.

Research Questions

Does intravenous tranexamic acid reduce blood loss during and after caesarean section in patients at high risk of primary postpartum hemorrhage?

Aim of The Study

To determine the efficacy of tranexamic acid in reducing blood loss during and after caesarean section in women with risk factors for primary postpartum hemorrhage.

Specific Objectives

1. To determine the effects of tranexamic acid at reducing change in hematocrit after caesarean section in women at increased risk of primary postpartum hemorrhage.
2. To determine if addition of tranexamic acid reduces the need for additional uterotonics at caesarean section in women at increased risk of primary postpartum hemorrhage.
3. To determine if addition of tranexamic acid reduces the need for blood transfusion following caesarean section in women at increased risk of primary postpartum hemorrhage

Null Hypothesis

Intravenous tranexamic acid does not have any effect on the quantity of blood loss during and after caesarean section in patients at increased risk of primary postpartum hemorrhage.

Alternative Hypothesis

Intravenous tranexamic acid reduces the quantity of blood loss during and after caesarean section in patients at increased risk of primary postpartum hemorrhage.

Materials and Method

Study Design

This was a double-blind randomized placebo-controlled trial on the efficacy and safety of intravenous tranexamic acid at reducing blood loss in women undergoing caesarean section, who are at increased risk of primary postpartum hemorrhage at the Federal Teaching Hospital Abakaliki (FETHA).

Study Population

Participants for this study were from the population of women who have increased risk for primary postpartum hemorrhage admitted for elective or emergency caesarean section at the Federal Teaching Hospital, Abakaliki.

Study Duration

The study lasted for a period of six months. Each patient was adequately counselled about the study by the researcher or any of the research assistant. Thereafter, an informed consent was obtained before they were recruited into the study. The signed informed consent was obtained on admission in the antenatal ward or Obstetrics and Gynecology emergency ward.

Research Assistants

The research assistants consisted of 5 residents from the various units of the Obstetrics and Gynecology department. Training sessions was held where the research was explained in details to them as regards the aim and objectives of the study, recruitment of eligible patients, filling the proforma forms, assisting with the estimation of the blood loss and monitoring of the mother, fetus and neonate after delivery. Weekly group meetings were held for the purpose of feedback and reappraisal.

A group page on a social media platform (whatsApp®) was opened by the researcher and all the research assistants was added to allow for continuous communication, feedback, questions, answers and subsequent directions as the need arises. Voice calls were also made as and when necessary.

Inclusion Criteria

Parturient at 37-42 weeks' gestational age, on admission for emergency or elective caesarean section with increased risk of primary postpartum haemorrhage such as antepartum haemorrhage, multiple gestation, polyhydramnios, grandmultipara, previous primary postpartum haemorrhage, previous caesarean scar, hypertensive disorder in pregnancy, obstructed labour, anaemia and prolonged use of oxytocin for induction or augumentation of labour, who give consent to participate in the study and do not have any contraindication to the use of tranexamic acid were included in the study.

Exclusion Criteria

1. Women who have known allergy to tranexamic acid.
2. Women with prior history of thromboembolism.
3. Women with bleeding disorders.
4. Patients with renal disease.
5. Patients with liver pathology.
6. Patients with varicose veins at increased risk of deep vein thrombosis.
7. Primary caesarean with no added risk.
8. Patients who do not consent to the study.

Sample Size Determination

The minimum sample size was determined using the formula for comparison between two groups when the end point was quantitative.52

$$\text{Sample size} = \frac{2SD_2\,(Z\alpha/_2 + Z\beta)^2}{d^2}$$

Where:

- **SD:** standard deviation in blood loss from treatment group 48.551= 0.485
- **$Z\alpha/_2$:** Standard normal deviate at 5% type 1 error= 1.96
- **$Z\beta$:** To increases accuracy of the study 90% power was used = 1.282
- **d:** Standardized effect size 25% reduction in blood loss51= 0.25

Therefore:

$$\text{Sample size per group} = \frac{2\,(0.485)^2 \times (1.96 + 1.282)^2}{(0.25)^2}$$

$$\text{M (size per group)} = \frac{0.47045 \times (3.242)^2}{(0.0625)}$$

$$\text{M (size per group)} = \frac{4.94469}{0.0625}$$

Size per group = 79.115

=79

10% of the minimum sample size per group (79/10=7.9) was added to correct for any attrition hence the final sample size would be 87 for each arm.

