Management of Initial Bleeding or Spotting After Levonorgestrel-Releasing Intrauterine System Placement

A Randomized Controlled Trial

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OBJECTIVE: To assess the efficacy of tranexamic acid or mefenamic acid in the management of the initial “nuisance” bleeding or spotting in the period immediately after placement of the levonorgestrel-releasing intrauterine system.

METHODS: Women were randomized after levonorgestrel-releasing intrauterine system placement to oral tranexamic acid (500 mg), mefenamic acid (500 mg), or placebo three times daily during bleeding or spotting episodes over a 90-day treatment period. Treatment was initiated from onset of a bleeding or spotting episode and continued until the first day after bleeding or spotting stopped and restarted with a new bleeding or spotting episode. The primary efficacy variable was reduction in the number of bleeding or spotting days. Tranexamic acid and mefenamic acid were compared with placebo using a one-sided Wilcoxon rank-sum test. Bonferroni-Holm adjustment was used to account for multiple testing.

RESULTS: A total of 204 women were screened; 187 were randomized to tranexamic acid (n = 63), mefenamic acid (n = 63), or placebo (n = 61). The median number of bleeding or spotting days experienced during treatment was 25, 29, and 33 days in the three groups, respectively. The median number of bleeding or spotting days was reduced by 6 days (95% confidence interval [CI] –14.0 to 1.0, P = .049) with tranexamic acid and by 3 days (95% CI –11.0 to 5.0, P = .229) with mefenamic acid compared with placebo. The relative risk of bleeding or spotting compared with placebo with tranexamic acid and mefenamic acid was 0.82 (95% CI 0.65–1.03) and 0.89 (95% CI 0.71–1.11), respectively. Most women (85% or more) were satisfied with the levonorgestrel-releasing intrauterine system across the groups.

CONCLUSIONS: Tranexamic acid and mefenamic acid during the first 90 days after levonorgestrel-releasing intrauterine system placement do not alleviate “nuisance” bleeding or spotting.


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LEVEL OF EVIDENCE: 1

Disturbance of uterine bleeding patterns, often anecdotally referred to as “nuisance bleeding,” is common during the first few months after placement of the levonorgestrel-releasing intrauterine system. During the first 3 months of use, prolonged bleeding has been reported by 22% and irregular bleeding by 67% of women after postmenstrual placement of the levonorgestrel-releasing intrauterine system, which declined to 3% and 19%, respectively, by the end of the first
year. To avoid unnecessary removals as a result of initial bleeding-related issues, women wishing to use the levonorgestrel-releasing intrauterine system need to be counseled regarding the expected bleeding pattern.

The limited data on the medical management of uterine bleeding disturbances after levonorgestrel-releasing intrauterine system placement suggest an inconclusive benefit with mifepristone or a progesterone receptor modulator. Tranexamic acid, which reduces menstrual blood loss by 28–58% in women with heavy menstrual blood loss, may be an effective treatment for irregular bleeding associated with depot medroxyprogesterone acetate or the subdermal levonorgestrel-releasing implant. Nonsteroidal anti-inflammatory drugs (NSAIDs) are superior to placebo for the treatment of heavy menstrual blood loss (reduce menstrual blood loss by 20–49%) and dysmenorrhea, and in the management of bleeding or spotting, or dysmenorrhea associated with copper intrauterine device (IUD) use. Naproxen was shown to achieve a 10% reduction in bleeding and spotting days compared with placebo in recent study.

We undertook this study to investigate whether counseling plus tranexamic acid or the NSAID, mefenamic acid, was superior to counseling plus placebo in the management of initial bleeding or spotting after levonorgestrel-releasing intrauterine system placement.

MATERIALS AND METHODS

This prospective, double-blind, three-arm, randomized placebo-controlled, phase IV study was conducted between March and December 2011 in 12 study centers in Denmark, Ireland, and Norway. The protocol and all protocol amendments were reviewed and approved by each study site’s institutional review board before the start of the study and before implementation of the amendment, respectively. The study was conducted according to the principles of Declaration of Helsinki of 1975, which was revised in 1983. All participants provided written, informed consent before entry into the study.

