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RESEARCH ARTICLE

Effect of tranexamic acid on coagulation and fibrinolysis in women with postpartum haemorrhage (WOMAN-ETAC): a single-centre, randomised, double-blind, placebo-controlled trial [version 1; referees: 2 approved]

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Abstract




Background: Postpartum haemorrhage (PPH) is a leading cause of maternal death. The WOMAN trial showed that tranexamic acid (TXA) reduces death due to bleeding in women with PPH. We evaluated the effect of TXA on fibrinolysis and coagulation in a sample of WOMAN trial participants.

Methods: Adult women with a clinical diagnosis of PPH were randomised to receive 1 g TXA or matching placebo in the WOMAN trial. Participants in the WOMAN trial at University College Hospital (Ibadan, Nigeria) also had venous blood taken just before administration of the first dose of trial treatment and again 30 (\pm 15) min after the first dose (the ETAC study). We aimed to determine the effects of TXA on fibrinolysis (D-dimer and rotational thromboelastometry maximum clot lysis (ML)) and coagulation (international normalized ratio and clot amplitude at 5 min). We compared outcomes in women receiving TXA and placebo using linear regression, adjusting for baseline measurements.

Results: Women (n=167) were randomised to receive TXA (n=83) or matching placebo (n=84). Due to missing data, seven women were excluded from analysis. The mean (SD) D-dimer concentration was 7.1 (7.0) mg/l in TXA-treated women and 9.6 (8.6) mg/l in placebo-treated women (p=0.09). After adjusting for baseline, the D-dimer concentration was 2.16 mg/l lower in

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TXA-treated women (-2.16, 95% CI -4.31 to 0.00, $p=0.05$). There was no significant difference in ML between TXA- and placebo-treated women (12.3% (18.4) and 10.7% (12.6), respectively; $p=0.52$) and no significant difference after adjusting for baseline ML (1.02, 95% CI -3.72 to 5.77, $p=0.67$). There were no significant effects of TXA on any other parameters.

Conclusion: TXA treatment was associated with reduced D-dimer levels but had no apparent effects on thromboelastometry parameters or coagulation tests.

Registration: [ISRCTN76912190](#) (initially registered 10/12/2008, WOMAN-ETAC included on 22/03/2012) and [NCT00872469](#) (initially registered 31/03/2009, WOMAN-ETAC included on 22/03/2012).

Keywords

Postpartum Haemorrhage, Fibrinolysis, Coagulation, Tranexamic Acid, Randomised Controlled Trial, Thromboelastogram

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Kuti M: Conceptualization, Data Curation, Methodology, Project Administration, Writing – Review & Editing; **Olayemi OO:** Conceptualization, Methodology, Project Administration, Writing – Review & Editing; **Bello A:** Conceptualization, Data Curation, Methodology, Writing – Review & Editing;

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Aimakhu C: Conceptualization, Data Curation, Writing – Review & Editing; **Okunade OA:** Data Curation, Writing – Review & Editing; **Olutogun T:** Data Curation, Writing – Review & Editing; **Adetayo CO:** Data Curation, Writing – Review & Editing; **Dallaku K:** Data Curation, Writing – Review & Editing;

Mansmann U: Data Curation, Writing – Review & Editing; **Hunt BJ:** Data Curation, Writing – Review & Editing; **Pepple T:** Data Curation, Writing – Review & Editing; **Balogun E:** Project Administration, Writing – Review & Editing

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List of abbreviations

APTT	activated partial thromboplastin time
ETAC	Effect of Tranexamic Acid on Coagulation
INR	International Normalized Ratio
MCF	maximum clot firmness
ML	maximum clot lysis
PPH	postpartum haemorrhage
PT	prothrombin Time
ROTEM	rotational thromboelastometry
SD	standard deviation
TXA	tranexamic acid
WOMAN Trial	World Maternal Antifibrinolytic Trial

Introduction

Primary postpartum haemorrhage (PPH) is the leading cause of maternal death worldwide, responsible for an estimated 100,000 deaths each year¹⁻³. Most of the deaths occur within the first 2–3 hours after giving birth and almost all (99%) are in low- and middle-income countries, with Sub-Saharan Africa accounting for the majority^{4,5}.