Drug Procurement, Storage and Disposal

The entire drug that was used for this study were procured from a reputable pharmacy company. The batch number, date of manufacture and expiry date and the NAFDAC registration number were noted. The placebo batch number and date of manufacture and expiry were also noted. Both drug and placebo are heat stable and were stored at room temperature. At the end of the study, following un-blinding, all the used drugs and placebo vial were properly disposed in the hospital's incinerator.

Randomization and Concealment

The participants were randomized by means of a computer generated random-number using the software Research Randomizer®. Using this software, eighty-seven numbers were randomly generated from a pool of one hundred and seventy-four numbers (1-174) and these numbers were assigned to group A (tranexamic acid group) while the remaining Eighty-seven numbers were automatically assigned to group B (the placebo group).

Group A received 1g tranexamic acid (Exacyl®; Sanofi Aventis Paris France) at the rate of 1ml/min over 10 minutes starting 20 minutes before the skin incision.

Group B received 10mls of water for injection (Biofem®; Juhel Anambra Nigeria) at the rate of 1ml/min over 10 minutes starting 20 minutes before the skin incision.

Concealment was done in sequentially numbered opaque sealed envelopes (SNOSE). These numbers (1-174) were inscribed on brown envelopes and a piece of paper with the inscription 'tranexamic acid' or 'placebo' will be placed with the respective drug or placebo accordingly inside these envelopes and sealed. The randomization would be done by a statistician, while the concealment would be done by a hospital pharmacist without revealing the outcome to the researcher. All the envelopes would be kept in a locker that would be made accessible to all the members of the research team.

Participants that meet the inclusion criteria, having signed the informed consent form will be given sequential study number and the corresponding numbered opaque sealed envelope will then be allocated to the patient.

Study Procedure

Women who had caesarean section were screened for inclusion. Clinical history and astute examination were done to confirm the indication for the surgery and rule out exclusion criteria while ancillary investigations; haematocrit, haemoglobin, group and cross matching of blood were done. Other investigations were carried out according to the indication of the surgery. The patients were reviewed by the anaesthetist. The surgeries were carried out by the Consultant or Senior Registrars as is the hospital policy. Data were collected using proforma in Appendix 1, using Appendix 2 and 3 to obtain inform consent.

The researcher or any of the research assistants took the allotted sealed envelope to the theatre and hand over same to the anaesthetist who administered the drug or the placebo over 10 min (starting 20 minutes before the skin incision) to the patient without telling the researcher or the patient the content of the envelope (double blinding). The envelopes with its used contents (resealed) were returned to the researcher who kept all the used envelopes/packs in a separate locker until the end of the study when un-blinding was done. All the surgeries were lower segment caesarean section, carried out under spinal anaesthesia by consultants and senior registrars. The surgery was carried out according to standard protocol.

Quality Control

To ensure that the blood loss estimate was as accurate as possible all the preoperative maternal weighing was done by the researcher or any of the research assistants. The haematocrit was analysed by the researcher and either of two laboratory scientists who were dedicated to the study. A third laboratory scientist also dedicated to this research, at intervals randomly selected specimen samples for cross checking for quality control. This was aimed to reduce intra- and inter-observer errors and ensure quality control.

Outcome Measures

Primary Outcome Measure was

1. Estimated blood loss at elective Caesarean section
2. Secondary Outcome Measures were
3. Excessive blood at Caesarean section loss defined as blood loss > 1000ml
4. Change in haematocrit after Caesarean section
5. The need for additional uterotonics to control bleeding
6. The need for blood transfusion during or after the surgery
7. Mild maternal side effects (nausea, vomiting, headache, skin rash)
8. Major maternal side effects (thromboembolism, maternal death)

Statistical Analysis

Data was collated, tabulated then statistically analysed using statistical Package for Social Science (IBM SPSS) software (version 20, Chicago II, USA). Continuous variables were presented as mean and standard deviation (Mean ± 2SD), while categorical variables were presented as numbers and percentages. Chi-square test (X2) was used for comparison between groups for qualitative variables while student 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 duration of six months, 201 patients were assessed for randomization into the study; twenty-seven patients were excluded while 174 patients were allocated to receive either the tranexamic acid or the placebo. Only 82 patients in the study (tranexamic acid) group and 83 in the control (placebo) group were available for the final analysis which was done with intention to treat.