Healthy women aged 18–45 years requesting contraception and who had a history of regular, cyclic menstrual cycles (cycle length 21–35 days) without use of hormonal contraceptives, normal or clinically insignificant cervical smear not requiring further follow-up, were recruited to the study. Ultrasonographic examination was not part of the trial procedures because routine vaginal ultrasound in these women was not standard practice before IUD placement in the participating countries. Women were excluded if they were pregnant or breastfeeding, had not had at least two complete menstrual cycles after removal of a previous levonorgestrel-releasing intrauterine system, had a vaginal or cesarean delivery or abortion within 6 weeks of initial screening, had an infected abortion or postpartum endometritis within 90 days of screening, had been indicated for treatment of idiopathic heavy menstrual bleeding or had a history of abnormal bleeding, had any pelvic, genital, or gynecologic abnormalities, had any malignancy or severe hypertension, or had used long-acting contraceptive methods within 90 days of screening. Women who had daily or frequent NSAID use for any condition or those unwilling to use non-NSAIDs (eg, paracetamol) for pain management were also excluded. Use of medications known to affect vaginal bleeding patterns (eg, gonadotropin-releasing hormone analogs, danazol, or anticoagulants as well as oral, vaginal, injectable, or transdermal hormonal contraception, copper IUDs, and implants) or other NSAIDs was prohibited during the study.

Women enrolled to the study received standardized structured preplacement counseling on the bleeding or spotting associated with levonorgestrel-releasing intrauterine system use. The women undertook a pregnancy test to exclude the possibility of pregnancy. The levonorgestrel-releasing intrauterine system was then placed within 7 days of the onset of menstruation or withdrawal bleeding. Women with successful levonorgestrel-releasing intrauterine system placement were randomized 1:1:1 to treatment with encapsulated (all study drug capsules were identical in appearance to maintain blinding) oral tranexamic acid (500 mg), mefenamic acid (500 mg), or placebo (lactose and magnesium stearate, encapsulated to appear identical to study treatments) three times daily during bleeding or spotting episodes. Randomization was performed in a sequential manner in blocks of six using a SAS-generated randomization list prepared by the study sponsor. Oral study treatment was scheduled to start on the first day of a bleeding or spotting episode [however, if the bleeding or spotting episode started in the afternoon or evening, the women were instructed to start study drug treatment the morning of the next day] until bleeding or spotting stopped (ie, first bleeding-free or spotting-free day) without restriction to treatment length. The first treatment was to be started on the day after levonorgestrel-releasing intrauterine system placement and continued as described and was to be restarted on occurrence of all bleeding or spotting episodes during the 90 days of study assessment followed by a 30-day follow-up period without oral study treatment. The women were also instructed to take a full day’s dose of study drug (ie, one capsule three times per day).
All women were given diary cards to record on a daily basis vaginal bleeding, study drug intake, and use of pain medication for dysmenorrhea. Occurrence of dysmenorrhea was also recorded at the end of study treatment and at the end of study. The intensity of vaginal bleeding was recorded according to bleeding intensity based on the woman’s subjective experience as follows: none, no vaginal bleeding; spotting, less than associated with normal menstruation relative to the woman’s experience with no need for sanitary protection (except for panty liners); light, less than associated with normal menstruation relative to the woman’s experience with need for sanitary protection; normal, like normal menstruation relative to the woman’s experience; and heavy, more than normal menstruation relative to the woman’s experience. Compliance to treatment was assessed through diary card recordings of the number of capsules taken, along with all used study drug packaging and any remaining unused study drug.

Bleeding and spotting days and episodes were assessed for the full analysis set (all randomized women with at least one clinical observation) using the terminology proposed by the World Health Organization. In our study, bleeding intensity rated as light, normal, or heavy was classified as bleeding to be consistent with the World Health Organization definitions. A one-sided, nonparametric Wilcoxon rank-sum test was used to compare the cumulative number of bleeding or spotting days during the 90-day treatment period observed in the placebo group pairwise with the two active study drug treatment groups. The Bonferroni-Holm procedure was used to adjust the significance level to account for the number of comparisons made. The Hodges-Lehmann estimates for the differences in the number of bleeding or spotting days between the treatment groups with active oral study drug and the placebo treatment group were accompanied by corresponding unadjusted exact 95% confidence intervals. The Hodges-Lehmann estimator is a robust estimator for the shift in the distribution of two groups. A direct comparison between tranexamic acid and mefenamic acid was also performed using a two-sided Wilcoxon rank-sum test providing the P-value, Hodges-Lehmann estimate, and corresponding 95% confidence interval. No α adjustments were performed between active treatments comparison because this analysis was considered to be secondary. The number of bleeding or spotting days was compared using univariable and multivariable Poisson regression models to estimate the relative risk (RR) between treatment groups along with 95% confidence intervals and to explore the effects of the following baseline characteristics: age (in years) or age category (younger than 35 years compared with 35 years or older); current smoker (yes or no); body mass index (as continuous variable, calculated as weight (kg)/ [height (m)]²); and parity status (number of births, zero compared with one or more).

