ORIGINAL ARTICLE

Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery

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ABSTRACT

BACKGROUND

The use of tranexamic acid reduces mortality due to postpartum hemorrhage. We investigated whether the prophylactic administration of tranexamic acid in addition to prophylactic oxytocin in women with vaginal delivery would decrease the incidence of postpartum hemorrhage.

METHODS

In a multicenter, double-blind, randomized, controlled trial, we randomly assigned women in labor who had a planned vaginal delivery of a singleton live fetus at 35 or more weeks of gestation to receive 1 g of tranexamic acid or placebo, administered intravenously, in addition to prophylactic oxytocin after delivery. The primary outcome was postpartum hemorrhage, defined as blood loss of at least 500 ml, measured with a collector bag.

RESULTS

Of the 4079 women who underwent randomization, 3891 had a vaginal delivery. The primary outcome occurred in 156 of 1921 women (8.1%) in the tranexamic acid group and in 188 of 1918 (9.8%) in the placebo group (relative risk, 0.83; 95% confidence interval [CI], 0.68 to 1.01; P=0.07). Women in the tranexamic acid group had a lower rate of provider-assessed clinically significant postpartum hemorrhage than those in the placebo group (7.8% vs. 10.4%; relative risk, 0.74; 95% CI, 0.61 to 0.91; P=0.004; P=0.04 after adjustment for multiple comparisons post hoc) and also received additional uterotonic agents less often (7.2% vs. 9.7%; relative risk, 0.75; 95% CI, 0.61 to 0.92; P=0.006; adjusted P=0.04). Other secondary outcomes did not differ significantly between the two groups. The incidence of thromboembolic events in the 3 months after delivery did not differ significantly between the tranexamic acid group and the placebo group (0.1% and 0.2%, respectively; relative risk, 0.25; 95% CI, 0.03 to 2.24).

CONCLUSIONS

Among women with vaginal delivery who received prophylactic oxytocin, the use of tranexamic acid did not result in a rate of postpartum hemorrhage of at least 500 ml that was significantly lower than the rate with placebo. (Funded by the French Ministry of Health; TRAAP ClinicalTrials.gov number, NCT02302456.)

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Postpartum hemorrhage is a major cause of maternal death and severe maternal complications after childbirth.[1] Currently, the prophylactic administration of a uterotonic agent immediately after delivery is recommended for all women[2] as the only procedure that has been proved to reduce rates of postpartum hemorrhage.[3,4] Tranexamic acid, an antifibrinolytic agent,[5] reduces the incidence of bleeding in elective surgery[6,7] and mortality among patients with trauma,[8] without increasing the incidence of vascular occlusive events, and is consequently recommended in these situations.[9,10]

Tranexamic acid was recently shown to reduce bleeding-related mortality among women with postpartum hemorrhage, especially when the drug was administered shortly after delivery.[11] A meta-analysis of data from individual patients,[12] including data from patients with trauma[8] and women with postpartum hemorrhage,[11] suggested the importance of early treatment. Every 15-minute delay in administration was associated with a reduction of approximately 10% in the benefit against bleeding-related deaths, and no significant benefit was noted when the drug was administered more than 3 hours after delivery. These findings suggest that tranexamic acid be considered as an intervention not only to treat but to prevent postpartum coagulopathy,[12] but evidence to support a prophylactic effect on postpartum hemorrhage is weak.

Several randomized, controlled trials, mostly involving women undergoing cesarean delivery, have shown that the prophylactic intravenous administration of 1 g of tranexamic acid after childbirth reduced blood loss.[5] Most were small, single-center trials with considerable methodologic limitations.[5,13-18] Moreover, they assessed the risk of adverse events only until hospital discharge, although the excess risk of thrombotic complications (as compared with nonpregnant women) persists through 12 weeks after delivery.[19] Thus, no guidelines advocate the use of tranexamic acid to prevent blood loss after vaginal delivery.[2,20-22] We designed this trial to investigate whether the administration of tranexamic acid in addition to a prophylactic uterotonic agent (oxytocin) would decrease the incidence of postpartum hemorrhage after vaginal delivery, as compared with a uterotonic agent alone.

Methods

Trial Design and Oversight

The Tranexamic Acid for Preventing Postpartum Hemorrhage Following a Vaginal Delivery (TRAAP) trial was a multicenter, randomized, placebo-controlled, double-blind trial with two parallel groups. Women who were scheduled to undergo vaginal delivery were randomly assigned to receive tranexamic acid or placebo immediately after delivery, along with the administration of a uterotonic agent. Details of the rationale and design of the trial have been published previously.[23]

The trial protocol (available with the full text of this article at NEJM.org) was approved by the Ouest II Committee for the Protection of Research Subjects and the French Health Products Safety Agency. The funder (the French Ministry of Health) had no role in the design and conduct of the trial; the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. The first and last authors take responsibility for the accuracy and completeness of the data and analyses and vouch for the fidelity of the trial to the protocol and statistical analysis plan. No company or manufacturer was involved in the trial.

Participants

Eligible participants were women 18 years of age or older who had a singleton pregnancy at 35 weeks 0 days of gestation or more and who were planning to undergo vaginal delivery. Women were recruited at 15 maternity units in French hospitals. Women with a known or possible increased risk of venous or arterial thrombosis or bleeding or who had a condition potentially impairing initial hemostasis, a history of epilepsy or seizure, or poor comprehension of oral French were excluded. (A detailed list of the exclusion criteria is provided in Table S1 in the Supplementary Appendix, available at NEJM.org.) Obstetricians, midwives, and anesthesiologists provided women with information about the trial during late-pregnancy prenatal visits. Women confirmed participation at the labor ward and provided written informed consent when the investigator considered that vaginal delivery was likely (≥4 cm of cervical dilation).

