Prophylactic tranexamic acid for the prevention of postpartum haemorrhage in women with placenta praevia: multicentre, double blind, randomised, placebo controlled, phase 3 trial

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ABSTRACT

OBJECTIVE

To investigate whether prophylactic tranexamic acid reduces the incidence of postpartum haemorrhage in women with placenta praevia compared with placebo.

DESIGN

Randomised, double blind, placebo controlled, phase 3 study.

SETTING

24 maternity units across China between July 2023 and March 2025.

PARTICIPANTS

1732 women with placenta praevia undergoing caesarean delivery.

INTERVENTIONS

Participants were randomly (1:1) assigned to receive prophylactic oxytocin and either tranexamic acid (1 g in 10 mL) or placebo (10 mL normal saline) diluted in 40 mL normal saline intravenously over 10 minutes, initiated within five minutes of umbilical cord clamping.

MAIN OUTCOME MEASURES

The primary outcome was postpartum haemorrhage, defined as calculated estimated blood loss ≥1000 mL or as red cell transfusion within two days after delivery. Serious adverse events included thromboembolic events, seizures, acute kidney or liver injury, and maternal death.

RESULTS

Of 1732 women with placenta praevia who were randomised, 38 were excluded because they withdrew consent or were determined to be ineligible after randomisation. Primary outcome data were available for 99.8% (1691/1694) of the remaining women. Placenta accreta spectrum was diagnosed in 303 participants (17.9%). The primary outcome occurred in 29.7% (251/845) of the tranexamic acid group and 35.1% (297/846) of the placebo group (relative risk 0.85, 95.2% confidence interval (CI) 0.75 to 0.96; P=0.01). The rates of serious adverse events were similar between the tranexamic acid group and placebo group (0.5% (4 of 837) *v* 0.5% (4 of 845); relative risk 1.01, 95% CI 0.25 to 4.00).

CONCLUSIONS

In women with placenta praevia who underwent caesarean delivery and received prophylactic oxytocin, treatment with tranexamic acid resulted in a statistically significant yet modest reduction in the incidence of postpartum haemorrhage, with no signal of increased serious adverse events.

TRIAL REGISTRATION

ClinicalTrials.gov NCT05811676.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Tranexamic acid is widely recommended for the treatment of postpartum haemorrhage

In caesarean deliveries at low risk of postpartum haemorrhage, tranexamic acid may reduce the risk of postpartum haemorrhage

Evidence on the prophylactic use of tranexamic acid to prevent postpartum haemorrhage in high risk women undergoing caesarean delivery is scarce

WHAT THIS STUDY ADDS

In a high risk population—specifically, women with placenta praevia undergoing caesarean delivery—prophylactic tranexamic acid leads to a statistically significant but modest reduction in the incidence of postpartum haemorrhage

Introduction

Postpartum haemorrhage remains a leading cause of maternal mortality, accounting for more than 20% of maternal deaths worldwide.[1] This life threatening complication substantially affects the health and survival of millions of women annually.[1] Hence, the development of effective preventive strategies is a clinical priority.[2]

Placenta praevia, a condition in which the lower edge of the placenta attaches to the lower uterine segment or covers the internal cervical os, increases the risk of postpartum haemorrhage.[3] Postpartum haemorrhage occurs in about one third of pregnancies complicated by placenta praevia, with the incidence increasing to 56% in pregnancies with co-existing placenta accreta spectrum disorders.[4] The prevalence of placenta praevia has been increasing in many countries,[5] particularly in China, where the incidence has nearly tripled after implementation of the universal two child policy—a change that resulted in an increased incidence of advanced maternal age and scarred uterus pregnancy.[6] This trend further underscores the importance and urgency to investigate an effective preventive strategy to reduce postpartum haemorrhage and improve outcomes in high risk populations.

Tranexamic acid, an antifibrinolytic agent that inhibits plasmin mediated fibrinolysis, has been shown to effectively reduce the incidence of postpartum haemorrhage during caesarean delivery in low risk populations.[7] However, no evidence exists for tranexamic acid reducing more severe maternal outcomes, including maternal mortality or the need for blood transfusion during caesarean section.[8] Notably, previous studies have predominantly enrolled participants from low risk or mixed risk (~50% unscheduled caesarean delivery) populations. Such selective enrolment has left a critical gap in prophylactic use of tranexamic acid in high risk patients, who have a considerably high risk of haemorrhage and may derive greater clinical benefit from preventive interventions.[9-11] Therefore, we conducted a randomised, double blind, placebo controlled trial to investigate whether tranexamic acid could reduce the incidence of postpartum haemorrhage without increasing the risk of adverse events in women with placenta praevia undergoing caesarean delivery.

Methods

Study design

The current trial of prophylactic tranexamic acid for prevention of postpartum haemorrhage in women with placenta praevia was a multicentre, double blind, randomised, placebo controlled trial with two parallel groups. The protocol[12] was developed with direct reference to the TRAAP[13] and TRAAP2 trials.[7] An independent data and safety monitoring board oversaw the trial.