The sample size (calculated using nQuery Advisor 6.01) was based on experience from a previous study with the levonorgestrel-releasing intrauterine system. Assuming a mean reduction in the number of bleeding or spotting days during the 90-day treatment period of at least 25% (consider the convention margin for superiority, corresponding to a reduction by 12.5 bleeding or spotting days) with active study drug treatment compared with placebo and a common standard deviation of 20 bleeding or spotting days, then 62 women per treatment group (assuming a 20% dropout rate) would be needed for a one-sided Wilcoxon rank sum test at a 5% α level to achieve a 90% power for a single comparison. Based on a Bonferroni adjustment, ie, a significance level of 2.5% per one-sided test, a power of more than 83% could be achieved for a single test based on the aforementioned assumptions.

RESULTS

The flow of participants through the study is shown in Figure 1. A total of 204 women were screened, of whom 187 were randomized after successful placement of the levonorgestrel-releasing intrauterine system to receive oral tranexamic acid (n=63), mefenamic acid (n=63), or placebo (n=61). Demographic and baseline characteristics of the women enrolled to the study are summarized in Table 1. There were no statistically significant differences between the treatment groups. There were 41 (22.3%) nulliparous women included in the study. Compliance to 80% or more of planned days (ie, the percentage of days with bleeding or spotting where study medication was taken) of oral study drug intake was recorded in 83.9%, 87.1%, and 90.0% of participants in the tranexamic acid, mefenamic acid, and placebo groups, respectively. Total average cumulative numbers of capsules taken were 80.5±50.2, 86.3±52.6, and 97.8±61.7 in the three groups, respectively.

Figure 2 shows the box–whisker plot of the number of bleeding or spotting days during the 90-day treatment period. The median number of bleeding or spotting days was lowest in the tranexamic acid group followed by the mefenamic acid and placebo groups, respectively. The median reduction in the number of bleeding or spotting days was estimated...
Potential participants screened n=204
Denmark: 93
Ireland: 34
Norway: 77

Participants randomized n=187
Tranexamic acid n=63
Mefenamic acid n=63
Placebo n=61

Excluded from full analysis set because of no observation after randomization n=1

Full analysis set n=62
Did not complete treatment phase: n=5
Adverse event: 3
Withdrawal of consent: 1
Lost to follow-up: 1

Completed treatment phase n=57
Did not complete follow-up period; adverse event n=1

Completed follow-up period n=56

Excluded from full analysis set because of no observation after randomization n=1

Full analysis set n=62
Did not complete treatment phase: n=6
Adverse event: 4
Lost to follow-up: 2

Completed treatment phase n=56
Did not complete follow-up period; adverse event n=1

Completed follow-up period n=55

Excluded from full analysis set because of no observation after randomization n=1

Full analysis set n=60
Did not complete treatment phase: n=3
Withdrawal of consent: 2
Lost to follow-up: 1

Completed treatment phase n=57
Did not complete follow-up period; withdrawal of consent n=1

Completed follow-up period n=56

Screening failures: n=17
Denmark: 4
Ireland: 6
Norway: 7

Table 2 summarizes the data for the additional bleeding or spotting parameters assessed. The number of bleeding-only days and the length of the bleeding or spotting episodes tended to be lower with tranexamic acid compared with mefenamic acid or placebo. The number of spotting-only days and number of bleeding or spotting episodes were similar between the groups. The change in the number of bleeding or spotting days between the last 30 days on study drug treatment and the 30-day follow-up period was also evaluated to determine whether the treatments assessed were only postponing the initial “nuisance” bleeding or spotting. There was no increase observed in the number of bleeding or spotting days in any of the treatment groups, suggesting that study treatments do not postpone the initial “nuisance” bleeding or spotting (Table 2).
Outcomes of univariable and multivariable analyses of the number of bleeding or spotting days during the 90-day treatment period using Poisson regression models are summarized in Table 3. There was no significant difference in the RR of bleeding or spotting with tranexamic acid compared with placebo. Variables such as age, body mass index, or smoking status did not have a marked influence on bleeding or spotting compared with placebo.

