Tranexamic Acid Treatment for Heavy Menstrual Bleeding

A Randomized Controlled Trial

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OBJECTIVE: To assess the efficacy and safety of an oral formulation of tranexamic acid for the treatment of heavy menstrual bleeding.

METHODS: Adult women with heavy menstrual bleeding (mean menstrual blood loss 80 mL or more per cycle) were enrolled in a double-blind, placebo-controlled study. After two pretreatment menstrual cycles, women were randomized to receive tranexamic acid 3.9 g/d or placebo for up to 5 days per menstrual cycle through six cycles. To meet the prespecified three-component primary efficacy end point, mean reduction in menstrual blood loss from baseline with tranexamic acid treatment needed to be 1) significantly greater than placebo, 2) greater than 50 mL, and 3) greater than a predetermined meaningful threshold (36 mL or higher). Health-related quality of life was measured using a validated patient-reported outcome instrument.

RESULTS: Women who received tranexamic acid (n=115) met all three primary efficacy end points: first, a significantly greater reduction in menstrual blood loss of −69.6 mL (40.4%) compared with −12.6 mL (8.2%) in the 72 women who received placebo ($P<.001$); reduction of menstrual blood loss exceeding a prespecified 50 mL; and last, reduction of menstrual blood loss considered meaningful to women. Compared with women receiving placebo, women treated with tranexamic acid experienced significant improvements in limitations in social or leisure and physical activities, work inside and outside the home, and self-perceived menstrual blood loss ($P<.01$). The majority of adverse events were mild to

For a list of investigators who enrolled patients in this study, see the Appendix online at http://links.lww.com/AOG/A198.

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moderate in severity, and the incidence of gastrointestinal adverse events was comparable with placebo.

CONCLUSION: In this study, a new oral tranexamic acid treatment was well tolerated and significantly improved both menstrual blood loss and health-related quality of life in women with heavy menstrual bleeding.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00386308.

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LEVEL OF EVIDENCE: I

Heavy menstrual bleeding is described as a condition that "interferes with the woman's physical, social, emotional, and/or material quality of life."[1] Although quantitatively defined as menstrual blood loss of 80 mL or more per menstrual cycle,[2–4] the diagnosis of heavy menstrual bleeding is typically based on personal perception of menstrual blood loss and its effect on daily life. The negative effects of heavy menstrual bleeding on health-related quality of life (eg, limitations in daily activities, work functions, and social interactions) are what often lead women to seek medical treatment.[5–9] Hormonal medications, nonsteroidal antiinflammatory drugs, and surgical procedures can effectively reduce menstrual blood loss; however, relative contraindications, variable efficacy, potential adverse effects, or undesired effects on fertility can limit the use of these therapies.[10]

Evidence of increased fibrinolytic activity in the menstrual blood of women with heavy menstrual bleeding prompted evaluation of hemostatic agents as potential therapeutic options.[11,12] Having established efficacy in reducing menstrual blood loss, tranexamic acid, a competitive plasminogen inhibitor, has been used for treatment of heavy menstrual bleeding outside of the United States for several decades.[13,14] Oral, immediate-release tranexamic acid is generally well tolerated; however, gastrointestinal adverse effects may limit its use.[13] A unique oral formulation of tranexamic acid (LYSTEDA) that provides a higher per-tablet dose and increases drug absorption time has been designed to maintain efficacy while minimizing gastrointestinal adverse effects and was recently approved by the U.S. Food and Drug Administration for the treatment of cyclic heavy menstrual bleeding. In this report, we describe quantitative and qualitative results from a phase 3 clinical trial of this novel tranexamic acid formulation.

MATERIALS AND METHODS

In this multicenter, double-blind, parallel-group study, women with heavy menstrual bleeding were randomized to receive tranexamic acid (LYSTEDA) 1.3 g per dose (two tablets, 650 mg each) or matching placebo. Women were instructed to begin treatment at the onset of heavy menstrual bleeding and to take the study medication three times daily at least 6 hours apart for up to 5 days per cycle over the course of six menstrual cycles. The maximum daily dose of tranexamic acid was 3.9 g.

Adult women (age 18 to 49 years) with heavy menstrual bleeding were enrolled at 40 clinical sites in the United States. Participants were required to have a history of three or more consecutive days of heavy menstrual bleeding over at least four of their last six menstrual periods. During a two-cycle pretreatment baseline phase, menstrual blood loss had to be at least 60 mL during the first menstrual period and had to average at least 80 mL over both pretreatment cycles. Participants were required to have normal findings on pelvic examination, no clinically important cervical cytology abnormalities, and no clinically important uterine pathologic findings by transvaginal ultrasonography. The transvaginal ultrasonogram was considered abnormal if the endometrial thickness was greater than 12 mm or if the endometrial thickness was 5 to 12 mm and the patient's clinical history suggested long-term unopposed estrogen exposure (1 year or longer). If the transvaginal ultrasonogram was considered abnormal, normal results on endometrial biopsy were required. Presence of leiomyomas was not considered an abnormal finding unless the leiomyomas were of a sufficient number and size to warrant surgical management. In addition, participants had to have a history of regularly occurring menstrual periods of no more than 10 days in duration and 21 to 35 days from the start of one period until the start of the next menstrual period. Women of childbearing potential were required to use an acceptable nonhormonal method of birth control.