The characteristics of the women in the two groups were similar and there was no significant difference in the maternal demographics characteristics; maternal age, weight, height, body mass index (BMI) on admission, gestational age and parity (p>0.05). There was also no statistically significant difference in the mean duration of the surgery, the birth weight and APGAR scores in the first and fifth minutes (p>0.05) table 1.

Table 1: Demographic Characteristic of the Patients and Some Surgery Determinant

Variables	Study group (mean ± SD)	Placebo group (mean ± SD)	P value
Maternal age (years)	30.27±4.10	31.18±5.55	0.2852
Weight (kg)	73.91±18.28	77.86±17.98	0.101
Height (m)	1.58±0.07	1.60±0.06	0.1025
Maternal BMI (kg/m2)	29.74±7.37	30.93±4.85	0.2665
Gestational age (weeks)	38.24±2.74	38.49±1.13	0.6547
Parity	2.87±2.15	2.52±1.97	0.3243
Mean duration of surgery (min)	46.43±5.6	48.61±7.5	0.1481
Fetal birth weight	3.11±0.58	3.18±0.42	0.7893
APGAR score			
First minute	6.8±1.2	6.7±1.4	0.6819
Fifth minute	9.6±0.8	9.7±0.6	0.4493
Mean platelet count	214±102	234±123	0.1278
Mean bleeding time (min)	5.5±0.9	5.1±1.1	0.6422

Table 2 shows some surgery determinants. There was no significant difference in the number of primary caesarean section and repeat caesarean sections, cadre of surgeon and the level of experience of the surgeon between the groups, P value >0.05.

Table 2: Some Surgery Determinants

Variable	Study group (n=82)	Placebo group (n=83)	Chi square	P value
No of previous scar			0.2427	0.6223
0	39	42		
1	21	19		
2	16	18		
≥3	6	4		
Cadre of surgeon			0.4037	0.5252
Senior registrar	65	69		
Consultant	17	14		
Years of experience			0.1802	0.6712
≤2 years	28	31		
>2 years	54	52		

The indication for the surgery was also similar between the two groups, see table 3.

Table 3: Risk Factors/ Indication for the Surgery

Indication	Study group	Control group	Chi square	P value
Two previous scars	25	21	0.6198	0.4311
≥3 previous scar	9	7		
1previous scar with another indication	19	18		
CPD/ obstructed labour	4	5		
Transverse lie at term	5	3		
Failed induction of labour	3	5		
Preeclampsia/ eclampsia	2	5		
Fetal macrosomia	6	8		
Multiple gestation	3	2		
Others	6	9		

The mean estimated blood loss was significantly lower in the tranexamic acid group compared with the placebo group (689.8±257.4mls versus 918.1±331.4mls, respectively; p<0.001). More so, blood loss > 1000mls was also significantly lower in the study group compared with the control group with 5(8.8%) versus 16(27.6%) respectively giving an Odd Ratio (OR) 0.25; 95% Confidence interval (CI) 0.09 to 0.74; p=0.012. There was no significant difference in the pre-operative haemoglobin and pre-operative haematocrit values between both group p >0.05, but the mean post-operative haematocrit was significantly higher in the tranexamic acid group compared with the control (29.5±2.1 versus 28.0±2.4; p=0.005) also the mean postoperative haemoglobin was significantly higher in the study group compared to the control group (9.8±0.7mg/dL versus 9.3±0.9mg/dL, P=0.001). The mean change in haematocrit and change in haemoglobin value were significantly less in the tranexamic acid group compared with the control group p<0.001.