Tranexamic acid (TXA) reduces bleeding by inhibiting the breakdown of fibrin and fibrinogen by the enzyme plasmin⁶. The WOMAN trial showed that TXA reduces death due to bleeding in women with PPH by about one-fifth. When given within 3 hours of giving birth it reduces maternal death due to bleeding by around one-third⁷. In trauma, TXA also reduces death due to bleeding by about one-third in patients treated within 3 hours of injury⁸. However, when given after 3 hours, there is no apparent benefit⁹. Early activation of fibrinolysis is common after trauma and is associated with increased mortality, and early administration of TXA in these patients inhibits fibrinolysis and reduces mortality¹⁰. Early activation of fibrinolysis is also observed after childbirth¹¹. Within an hour of giving birth, there is a doubling of the plasma concentration of tissue plasminogen activator¹⁰. Thereafter, the concentration falls rapidly¹¹. Active PPH is associated with an early increase in levels of D-dimer and plasmin-anti-plasmin complexes¹².

We conducted a randomised double blind placebo controlled trial (Effect of Tranexamic Acid on Coagulation, ETAC) to examine the effect of TXA on fibrinolysis and coagulation in women with PPH at the University College Hospital, Ibadan, Nigeria. We hypothesised that TXA would reduce fibrin clot breakdown (fibrinolysis) thus reducing the severity of bleeding and the risk of death.

Methods

The aims and methods of the WOMAN¹³ and the ETAC¹⁴ trials are described in detail elsewhere. Briefly, adult women with clinically diagnosed primary PPH after vaginal or caesarean delivery were eligible Ref 7 & 13 for inclusion.

Intervention

After the appropriate consent procedure was completed, each woman was randomly allocated to receive 1 g TXA or matching

placebo by intravenous injection. If bleeding continued after 30 min, or if bleeding stopped and restarted within 24 h, a second dose of 1 g of TXA or placebo was given. We collected patient entry and outcome data as per the WOMAN trial protocol¹³.

Participants and blood sampling

WOMAN trial participants at University College Hospital, Ibadan, Nigeria were also considered for inclusion in the ETAC trial. In addition to the WOMAN trial procedures, women had 15 ml venous blood taken after randomisation and before administration of the first dose of trial treatment. A second venous blood sample of about 15 ml was taken 30 (± 15) min after the first dose and before a second dose was given.

Sample analysis

We divided each venous blood sample into three vacutainer tubes. We collected one 5 ml sample in a tube containing potassium EDTA for full blood count analysis and two 4.5 ml samples in tubes containing 0.5 ml sodium citrate (0.109 mol/l) for coagulation and rotational thromboelastometry (ROTEM). We used a five-parameter particle counter Sysmex KN analyser (Sysmex Corporation, Kobe, Japan) for the full blood count analysis.

After centrifuging the blood at 3000g for 20 min, we extracted the plasma without disturbing the buffy coat layer, and measured prothrombin time (PT), activated partial thromboplastin time (APTT), Clauss fibrinogen and D-dimers using a HumaClot Junior automated coagulation analyser. We measured ROTEM parameters at 37°C using two of the four channels (EXTEM, APTEM) of the ROTEM coagulation analyser (TEM®, Munich, Germany)). The ROTEM was allowed to run for 60 min. The following ROTEM variables were examined from the EXTEM and APTEM traces: clotting Time), clot amplitude at 5 and 10 min (CA-t), maximum clot firmness (MCF), maximum clot lysis (ML) and lysis index (LI). We stored the ROTEM reagents at 2–8°C with temperature monitoring and we used in-date reagents. The clinical staff had no access to the results of ROTEM analysis carried out for the ETAC trial.

In addition, we collected the following information: time of blood samples, time the trial treatment was administered, time laboratory analysis started and ended, any treatment given that may affect coagulation, adverse events, and technical problems with analysis.

Analyses

We published a statistical analysis plan before the allocation was unblinded¹⁴. We assumed that D-dimer mean and standard deviation in the control group would be 9,000 ng/ml and 7,200 ng/ml, respectively. Taking into account that we would adjust for baseline measurement and assuming a correlation between baseline and follow-up of 0.4, we estimated that a study with about 180 patients would have 90% power (two-sided $\alpha=5\%$) to detect a reduction of 30% in the mean D-dimer value in the tranexamic group.