Women were excluded from the study if they had a history or presence of significant medical problems (eg, thromboembolic disease, coagulopathy, subarachnoid hemorrhage, endocrinopathy, or ocular disease); had severe anemia (hemoglobin less than 8 g/dL); were pregnant or lactating; had a history or presence of endometrial abnormalities or cervical carcinoma; or had anovulatory dysfunctional uterine bleeding, metrorrhagia, menometrorrhagia, or polymenorrhea. Participants were required to have normal color vision and could not have glaucoma, ocular hypertension, macular degeneration, or retinopathies (see Discussion for rationale).

Participants were not permitted to use anticoagulants, aspirin, dong quai, aminocaproic acid, or hy-

droxychloroquine during the study. Cyclooxygenase-2 inhibitors and nonsteroidal antiinflammatory drugs were not allowed during menstrual periods, but were permitted during the intermenstrual phase of the cycle. Use of acetaminophen, analgesic opioids, oral iron therapy, and vitamins was permitted throughout the study. Oral iron therapy was prescribed at the investigator's discretion for women with hemoglobin levels between 11 g/dL and 12 g/dL at baseline. Oral iron therapy was required for women with baseline hemoglobin levels lower than 11 g/dL and for those individuals whose hemoglobin levels declined to less than 11 g/dL during the study.

The protocol received approval from each site's Institutional Review Board and was conducted in compliance with the principles of the Declaration of Helsinki and guidelines for Good Clinical Practice. All participants provided signed informed consent.

The prespecified three-component primary efficacy end point was mean reduction in menstrual blood loss with tranexamic acid treatment that was 1) significantly greater than that of the placebo group, 2) greater than 50 mL from baseline, and 3) greater than a reduction in menstrual blood loss previously established to be perceived as meaningful to women (36 mL or higher; unpublished data). The change in menstrual blood loss was calculated by subtracting the mean blood loss during the two pretreatment cycles from the mean blood loss during four of the on-treatment cycles (first, second, third, and sixth cycles). Quantification of a "meaningful" change was performed by constructing a receiver operating characteristic curve based on change in menstrual blood loss from baseline data and responses to Menorrhagia Impact Questionnaire (MIQ) question 6 (see Table 1) in a separate, double-blind, placebo-controlled heavy menstrual bleeding study. Sensitivity and specificity were computed by dichotomizing the change in menstrual blood loss from baseline values as above and below various thresholds (cutoff points) in 1-mL increments and the MIQ question 6 responses as meaningful or not meaningful. The optimum balance of sensitivity and specificity was used as the minimum value for a meaningful improvement in menstrual blood loss.

Participants were instructed to collect and return all menses captured on sponsor-provided sanitary products for analysis; emphasis was placed on preventing loss of menstrual fluid. Individually labeled bags containing each woman's daily used sanitary products were shipped by the study sites to a central laboratory for quantification of menstrual blood loss. The volume of menstrual blood was objectively measured using a validated alkaline hematin method.[15]

Secondary end points included change from baseline in health-related quality-of-life parameters, the occurrence of large blood stains, and hemoglobin and ferritin concentrations. Qualitative health-related quality-of-life assessments were based on responses to the MIQ, a disease-specific, validated patient-reported outcome instrument (Table 1) that was completed by participants after all screening and treatment cycles. Among the parameters measured by the MIQ were limitations on social or leisure activities, limitations on physical activities, limitation in work outside or inside the home, and patient perception of treatment-induced changes in menstrual blood loss. The number and size of blood stains were recorded by participants in menstrual bleeding diaries. Hemoglobin and ferritin concentrations were determined from routine laboratory evaluations. Normal hemoglobin concentrations were defined as more than 12 g/dL and normal ferritin levels were defined as more than 10 ng/mL. Data for all prespecified secondary end points and additional secondary end points (with the exception of hemoglobin and ferritin levels) were collected during all study menstrual cycles. Blood samples for determining hemoglobin and ferritin concentrations were collected at baseline and treatment menstrual periods 3 and 6.

Medication safety was assessed by evaluating laboratory data, performing physical examinations, measuring vital signs, evaluating data from 12-lead electrocardiography, performing ophthalmologic examinations, and monitoring adverse events. Medication adherence was assessed by study personnel who reviewed participant study diaries and counted returned tablets.

The sample size was calculated using a two-to-one allocation and a 90% chance of detecting a 50-mL difference in the mean change in menstrual blood loss from baseline to end of study between groups. The standard deviation of $\sigma=85$ mL used in the calculation was derived from previous tranexamic acid studies.[16–18] The sample size was based on a two-sided $\alpha=0.05$ level of significance and assumed normal distribution of the data. An interim analysis by the Data Safety Monitoring Board resulted in an increase in the planned sample size by 28 participants (total 120 participants) in the tranexamic acid treatment group and 18 participants (total 64 participants) in the placebo treatment group to achieve appropriate power for detecting between-group differences in the prespecified secondary variables.