Participants

Women with confirmed placenta praevia during their last prenatal ultrasound examination who presented to 24 maternity units across 10 Chinese provinces were screened for eligibility after admission. The largest centre manages about 400 pregnancies with placenta praevia annually, with a median of 212 (interquartile range (IQR) 100-300) such pregnancies each year across all participating sites. Placenta praevia was diagnosed when the lower placental edge was attached within the lower uterine segment (≤2 cm from the internal cervical os) or covering the internal cervical os. It was further categorised as either placenta praevia (where placental tissue partially or completely covered the internal os) or low lying placenta (where the placental edge was within 2 cm of the internal os but not covering it).[14] Placenta accreta spectrum disorders were diagnosed based on the International Federation of Gynecology and Obstetrics (FIGO) guideline (see supplementary appendix table S1).[15] For women who underwent hysterectomy or partial myometrial resection of the increta area, the diagnosis was confirmed histologically. In all other women, the diagnosis was based on clinical criteria. To ensure diagnostic accuracy of placenta accreta spectrum disorders, two senior obstetricians independently reviewed the surgical records and pathology reports post hoc for all affected pregnancies. A third senior obstetrician served as the final arbiter when consensus was not reached. Inclusion criteria were age ≥18 years, singleton or multiple pregnancy at ≥34 weeks' gestation, undergoing caesarean delivery, and haemoglobin level >90 g/L within the preceding week. Key exclusion criteria were thromboembolic risk factors, history of epilepsy or seizures, active malignancy, cardiovascular disorders, kidney or liver dysfunction, autoimmune diseases, and hypersensitivity to tranexamic acid (see supplementary appendix table S2). Eligible patients received information on the trial from trained clinical staff and provided written informed consent.

Randomisation and masking

Study investigators randomly assigned patients in a 1:1 ratio using a centralised computer generated randomisation (Sun Yat-sen University Cancer Centre, Guangzhou, China) with a block size of six to receive either tranexamic acid or placebo. Randomisation was stratified according to the study site, maternal age group (≥35 or <35 years), and placenta praevia type (low lying placenta or placenta praevia). The information on randomisation was sent to the pharmacy department of The Third Affiliated Hospital, Guangzhou Medical University, which prepared and distributed the tranexamic acid (Chengdu Lier Pharmaceutical, Dujiangyan, Sichuan, China) and placebo (Hebei Tiancheng Pharmaceutical, Cangzhou, Hebei, China). All vials were labelled as "tranexamic acid 10 mL (1 g) / placebo 10 mL" with expiry dates and randomisation numbers. Study drugs were packaged in sequentially numbered, identical boxes distinguishable only by randomisation number. Participants, investigators, clinical staff, the study sponsor, and the data analysts were masked to treatment assignment.

Procedures

Tranexamic acid (1 g in 10 mL) or placebo (10 mL normal saline) of identical appearance was diluted in 40 mL normal saline and administered intravenously over 10 minutes, initiated within five minutes of umbilical cord clamping. Prophylactic oxytocin (10 IU) was administered immediately after delivery. Haemodynamic variables, including heart rate and blood pressure, were recorded before and after administration of the study drug. Adverse events occurring in the operating room were documented. Laboratory assessments were performed during screening and repeated closest to day 2 after delivery. Maternal psychological status using the Edinburgh postnatal depression scale was evaluated before caesarean delivery (after randomisation) and at six weeks post partum (via telephone). Patient satisfaction was assessed at two days and six weeks after delivery (via telephone). Surveillance for severe adverse effects continued until six weeks post partum.

Standardised protocols and uniform training were implemented for both transfusion management in bleeding and surgical procedures for placenta praevia and placenta accreta spectrum disorders (see protocol[12] and supplementary appendix tables S3

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and S4) across all participating centres before trial initiation. These protocols were designed to adhere to Chinese guidelines[16] and institutional protocols, while remaining aligned with international standards.[3 17 18] If open label tranexamic acid was used because of excessive intraoperative bleeding, it was recommended to be delayed for at least 30 minutes after the trial infusion. No more than two doses in total (trial infusion plus one dose of open label tranexamic acid) were allowed within the first 24 hours after delivery.

Outcomes

The primary outcome was postpartum haemorrhage, defined as either calculated estimated blood loss ≥1000 mL or as red cell transfusion within two days after delivery. The calculated estimated blood loss was determined as estimated blood volume×(preoperative packed cell volume−postoperative packed cell volume)/preoperative packed cell volume. Estimated blood volume (mL) was calculated by multiplying the body weight (kg) by 85, as described in a previous study.[19] The preoperative level of packed cell volume was measured within one week before delivery, and the postoperative measurement was taken closest to day 2 after delivery if transfusion was not required.

Secondary outcomes included clinical and laboratory measures of postpartum blood loss during hospital admission, as well as interventions for the management of haemorrhage. We also assessed adverse events; these included the occurrence of at least one of the following in the operating room: nausea, vomiting, photopsia, dizziness, or diarrhoea. Serious adverse events such as thrombosis, seizure, acute liver or kidney injury, and maternal death from any cause were monitored up to six weeks after delivery. Supplementary appendix table S5 lists additional secondary efficacy and safety outcomes.

Trained staff, blinded to treatment assignments, extracted data from medical records. Participants were interviewed six weeks after delivery via telephone. They were asked about any hospital admissions since discharge, emergency department visits, and the development of adverse events.

A web based electronic data capture system with hierarchical access controls and audit trail functionality was used to ensure data integrity. Routine clinical data, defined as information routinely contained in medical records, were entered directly into the system. Non-routine variables, such as assessments of maternal psychological status and satisfaction, were first captured on paper case report forms before electronic transcription. To ensure data quality, constraints were implemented at the database level alongside input validation on the user interface. In addition to these automated checks, the lead research team performed online data quality control twice monthly and conducted regular on-site supervision visits at the participating hospitals.