We conducted a per-protocol analysis that included all participants who satisfied the eligibility criteria, received the allocated treatment, had follow up samples and at least one measurement

of the primary outcome. We did not exclude outliers or impute missing data as it would be inappropriate in a study aimed at understanding the biological effects of TXA.

Outcomes

We assessed the effect of TXA on fibrinolysis by assessing D-dimer and ML as our co-primary outcome. For each co-primary outcome, we compared the follow up results of each treatment group (t-test).

Our secondary outcomes included INR, PT, APTT, fibrinogen, haemoglobin and the following ROTEM EXTEM parameters: clotting time (CT), clot amplitude at 5 (A5) and 10 min (A10), LI at 30 and 60 min and MCF. We compared the mean follow-up result in women receiving TXA and those receiving placebo using the t-test. We also compared follow-up results of each treatment group using linear regression, adjusting for the corresponding baseline measurement.

Statistical analysis

The effect of TXA on our co-primary outcomes, D-dimer and maximum lysis, were explored stratified by time since delivery, type of delivery, cause of postpartum haemorrhage and maternal anaemia. A t-test was conducted to compare means between treatment arms, and the likelihood ratio test was used to test for interaction between subgroups. We defined hyperfibrinolysis as $ML > 15\%$ on ROTEM EXTEM and coagulopathy as an $INR > 1.2$ and $A5 \leq 40$ mm. We used logistic regression to assess multivariate odds ratios between baseline variables and hyperfibrinolysis and coagulopathy. Stata 15 was used for all statistical analyses¹⁵.

To set the results of the ETAC study in context of an almost identical haematological sub-study conducted within the WOMAN trial but in a different location (Albania) and provide a more robust estimate of the effect of TXA on D-dimer, we conducted a meta-analysis of the two studies. Data from the ETAC trial and ETAPlaT (a single centre sub-study of the WOMAN trial) were pooled. Eligibility criteria for both trials were the same and blood samples were collected for D-dimer in the same way in both trials¹⁶. We computed the pooled ratio of D-dimers in women receiving TXA compared to women receiving placebo. We log-transformed individual patient data for D-dimer, and calculated the arithmetic mean (SD) of the log-transformed values for each study. A meta-analysis of the arithmetic means of transformed data gives a mean difference, which after back-transforming, corresponds to a meta-analysis of the ratio of geometric means in the original scale. Statistical heterogeneity was examined by visual inspection of forest plots, the I^2 statistic and χ^2 test. This analysis was not included in the statistical analysis plan for the ETAC trial.

Ethical approval and consent to participate

The trial was conducted in accordance with the ICH-GCP¹⁷. Approvals were obtained from the Ethics Committees of London school of Hygiene and Tropical Medicine (Reference A275 5536) and the University of Ibadan & University College Hospital Ethics Committee (Reference UI/EC/09/0131).

Regulatory approval was obtained from the Nigerian National Agency for Food and Drug Administration and Control.

The consent procedures are described in detail in the WOMAN Trial protocol¹³. In summary, consent was obtained from women if their physical and mental capacity allowed. If a woman was unable to give consent, proxy consent was obtained from a relative or representative. If a proxy was unavailable, then consent was deferred or waived. When consent was deferred or given by a proxy, the woman was informed about the trial as soon as possible, and consent obtained for on-going data collection, if needed.