Table 4A: Intraoperative and Postoperative Variables in the Study Group and in the Control Group

Variables	Study group (mean ± SD)	Placebo group (mean ± SD)	P value
Blood loss at the Caesarean Section	689.8±257.4	918.1±331.4	<0.001
Maternal haematocrit			
Preoperative	32.3±2.5	32.2±1.8	0.5951
Postoperative	29.5±2.1	28.0±2.4	0.005
Change in haematocrit	2.8±1.4	3.8±1.8	0.0012

There was no statistical difference in the number of patients that had blood transfusion between both groups 2(3.5%) versus 5 (8.6%) respectively OR 0.38; 95% CI 0.07 to 2.07; p=0.2668. The need for additional uterotonics was significantly lower among women in the tranexamic acid group compared to the control group 13 (22.8%) versus 25 (43.1%) OR 0.39; 95% CI 0.17 to 0.87; p=0.021. No patient needed additional surgical procedure, such as a brace suture, uterine artery ligation, or caesarean hysterectomy. There was no thromboembolism reported in either of the tranexamic acid group or in the control group. There was also no maternal death. However, the cases of gastrointestinal side effects (nausea and vomiting) were more in the tranexamic acid group but the difference was not statistically significant; 11(19.3%) versus 8(13.8%) OR 1.49 95% CI; 0.5 to 4.04; p=0.4286), table 4b

Table 4B: Intraoperative and Postoperative Variables in the Study Group and in the control Group

Variables	Study group N (%)	Placebo group N (%)	P value	OR 95% CI
Blood loss ≥ 1000ml	9(10.9%)	19(22.9%)	0.0414	0.42 (0.17 to 0.98)
Patients requiring additional oxytocics	13(15.8%)	27(32.5%)	0.0122	0.39 (0.18 to 0.82)
Patients requiring blood transfusion	11(13.4%)	19(22,9%)	0.1145	0.52 (0.23 to 1.18)
Patients with minor side effects				
Nausea/vomiting	13	8	0.231	1.77(0.69 to 4.51)
Nil	69	75		
Patients with major side effects				
Thromboembolism	0	0		
Maternal deaths	0	0		

Table 5 shows the vital signs of the patients at specific times from admission through 2 hours post operation. There was no statistically significant difference in the mean vital signs (respiratory rate, pulse rate, systolic and diastolic blood pressure) on admission, pre-operatively, immediately after placental delivery, or 1 hour and 2 hours after CS between both groups.

Table 5: Maternal Vital Signs at Different times During and Post Caesarean Section

Maternal vital signs	Study group	Placebo	P value
On admission			
Respiratory rate	21.9±2.5	21.5±2.2	0.3641
Pulse rate	79.9±6.6	81.5±6.4	0.1896
Systolic blood pressure	123.4±16.7	121.7±14.4	0.5597
Diastolic blood pressure	75.1±11.33	72.0±12.9	0.1734

Preoperative			
Respiratory rate	21.4±1.8	21.4±2.7	0.9511
Pulse	80.3±8.0	80.8±8.0	0.7382
Systolic blood pressure	118.3±12.11	116.9±10.8	0.5139
Diastolic blood pressure	75.9±10.1	74.9±7.9	0.555
At placental delivery			
Respiratory rate	22.4±1.5	22.3±2.2	0.7767
Pulse	83.6±7.2	82.2±8.6	0.7382
Systolic blood pressure	117.9±13.7	118.4±11.0	0.8294
Diastolic blood pressure	76.9±11.0	75.6±9.5	0.4988
1h after surgery			
Respiratory rate	22.6±1.9	22.8±1.7	0.3739
Pulse	78.6±15.4	82.0±8.4	0.1435
Systolic blood pressure	115.8±9.3	116.7±11.2	0.6404
Diastolic blood pressure	72.9±8.4	74.1±9.9	0.4852
2 h after surgery			
Respiratory rate	22.8±1.6	22.7±2.0	0.768
Pulse	80.2±5.4	80.6±7.9	0.7522
Systolic blood pressure	114±9.8	115.1±10.7	0.7153
Diastolic blood pressure	74.3±7.5	75.4±6.3	0.3959

Discussion

Increased risk of blood loss is the most feared complication associated with caesarean section, this is often time compounded by additional risk that some parturients possess. This problem is worsened by the prevalent anaemia in pregnancy in our environment. Despite the efficacy of uterotonics in preventing excessive blood loss following delivery, excessive blood loss remains a major cause of maternal morbidity and mortality worldwide. Hence, there is an urgent need to evaluate additional preventive and treatment interventions especially in high risk patients.