Sample size calculation

Based on a systematic review of PubMed from database inception to 7 March 2023, a pooled analysis of 13 studies (see supplementary appendix table S6) estimated the incidence of the primary outcome to be 33% in the placebo group. To achieve 80% power in detecting a ≥20% relative difference in incidence (33% in the placebo group versus 26.4% in the tranexamic acid group) at a two sided type I error rate of 5%, the required sample size was determined to be 1500 (750 in each group) based on a standard two sample test for comparing proportions. To account for a projected 10% attrition rate, including insufficient postpartum blood samples for primary outcome assessment and participant loss to follow-up, the final sample size was set at 840 women in each treatment arm, totalling 1680 participants. A post hoc simulation based power analysis indicated that with this sample size, the study had 86.7% power to detect the target effect size using a log-binomial mixed effects regression model—the prespecified method for the primary outcome analysis.

Statistical analysis

The main analysis of the primary and secondary outcomes was performed following the intention-to-treat principle, and included all women who had undergone randomisation, except for those who withdrew consent or were deemed ineligible after randomisation. The safety population included all women who received the study drug.

Baseline continuous variables are presented as means with standard deviations (SDs) or as medians with IQRs, and categorical variables are presented as frequencies with percentages. For binary outcomes, we used log-binomial mixed effects regression models with study centre as a random effect, adjusting for maternal age group and placenta praevia type, to estimate relative risks with 95% confidence intervals (CIs) for the tranexamic acid group versus placebo group. When these models failed to converge, we estimated adjusted relative risks using a modified Poisson regression model with generalised estimating equations, clustering by study centre and using robust sandwich standard errors. For continuous outcomes, we used linear mixed effects models to estimate mean differences with 95% CIs. Participants with missing data for the primary outcome were excluded from the analyses. Sensitivity analysis was conducted using the per protocol population, which excluded participants who received the study drug more than five minutes after cord clamping, as well as those who received open label tranexamic acid. Moreover, subgroup analyses were conducted to assess the primary outcome, stratified by maternal age group (≥35 or <35 years), type of placenta praevia (low lying placenta or placenta praevia), and the presence or absence of placenta accreta spectrum disorders. Post hoc analyses included a sensitivity analysis using mean imputation for missing values for packed cell volume, a subgroup analysis based on antepartum haemorrhage (presence versus absence), as well as evaluations of hysterectomy

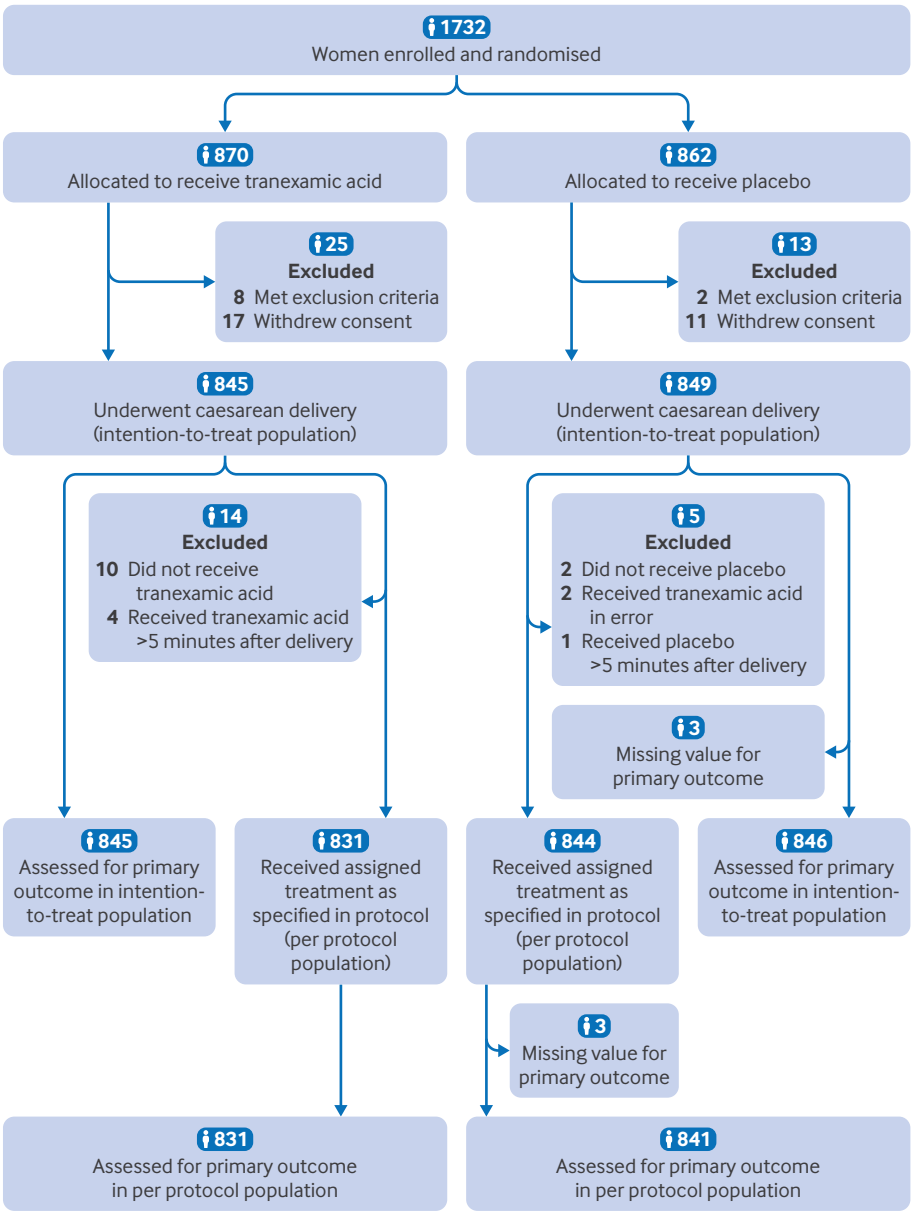

Fig 1 | Randomisation and treatment. Patients with missing primary outcome data lacked postoperative measurement of packed cell volume. The per protocol population consisted of women in the intention-to-treat group who received tranexamic acid or placebo within five minutes of umbilical cord clamping

rate and length of hospital stay; all these analyses were exploratory and not prespecified in the study protocol. No adjustments for multiple comparisons were performed. An interim analysis using the O'Brien-Fleming boundary was conducted and reviewed by an independent data and safety monitoring board.[20] In the final analysis of the primary outcome, statistical significance was defined as a two tailed P<0.048. All statistical analyses were performed using R version 4.4.3.