A randomization schedule was generated for packaging, labeling, and treatment group assignment using a permuted block randomization scheme. The randomization block size was eight, with five partici-

Table 1. Menorrhagia Impact Questionnaire

Questions	Response Options
1. During your most recent menstrual period, your blood loss was: (perceived MBL)	1. Light 2. Moderate 3. Heavy 4. Very heavy
2. During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home? (LWH)	1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely
3. During your most recent menstrual period, how much did your bleeding limit you in your physical activities? (LPA)	1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely
4. During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities? (LSLA)	1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely
5. Please mark all activities that were limited by bleeding during your most recent menstrual period.	Walking, standing, climbing stairs, squatting or bending down, childcare, shopping, home management, leisure, exercise, sports, gardening, traveling/vacation, or other
6. Compared with your previous menstrual period, would you say your blood loss during this period was:	
6a. If your menstrual bleeding "improved" since your last period, please indicate how much.*	0. About the same (survey complete) 1. Better (proceed to questions 6a and 6c) 2. Worse (proceed to question 6b and 6c)
6b. If your menstrual bleeding "worsened" since your last period, please indicate how much.*	1. Almost the same, hardly better at all 2. A little better 3. Somewhat better 4. An average amount better 5. A good deal better 6. A great deal better 7. A very great deal better
6c. Was this a meaningful or important change for you?	0. No 1. Yes

MBL, menstrual blood loss; LWH, limitation in work outside or inside the home; LPA, limitation of physical activities; LSLA, limitation of social or leisure activities.

* Response options shown for question 6a. Response choices were the same for question 6b, with "worse" substituted for "better."

pants assigned to tranexamic acid and three participants assigned to placebo per block. Fisher Clinical Services was responsible for generating the randomization and allocation sequence and enrolling and assigning blinded study medication to individuals. Participants, investigators, sponsor, statisticians, clinical data management staff, and clinical monitors were blinded to study group allocation. Study drug was individually packaged for each visit and labeled with the study code. The tranexamic acid and placebo tablets were identical in appearance.

Efficacy analyses were conducted using data from the modified intent-to-treat population, which included participants who had sufficient data at baseline and for at least one treatment cycle. The primary efficacy analysis included a between-treatment group comparison using an analysis of covariance (ANCOVA) model and a within-treatment difference assessment using paired *t* tests for the mean change from baseline in menstrual blood loss. To address differences in baseline characteristics, baseline menstrual blood loss was used as a covariate in the ANCOVA analysis. The calculations of least-squares mean changes from baseline did not include adjustment for baseline menstrual blood loss. Treatment effect was confirmed using a linear regression

analysis of menstrual blood loss over time by statistical testing of the significance and direction of the regression slope. Additional comparative treatment analyses included the percentage of menstrual cycles with 1) menstrual blood loss of 80 mL or less, 2) decrease of 36 mL or more in menstrual blood loss from baseline (calculated by receiver operating characteristic analysis to be the threshold for a meaningful reduction in menstrual blood loss), 3) 50-mL or more decrease in menstrual blood loss from baseline, and 4) 50% or more decrease in menstrual blood loss from baseline.

Prespecified secondary end-point analyses were performed under a sequential step-down procedure in the following order of importance: 1) changes in limitations on social or leisure activities scores, 2) changes in limitations on physical activities scores, and 3) large stain responder (percentage of participants with a decrease from baseline in the number of large stains). The sequence was fixed before unblinding. The hypotheses were to be tested at $\alpha=0.05$ level of significance. If at any point of the testing sequence results were not statistically significant, then any remaining prespecified analyses were to be exploratory in nature. All secondary end points were comparisons of the mean of the two baseline cycles and the mean of the six treatment cycles. Between-treatment differences in the prespecified and other secondary end points were evaluated using ANCOVA, with the study group treatment cycle value and the baseline value included as covariates in their respective analyses. Using general linear models, least-squares means change (adjusted mean) was computed with the respective baseline health-related quality-of-life score as the covariate and reported as a positive value. The within-treatment test was conducted using a paired difference *t* test. The intraparticipant differences for the number of large stains were calculated as the average number of stains recorded during treatment minus the baseline average. The percentage of participants with a reduction from baseline in the number of large stains was compared between treatment groups using a two-tailed Fisher exact test.

Demographic and safety data were described using summary statistics. Analysis of variance was used to assess between-group differences in these parameters. Safety evaluations were conducted using data from the intent-to-treat population, which included all randomized participants who took at least one dose of study drug. All statistical analyses were performed using SAS 9.1.3.