RANDOMIZATION AND PROCEDURES

Eligible women were randomly assigned in a 1:1 ratio to receive 1 g of tranexamic acid (purchased at full cost from Sanofi Aventis) or placebo (normal saline, Fresenius Kabi), administered intravenously. Randomization was performed by means of a computer-generated code that produced permuted blocks of randomly varying sizes, stratified according to trial site. The randomization procedure was supervised by the Angers Clinical Research Unit and transmitted to the PPRIGO (Production Pharmaceutique pour la Recherche Institutionnelle du Grand Ouest) hospital pharmacists' consortium, which prepared the blinded ampules. Tranexamic acid and placebo were prepared at a single site in numbered and labeled boxes, each containing a 10-ml vial of the trial regimen (1 g of tranexamic acid or placebo, depending on randomization number). All the boxes and vials were identically labeled, and only the randomization number differentiated the packs. Neither the participants nor the investigators were aware of the trial-group assignments.

The intravenous trial regimen was administered slowly (over a period of 30 to 60 seconds) during the 2 minutes after delivery, after the routine prophylactic intravenous injection of oxytocin at delivery of the anterior shoulder[20] and clamping of the umbilical cord. All other aspects of managing the third stage of labor were identical in the two groups and adhered to the national guidelines issued by the French College of Gynecologists and Obstetricians.[20] A graduated bag (with 100-ml graduations) to collect and measure postpartum vaginal blood loss objectively[24-26] was placed just after delivery and remained in place for at least 15 minutes and until the birth attendant considered that the bleeding had stopped. Adverse events were assessed in all the women until hospital discharge and by means of a telephone interview at 3 months post partum.

TRIAL OUTCOMES

The primary outcome was postpartum hemorrhage, defined as blood loss of at least 500 ml, as measured with the collector bag,[24,27] in all the women during immediate postpartum surveillance in the delivery room. Secondary outcome measures describing postpartum blood loss were the following: blood loss measured at 15 minutes after delivery and at bag removal; the incidence of measured blood loss of more than 500 ml and of at least 1000 ml; the incidence of provider-assessed clinically significant postpartum hemorrhage (defined according to the provider's response to a self-administered questionnaire completed at the time of the woman's discharge from the labor ward by one unguided question: "Was there a PPH [postpartum hemorrhage]?"); total estimated blood loss; the proportion of women receiving supplementary uterotonic treatment; the incidence of postpartum transfusion (until discharge); the incidence of arterial embolization or emergency surgery for postpartum hemorrhage; hemodynamic variables (heart rate and blood pressure) at 15, 30, 45, 60, and 120 minutes after delivery; and peripartum changes in venous hemoglobin and hematocrit measurements (difference between these measurements before delivery and at day 2). An additional secondary outcome of blood loss of more than 500 ml, which had not been initially planned in the protocol, was added in the final statistical analysis plan before data unblinding owing to the possibility of a threshold effect in blood-loss reporting — that is, providers might be more likely to report a 500-ml loss rather than one slightly higher, because 500 ml is considered to be the line between a physiologic condition and a pathologic condition.[20]

Other outcomes included adverse events that were potentially related to tranexamic acid: nausea, vomiting, photopsia (sensation of seeing lights, sparks, or flashes of color), or dizziness in the delivery room; the prothrombin time, active prothrombin time, and levels of venous urea, creatinine, aspartate and alanine aminotransferases, total bilirubin, and fibrinogen on day 2; and postpartum thromboembolic events, seizure, kidney failure, and any other unexpected adverse event through 3 months (reported by the women after discharge and documented by means of review of medical files transmitted by the woman or her physician). Finally, women completed a self-administered questionnaire that had previously been used in the Traction of the Cord (TRACOR) trial[24] to evaluate maternal satisfaction on day 2 and another questionnaire that was mailed at 2 months to assess their psychological status with the use of scales including the Edinburgh Postnatal Depression Scale (EPDS).[28]

The midwife or obstetrician handling the delivery prospectively collected information about

the procedures that were used during the third stage of labor and clinical outcomes that were identified before discharge. A research assistant, who was independent of the local medical team, collected all the other data from medical charts. A data and safety monitoring committee met monthly to review safety data and yearly to review adherence to trial procedures. The quality of the outcome data was checked at each center in a random sample of 10% of the participants and in all the women who had postpartum hemorrhage.

STATISTICAL ANALYSIS

We based the expected primary-outcome rate in the placebo group on the results of previous studies, notably the TRACOR trial.[23,29] We estimated that 3628 women with a vaginal delivery would provide the trial with a power of at least 90% to detect a primary-outcome rate that was 30% lower in the active-intervention group than in the placebo group (7% in the tranexamic acid group vs. 10% in the placebo group), at a two-sided type I error of 5%. Given the expected percentage of women who would undergo cesarean section after randomization (estimated at 5 to 10% [6.8% in the TRACOR trial]),[24] we aimed to recruit 4000 women in order to include the necessary number of women with a vaginal delivery.

The main analysis of the primary and secondary outcomes was performed in the modified intention-to-treat population, which was defined as women who had undergone randomization and had a vaginal delivery (except for those who withdrew consent or were deemed to be ineligible after randomization). Women who had missing data for the primary outcome were to be excluded from the analysis of the primary outcome. We also analyzed two per-protocol populations: one included women from the modified intention-to-treat population who received oxytocin and then received tranexamic acid or placebo in the first 2 minutes after delivery (as prespecified in the protocol)[23] (per-protocol group 1); and the other included women from the modified intention-to-treat population who received oxytocin and then received tranexamic acid or placebo in the first 10 minutes after delivery (per-protocol group 2; this group was included in the final statistical analysis plan because this situation is more consistent with routine clinical practice).