Patient and public involvement

No patients or members of the public were involved in the design, conduct, or reporting of the research. This was primarily because the study was initiated and completed within a short timeframe as a pragmatic, investigator led trial, and we did not have the necessary infrastructure or funding to establish a formal patient and public involvement group.

Results

Trial participants

Between July 2023 and March 2025, we enrolled 1732 eligible participants and randomly assigned them to receive tranexamic acid (870 women) or placebo (862 women), masked to treatment group. Of these, 38 women were excluded because they withdrew consent or were determined to be ineligible after randomisation (see supplementary appendix table S7). Of the remaining 1694 women, 845 were in the tranexamic

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Table 1 | Baseline characteristics of participants with placenta praevia undergoing caesarean delivery, by treatment group. Values are number (percentage) unless stated otherwise

Characteristic	Tranexamic acid (n=845)	Placebo (n=849)
Mean (SD) age (years)	33.8 (4.3)	34.0 (4.4)
Mean (SD) BMI	22.1 (3.5)	22.2 (3.6)
Education:		
Master's degree	28 (3.3)	40 (4.7)
Bachelor's degree	592 (70.1)	577 (68.0)
High school or below	202 (23.9)	200 (23.6)
Unknown	23 (2.7)	32 (3.8)
Mode of conception:		
Natural conception	722 (85.4)	731 (86.1)
Artificial insemination	21 (2.5)	19 (2.2)
IVF/ICSI	102 (12.1)	99 (11.7)
Primiparous	133 (15.7)	124 (14.6)
No of previous caesarean deliveries:		
1	221 (26.2)	227 (26.7)
≥2	98 (11.6)	104 (12.2)
Polyhydramnios	23 (2.7)	14 (1.6)
History of postpartum haemorrhage	51 (6.0)	49 (5.8)
Antepartum haemorrhage	293 (34.7)	260 (30.6)
Multiple pregnancy	13 (1.5)	15 (1.8)
Gestational/prepregnancy diabetes	229 (27.1)	226 (26.6)
Gestational hypertensive disorders	33 (3.9)	37 (4.4)
Median (IQR) gestational age at delivery (weeks)	37 (36-37)	37 (36-37)
Median (IQR) duration of caesarean delivery (mins)	63 (45-90)	65 (45-95)
General anaesthesia	158 (18.7)	151 (17.8)
Epidural or spinal anaesthesia	653 (77.3)	671 (79.0)
Type of placenta praevia:		
Low lying placenta	217 (25.7)	221 (26.0)
Placenta praevia	628 (74.3)	628 (74.0)
Median (IQR) distance from placental edge to cervical os for low lying placenta (mm)	0 (0-13)	0 (0-13)
Median (range) gestational age at last ultrasonography (weeks)	37 (33-40)	37 (33-40)
Interval between last ultrasonography and delivery (weeks):		
≤1	785 (92.9)	789 (92.9)
1~2	60 (7.1)	58 (6.8)
>2	0 (0)	2 (0.2)
PAS disorder	148 (17.5)	155 (18.3)
Grade of PAS disorder*:		
1	71 (48.0)	77 (49.7)
2	54 (36.5)	55 (35.5)
3	23 (15.5)	23 (14.8)
Clinical diagnosis of PAS	84 (56.8)	94 (60.6)
Histological diagnosis of PAS	64 (43.2)	61 (39.4)
Hysterectomy	17 (26.6)	9 (14.8)
Partial myometrial resection of increta area	47 (73.4)	52 (85.2)
Median (IQR) infant birth weight (g)	2900 (2620-3140)	2900 (2650-3160)

Data on BMI were missing for three participants in the tranexamic acid group and five in the placebo group, and data on infant birth weight were missing for one participant in the tranexamic acid group.
BMI=body mass index; ICSI=intracytoplasmic sperm injection; IQR=interquartile range; IVF=in vitro fertilisation; PAS=placenta accreta spectrum; SD=standard deviation.
*Diagnosis based on FIGO (International Federation of Gynecology and Obstetrics) guideline. For participants who underwent hysterectomy or partial myometrial resection of the increta area, the diagnosis was confirmed using histological criteria. For all other participants with PAS, the diagnosis relied exclusively on clinical criteria.

acid group and 849 were in the placebo group (fig 1). The median gestational age at last ultrasound diagnosis of placenta praevia was 37 weeks (range 33-40 weeks) in both groups, with 93% of all participants delivering within one week of the last ultrasound examination. The incidence of placenta accreta spectrum disorders was 17.5% (148 of 845) in the tranexamic acid group and 18.3% (155 of 849) in the placebo group. Table 1 shows the baseline characteristics of the participants, and supplementary appendix table S8 additionally shows adherence to the protocol. Tranexamic acid or placebo was administered within five minutes of umbilical cord clamping in 98.9% of participants.