Results

Participation

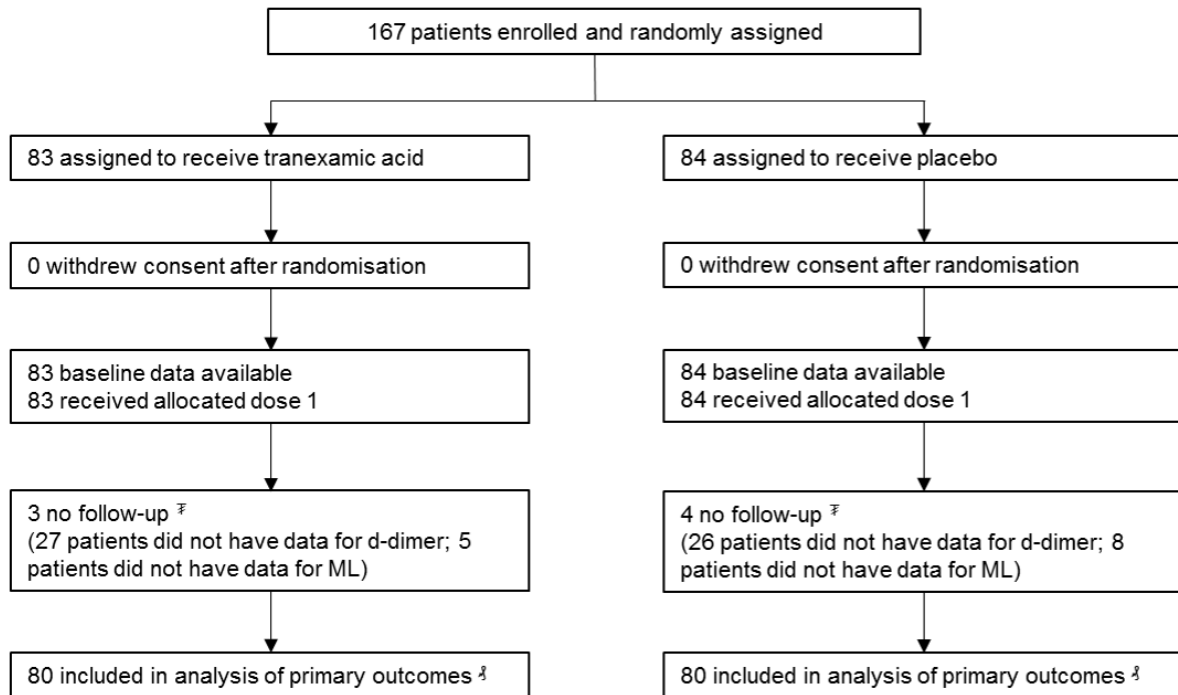
The ETAC trial recruited patients from April 2012 to March 2016. A total of 205 women were recruited into the WOMAN trial at University College Hospital, Ibadan during this period of whom 167 were included in the ETAC trial. The planned sample size of 180 participants was not reached due to occasional equipment failures and interruptions in the supply of reagents. Participants were randomly assigned to receive TXA (n=83) or placebo (n=84). All participants received the first dose of the allocated treatment, and no one withdrew their consent. Data on both co-primary outcomes were missing for 7 women, and they were excluded from the primary analysis. The CONSORT flow diagram is shown in [Figure 1](#). The dataset generated for this study is available online following registration¹⁸.

Participant characteristics

[Table 1](#) reports baseline characteristics of trial participants by treatment group. A total of 128 (77%) gave birth in the hospital, whereas 39 (23%) gave birth in other settings and were admitted to hospital after PPH onset. Age and systolic blood pressure were normally distributed; all other continuous variables had a skewed distribution. Therefore, we present means, medians and interquartile ranges for all variables. The mean ROTEM CT at baseline was higher in women randomised to TXA (180 s) compared to placebo (78 s). All other baseline parameters were similar between the two treatment arms.

Follow-up venous blood was collected at 31 (6) (mean (SD)) minutes after administration of TXA or matching placebo and all samples were obtained before a second dose was given. The mean (SD) time between treatment and collection of the follow up blood sample was 30 (4) min in the TXA arm and 33 (8) minutes in the placebo arm.

The effect of TXA on fibrinolysis and coagulation is reported in [Table 2](#). The mean (SD) D-dimer level after treatment was 7.1 (7.0) mg/l in women receiving TXA and 9.6 (8.6) in women receiving the placebo. After adjusting for baseline D-dimer level, the difference in mean D-dimer between women receiving TXA and placebo was -2.16 (95% CI: -4.31 to 0.00, p=0.05). There was no significant difference in ML between TXA- and placebo-treated women (12.3% (18.4) and 10.7% (12.6), respectively; p = 0.52) and no significant difference after adjusting for baseline ML (1.02, 95% CI -3.72 to 5.77, p= 0.67).



¶ 3 patients allocated to TXA and 4 patients allocated to placebo did not have data for both primary outcomes, d-dimer and maximum lysis (ML).

§ All 167 patients were included in description of baseline characteristics and analysis of secondary outcomes.

Figure 1. Consort diagram.

Table 1. Baseline characteristics by treatment group (N=167).