Descriptive statistics were used to compare the baseline characteristics of the trial participants, the management of the third stage of labor, and adherence to the protocol. Quantitative variables were expressed, as appropriate, as means with standard deviations and compared by Student's t-test or as medians with interquartile ranges and compared by the Wilcoxon rank-sum test. Chi-square or Fisher's exact tests were used, as appropriate, to compare categorical variables. The effects of tranexamic acid were expressed as relative risks with 95% confidence intervals for categorical outcomes and as mean differences with 95% confidence intervals for quantitative outcomes. The results were also expressed as absolute risk differences with 95% confidence intervals for binary outcomes. Missing data for the primary outcome were imputed as failures in a secondary analysis.

Four prespecified subgroup analyses examined the primary outcome in subgroups of women who were at increased risk for postpartum hemorrhage. The subgroups included women who had a history of postpartum hemorrhage, those who received an episiotomy, those who had an operative vaginal delivery, and those who were at risk for postpartum hemorrhage according to a composite definition (having at least one risk factor with an odds ratio of 3 or greater in the literature[30]: previous postpartum hemorrhage, pregnancy-related hypertensive disorder, or episiotomy). To determine whether there was a significant effect of tranexamic acid on the primary outcome within the prespecified subgroups, we performed the Mantel–Haenszel interaction test in which a P value of less than 0.05 was considered to indicate statistical significance.

Our statistical analysis plan did not include a plan to adjust for multiple comparisons of secondary outcomes or subgroups, but we performed post hoc adjustment in these analyses using the Benjamini–Hochberg procedure.[31] We used Stata software, version 14.0 (StataCorp), for all the analyses.

RESULTS

TRIAL POPULATION

From January 2015 through December 2016, we recruited 4079 eligible participants and randomly assigned them to receive tranexamic acid (2040 women) or placebo (2039); 46 women were excluded because they were found after randomization to be ineligible or they withdrew consent. Of the remaining 4033 women (intention-to-treat

population), 142 had an intrapartum cesarean delivery, which resulted in a modified intention-to-treat population of 3891 women (1945 women in the tranexamic acid group and 1946 in the placebo group) (Fig. 1). The groups did not differ significantly with regard to baseline characteristics or adherence to the assigned intervention and other aspects of third-stage labor management (Table 1, and Table S2 in the Supplementary Appendix).

PRIMARY OUTCOME

Postpartum hemorrhage, defined as blood loss of at least 500 ml, as measured with a graduated collector bag, occurred in 156 of 1921 women (8.1%) in the tranexamic acid group and in 188 of 1918 (9.8%) in the placebo group (relative risk, 0.83; 95% confidence interval [CI], 0.68 to 1.01; P=0.07) (Table 2). Data on the primary outcome were missing for 24 women in the tranexamic acid group and for 28 in the placebo group because no collector bag was available. The effect of the intervention did not differ among centers. The analysis that used imputed data for missing values yielded similar results (Table S3 in the Supplementary Appendix).

The results of subgroup analyses are shown in Table 3. There were no significant differences regarding the effects of tranexamic acid according to the participants' type of vaginal delivery (operative or spontaneous), history of postpartum hemorrhage, presence or absence of episiotomy, or presence or absence of known risk factors for postpartum hemorrhage (P>0.05 for interaction for all comparisons).

SECONDARY OUTCOMES

The tranexamic acid group had lower rates than the placebo group for the following outcomes related to postpartum hemorrhage: provider-assessed clinically significant postpartum hemorrhage (7.8% vs. 10.4%; relative risk, 0.74; 95% CI, 0.61 to 0.91; P=0.004; P=0.04 after adjustment for multiple comparisons post hoc) and the use of additional uterotonic agents (7.2% vs. 9.7%; relative risk, 0.75; 95% CI, 0.61 to 0.92; P=0.006; adjusted P=0.04) (Table 2). Blood loss of more than 500 ml in the collector bag was also significantly less frequent in the tranexamic acid group than in the placebo group (6.6% vs. 8.8%; relative risk, 0.75; 95% CI, 0.60 to 0.94; adjusted P=0.046).

The two groups did not differ significantly with regard to mean postpartum blood loss or peripartum changes in the hemoglobin level or hematocrit (Table 2). The tranexamic acid group had significantly higher systolic, mean, or diastolic blood pressures than the placebo group at some time points between 0 and 120 minutes (Fig. S1 in the Supplementary Appendix), but there was no significant difference in the rate of women within the hypertensive range (Table 4).

ADVERSE EVENTS

The frequency of vomiting or nausea in the delivery room was higher in the tranexamic acid group than in the placebo group (7.0% vs. 3.2%, P<0.001), but no cases were graded as severe (Table 4). Women in the tranexamic acid group had higher mean liver aminotransferase levels than those in the placebo group, but there were no significant between-group differences in the proportions of women with levels above the clinically relevant threshold of twice the normal value or in the prothrombin time, active prothrombin time, fibrinogen level, total bilirubin level, or kidney-function tests measured on day 2 (Table S4 in the Supplementary Appendix).

Adverse events could be assessed at 3 months for 95% of the participants. The incidence of thromboembolic events during those months did not differ significantly between the tranexamic acid group and the placebo group (0.1% [1 of 1844 participants] and 0.2% [4 of 1849], respectively; relative risk, 0.25; 95% CI, 0.03 to 2.24; P=0.37) (Table 4).