Primary outcome

Data on postpartum haemorrhage were not available for three women in the placebo group owing to missing values for postoperative packed cell volume. Postpartum haemorrhage occurred in 251 of 845 participants (29.7%) in the tranexamic acid group and 297 of 846 (35.1%) in the placebo group (relative risk 0.85, 95.2% CI 0.75 to 0.96; P=0.01) (table 2). The

Table 2 | Primary and secondary outcomes in participants with placenta praevia undergoing caesarean delivery, by treatment group. Values are number (percentage) unless stated otherwise

Outcomes	Tranexamic acid (n=845)	Placebo (n=849)	Relative risk (95% CI)*	Mean difference (95% CI)†
Primary outcome				
Postpartum haemorrhage‡	251 (29.7)	297 (35.1)	0.85 (0.75 to 0.96)§	–
Calculated estimated blood loss ≥1000 mL	217 (25.7)	267 (31.6)	0.81 (0.70 to 0.93)	–
Red cell transfusion <2 days after delivery	159 (18.8)	183 (21.6)	0.88 (0.74 to 1.03)	
Secondary outcomes				
Mean (SD) gravimetrically estimated blood loss within 24 hours after delivery (mL)	790 (767)	813 (688)	–	−23.98 (−88.86 to 40.90)
Gravimetrically estimated blood loss ≥1000 mL	127 (15.0)	175 (20.6)	0.80 (0.66 to 0.96)	–
Uterotonic agent other than oxytocin by discharge	786 (93.0)	800 (94.2)	0.99 (0.97 to 1.00)	–
Postoperative iron sucrose infusion by discharge	63 (7.5)	72 (8.5)	0.88 (0.65 to 1.20)	–
Transfer to intensive care unit by discharge¶	113 (13.4)	115 (13.5)	0.93 (0.62 to 1.39)	–
Haemoglobin**:				
Mean (SD) peripartum decrease (g/L)	11 (14)	13 (15)	–	−1.79 (−3.10 to −0.47)
Peripartum decrease >20 g/L	151 (17.9)	194 (22.9)	0.77 (0.64 to 0.93)	
Packed cell volume††:				
Mean (SD) peripartum decrease (%)	3.5 (5.1)	4.0 (5.3)	–	−0.53 (−0.99 to −0.07)
Peripartum decrease >10%	61 (7.2)	72 (8.5)	0.84 (0.62 to 1.13)	–
Mean (SD) calculated estimated blood loss (mL)	841 (1397)	1003 (1440)	–	−161.78 (−292.17 to −31.40)
Transfusion by discharge	164 (19.4)	185 (21.8)	0.90 (0.77 to 1.05)	
Additional operations by discharge‡‡	493 (58.3)	492 (58.0)	1.00 (0.95 to 1.06)	–
Hysterectomy by discharge	19 (2.2)	18 (2.1)	1.06 (0.57 to 1.97)	–
Hypovolaemic shock related to postpartum haemorrhage by discharge	8 (0.9)	8 (0.9)	1.01 (0.39 to 2.62)	–
Open label use of tranexamic acid by discharge§§	98 (11.6)	103 (12.1)	1.02 (0.84 to 1.25)	–
Maternal thromboembolic events by 6 weeks after delivery	1 (0.1)	3 (0.4)	0.34 (0.03 to 3.22)	–
Readmission after discharge	2 (0.2)	1 (0.1)	1.80 (0.38 to 8.46)	–
Mean (SD) hospital stay (days)	7 (6)	7 (5)	–	0.00 (−0.44 to 0.45)
Maternal death by 6 weeks after delivery	0 (0)	0 (0)	–	–

Data on calculated estimated blood loss, haemoglobin, and packed cell volume were available for 846 participants in the placebo group.
CI=confidence interval; SD=standard deviation.
*Relative risks were estimated using log-binomial mixed effects regression, with study centre as a random effect and adjustment for maternal age group and placenta praevia type. When models did not converge, a modified Poisson regression model was used.
†Mean differences were estimated using linear mixed effects models, with study centre as a random effect and adjustment for maternal age group and placenta praevia type.
‡Defined as calculated estimated blood loss ≥1000 mL or as red cell transfusion within two days after delivery.
§ For postpartum haemorrhage, a 95.2% CI was used with a predefined threshold of P<0.048. For postpartum haemorrhage the adjusted P=0.01. CIs for outcomes other than the primary outcome were not adjusted for multiplicity and therefore should not be used for hypothesis testing.
¶The composite outcome of transfer to intensive care unit was defined as admission to an intensive care unit or the obstetric high dependency unit. In the tranexamic acid group, 25 participants were admitted to the intensive care unit and 88 to the obstetric high dependency unit; the corresponding numbers in the placebo group were 30 and 85 participants.
**Preoperative levels of haemoglobin reflect the most recent measurement within seven days before delivery, whereas postpartum levels are derived from the measurement closest to day 2 after delivery. For participants who received transfusions before the blood sample was obtained, postpartum levels were calculated as haemoglobin levels at day 2 after delivery (g/L)−(5×number of units of red cells transfused); see supplementary appendix table S5 for details. For those who received blood transfusions after delivery, one unit of packed red cells was considered to indicate a 5 g/L decrease in haemoglobin levels.
††Preoperative levels of packed cell volume reflect the most recent measurement within seven days before delivery, whereas postoperative levels are derived from the measurement closest to day 2 after delivery. For patients who received transfusions before the blood sample was obtained, postoperative levels were calculated as packed cell volume levels at day 2 (%) after delivery−(2.5×number of units of red cells transfused). In those who received transfusions after delivery, one unit of packed red cells was considered to indicate a 2.5% decrease in packed cell volume levels.
‡‡Intraoperative use of any of uterine gauze or balloon tamponade, uterine artery ligation, uterine compression sutures, or endovascular interventional.
§§If excessive intraoperative bleeding occurred, open label tranexamic acid was used at least 30 minutes after the trial infusion.