RESULTS

A total of 196 participants were randomized to receive tranexamic acid (n=123) or placebo (n=73; Fig. 1). The intent-to-treat population consisted of 189 women, 117 in the tranexamic acid group and 72 in the placebo group. Six participants in the tranexamic acid group and 1 in the placebo group were excluded from the intent-to-treat analyses because they did not ingest at least one dose of study drug. The modified intent-to-treat population consisted of 187 women, 115 in the tranexamic acid group and 72 in the placebo group. Two individuals in the tranexamic acid group were excluded from the modified intent-to-treat analyses because posttreatment data were unavailable. In all, 148 women completed the study, 94 in the tranexamic acid group and 54 in the placebo group. Forty-eight participants withdrew from the study; the majority were lost to follow-up (16 individuals). Two participants in the placebo group and no individuals in the tranexamic acid group discontinued because of unsatisfactory efficacy response. The first participant was screened on October 16, 2006, and the last study visit was May 8, 2008.

Both groups had comparable baseline and demographic characteristics, with the exception of baseline menstrual blood loss (Table 2). Participants in the modified intent-to-treat population randomized to receive tranexamic acid (n=115) had a slightly higher baseline menstrual blood loss compared with the 72 women randomized to receive placebo (172.3±95.6 and 153.0±66.6 mL/cycle, respectively); however, the difference was not statistically significant ($P=.11$). The mean number of treatment days per cycle was 3.4 days for tranexamic acid and 3.3 days for participants taking placebo. Among the 188 individuals with treatment compliance data, 96.3% of tablets were taken in both treatment groups.

Women with heavy menstrual bleeding treated with tranexamic acid achieved the prespecified three-part primary efficacy outcome. A statistically significant reduction in mean menstrual blood loss occurred among women in the modified intent-to-treat population receiving tranexamic acid compared with those receiving placebo (−69.6 mL [40.4% reduction] compared with −12.6 mL [8.2% reduction]; $P<.001$), and the reduction in menstrual blood loss from baseline for those receiving tranexamic acid was greater than 50 mL and also exceeded the threshold of menstrual blood loss reduction (36 mL and greater) considered meaningful to women. Least-squares mean change in menstrual blood loss was also significantly greater in the tranexamic acid group (−66.3 mL [38.5% reduc-

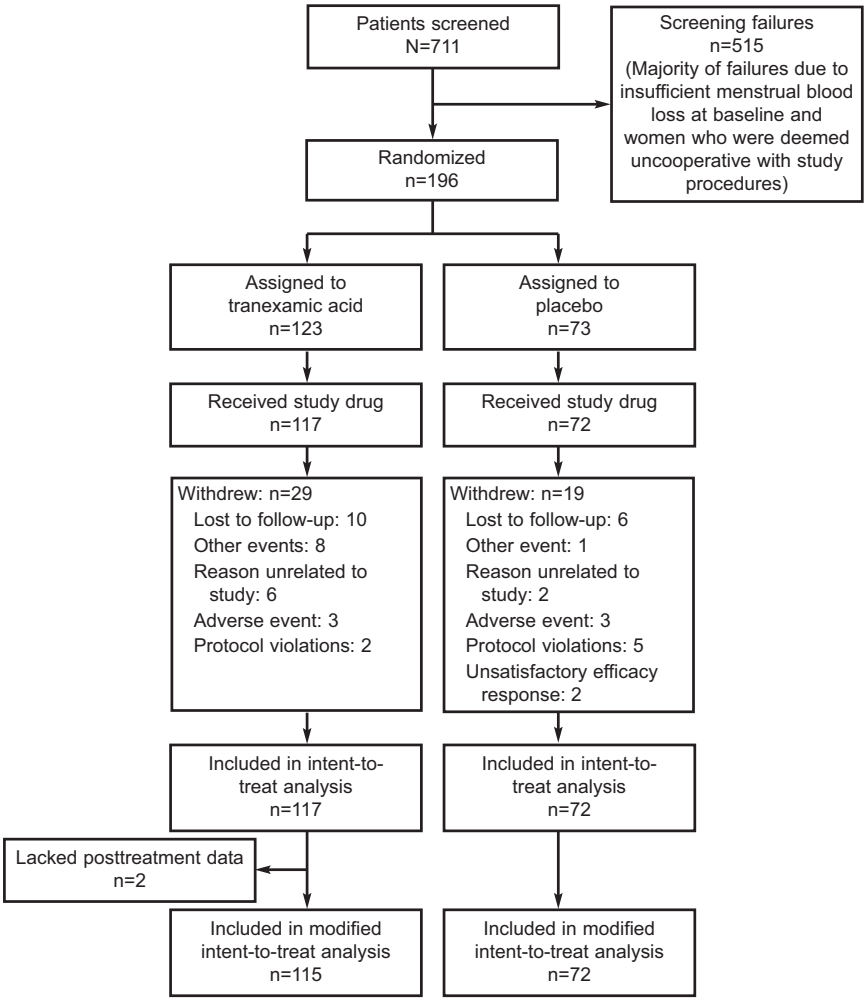

Fig. 1. Study flow chart.
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tion]) compared with placebo group (−17.8 mL [11.6% reduction]; $P<.001$).