The proportion of women who reported being satisfied with the study drug (ie, when specifically questioned about satisfaction with study drug) used to manage initial bleeding or spotting ranged between 63.8% and 66.4% across the three study groups (Fig. 3). In addition, there were no marked differences in participant satisfaction with the levonorgestrel-releasing intrauterine system (ie, when specifically questioned about satisfaction with the levonorgestrel-releasing intrauterine system) between the treatment groups with 85% or more women reporting being satisfied across the groups. This indicates that satisfaction with the study drug does not influence overall satisfaction with the levonorgestrel-releasing intrauterine system. Continuation rates after 16 weeks were 96.7%, 96.6%, and 98.3% in the tranexamic acid, mefenamic acid, and placebo groups, respectively, indicating no influence of study drug on early discontinuation among the treatment groups.

The proportion of women with dysmenorrhea decreased from 40% at baseline to approximately 20% in all three groups at the end of treatment and at the end of the study (data not shown). Only one woman

![Fig. 2. Box–whisker plot of the number of bleeding or spotting days during the 90-day treatment period by treatment group (full analysis set). The lower and upper ends of the box indicate the first to third quartile, respectively; the horizontal line indicates the median and the cross indicates the mean. Vertical lines (whiskers) indicate the minimum to maximum.](image-url)
reported severe dysmenorrhea at the end of treatment and none at the end of the study compared with nine women (approximately 5%) at baseline. Inversely, the proportion of women free of dysmenorrhea increased from approximately 60% at screening to approximately 80% at the end of the study, showing the effect of the levonorgestrel-releasing intrauterine system in the alleviation of dysmenorrhea. The median number of days of pain medication use to alleviate dysmenorrhea during the treatment period was zero in all groups.

The treatment-emergent adverse events are summarized in Table 4. Adverse events related to the gastrointestinal tract tended to be higher in the tranexamic acid group compared with the other two groups, and occurrence of headache tended to be lower in the mefenamic acid group compared with the other groups; however, there was no statistically significant difference in the occurrence of any single adverse event nor in the occurrence of different adverse events belonging to the same organ class between the treatment groups. Two women receiving tranexamic acid experienced a serious adverse event. One had a previously inserted, asymptomatic intraabdominal copper IUD that was assumed spontaneously expelled (it was not removed according to investigator clinical judgment). Another had endometritis resulting in hospitalization, which resolved completely after antibiotic treatment and removal of the levonorgestrel-releasing intrauterine system.

**DISCUSSION**

Tranexamic acid and mefenamic acid during the first 90 days after levonorgestrel-releasing intrauterine system placement do not alleviate the initial “nuisance” bleeding or spotting associated with the intrauterine system to a clinically meaningful degree. We do not believe that there were any relevant “placebo effects” to confound our results because the mean number of bleeding or spotting days observed in the placebo group in this study was consistent with those reported in a similar group of patients in another study that assessed the contraceptive effectiveness of the levonorgestrel-releasing intrauterine system (35 days compared with 36 days).11

The strengths of our study include the randomized, blinded, placebo-controlled design, use of standardized structured levonorgestrel-releasing intrauterine system preplacement counseling, and the careful monitoring of compliance with study drug treatment. Potential weaknesses included patient selection, more than 95% of the women recruited were white, and it is possible that our results may not be generally applicable to other ethnic groups. In addition, a greater reduction in bleeding or