incidence of calculated estimated blood loss ≥1000 mL was 25.7% (217 of 845) in the tranexamic acid group versus 31.6% (267 of 846) in the placebo group (relative risk 0.81, 95% CI 0.70 to 0.93). The red cell transfusion rate within two days after delivery was 18.8% (159 of 845) in the tranexamic acid group versus 21.6% (183 of 849) in the placebo group (relative risk 0.88, 95% CI 0.74 to 1.03). The number needed to treat was 19 (95% CI 10 to 104)for postpartum haemorrhage, 17 (10 to 63) for calculated estimated blood loss ≥1000 mL, and 37 (92 (harm) to ∞ to 15 (benefit)) for red cell transfusion within two days after delivery. Figure 2 presents the results of subgroup analyses. No statistically significant variation was observed across maternal age groups (≥35 or <35 years), placenta praevia types (low lying placenta or placenta praevia), and the presence or absence of antepartum haemorrhage and placenta accreta spectrum disorders. In post hoc sensitivity analyses excluding participants who received tranexamic acid or placebo more than five minutes after umbilical cord clamping or received open label tranexamic acid, and using mean imputation for missing values for packed cell volume, the results remained consistent with those of the primary analysis (see supplementary appendix tables S9-11).

Secondary outcomes

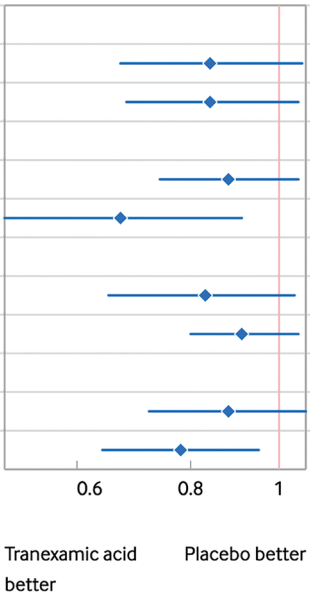
Overall, 15.0% (127 of 845) and 20.6% (175 of 849) of the tranexamic acid and placebo groups, respectively, had gravimetrically estimated blood loss ≥1000 mL (relative risk 0.80, 95% CI 0.66 to 0.96).

Subgroup analyses for the primary outcome of calculated estimated blood loss ≥1000 mL or of red cell transfusion within two days after delivery

Postpartum haemorrhage according to subgroup: maternal age groups (≥35 *v* <35 years), placenta praevia types (low lying placenta *v* placenta praevia), presence or absence of antepartum haemorrhage, and PAS disorders, comparing tranexamic acid with placebo

Relative risks were estimated using log-binomial mixed effects regression models, with study centre as a random effect and adjustment for maternal age group and placenta praevia type. When models did not converge, a modified Poisson regression model was used. CIs for estimates in the prespecified subgroups are not adjusted for multiplicity and may not be used for hypothesis testing

Subgroup	Tranexamic acid No/Total No (%)	Placebo No/Total No (%)	Equivalent relative risk (95% CI)	P value for interaction
Maternal age				1
<35	126/474 (26.6)	146/468 (31.2)	0.84 (0.67 to 1.06)	
≥35	125/371 (33.7)	151/378 (39.9)	0.84 (0.68 to 1.05)	
Type of placenta praevia				0.06
Placenta praevia	216/628 (34.4)	246/626 (39.3)	0.88 (0.74 to 1.05)	
Low lying placenta	35/217 (16.1)	51/220 (23.2)	0.67 (0.50 to 0.91)	
PAS disorders				0.39
No	146/697 (20.9)	175/691 (25.3)	0.83 (0.65 to 1.04)	
Yes	105/148 (70.9)	122/155 (78.7)	0.91 (0.80 to 1.05)	
Antepartum haemorrhage				0.28
No	159/552 (28.8)	192/586 (32.8)	0.88 (0.72 to 1.07)	
Yes	92/293 (31.4)	105/260 (40.4)	0.78 (0.64 to 0.95)	



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CI=confidence interval; PAS=placenta accreta spectrum

Fig 2 | Subgroup analyses for the primary outcome. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/28574562/

Mean gravimetrically estimated blood loss was similar between the two groups (mean difference −23.98 mL, 95% CI −88.86 to 40.90). The respective decreases in haemoglobin and packed cell volume levels were 11 g/L and 3.5% and 13 g/L and 4.0%, respectively. The mean between group differences were −1.79 g/L (95% CI −3.10 to −0.47) for haemoglobin and −0.53% (95% CI −0.99% to −0.07%) for packed cell volume. A decrease in haemoglobin >20 g/L occurred in 17.9% (151 of 845) of the tranexamic acid group and 22.9% (194 of 846) of the placebo group (relative risk 0.77, 95% CI 0.64 to 0.93), and a decrease in packed cell volume >10% occurred in 7.2% (61 of 845) and 8.5% (72 of 846), respectively (0.84, 95% CI 0.62 to 1.13). The mean hospital stay was seven days in both groups (mean difference 0.00, 95% CI −0.44 to 0.45). Table 2 presents the results for other secondary outcomes.