The reduction in menstrual blood loss from baseline with tranexamic acid use was reported by women after the first treatment cycle (Fig. 2) and this reduction was maintained in each measured treatment cycle (confirmed by linear regression analyses). Treatment of heavy menstrual bleeding with tranexamic acid was effective in reducing menstrual bleeding regardless of presence of leiomyomas or baseline menstrual blood loss (Fig. 3). The blood loss on treatment declined to less than 80 mL (standard definition of heavy menstrual bleeding) in 43% (181/426) of menstrual cycles in women receiving tranexamic acid, compared with 17% (43/254) of cycles in women receiving placebo ($P<.001$).

The percentage of cycles with clinically meaningful reduction in menstrual blood loss of at least 36 mL was greater with tranexamic acid treatment (69%) compared with placebo use (29%; $P<.001$). Further, a significantly greater percentage of menstrual cycles had a reduction of at least 50 mL in the tranexamic acid group (56%) compared with the placebo group (19%; $P<.001$). In terms of the percentage of menstrual blood loss reduction, the proportion of women with at least a 50% reduction of menstrual blood loss from baseline was greater in the tranexamic acid group (35%) compared with placebo (7%; $P<.001$).

Two of the three prespecified secondary end points were met by women receiving tranexamic acid. Mean improvements in scores for limitations on social or leisure activities and limitations on physical activities were significantly greater in the tranexamic acid group compared with the placebo group, respectively ($P<.001$; Fig. 4A). The change in least-squares means in scores for limitations on social or leisure activities (0.85 ± 0.13 compared with 0.44 ± 0.12; $P<.001$) and limitations on physical activities (0.87 ± 0.13 compared with 0.40 ± 0.14; $P<.001$) was significantly greater in the tranexamic acid group compared with placebo group, respectively. The percentage of women who experienced reductions

Table 2. Demographic and Baseline Characteristics (Intent-to-Treat Population)

Parameter	Tranexamic Acid (n=117)	Placebo* (n=72)
Age (y)	38.7 ± 6.4†	38.7 ± 6.8
Race		
White	86 (73.5)	51 (70.8)
African American	23 (19.7)	18 (25.0)
Asian	1 (0.9)	1 (1.4)
Other	7 (6.0)	2 (2.8)
Duration of heavy menstrual bleeding (y)	9.9 ± 9.3†	10.1 ± 8.6
Uterine leiomyomas present at baseline	42 (36.5)†	26 (36.1)
Menstrual blood loss (mL)	172.3 ±95.6† (83.1–747.3)	153.0 ±66.6 (80.7–385.4)
Alcohol use (y)		
Less than 1	1 (1.9)	1 (2.9)
1–5	9 (17.0)	7 (20.0)
More than 5	43 (81.1)	27 (77.1)
Tobacco use (y)		
Less than 1	1 (2.4)	1 (3.7)
1–5	9 (22.0)	5 (18.5)
More than 5	31 (75.6)	21 (77.8)

Data are mean±standard deviation, n (%), or baseline (range).

Intent-to-treat population includes all randomized participants who ingested at least one dose of study medication; modified intent-to-treat population includes all randomized participants who have received at least one dose of study medication, have a baseline primary efficacy evaluation, and have sufficient daily blood-loss data to construct one cycle of data after the first dose of study medication.

* Differences between groups were not statistically significant ($P<.05$). *P* was calculated using two-sided *t* test.

† Modified intent-to-treat population (n=115).

in the number of large stains reported from baseline (large stain responder) was slightly higher among women treated with tranexamic acid than with placebo; however, the difference was not statistically significant ($P=.45$; Fig. 4B). Improvements in scores for limitations on social or leisure activities and limitations on physical activities were evident during the first treatment cycle and were maintained throughout the study (Fig. 5A and 5B). For women receiving tranexamic acid, scores for limitations on social or leisure activities and limitations on physical activities improved from "moderate impairment" at baseline to "slight impairment" after treatment.

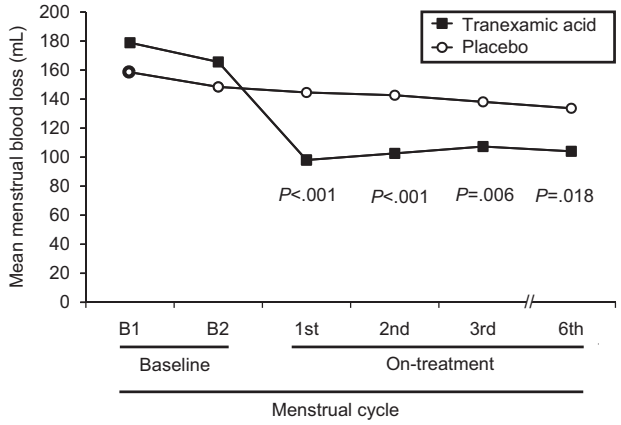

Fig. 2. Menstrual blood loss change over study course. Effects of tranexamic acid (n=115) and placebo (n=72) use on menstrual blood loss as measured by the alkaline hematin method are illustrated over the time course of the study. *P* values are for the comparison between tranexamic acid and placebo.