Findings from this study showed that pre-operative administration of 1g intravenous tranexamic acid in high risk patients was associated with a 228.3mL (24.9%) reduction in blood loss in high risk patients compared with placebo; the mean blood loss in the study group was 689.8±257.4 while the mean blood loss in the control group was 918.1±331.4 (p value <0.001). This is similar to the 26.9% reported by Goswani and coworkers in New Delhi India among anaemic patients who had caesarean section. A blood loss reduction of between 39.1- 43.7% had been reported in similar studies among low risk patients who had elective caesarean section. These differences in blood loss reduction may be due to the inherent risk of blood loss among high risk patients compared with those without additional risks.

Additionally, blood loss >1000mls was significantly reduced in the study group compared to the placebo group. This reduction in the risk of primary postpartum haemorrhage had been reported in similar randomized control studies in which risk of primary postpartum haemorrhage was an assessed outcome. This significant reduction in blood loss is particularly important for Abakaliki South east Nigeria where anaemia, caused by either nutritional or environmental factors, is prevalent among pregnant women in whom even a relatively small reduction of postpartum blood loss is clinically relevant [39].

This study also demonstrated that preoperative intravenous tranexamic acid reduced the need for additional uterotonics during caesarean section. This finding is consistent in the studies that evaluated the efficacy of tranexamic acid in high risk parturients and those that compared the efficacy of tranexamic acid to placebo in low risk caesarean section. No patient needed additional surgical procedure, such as a brace suture, uterine artery ligation, or caesarean hysterectomy during the procedure. There was a statistically significant difference in the mean postoperative haematocrit between the two groups. This is also reflected in the smaller mean change in the haematocrit in the tranexamic acid groups. These findings are consistent in most similar studies. There was no difference in the number of patients that received blood transfusion between both groups. This was similar to the finding by Suseela et al. However, Goswan et al and a systemic review and meta-analysis had shown that tranexamic acid reduced the need for blood transfusion in patient who had caesarean section. This lack of difference in blood transfusion in this study may be as a result of the high unmet need for blood transfusion in our environment.

This study demonstrated that preoperative tranexamic acid was not associated with any change in maternal vital signs and this confirm that it is safe to use it on parturient mothers. However, it is associated with a small increase in the risk of frequent maternal side effects (majorly nausea and vomiting) although this is not statistically significance. While some other studies did not demonstrate any difference in minor maternal gastro-intestinal side effects, others had observed significant difference. This difference may be as a result of the differences in the dosage and the

rate of administration of the medication; higher doses have been associated with increased in the rate of common maternal side effects. There were no major maternal side effects in this study and no maternal death occurred between the study groups. There was no difference in the neonatal APGAR scores in the first and fifth minutes between the two groups and there was no recorded neonatal admission into the new born intensive care unit for birth asphyxia. This further suggests that tranexamic acid did not have any adverse maternal or neonatal outcome. This safety profile had been demonstrated in other similar studies.

Conclusion

This study demonstrated that pre-operative intravenous tranexamic acid significantly reduced blood loss in women at increased risk of blood loss during caesarean section and it further reduced the risk of primary postpartum haemorrhage. It also significantly reduced the need for additional uterotonics. Although the common maternal side effects are slightly more, the difference was not statistically significant. There was no major maternal side effect and there was no maternal death.

Ethical Considerations

Ethical clearance was sought and obtained from the Health Research and Ethics committee of the Federal Teaching Hospital. All ethical parameters were put into consideration during this study.

Funding

All the financial costs were borne by the researchers.

Conflict of Interest

There was no conflict of interest as all the drugs used in the study were obtained from a reputable pharmacy store without any incentives from any drug company.

Dissemination of Results from Study

A dissertation was made out from the findings of this study and presented at the departmental clinical conference. It has also been presented during hospital grand round meeting. Recommendations from this study has been included in the departmental protocol.

Recommendation

- This result showed that intravenous tranexamic acid safely and effectively reduced the risk of primary postpartum haemorrhage among high risk women without increasing maternal risks and hence it could be an adjunctive therapy among these parturients.
- There is need to confirm these findings in a larger multi-centre trial involving larger number of women.

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