MATERNAL SATISFACTION AND PSYCHOLOGICAL STATUS

Maternal satisfaction on day 2 did not differ significantly between the two groups, nor did the EPDS scores at 2 months. Details are provided in Table S4 in the Supplementary Appendix.

PER-PROTOCOL ANALYSES

Results in the two per-protocol populations did not differ materially from those in the modified intention-to-treat population. Details are provided in Tables S5 through S8 in the Supplementary Appendix.

DISCUSSION

In this trial involving women with vaginal delivery who received prophylactic oxytocin, the use

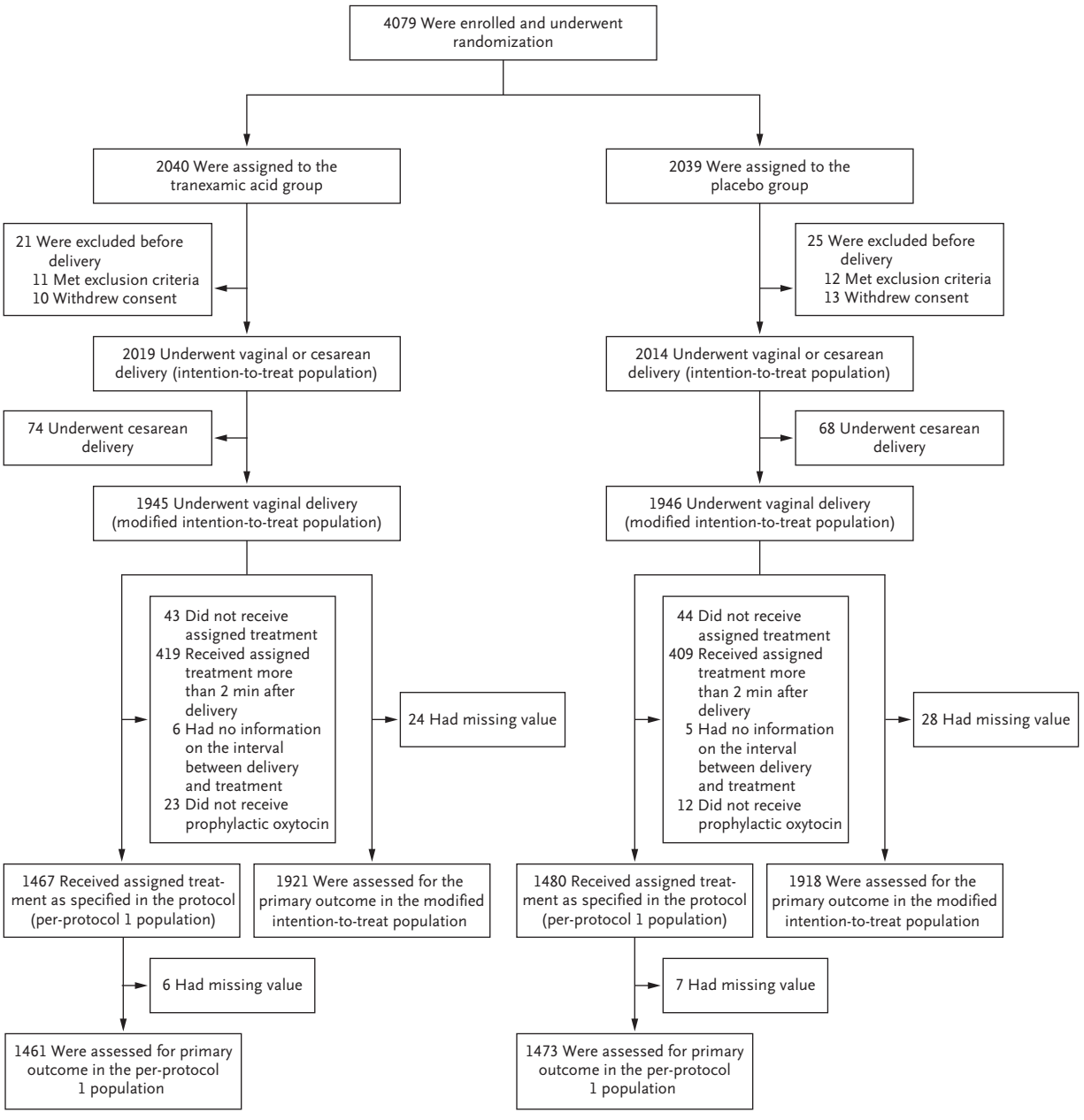

Figure 1. Randomization and Trial Populations.

A total of 24 women in the tranexamic acid group (including 6 women in the per-protocol 1 population) and 28 in the placebo group (including 7 in the per-protocol 1 population) had a missing value for the primary outcome because no collector bag was available. The population in the per-protocol 1 analysis was defined as women in the modified intention-to-treat population who received oxytocin and then received tranexamic acid or placebo within the first 2 minutes after delivery. A total of 13 women in the tranexamic acid group and 4 in the placebo group had more than one reason to be excluded from the per-protocol 1 population. (The per-protocol 2 population [data not shown] included women in the modified intention-to-treat population who received oxytocin and then received tranexamic acid or placebo within the first 10 minutes after delivery.)