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Secondary end-point analyses revealed that participants in the tranexamic acid treatment group experienced a larger reduction (indicating improvement) in mean scores for limitation in work outside or inside the home compared with women taking placebo (−0.71±0.85 compared with −0.16±0.87, respectively; $P<.001$); improvements were evident during the first treatment cycle and were maintained throughout the study (Fig. 5C). Statistically significant between-group treatment differences were observed for mean changes in perceived menstrual blood loss scores from baseline (−0.47±0.59 and 0.15±0.67 for tranexamic acid and placebo participants, respectively, $P<.001$; Fig. 5D).

Anemia was more prevalent at baseline in the tranexamic acid group (33.9% [39/115]) than in the placebo group (18.1% [13/72]). Mean hemoglobin levels did not appreciably increase from baseline in the tranexamic acid treatment group (0.02±1.10

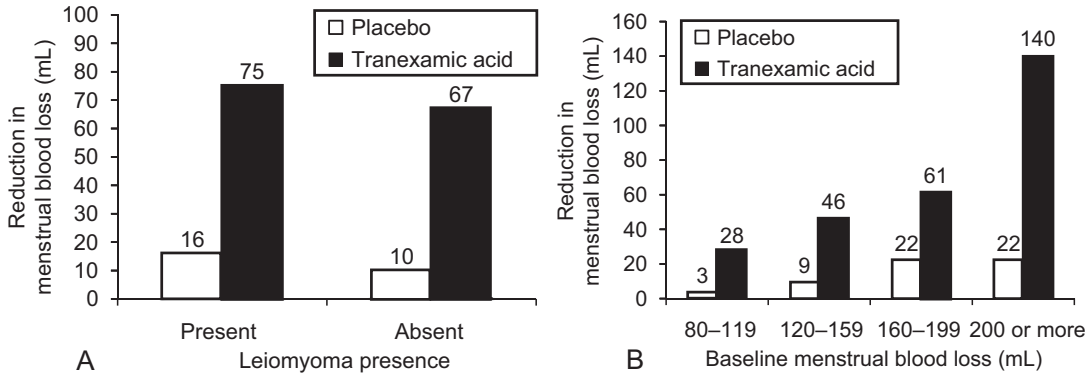

Fig. 3. Reduction in menstrual blood loss from baseline stratified by presence of uterine leiomyomas **(A)** and by baseline menstrual blood loss **(B)**. For all comparisons between tranexamic acid and placebo, $P<.05$.

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g/dL); a slight but statistically significant increase was observed in the placebo group (0.34 ± 0.66 g/dL; $P<.001$); this change is not considered clinically significant. Mean changes from baseline ferritin concentrations were not significant in either group (-1.21 ± 12.70 and -2.68 ± 16.15 ng/mL for tranexamic acid and placebo groups, respectively).

This formulation of tranexamic acid was generally well tolerated, and the majority of adverse events in the intent-to-treat population were mild to moderate in severity. The most common adverse events reported were menstrual discomfort or cramps, headache, and back pain (Table 3). Sinus headache and anemia were reported more often with tranexamic acid use than with placebo. The frequency of gastrointestinal-related adverse events was similar between groups. Six serious adverse events were reported during the study: in the tranexamic acid group, one incident each of tachycardia, acute bronchitis, hypoglycemia, posttraumatic stress disorder, and urticaria; in the placebo group, one incident of deep vein thrombosis. All of these events were judged to be unrelated to study treatment. No thrombotic events were reported in the participants treated with tranexamic acid and no deaths occurred during the study. Seven study participants reported or experienced an ocular-related adverse effect that was considered possibly or probably treatment related; two of these individuals were receiving tranexamic acid and five were receiving placebo. In the tranexamic acid group, a woman missed one blue-yellow color vision plate (right eye) during an eye examination and another woman complained of a nonspecific visual disturbance; these conditions were not considered clinically significant. No clinically significant changes in blood pressure, pulse rate, physical or gynecologic findings,