	TXA (N = 83)			Placebo (N = 84)		
	n ^a	Mean (SD)/ count (%)	Median (IQR)	n ^a	Mean (SD)/ Count (%)	Median (IQR)
Age	83	32.1 (5.8)	32 (29, 36)	84	31.6 (5.4)	31 (28, 35)
>35 years		28 (33.7%)			21 (25.0%)	
Time since delivery	83	4.5 (6.2)	1.7 (0.8, 6.3)	84	3.9 (4.5)	1.9 (0.9, 5.0)
≤3 hours		52 (62.7%)			51 (60.7%)	
>3 hours		31 (37.3%)			33 (39.3%)	
Type of delivery	83			84		
Vaginal		37 (44.6%)			43 (51.2%)	
Caesarean section		46 (55.4%)			41 (48.8%)	
Delivery in randomising hospital	83			84		
Yes		62 (74.7%)			66 (78.6%)	
No		21 (25.3%)			18 (21.4%)	
Cause of Haemorrhage	83			84		
Uterine Atony		41 (49.4%)			33 (39.3%)	
Other		42 (50.6%)			51 (60.7%)	
Systolic blood pressure (mmHg)	83	108.2 (26.7)	110 (90, 120)	83	111.7 (27.4)	110 (90, 130)
<90 mmHg		17 (20.5%)			14 (16.9%)	

	TXA (N = 83)			Placebo (N = 84)		
	n ^a	Mean (SD)/ count (%)	Median (IQR)	n ^a	Mean (SD)/ Count (%)	Median (IQR)
Blood loss volume	83	1638.9 (1016.9)	1300 (1000, 2000)	84	1423.8 (751.7)	1200 (825, 1950)
>1000 ml		56 (67.5%)			52 (61.9%)	
Clinical signs of shock	83			84		
Yes		54 (65.1%)			51 (60.7%)	
No		29 (34.9%)			33 (39.3%)	
Full Blood Count Variables						
Haemoglobin (g/l)	65	72.6 (32.6)	72 (55, 95)	67	83.4 (37.8)	84 (63, 100)
<110 g/l		59 (90.8%)			57 (85.1%)	
White cell count (x10 ⁹ /l)	66	12.2 (7.6)	11.5 (6, 17.3)	65	11.7 (8.7)	10.7 (5.3, 15.4)
Platelet count (x10 ⁹ /l)	65	151.6 (114.9)	126 (84, 203)	65	158.9 (87.2)	161 (86, 212)
Coagulation Variables						
INR	67	1.6 (1.4)	1.2 (1, 1.6)	70	1.4 (0.8)	1.1 (1.0, 1.3)
INR>1.2		33 (49.3%)			24 (34.3%)	
PT (s)	67	20.5 (15.6)	15.8 (13.5, 19.8)	70	17.6 (8.6)	14.8 (13.5, 16.8)
APTT (s)	64	36.4 (24.7)	29.9 (26.8, 37.0)	69	35.4 (21.3)	30.7 (27.1, 33.5)
Fibrinogen (g/l)	66	8.9 (7.1)	7.2 (3.2, 12.7)	70	8.0 (6.1)	6.0 (3.3, 11.9)
D-dimer (mg/l)	59	7.7 (8.6)	4.3 (1.5, 11.1)	60	9.5 (7.7)	6.8 (3.4, 15.2)
Thromboelastometry (ROTEM® EXTEM) variables						
CT (seconds)	73	179.9 (469.9)	54 (45, 82)	78	78.3 (97.5)	54.5 (45, 68)
ML (%)	72	17.0 (25.0)	9 (4, 18)	78	12.6 (14.9)	9 (4, 14)
ML>15%		20 (27.8%)			15 (19.2%)	
A5 (mm)	69	39.4 (18.0)	44 (29, 52)	77	44.6 (13.2)	48 (38, 53)
A5<40		28 (40.6%)			21 (27.3%)	
A10 (mm)	72	48.2 (20.5)	55 (39, 63)	77	54.7 (13.6)	59 (51, 63)
LI30 (%)	68	96.5 (15.6)	100 (100, 100)	77	99.3 (1.8)	100 (100, 100)
LI60 (%)	46	93.7 (11.6)	97.5 (92, 99)	55	93.0 (8.7)	95 (91, 99)
MCF (mm)	69	56.1 (20.6)	64 (51, 70)	77	62.0 (13.6)	65 (61, 69)

^aNumber of women with available data. ^bTwo women in the tranexamic acid arm had outlying ROTEM EXTEM clotting time values of 1814 and 3468 seconds. TXA, tranexamic acid; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial prothromboplastin time; CT, clotting time; ML, maximum lysis; A5, clot amplitude at 5 min; LI30, lysis index at 30 min; MCF, maximum clot firmness.