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### Table 2. Bleeding or Spotting Parameters During the 90-Day Treatment Phase (Full Analysis Set)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tranexamic Acid (n=55)</th>
<th>Mefenamic Acid (n=57)</th>
<th>Placebo (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of bleeding or spotting days</td>
<td>25.0 (13.0, 40.0)</td>
<td>29.0 (15.0, 44.0)</td>
<td>33.0 (15.0, 53.5)</td>
</tr>
<tr>
<td>No. of bleeding-only days</td>
<td>8.0 (4.0, 16.0)</td>
<td>10.0 (5.0, 18.0)</td>
<td>11.5 (6.0, 19.5)</td>
</tr>
<tr>
<td>No. of spotting-only days</td>
<td>15.0 (7.0, 22.0)</td>
<td>16.0 (8.0, 25.0)</td>
<td>16.0 (7.0, 27.0)</td>
</tr>
<tr>
<td>No. of bleeding or spotting episodes</td>
<td>5.0 (3.0, 6.0)</td>
<td>4.0 (3.0, 5.0)</td>
<td>4.0 (3.0, 5.0)</td>
</tr>
<tr>
<td>Length of bleeding or spotting episodes (d)</td>
<td>5.2 (3.5, 7.0)</td>
<td>7.0 (4.7, 9.6)</td>
<td>7.0 (4.0, 12.0)</td>
</tr>
<tr>
<td>Change in the no. of bleeding or spotting days*</td>
<td>0 (–1.0, 3.0)</td>
<td>1.0 (–1.0, 4.0)</td>
<td>0 (–4.0, 3.0)</td>
</tr>
</tbody>
</table>

Data are median (quartile 1, quartile 3).

* Change in the number of bleeding or spotting days from the last 30 days of oral blinded treatment to the first 30 days without blinded treatment.

### Table 3. Univariable and Multivariable Poisson Regression Analyses of the Number of Bleeding or Spotting Days During the 90-Day Treatment Period (Full Analysis Set)

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Univariable (n=168)</th>
<th>Multivariable (n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tranexamic acid vs placebo</td>
<td>0.81 (0.64–1.02)</td>
<td>0.82 (0.65–1.03)</td>
</tr>
<tr>
<td>Mefenamic acid vs placebo</td>
<td>0.90 (0.72–1.12)</td>
<td>0.89 (0.71–1.11)</td>
</tr>
<tr>
<td>Tranexamic acid vs mefenamic acid</td>
<td>0.90 (0.71–1.14)</td>
<td>0.92 (0.72–1.17)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.00 (0.98–1.01)</td>
<td>1.00 (0.98–1.02)</td>
</tr>
<tr>
<td>BMI at baseline (kg/m²)</td>
<td>0.98 (0.95–1.00)</td>
<td>0.98 (0.96–1.00)</td>
</tr>
<tr>
<td>Current smoker (yes vs. no)</td>
<td>0.89 (0.69–1.15)</td>
<td>0.91 (0.70–1.17)</td>
</tr>
</tbody>
</table>

BMI, body mass index.

Data are relative risk (95% confidence interval).
spotting days may have been easier to show in women using the levonorgestrel-releasing intrauterine system for treatment of heavy menstrual blood loss. However, this would have resulted in a highly selected patient population, preventing extrapolation of our results to the general population of women using the levonorgestrel-releasing intrauterine system for contraception. Alternatively, we could have selected only women with a high number of bleeding or spotting days during the first month after levonorgestrel-releasing intrauterine system placement or women with a subjective complaint of irregular bleeding or spotting (two overlapping but not identical groups). However, this may have increased the screening phase to at least 30 days, after which the condition may have resolved without intervention; most “nuisance” bleeding or spotting occurs during the first month followed by a rapid reduction in these events.

Treatment of bleeding or spotting with tranexamic acid tended to be associated with fewer bleeding or spotting days, shorter bleeding or spotting episodes, compared with mefenamic acid or placebo. It may be argued that the dose of tranexamic acid (1.5 g/d) used in this study was too low and that a higher dose may have resulted in a higher treatment effect. However, 1 g tranexamic acid per day has been previously shown to be more effective than

Fig. 3. Satisfaction with the levonorgestrel-releasing intrauterine system (full analysis set). There was no statistically significant difference in women who were “very satisfied” or “satisfied” compared with those who were “very dissatisfied” or “dissatisfied” among the three treatment-groups (P values not shown).

Table 4. Treatment-Emergent Adverse Events Reported for 2% or More of Participants by Primary System Organ Class and Preferred Term (Full Analysis Set)