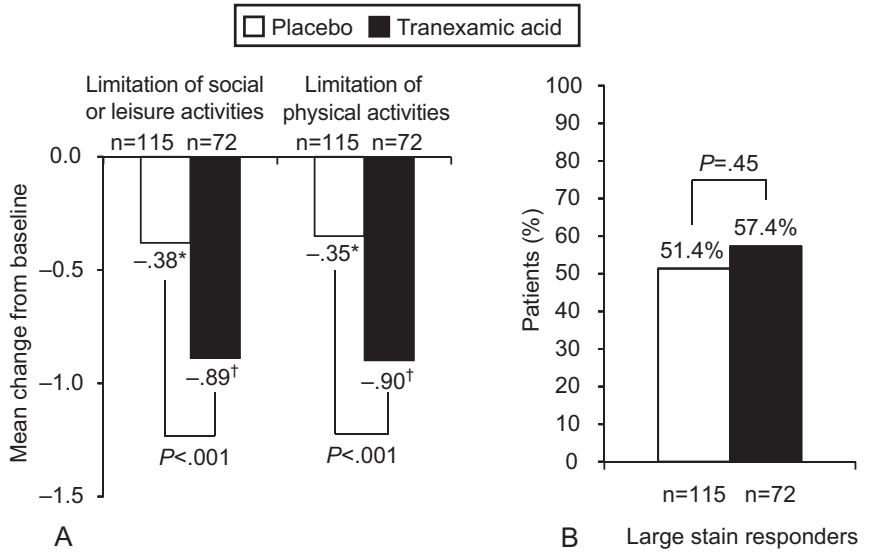

Fig. 4. Prespecified secondary efficacy end-point analysis. Effects of tranexamic acid and placebo on mean reductions from baseline in scores for limitation of social or leisure activities and limitation of physical activities **(A)** and percentage of women who experienced a decrease from baseline in the number of large stains **(B)**. *$P<.01$ compared with baseline; †$P<.001$ compared with baseline.

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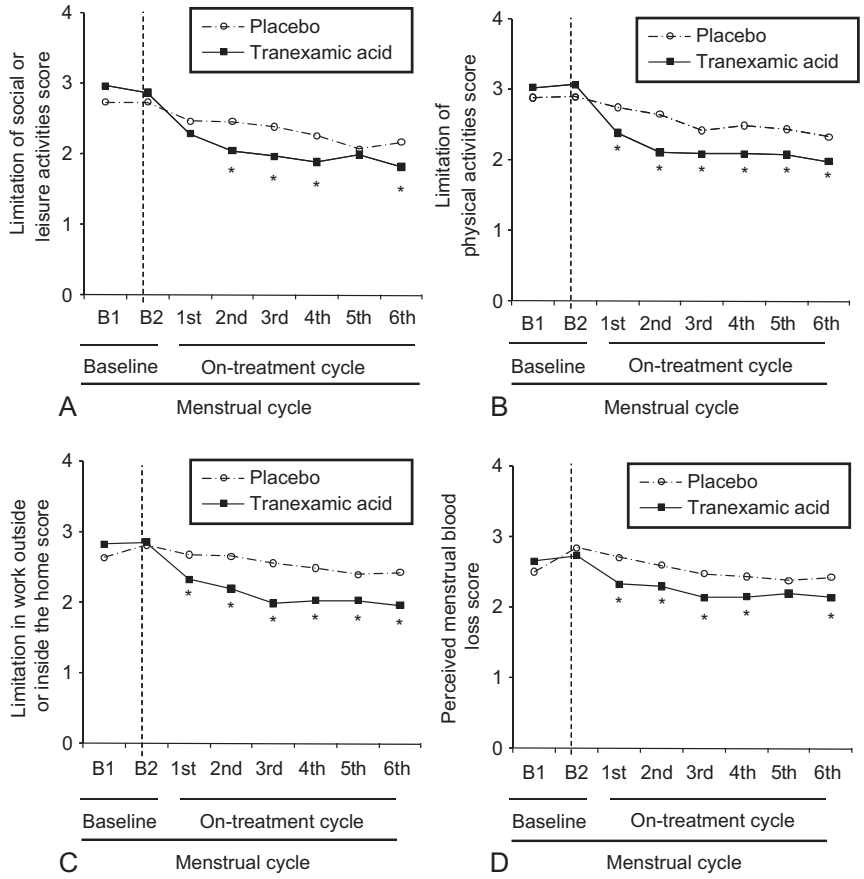

Fig. 5. Health-related quality-of-life question scores at baseline and during study. Effects of tranexamic acid and placebo on mean scores for limitation of social or leisure activities **(A)**, limitation of physical activities **(B)**, limitation in work outside or inside the home **(C)**, and perceived menstrual blood loss **(D)**. **P*<.05 compared with placebo.

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or electrocardiograph parameters were observed during the study.

DISCUSSION

In this phase 3 trial, a new oral tranexamic acid formulation provided quantitative and qualitative relief for women with heavy menstrual bleeding. In terms of menstrual blood loss, the three-part primary efficacy end point was achieved in significantly more women treated with tranexamic acid than with placebo, and tranexamic acid treatment resulted in consistent improvement irrespective of baseline menstrual blood loss or the presence of uterine leiomyomas. More than two thirds of women treated with tranexamic acid experienced clinically meaningful reductions in menstrual blood loss (36 mL and greater), with a significantly greater proportion of tranexamic acid–treated menstrual cycles reaching menstrual blood loss volumes within the normal range (less than 80 mL) compared with placebo. Moreover, women receiving tranexamic acid reported statistically and, most likely, clinically significant improvements in health-related quality-of-life parameters compared with those receiving placebo. Improvements in both menstrual blood loss and health-related quality-of-life parameters were observed during the first treatment cycle and were maintained throughout the 6-month study duration.