There were no significant effects of TXA on any other parameters. There were no adverse events associated with this sub-study reported.

There was no evidence of heterogeneity in the effect of TXA on fibrinolysis (D-dimer and ML) by time since delivery, type of delivery, cause of haemorrhage and severity of anaemia.

Discussion

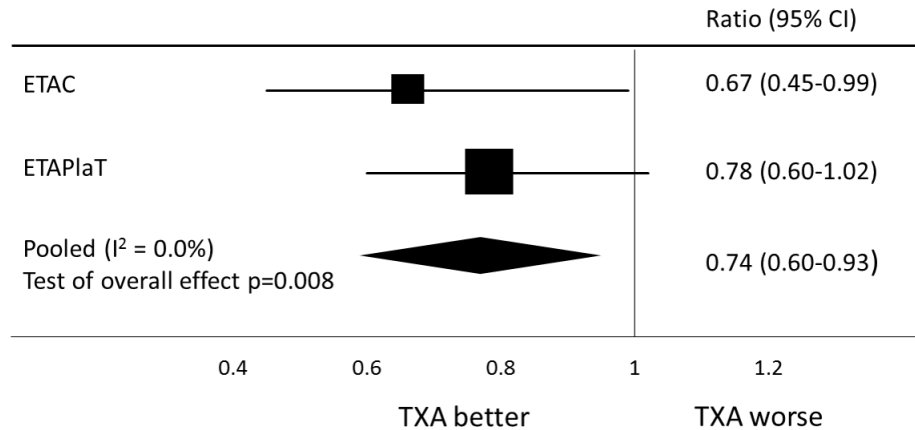
TXA treatment was associated with reduced D-dimer levels, but had no apparent effects on ROTEM parameters or coagulation

tests. The effect of TXA on D-dimer levels in this study is similar to that observed in an almost identical WOMAN trial sub-study that aimed to assess the effects of TXA on platelet function (ETAPLAT-study)¹⁶. The eligibility criteria for both studies were the same and blood samples for D-dimer were collected in the same way. When the results of the two sub-studies are pooled in a meta-analysis (Figure 2), there is a 26% reduction in D-dimer levels with TXA (pooled D-dimer ratio 0.74, 95% CI 0.60 to 0.93, p=0.008). These results concur with a study in France that showed the early increase in D-dimer values in women with PPH can be inhibited by TXA¹¹.

Table 2. Effect of tranexamic acid (TXA) on coagulation and fibrinolysis in women with postpartum haemorrhage.

	n	TXA	n	Placebo	Difference (95% CI)	p-value†	Baseline adjusted difference (95% CI)*	p-value‡
		Mean (SD)		Mean (SD)				
Primary outcomes								
D-dimer (mg/l)	56	7.1 (7.0)	58	9.6 (8.6)	-2.5 (-5.4, 0.4)	0.09	-2.2 (-4.3, 0.0)	0.05
ML (%)	78	12.3 (18.4)	76	10.7 (12.6)	1.6 (-3.4, 6.7)	0.52	1.0 (-3.7, 5.8)	0.67
Secondary outcomes								
INR	71	1.6 (1.8)	70	1.2 (0.4)	0.4 (-0.1, 0.8)	0.09	0.4 (-0.1, 0.9)	0.11
PT (s)	71	18.5 (15.6)	70	15.8 (4.7)	2.7 (-1.1, 6.5)	0.17	2.5 (-1.6, 6.6)	0.22
APTT (s)	71	36.3 (20.7)	69	33.2 (12.6)	3.0 (-2.7, 8.8)	0.30	1.0 (-3.9, 5.8)	0.69
Fibrinogen (g/l)	68	8.8 (6.1)	69	8.8 (6.5)	-0.03 (-2.2, 2.1)	0.98	-1.1 (-2.3, 0.2)	0.08
Haemoglobin (g/l)	71	75.4 (30.9)	67	83.2 (31.1)	-7.8 (-18.3, 2.6)	0.14	-1.0 (-8.8, 6.8)	0.79
Thromboelastometry (ROTEM® EXTEM)								
CT (s)	78	151.3 (528.4)	77	104.7 (385.9)	46.6 (-100.4, 193.6)	0.53	-8.8 (-150.1, 132.4)	0.90
A5 (mm)	75	39.5 (16.7)	76	45.3 (12.9)	-5.8 (-10.6, -1.0)	0.02	-2.0 (-5.7, 1.7)	0.27
A10 (mm)	78	49.6 (18.1)	76	55.3 (13.1)	-5.7 (-10.8, -0.7)	0.03	-1.7 (-5.9, 2.5)	0.41
LI30 (%)	71	98.3 (11.3)	75	99.2 (3.6)	-0.8 (-3.5, 1.9)	0.54	-0.9 (-3.9, 2.0)	0.52
LI60 (%)	49	93.6 (13.0)	49	93.3 (11.5)	0.2 (-4.7, 5.2)	0.92	-0.3 (-5.6, 4.9)	0.90
MCF (mm)	72	57.4 (18.1)	70	62.6 (11.1)	-5.2 (-10.2, -0.2)	0.04	-1.8 (-6.2, 2.5)	0.40