Table 1. Characteristics of the Participants at Baseline and Management of the Third Stage of Labor (Modified Intention-to-Treat Population).*

Characteristic	Tranexamic Acid Group (N=1945)	Placebo Group (N=1946)
Age — yr	30.3±4.7	30.2±5.0
Non-French nationality — no./total no. (%)	161/1830 (8.8)	162/1824 (8.9)
Body-mass index before pregnancy†	23.3±4.4	23.5±4.6
Primiparous — no. (%)	1025 (52.7)	1048 (53.9)
Any uterine scar — no. (%)	122 (6.3)	114 (5.9)
Previous cesarean delivery — no. (%)	101 (5.2)	107 (5.5)
History of postpartum hemorrhage — no. (%)	92 (4.7)	85 (4.4)
Gestational diabetes — no. (%)	198 (10.2)	222 (11.4)
Gestational hypertensive disorder — no. (%)	37 (1.9)	47 (2.4)
Hospitalization during pregnancy >24 hr — no. (%)	106 (5.4)	103 (5.3)
Induction of labor — no. (%)	384 (19.7)	410 (21.1)
Epidural analgesia — no. (%)	1908 (98.1)	1900 (97.6)
Oxytocin during labor — no. (%)	1135 (58.4)	1171 (60.2)
Duration of active phase of labor — hr		
Median	2.3	2.3
Interquartile range	1.3–3.5	1.3–3.5
Operative vaginal delivery — no. (%)	346 (17.8)	332 (17.1)
Episiotomy — no. (%)	456 (23.4)	444 (22.8)
Perineal tear — no. (%)	1099 (56.5)	1119 (57.5)
Infant's birth weight ≥4000 g — no. (%)	165 (8.5)	142 (7.3)
Prophylactic oxytocin at delivery — no. (%)	1922 (98.8)	1934 (99.4)
Interval between delivery and administration of trial regimen — min		
Median	2	1
Interquartile range	1–2	1–2
Controlled traction of umbilical cord — no./total no. (%)	738/1735 (42.5)	742/1735 (42.8)
Duration of use of collector bag — min		
Median	26	27
Interquartile range	17–38	18–40

* Plus-minus values are means ±SD. There were no significant differences between the two groups. Data on the duration of the active phase of labor were missing for 206 women in the tranexamic group and for 197 in the placebo group; on the interval between delivery and administration of the trial regimen for 47 and 47, respectively; and on the duration of use of the collector bag for 109 and 112, respectively.

† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 16 women in the tranexamic acid group and for 19 in the placebo group.

of tranexamic acid did not result in a rate of the primary outcome — postpartum hemorrhage of at least 500 ml — that was significantly lower than the rate with placebo. On the basis of the 95% confidence interval around the relative risk of the primary outcome (relative risk, 0.83; 95% CI, 0.68 to 1.01), plausible results range from a 1% higher incidence to a 32% lower incidence of postpartum hemorrhage with tranexamic acid than with placebo.

Table 2. Primary and Secondary Outcomes (Modified Intention-to-Treat Population).

Outcome or Event	Tranexamic Acid Group (N=1945)	Placebo Group (N=1946)	Risk Ratio (95% CI)	Difference (95% CI)*	P Value	
					Unadjusted	Adjusted†
Primary outcome — no./total no. (%)‡	156/1921 (8.1)	188/1918 (9.8)	0.83 (0.68 to 1.01)	−1.7 (−3.5 to 0.1)	0.07	—
Clinically significant postpartum hemorrhage, according to provider — no. (%)	151 (7.8)	203 (10.4)	0.74 (0.61 to 0.91)	−2.7 (−4.5 to −0.7)	0.004	0.04
Additional uterotonic agent for excessive bleeding — no. (%)	141 (7.2)	189 (9.7)	0.75 (0.61 to 0.92)	−2.5 (−4.2 to −0.7)	0.006	0.04
Severe postpartum hemorrhage — no./total no. (%)§	47/1921 (2.4)	57/1918 (3.0)	0.82 (0.56 to 1.21)	−0.5 (−1.6 to 0.5)	0.32	0.59
Blood loss — ml¶						
At 15 min	130.5±144.3	135.3±149.8	—	−4.7 (−14.1 to 4.6)	0.32	0.59
At bag removal	199.1±261.2	210.4±256.1	—	−11.3 (−27.7 to 5.0)	0.17	0.46
Estimated total	220.3±280.4	236.9±291.6	—	−16.7 (−34.7 to 1.4)	0.07	0.23
Blood transfusion — no. (%)	17 (0.9)	18 (0.9)	0.94 (0.49 to 1.83)	−0.1 (−0.6 to 0.5)	0.87	0.88
Arterial embolization or surgery for postpartum hemorrhage — no. (%)	3 (0.2)	5 (0.3)	0.60 (0.14 to 2.51)	−0.1 (−0.4 to 0.2)	0.73	0.86
Hemoglobin‖						
Peripartum change — g/dl	−0.77±1.23	−0.79±1.28	—	0.02 (−0.06 to 0.10)	0.64	0.83
Decrease >2 g/dl	269 (14.6)	274 (15.2)	0.96 (0.82 to 1.12)	−0.6 (−2.9 to 1.8)	0.63	0.83
Hematocrit**						
Peripartum change — percentage points	−2.05±3.89	−2.03±4.11	—	−0.02 (−0.29 to 0.25)	0.88	0.88
Decrease >10 percentage points — no. (%)	47 (2.7)	53 (3.1)	0.88 (0.59 to 1.29)	−0.4 (−1.5 to 0.7)	0.50	0.82

* Differences between rates are presented in percentage points, and differences between mean values are presented in the unit of the mean values.

† The P value was adjusted post hoc for multiple testing with the use of the Benjamini–Hochberg procedure.

‡ The primary outcome was postpartum hemorrhage, defined as blood loss of at least 500 ml, measured with a graduated collector bag. In the modified intention-to-treat population, data on the primary outcome were missing for 24 women in the tranexamic acid group and for 28 in the placebo group because no collector bag was available.