Adverse events

Table 3 shows results for the safety outcomes (see supplementary appendix fig S1 and table S12). In the operating room, adverse events occurred in 2.2% (18 of 837) of participants in the tranexamic acid group and 1.7% (14 of 845) in the placebo group (relative risk 1.31, 95% CI 0.67 to 2.59). At six weeks after delivery, data on serious adverse events were available for all participants. Overall, 0.5% (4 of 837) of participants in the tranexamic acid group and 0.5% (4 of 845) in the placebo group experienced a serious adverse event (relative risk 1.01, 0.25 to 4.00). Maternal satisfaction was comparable between the two groups at day 2 and six weeks after delivery. At day 2 after delivery, 90.1% and 96.8% of participants reported little or no tiredness and anxiety, increasing to 94.7% and 98.1% at six weeks after delivery. At six weeks, more than

Table 3 | Adverse events (safety population) in participants with placenta praevia undergoing caesarean delivery, by treatment. Values are number (percentage) unless stated otherwise

Adverse events	Tranexamic acid (n=837)	Placebo (n=845)	Relative risk* (95% CI)
In the operating room			
Adverse event†	18 (2.2)	14 (1.7)	1.31 (0.67 to 2.59)
Nausea or vomiting	11 (1.3)	10 (1.2)	1.14 (0.49 to 2.61)
Photopsia	1 (0.1)	1 (0.1)	1.02 (0.11 to 9.36)
Dizziness	5 (0.6)	3 (0.4)	1.68 (0.41 to 6.88)
Diarrhoea	2 (0.2)	0 (0)	–
At 6 weeks after delivery			
Completed interviews	837 (100.0)	845 (100.0)	–
Postpartum infection‡	12 (1.4)	11 (1.3)	1.09 (0.49 to 2.44)
Endometritis	4 (0.5)	4 (0.5)	1.02 (0.26 to 4.06)
Surgical site infection	8 (1.0)	5 (0.6)	1.58 (0.53 to 4.78)
Pelvic abscess	1 (0.1)	2 (0.2)	0.50 (0.05 to 5.48)
Serious adverse event§	4 (0.5)	4 (0.5)	1.01 (0.25 to 4.00)
Thromboembolic event (venous or arterial)	1 (0.1)	3 (0.4)	0.34 (0.04 to 3.23)
Acute liver injury	3 (0.4)	1 (0.1)	3.05 (0.32 to 29.13)

The safety population included all participants who received either tranexamic acid or placebo.
*Estimated using log-binomial mixed effects regression models, with study centre as a random effect and adjustment for maternal age group and placenta praevia type. When models did not converge, a modified Poisson regression model was used.
†Defined as the occurrence of at least one of nausea, vomiting, photopsia, dizziness, or diarrhoea.
‡Included endometritis, surgical site infection, or pelvic abscess.
§Included thromboembolic events (venous or arterial), myocardial infarction, seizure, acute kidney or liver injury, and any other unexpected serious adverse events. In the tranexamic acid group, one participant had deep vein thrombosis of the leg. In the placebo group, one participant had pulmonary embolism and two had deep vein thrombosis of the leg. Acute liver injury, defined as impairment of liver function requiring treatment, was observed in four participants. Diagnosis was confirmed by raised transaminase levels detected during postoperative liver function testing, and hepatoprotective treatment was administered accordingly. Neither group experienced maternal death, myocardial infarction, seizure, or impairment of kidney function requiring treatment.

96.0% of women in both groups reported satisfaction with their delivery experience and remained positive about it (see supplementary appendix table S13). The proportion of women with an Edinburgh postnatal depression scale score ≥12 was comparable between the tranexamic acid group (2.2%, 18 of 829) and placebo group (1.8%, 15 of 833) (see supplementary appendix table S13).

Discussion

In this randomised controlled trial comprising pregnant participants at high risk of postpartum haemorrhage undergoing caesarean delivery with prophylactic oxytocin—specifically those with a diagnosis of placenta praevia, of whom 17.9% had co-existing placenta accreta spectrum—tranexamic acid treatment resulted in a statistically significant yet modest reduction in the incidence of postpartum haemorrhage. Sensitivity analyses produced consistent effect estimates, confirming the robustness of the primary findings. Furthermore, subgroup analyses indicated no difference in treatment effect across maternal age, type of placenta praevia, and presence or absence of antepartum haemorrhage and placenta accreta spectrum disorders.

Comparison with other studies

Notably, the proportion of patients with placenta accreta spectrum disorders in this trial was 17.9%, considerably higher than reported in previous studies.[21 22] This primarily reflects the tertiary, high risk obstetric setting of all participating centres, which receive referrals of women with complex placenta praevia and with placenta accreta spectrum disorders from secondary hospitals. Therefore, this proportion does not reflect the incidence in the general population. Despite the high proportion of participants with placenta accreta spectrum, the overall hysterectomy rate in our trial was low (2%), consistent with reports from other specialised centres in China.[4 23] This can be attributed to two key factors. Firstly, influenced by Confucian values emphasising family continuity, families typically consent to hysterectomy only under clear and imminent maternal threat. Consequently, when technically feasible, partial myometrial resection of the increta area was the preferred surgical approach (160 of 303 (53%) participants). Secondly, in this trial the strategy of intentional partial or total placental retention was seldom used for women with placenta accreta spectrum (see supplementary appendix table S10). The number needed to treat to prevent one event was 19 for postpartum haemorrhage, 17 for calculated estimated blood loss ≥1000 mL, and 37 for red cell transfusion within two days after delivery. These values are lower than those reported in two previous trials involving low risk or mixed risk populations (~50% unscheduled caesarean delivery),[7 8] suggesting that tranexamic acid may have greater clinical utility in patients at high risk of postpartum haemorrhage.