†p-value from t-test. *Adjusted for the corresponding baseline parameter e.g. effect of TXA on D-dimer adjusted for pre-treatment D-dimer values. ‡p-value from likelihood ratio test (linear regression). INR, international normalized ratio; PT, prothrombin time; APTT, activated partial prothromboplastin time; CT, clotting time; A5, clot amplitude at 5 min; LI30, lysis index at 30 min; MCF, maximum clot firmness.

**Figure 2.** Forest plot of the effect of tranexamic acid (TXA) on D-dimer values in women with postpartum haemorrhage.

Although we planned to include 180 women in our study, due to equipment and power failures, and interruptions in the supply of reagents, only 167 women were recruited. Power cuts are common in Nigeria and although back-up power packs were supplied with the ROTEM delta analyser, these also failed on occasions. ROTEM reagents have a short shelf-life and were

sourced in Europe since they are not readily available in Nigeria. Moreover, due to technical problems with blood samples or measurement instruments, the number of women with useable outcome data was less than the number of women enrolled. As a result, the power of the study to detect differences between treatment arms was lower than anticipated.

This lack of power may at least partially explain the absence of any significant effects of TXA on thromboelastometry parameters and coagulation tests.

Increased fibrinolysis is common in women with PPH¹⁹. Our results show that this increase can be inhibited with TXA. Larger studies into the effects of TXA on fibrinolysis and coagulation in women with or at risk from PPH are required.

Data availability

The anonymised trial data is available from the freeBIRD data portal at <https://ctu-app.lshtm.ac.uk/freebird/index.php/data-sharing/downloads/woman-etac/> following free registration: <http://dx.doi.org/10.17037/DATA.00000788>¹⁸. Data are available under an [Open Data Commons Attribution License \(ODC-By\) licence](#).

The trial protocol, statistical analysis plan and trial publications will be made freely available at <http://www.txacentral.org/> and <http://womantrial.lshtm.ac.uk/>

Author contributions

I.R. and H.S-S. conceived the study, contributed data cleaning, statistical analysis and writing of the manuscript. B.F. contributed to protocol development and had overall responsibility for the study at the trial site and review of the manuscript. O.O.O. contributed to protocol development and is the site principal investigator for WOMAN trial and review of the manuscript. M.K. contributed to the protocol development and was responsible for overseeing laboratory tests, laboratory standard operating procedures and staff training and review of the manuscript. A.B. contributed to protocol development and was responsible for data transfer and review of the manuscript. O.O. contributed to the protocol development, development of the standard operating procedures and was responsible for participant recruitment and review of the manuscript. C. A. contributed to the protocol development and was responsible

for participant recruitment and review of the manuscript. T.K. contributed to the protocol development and was responsible for routine laboratory tests and review of the manuscript. B.J.H. contributed to data cleaning and writing of the manuscript. S.H. conducted the statistical analysis and contributed to the writing of the manuscript. T.O. was responsible for overseeing laboratory tests, laboratory standard operating procedures and staff training and review of the manuscript. B.J.H. contributed to data cleaning and contributed to the writing of the manuscript, T.O., O.A.O. and C.O.A. carried out some laboratory tests and review of the manuscript, T.P. and E.B. assisted with data management and review of the manuscript.