§ Severe postpartum hemorrhage was defined as blood loss of at least 1000 ml.

¶ Data on blood loss at 15 minutes were available for 1898 participants in the tranexamic acid group and for 1900 in the placebo group; data on blood loss at bag removal were available for 1921 and 1918, respectively; and data on estimated total blood loss were available for 1931 and 1927, respectively.

‖ Data on hemoglobin levels were available for 1837 participants in the tranexamic acid group and for 1802 in the placebo group. The prepartum hemoglobin level was measured between 8 months of gestation and arrival at the labor ward in 1459 women (79.4%) in the tranexamic acid group and in 1451 (80.5%) in the placebo group; at arrival in the labor ward in 159 (8.7%) and 124 (6.9%), respectively; and between 5 and 7 months of gestation in 202 (11.0%) and 209 (11.6%), respectively. The postpartum hemoglobin level was measured on day 2 in 1656 women (90.1%) in the tranexamic acid group and in 1642 (91.1%) in the placebo group and on day 1 or day 3 in 164 (8.9%) and 142 (7.9%), respectively. In women who underwent blood transfusion after delivery (17 women in the tranexamic acid and 18 in the placebo group), one unit of packed red cells was considered to indicate a decrease in the hemoglobin level of 1 g per deciliter.

** Data on the hematocrit were available for 1746 participants in the tranexamic acid group and for 1725 in the placebo group. The prepartum hematocrit was measured from 8 months of gestation until arrival at the labor ward in 1382 women (79.2%) in the tranexamic acid group and in 1386 (80.3%) in the placebo group; at arrival at the labor ward in 168 (9.6%) and 129 (7.5%), respectively; and between 5 and 7 months of gestation in 179 (10.3%) and 192 (11.1%), respectively. The postpartum hematocrit was measured on day 2 in 1581 (90.5%) women in the tranexamic acid and in 1573 (91.2%) in the placebo group and on day 1 or day 3 in 148 (8.5%) and 134 (7.8%), respectively. In women who underwent blood transfusion after delivery, one unit of packed red cells was considered to indicate a decrease in the hematocrit of 5 percentage points.

Table 3. Prespecified Subgroup Analyses for the Primary Outcome (Modified Intention-to-Treat Population).

Subgroup	Tranexamic Acid Group	Placebo Group	Relative Risk (95% CI)	P Value		
				Interaction*	Unadjusted	Adjusted†
	no./total no. (%)					
Type of vaginal delivery				0.17		
Operative	32/340 (9.4)	48/327 (14.7)	0.64 (0.42–0.98)		0.04	0.20
Spontaneous	124/1581 (7.8)	140/1591 (8.8)	0.89 (0.71–1.12)		0.33	0.43
Episiotomy				0.34		
Yes	57/452 (12.6)	76/439 (17.3)	0.73 (0.53–1.00)		0.049	0.20
No	99/1469 (6.7)	112/1479 (7.6)	0.89 (0.69–1.15)		0.38	0.43
History of postpartum hemorrhage‡				0.25		
Yes	23/91 (25.3)	14/82 (17.1)	1.48 (0.82–2.68)		0.19	0.38
No	48/817 (5.9)	48/801 (6.0)	0.98 (0.67–1.45)		0.92	0.92
Known risk factors for postpartum hemorrhage§				0.75		
Yes	80/557 (14.4)	92/545 (16.9)	0.85 (0.65–1.12)		0.25	0.40
No	76/1364 (5.6)	96/1373 (7.0)	0.80 (0.60–1.07)		0.13	0.35

* The P value for interaction was determined by the Mantel–Haenszel test.
† The P value was adjusted post hoc for multiple testing with the use of the Benjamini–Hochberg procedure.
‡ History of postpartum hemorrhage was assessed in multiparous women.
§ This subgroup was defined according to whether the participant had at least one risk factor for postpartum hemorrhage with an odds ratio of 3 or more in the literature (i.e., history of postpartum hemorrhage, gestational hypertensive disorder, or episiotomy).[30]

This trial included a large population of pregnant women, including many women who had risk factors for postpartum hemorrhage, and applied relatively few exclusion criteria; thus, the results appear to be generalizable to women with vaginal delivery who are receiving care in similar facilities. Postpartum blood loss was determined objectively,[23,24] since it was measured in a graduated collector bag[24,27] rather than being visually estimated. Several studies have shown visual estimation to be an unreliable method.[25,32-36]

Vomiting or nausea was significantly more frequent in the tranexamic acid group than in the placebo group, but none of the cases were judged to be severe. There were no significant between-group differences in the rates of thromboembolic events within 3 months after treatment. Although the trial was not powered to detect between-group differences in the rates of these events, the very low frequency of these events provides reassurance regarding the safety of tranexamic acid.

This trial has some limitations. Blood tests for the measurement of the hemoglobin level and hematocrit before delivery were performed as part of routine prenatal care, mostly in out-of-hospital laboratories and therefore without standardized timing. The trial did not have sufficient power to assess the effect of tranexamic acid on the rates of severe postpartum hemorrhage and of the use of interventions to treat it. Moreover, the definition of postpartum hemorrhage as blood loss of more than 500 ml instead of as blood loss of at least 500 ml might have affected the result for the primary outcome; this suspected threshold effect is an important consideration in the definition of outcomes in future trials. Finally, our trial was not designed to account for multiple testing. We conducted a post hoc adjustment for multiple testing for the analysis of secondary outcomes and for subgroup analyses. Nevertheless, these results should be viewed as exploratory in nature.

We found lower rates of provider-assessed clinically significant postpartum hemorrhage and of the use of additional uterotonic agents for bleeding — markers of postpartum hemorrhage that reflected the clinical judgment of health

Table 4. Adverse Events (Modified Intention-to-Treat Population).