Although this trial comprised only patients with placenta praevia and included a high proportion with placenta accreta spectrum disorders, the incidence of the primary outcome (35.1%) was only slightly higher than in the TRAAP2 trial (31.6%),[7] which excluded patients with placenta praevia and placenta accreta spectrum disorders. Given that both trials used the same formula for calculating blood loss, we speculate that the difference in mean body weight between the two trial populations might partly explain this discrepancy (see supplementary appendix table S14).

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The mean body mass index (BMI) in our trial was substantially lower than in TRAAP2 (22.2 (SD 3.6) *v* 26.1 (6.2)),[7] supporting our speculation given the close correlation between body weight and BMI.

In this trial, we used a composite primary outcome because no single measure alone could adequately identify all patients with postpartum haemorrhage. Gravimetrically estimated blood loss is widely used in clinical practice, but it often substantially underestimates true blood loss due to contamination with amniotic fluid and variability in provider judgement.[24] Calculated estimated blood loss, an alternative to gravimetric estimation, is more objective for research purposes; however, it can be influenced by physiological factors such as haemoconcentration and fluid resuscitation. Red cell transfusion captures patients who experienced severe bleeding without exhibiting an increase in calculated estimated blood loss (see supplementary appendix tables S15 and S16). Both calculated estimated blood loss and red cell transfusion may be affected by antepartum bleeding, potentially overestimating rates of postpartum haemorrhage (see supplementary appendix table S17). The results of a stratified analysis excluding patients with antepartum bleeding, however, were consistent with the primary analysis. In addition, transfusion practices may vary by threshold and centre. To minimise this subjectivity, we implemented standardised transfusion criteria (see supplementary appendix table S4) and uniform training across all participating centres before the start of the trial. We did not, however, investigate adherence to these criteria across centres. The intraclass correlation coefficient for calculated estimated blood loss ≥1000 mL among patients who underwent red cell transfusion within two days after delivery was 0.12, indicating modest heterogeneity between centres.

The risk of thromboembolic events and other adverse events was not higher in the tranexamic acid group compared with placebo group. A previous study reported a higher incidence of postpartum infections with tranexamic acid (3.2% *v* 2.5%, relative risk 1.28, 95% CI 1.02 to 1.61)[8]; however, in our study, the incidence of postpartum infections was similar between the groups (1.4% *v* 1.3%, relative risk 1.09, 95% CI 0.49 to 2.44). The incidence of nausea and vomiting was lower in our trial, which may be attributable to potential underreporting. Nevertheless, this finding remains consistent with previous literature,[7 8] indicating no statistically significant difference in the risk of nausea and vomiting between the tranexamic acid group and control group.

Strengths and limitations of this study

Although tranexamic acid may reduce the risk of postpartum haemorrhage after caesarean delivery, high quality evidence specific to high risk populations remains scarce.[25] The current trial addressed this gap by focusing on the high risk group of women with placenta praevia undergoing caesarean delivery and showed that prophylactic tranexamic acid leads to a statistically significant yet modest reduction in the incidence of postpartum haemorrhage.

The main limitation of this study was that, despite intending to systematically record all ineligible women and reasons for exclusion, comprehensive data collection was not feasible owing to practical constraints during the trial. This may affect the assessment of the study's generalisability. Secondly, findings on secondary outcomes should be interpreted with caution because of their exploratory nature and potentially increased risk of type I error in lack of adjustment for multiple comparisons. Thirdly, follow-up data at six weeks postpartum were obtained via telephone interview and were based solely on participant recall of either doctor diagnosed conditions during the routine 42 day postnatal visit (at a community health centre or hospital) or any medical care sought after discharge. In the absence of corroboration from medical records, these data are susceptible to recall bias. Furthermore, women with mild symptoms who did not seek medical care may not have been captured. Finally, as this trial was conducted within a single country, the applicability of our findings may be limited by differences in population characteristics, including lower BMI[7 8] and higher rate of placenta accreta spectrum disorders,[22] as well as variations in clinical practices for managing placenta accreta spectrum disorders.[26] Future studies in diverse international settings are warranted to validate these results and to identify specific patient subgroups most likely to benefit from prophylactic use of tranexamic acid.

Conclusion

This trial found that among women with placenta praevia who underwent caesarean delivery and received prophylactic oxytocin, treatment with tranexamic acid resulted in a statistically significant yet modest reduction in the incidence of postpartum haemorrhage.

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Ethical approval: The trial was approved the Clinical Research and Applied Ethics Committee of The Third Affiliated Hospital, Guangzhou Medical University on 30 May 2023 (ethics review No 045). Ethical approval from the other participating centres was obtained before patient enrolment. All patients or their legally authorised representatives (ie, spouse or parents) provided written informed consent before randomisation.For patients who presented with altered consciousness or haemodynamic instability due to active postpartum haemorrhage, consent was obtained from their legally authorised representative.

Data sharing: The code used to analyse the data in the paper are in the supplementary file. The data underlying the findings in this paper are openly and publicly available and can be found at https://github.com/ChenDunjin-GZHMU. The corresponding author can be contacted if there are problems accessing the data.

Transparency: The corresponding author (DJC) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Dissemination to participants and related patient and public communities: Once the trial has been published, the findings will be shared via the WeChat official accounts of all participating study sites. A press release will also be issued. The results will be presented at both international and national conferences and possibly be used as evidence to inform future guidelines on the prophylactic use of tranexamic acid in populations at high risk of postpartum haemorrhage.

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Supplementary information: Members of the study's collaborator group, figure S1, tables S1-18, references, and R code