Quantitative measurements of menstrual blood loss used in clinical trials are typically not practical in routine clinical care, as women are required to collect and return all menses captured on sanitary products for laboratory analysis. Previous studies had suggested that tranexamic acid improves health-related quality of life in women with heavy menstrual bleeding, although limitations in study design (eg, open-label, nonspecific health-related quality-of-life assessment tool, lack of a placebo group) hindered interpretation of clinical relevance.[19–21] By using a validated patient-reported outcomes tool in a placebo-controlled, double-blind study, we feel that the statistically significant improvements in health-related quality of life with tranexamic acid compared with placebo in our study represent a clinically significant and meaningful finding for women with heavy menstrual bleeding.

Mean hemoglobin or ferritin levels did not appreciably improve from baseline in the tranexamic

Table 3. Frequently Reported Treatment-Emergent Adverse Events* (Intent-to-Treat Population)

Adverse Event	Tranexamic Acid (n=117)	Placebo (n=72)	P†
Menstrual discomfort/ cramps	72 (61.5)	36 (50.0)	.120
Headache	65 (55.6)	36 (50.0)	.457
Back pain	28 (23.9)	14 (19.4)	.471
Nausea	17 (14.5)	11 (15.3)	.888
Anemia	12 (10.3)	4 (5.6)	.260
Arthralgia	11 (9.4)	5 (6.9)	.556
Viral upper respiratory tract infection	9 (7.7)	7 (9.7)	.626
Multiple allergies	10 (8.5)	5 (6.9)	.692
Abdominal discomfort	8 (6.8)	6 (8.3)	.703
Cough	7 (6.0)	5 (6.9)	.792
Insomnia	6 (5.1)	6 (8.3)	.380
Fatigue	8 (6.8)	3 (4.2)	.446
Muscle cramps	8 (6.8)	3 (4.2)	.446
Dyspepsia	3 (2.6)	8 (11.1)	.015
Migraine	7 (6.0)	4 (5.6)	.903
Sinus headache	9 (7.7)	2 (2.8)	.161

Data are n (%) unless otherwise specified.
* Events that occurred in more than 10 participants irrespective of causality.
† *P* was determined using a χ^2 test.

acid treatment group and were not significantly different from the placebo group. These findings may be due in part to the use of oral iron therapy in individuals with low baseline hemoglobin and ferritin levels, the greater number of participants in the tranexamic acid group with anemia at baseline, and the higher mean baseline menstrual blood loss measured in the placebo group. In addition, changes in hemoglobin and ferritin concentrations are more likely to be observed over the long term (more than 6 months) in a population with chronic cyclic heavy menstrual bleeding such as ours (mean duration of heavy menstrual bleeding, 10 years). Future studies should assess the long-term efficacy of tranexamic acid.

The formulation of tranexamic acid used in this study was well tolerated. Previous studies of an immediate-release tranexamic acid formulation indicate that therapy-limiting gastrointestinal adverse effects occurred.[16,22] The novel, oral formulation of tranexamic acid studied here was designed to decrease the rate of drug delivery to the gastric mucosa and therefore facilitate gastrointestinal tolerability. In the current study, the frequency of gastrointestinal-related adverse events was comparable between tranexamic acid and placebo groups. Eye examinations were included in our evaluation of safety because focal areas of retinal degeneration have been observed in animal studies of intravenous tranexamic acid and visual abnormalities have been noted in postmarketing surveys. Treatment-related ocular findings in this study were not considered clinically significant.

In women with heavy menstrual bleeding, tranexamic acid appears to stabilize the deposition of endometrial vascular wall fibrin that occurs with menstruation,[13] but is unlikely to increase thrombosis. Thrombosis has not been observed in men or women receiving tranexamic acid for the management of bleeding secondary to cardiac or oral surgery, acute upper gastrointestinal bleeding, or ocular trauma,[13,14,23] and the use of tranexamic acid is not associated with an increased risk or incidence of thromboembolic events compared with the background rate of thrombotic events in women of childbearing age.[14,24,25] The results from the tranexamic acid clinical program, including a long-term, open-label safety study in women treated with tranexamic acid for up to 27 months (data not shown), support these studies and retrospective evaluations. Although one thrombotic event was reported in this clinical study, it occurred in a participant receiving placebo.

One limitation of the study was the prohibition of certain medications during the entire study period (eg, hormonal contraceptives) or during the women's menstrual cycle (eg, nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors) to avoid potential confounding effects on menstrual blood loss or adverse events[12] (Mirena package insert, Bayer HealthCare Pharmaceuticals, Wayne, NJ, October 2009). Additional data are needed to determine whether concomitant use of these medications with tranexamic acid would influence the risk of certain adverse events.

In the current study, use of tranexamic acid significantly reduced menstrual blood loss from baseline and improved health-related quality of life while maintaining safety and tolerability. The adverse events were predominantly mild to moderate, with an incidence of gastrointestinal events that was comparable with placebo. Tranexamic acid offers a first-line, nonhormonal, nonsurgical treatment option for women with cyclic heavy menstrual bleeding that may become an important alternative to surgical procedures and medical treatments.

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