Event	Tranexamic Acid Group (N=1945)	Placebo Group (N=1946)	Relative Risk (95% CI)	P Value
In the delivery room				
Vomiting or nausea — no. (%)	136 (7.0)	63 (3.2)	2.16 (1.61–2.89)	<0.001
Nausea — no. (%)	103 (5.3)	49 (2.5)	2.10 (1.51–2.94)	<0.001
Vomiting — no. (%)	73 (3.8)	33 (1.7)	2.21 (1.47–3.32)	<0.001
Photopsia — no. (%)*	4 (0.2)	6 (0.3)	0.67 (0.19–2.36)	0.53
Dizziness — no. (%)	40 (2.1)	30 (1.5)	1.33 (0.83–2.13)	0.23
Blood pressure — no./total no. (%)				
Systolic ≥140 mm Hg	415/1597 (26.0)	378/1590 (23.8)	1.09 (0.97–1.23)	0.15
Diastolic ≥90 mm Hg	411/1594 (25.8)	406/1600 (25.4)	1.02 (0.90–1.14)	0.79
At 3 mo after delivery				
Completed interviews at 3 mo — no. (%)	1844 (94.8)	1849 (95.0)		
Thromboembolic event — no./total no. (%)				
Any†	1/1844 (0.1)	4/1849 (0.2)	0.25 (0.03–2.24)	0.37
Deep-vein thrombosis	0/1844	1/1849 (0.1)	—	—
Pulmonary embolism	0/1844	0/1849	—	—
Ovarian-vein thrombosis	0/1844	2/1849 (0.1)	—	—
Superficial-vein thrombosis	1/1844 (0.1)	1/1849 (0.1)	—	—
Seizure — no./total no. (%)‡	1/1844 (0.1)	0/1849	—	—
Readmission after discharge — no./total no. (%)	18/1844 (1.0)	16/1849 (0.9)	1.13 (0.58–2.21)	0.72
Anticoagulant therapy at and after discharge — no./total no. (%)	57/1830 (3.1)	56/1842 (3.0)	1.02 (0.71–1.47)	0.90

* Photopsia was defined as a sensation of seeing lights, sparks, or flashes of color.
† One woman in the tranexamic acid group had superficial phlebitis along a peripheral venous line at day 1 post partum. In the placebo group, one woman had superficial phlebitis along a peripheral venous line in the immediate postpartum period, two had thrombosis of the ovarian vein in the immediate postpartum period, and one had deep-vein thrombosis of the leg at day 30 post partum. No retinal vascular occlusion, myocardial infarction, stroke, or kidney failure occurred in either group.
‡ One woman in the tranexamic acid group had seizures at day 30 post partum in a context of sleep deprivation and acute alcohol intake. The clinical examination, computed tomographic scan of the head, and electroencephalogram were normal, and she received no additional treatment.

care providers — in the tranexamic acid group than in the placebo group, but such findings were not observed in other secondary measures of blood loss. Three smaller, randomized trials have assessed the use of tranexamic acid to prevent blood loss after vaginal delivery.[37-39] A meta-analysis combining these trials showed that the risk of postpartum hemorrhage, defined as blood loss of more than 400 ml or blood loss of more than 500 ml, was 58% lower with tranexamic acid than with control (placebo or standard care) (relative risk, 0.42; 95% CI, 0.28 to 0.63).[40] However, substantial methodologic deficiencies relating to blinding, methods for outcome assessment, and attrition bias make these results inconclusive.[5,13-18,40]

Given the proven preventive effect of tranexamic acid against blood loss in various elective surgeries,[6,7] we had anticipated that this agent might be more likely to reduce the incidence of the primary outcome among women in whom vaginal delivery involved interventions (episiotomy or operative vaginal delivery) than among those in whom delivery did not involve such interventions. However, we did not find significant interactions with these variables, with a history of postpartum hemorrhage, or with a known risk of postpartum hemorrhage. Our trial was not powered to perform analyses in these subgroups. Large trials are needed to test the preventive effect of tranexamic acid in traumatic deliveries, such as vaginal delivery with episiotomy or instruments and cesarean delivery.

In conclusion, among women with vaginal delivery who received prophylactic oxytocin, the use of tranexamic acid did not result in a rate of the primary outcome of postpartum hemorrhage of at least 500 ml that was significantly lower than the rate with placebo.

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APPENDIX

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REFERENCES

1. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;2(6):e323-e333.
2. Sentilhes L, Goffinet F, Vayssière C Deneux-Tharaux C. Comparison of postpartum haemorrhage guidelines: discrepancies underline our lack of knowledge. BJOG 2017;124:718-22.
3. Begley CM, Gyte GM, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev 2015;3:CD007412.
4. Sentilhes L, Merlot B, Madar H, Sztark F, Brun S, Deneux-Tharaux C. Postpartum haemorrhage: prevention and treatment. Expert Rev Hematol 2016;9:1043-61.
5. Sentilhes L, Lasocki S, Ducloy-Bouthors AS, et al. Tranexamic acid for the prevention and treatment of postpartum haemorrhage. Br J Anaesth 2015;114:576-87.
6. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ 2012;344:e3054.
7. Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. N Engl J Med 2017;376:136-48.
8. Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376:23-32.
9. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care 2016;20:100.
10. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. Eur J Anaesthesiol 2017;34:332-95.
11. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017;389:2105-16.
12. Gayet-Ageron A, Prieto-Merino D, Ker K, et al. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. Lancet 2018;391:125-32.
13. Ker K, Shakur H, Roberts I. Does tranexamic acid prevent postpartum haemorrhage? A systematic review of randomised controlled trials. BJOG 2016;123:1745-52.
14. Sentilhes L, Brun S, Madar H, Merlot B, Deneux-Tharaux C. Does tranexamic acid prevent postpartum haemorrhage? A systematic review of randomised controlled trials: a very welcome publication. BJOG 2017;124:982.
15. Pacheco LD, Hankins GDV, Saad AF, Costantine MM, Chiossi G, Saade GR. Tranexamic acid for the management of obstetric hemorrhage. Obstet Gynecol 2017;130:765-9.
16. Sentilhes L, Brun S, Madar H, Deneux-Tharaux C. Tranexamic acid for preventing postpartum blood loss at cesarean delivery: is evidence sufficient? Acta Obstet Gynecol Scand 2016;95:836.
17. Alam A, Choi S. Prophylactic use of tranexamic acid for postpartum bleeding