<table>
<thead>
<tr>
<th>Primary System Organ Class Preferred Term</th>
<th>Tranexamic Acid (n=62)</th>
<th>Mefenamic Acid (n=62)</th>
<th>Placebo (n=60)</th>
<th>Total (N=184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with any adverse event</td>
<td>29 (46.8)</td>
<td>29 (46.8)</td>
<td>26 (43.3)</td>
<td>84 (45.7)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>12 (19.4)</td>
<td>4 (6.5)</td>
<td>6 (10.0)</td>
<td>22 (12.0)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>3 (4.8)</td>
<td>1 (1.6)</td>
<td>0</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (1.6)</td>
<td>2 (3.2)</td>
<td>3 (5.0)</td>
<td>6 (3.3)</td>
</tr>
<tr>
<td>Abdominal pain lower</td>
<td>3 (4.8)</td>
<td>0</td>
<td>2 (3.3)</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3.2)</td>
<td>0</td>
<td>3 (5.0)</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td>General disorders and administration site conditions*</td>
<td>2 (3.2)</td>
<td>1 (1.6)</td>
<td>2 (3.3)</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>7 (11.3)</td>
<td>7 (11.3)</td>
<td>6 (10.0)</td>
<td>20 (10.9)</td>
</tr>
<tr>
<td>Influenza</td>
<td>1 (1.6)</td>
<td>3 (4.8)</td>
<td>0</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>4 (6.5)</td>
<td>0</td>
<td>2 (3.3)</td>
<td>6 (3.3)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>5 (8.1)</td>
<td>2 (3.2)</td>
<td>7 (11.7)</td>
<td>14 (7.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (8.1)</td>
<td>2 (3.2)</td>
<td>7 (11.7)</td>
<td>14 (7.6)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>3 (4.8)</td>
<td>2 (3.2)</td>
<td>1 (1.7)</td>
<td>6 (3.3)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>13 (21.0)</td>
<td>15 (24.2)</td>
<td>15 (25.0)</td>
<td>43 (23.4)</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>2 (3.3)</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>8 (12.9)</td>
<td>10 (16.1)</td>
<td>10 (16.7)</td>
<td>28 (15.2)</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>3 (4.8)</td>
<td>3 (4.8)</td>
<td>2 (3.3)</td>
<td>8 (4.3)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>0</td>
<td>2 (3.2)</td>
<td>4 (6.7)</td>
<td>6 (3.3)</td>
</tr>
</tbody>
</table>

Data are n (%).

* The general disorders and administration site conditions were: expulsion (n=2), previously inserted copper intrauterine device diagnosed as intraabdominal (n=1), and fatigue (n=2).
placebo in stopping bleeding episodes in women using subdermal contraceptive implants and depot medroxyprogesterone acetate.\textsuperscript{5,6} Moreover, in our study, treatment with a higher tranexamic acid dose may have resulted in lower compliance and more frequent adverse events as a result of the increased pill burden.

A recently published, placebo-controlled study with naproxen showed a nonsignificant reduction in bleeding or spotting of 4.5 days during the first 90 days after levonorgestrel-releasing intrauterine system placement.\textsuperscript{9} In that study, women received 500 mg naproxen or placebo twice daily for 5 days every 4 weeks during three 4-week periods. As such, the drug intake could have occurred at a time without any bleeding (expected menstrual bleeding or irregular bleeding or spotting). The relative risk of bleeding or spotting for naproxen compared with placebo was 0.90 (95% CI 0.84–0.97). Despite the difference in treatment regimen, the RR reported by Madden et al is similar to that observed for mefenamic acid (0.89, 95% CI 0.7–1.11) in our study, although our CI was wider despite the larger sample size and similar distribution of bleeding or spotting days. The narrower 95% CI reported by Madden et al suggests that they used a Poisson regression analysis without accounting for overdispersion. We believe that a statistical model of these data accounting for overdispersion would not have resulted in a significant effect for NSAIDs in reducing the initial bleeding or spotting associated with the levonorgestrel-releasing intrauterine system in the first few months after placement. None of our comparisons resulted in statistically significant differences, because we accounted for the additional variability in the bleeding or spotting days in our Poisson regression analysis. Had we not done so, the 95% CI for the RR would have excluded 1 as well and would have indicated a significant effect.

In conclusion, considering the overall risk benefit, we cannot recommend either tranexamic acid or mefenamic acid for prophylactic use in the management of initial “nuisance” bleeding or spotting with the levonorgestrel-releasing intrauterine system, because both drugs did not result in at least 25% reduction in the number of bleeding or spotting days during the first 3 months of levonorgestrel-releasing intrauterine system use. Future trials are needed to confirm whether tranexamic acid or other drugs can be used for the management of bleeding or spotting among levonorgestrel-releasing intrauterine system users with a subjective complaint of bleeding or spotting.

REFERENCES