All authors have read and approved the final version of the manuscript.

Competing interests

No competing interests were disclosed.

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Supplementary information

Supplementary File 1. Completed CONSORT checklist.

[Click here to access the data.](#)

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Current Referee Status:  

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Referee Report 24 September 2018

doi:[10.21956/wellcomeopenres.16038.r33855](https://doi.org/10.21956/wellcomeopenres.16038.r33855)



Stanislas Grassin-Delyle 

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Shakur-Still and colleagues investigated the effect of tranexamic acid on fibrinolysis and coagulation parameters in women with primary postpartum haemorrhage. The study was a randomised double-blind placebo-controlled trial and the inclusion criteria were the same as in the WOMAN clinical trial previously published by this team. Female participants were randomized to receive 1g intravenous tranexamic acid or placebo, and blood samples were taken before administration and 30 minutes later to assess coagulation and fibrinolysis parameters. On these samples, the results show a lower D-dimer concentration in the treated group than in the placebo group, after correction of the baseline concentration. These results are confirmed by the presentation of a meta-analysis including the results of a similar study conducted in another centre. This work is remarkable for the implementation of specialized methods of off-site biology under non-ideal conditions. The study is very well conducted and all methods and results are clearly reported. This study provides additional evidence on the action of tranexamic acid on fibrinolysis, which is the main mechanism involved in reducing bleeding and mortality. This work therefore further strengthens the interest in tranexamic acid for the treatment of haemorrhagic diseases, even if its pharmacology remains poorly known, in particular the optimal dose and administration method.

One of the technical aspects that could be clarified concerns the taking of blood samples. Each 15 ml sample was divided into three fractions: one 5 ml sample in a tube containing potassium EDTA for full blood count analysis and two 4.5 ml samples in tubes containing 0.5 ml sodium citrate for coagulation and rotational thromboelastometry. It would be interesting to know the nature of the primary tube used for sampling and the time frame within which the distribution between the three tubes was then carried out, in order to be able to assess the risk of initial coagulation activation.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 13 September 2018

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Summary: This article by Shakur-Still et al. studies the coagulation markers affected by tranexamic acid administration to women with clinically diagnosed postpartum hemorrhage using traditional and newer methods of laboratory analysis. This is a timely study as very limited data exists what happens in women with actual diagnosed postpartum hemorrhage and their coagulation parameters with and without antifibrinolytic therapy.

Introduction:

While it is true that coagulation parameters are affected after childbirth, as described, the wrong citation is provided for the statement 'within an hour of giving birth, there is a doubling of the plasma concentration of tissue plasminogen activator'.

Statistical analysis:

Would be prudent to provide the citation/rationale for using $ML > 15\%$ as 'hyperfibrinolysis' as well as the other parameters/values cited.

Results:

Would be good to cite original trial methods or briefly describe randomization scheme employed for who got TXA versus placebo.

Table 1-Please provide statistical statement specifically how baseline parameters were similar (i.e. $p > 0.05$) either in text or footnote other than the baseline CT values.

When making the statement 'no evidence of heterogeneity in the effect of TXA on fibrinolysis by time since delivery, etc' please provide actual data/analysis to support this finding.

Although the authors state no outlier was excluded, it may be worth examining in a subgroup analysis or sensitivity analysis what the ROTEM parameter differences would be if the outlier groups were not included - for example in the footnote in table 1 it states CT values for two women were 1814 and 3468

seconds. This either means the test was run in error by the user or that the coagulopathy makes it difficult to interpret ML parameter.

Also, where these two women (from Table 1 in the footnote) included for the final comparison for ML?

Also one other key question is if the CONSORT flow chart states 80 women were included for primary outcome analysis - why are only 56/58 women shown data for d-dimer values in Table 2? Also it is interesting that only 49 patients per group were included for the LI60%. Were there technical issues that made it not possible to report out the LI60% parameter - if so then that could mean the ML parameter may also be less reliable.

If these are correct interpretations, please include in limitations section of discussion.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