outcomes: a systematic review and meta-analysis of randomized controlled trials. Transfus Med Rev 2015;29:231-41.
18. Sentilhes L, Brun S, Madar H, Deneux-Tharaux C. Tranexamic acid for prevention PPH: a promising drug but today only a promising drug. Transfus Med Rev 2016;30:100.
19. Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MSV. Risk of a thrombotic event after the 6-week postpartum period. N Engl J Med 2014;370:1307-15.
20. Sentilhes L, Vayssière C, Deneux-Tharaux C, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). Eur J Obstet Gynecol Reprod Biol 2016;198:12-21.
21. Practice bulletin no. 183: postpartum hemorrhage. Obstet Gynecol 2017;130(4):e168-e186.
22. Mavrides E, Allard S, Chandraharan E, et al. Prevention and management of postpartum haemorrhage: green-top guideline no. 52. BJOG 2017;124(5):e106-e149.
23. Sentilhes L, Daniel V, Darsonval A, et al. Study protocol: TRAAP — TRAnexamic acid for Preventing postpartum hemorrhage after vaginal delivery: a multicenter randomized, double-blind, placebo-controlled trial. BMC Pregnancy Childbirth 2015;15:135.
24. Deneux-Tharaux C, Sentilhes L, Maillard F, et al. Effect of routine controlled cord traction as part of the active management of the third stage of labour on postpartum haemorrhage: multicentre randomised controlled trial (TRACOR). BMJ 2013;346:f1541.
25. Brooks M, Legendre G, Brun S, et al. Use of a visual aid in addition to a collector bag to evaluate postpartum blood loss: a prospective simulation study. Sci Rep 2017;7:46333.
26. Legendre G, Richard M, Brun S, Chancerel M, Matuszewski S, Sentilhes L. Evaluation by obstetric care providers of simulated postpartum blood loss using a collector bag: a French prospective study. J Matern Fetal Neonatal Med 2016;29:3575-81.
27. Kerr R, Eckert LO, Winikoff B, et al. Postpartum haemorrhage: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2016;34:6102-9.
28. Guedeney N, Fermanian J. Validation study of the French version of the Edinburgh Postnatal Depression Scale (EPDS): new results about use and psychometric properties. Eur Psychiatry 1998;13:83-9.
29. Calvert C, Thomas SL, Ronsmans C, Wagner KS, Adler AJ, Filippi V. Identifying regional variation in the prevalence of postpartum haemorrhage: a systematic review and meta-analysis. PLoS One 2012;7(7):e41114.
30. Royal College of Obstetricians and Gynaecologists. Postpartum haemorrhage, prevention and management (Green-top Guideline No. 52). London: Royal College of Obstetricians and Gynaecologists, 2009:1-24.
31. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B 1995;57:289-300.
32. Glover P. Blood loss at delivery: how accurate is your estimation? Aust J Midwifery 2003;16:21-4.
33. Dildy GA III, Paine AR, George NC, Velasco C. Estimating blood loss: can teaching significantly improve visual estimation? Obstet Gynecol 2004;104:601-6.
34. Duthie SJ, Ven D, Yung GL, Guang DZ, Chan SY, Ma HK. Discrepancy between laboratory determination and visual estimation of blood loss during normal delivery. Eur J Obstet Gynecol Reprod Biol 1991;38:119-24.
35. Razvi K, Chua S, Arulkumaran S, Ratnam SS. A comparison between visual estimation and laboratory determination of blood loss during the third stage of labour. Aust N Z J Obstet Gynaecol 1996;36:152-4.
36. Stafford I, Dildy GA, Clark SL, Belfort MA. Visually estimated and calculated blood loss in vaginal and cesarean delivery. Am J Obstet Gynecol 2008;199(5):519.e1-519.e7.
37. Yang H, Zheng S, Shi C. Clinical study on the efficacy of tranexamic acid in reducing postpartum blood lose: a randomized, comparative, multicenter trial. Zhonghua Fu Chan Ke Za Zhi 2001;36:590-2. (In Chinese.)
38. Gungorduk K, Asıcıoğlu O, Yıldırım G, Ark C, Tekirdağ Aİ, Besımoglu B. Can intravenous injection of tranexamic acid be used in routine practice with active management of the third stage of labor in vaginal delivery? A randomized controlled study. Am J Perinatol 2013;30:407-13.
39. Mirghafourvand M, Mohammad-Alizadeh S, Abbasalizadeh F, Shirdel M. The effect of prophylactic intravenous tranexamic acid on blood loss after vaginal delivery in women at low risk of postpartum haemorrhage: a double-blind randomised controlled trial. Aust N Z J Obstet Gynaecol 2015;55:53-8.
40. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2015;6:CD007872.