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Consider this option for heavy menstrual bleeding

Women who fail to respond to—or are unable to tolerate—other treatments for heavy menstrual blood loss now have another choice.

PRACTICE CHANGER

Offer tranexamic acid to patients with heavy menstrual bleeding. The extended-release formulation is effective and well tolerated.[1]

STRENGTH OF RECOMMENDATION

A: Based on 1 good-quality randomized controlled trial (RCT).

Lukes AS, Moore KA, Muse KN, et al. Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial. *Obstet Gynecol.* 2010;116:865-875.

ILLUSTRATIVE CASE

A 32-year-old woman comes to your office complaining of heavy, but regular, menstrual bleeding, accompanied by clots and heavy cramping that often leave her drained and unable to work. She has taken oral contraceptives in the past, but they caused nausea, and nonsteroidal anti-inflammatory drugs (NSAIDs) did not provide adequate symptom relief.

A pelvic ultrasound shows that the patient has normal endometrial thickness and no fibroids. Aside from surgical intervention or the placement of a hormonal intrauterine device (IUD), what can you offer her?

Heavy menstrual bleeding is a frequent problem, common enough to cause an estimated 10% to 30% of women of reproductive age to seek treatment.[2-4] Often the bleeding is severe enough to adversely affect the patient's social, physical, and emotional well-being.

Adverse effects, variable efficacy limit use of other treatments

Quantitatively defined as blood loss ≥80 mL per cycle, heavy menstrual bleeding can also be diagnosed based on a patient's perception of menstrual blood loss and its effect on her daily life.[5,6] NSAIDs, hormonal medications, the placement of a hormonal IUD, and surgical procedures are all treatment options, but potential adverse effects, contraindications, personal preference, and variable efficacy can limit their use.[7]

The fibrinolysis-blood loss link

Fibrinolytic activity in menstrual blood, leading to increasing blood loss, has prompted the evaluation of hemostatic agents as potential therapeutic options.[8] Oral tranexamic acid decreases fibrinolysis, thereby reducing menstrual blood loss;[9] however, gastrointestinal (GI) side effects limit the usefulness of immediate-release tranexamic acid.[9,10]

This formulation of tranexamic acid has been used in Europe for heavy menstrual bleeding. A Cochrane review published in 2000 included 4 studies that compared immediate-release tranexamic acid therapy with placebo. The meta-analysis found a significant reduction in mean blood loss compared with placebo (weighted mean difference [WMD]=-94.0 mL; 95% confidence interval [CI], -151.4 to -36.5) and a significant change in mean reduction of blood loss (WMD=-110.2 mL; 95% CI, -146.5 to -73.8) compared with baseline in

the treatment group. However, only one of the studies measured perceived improvement in monthly menstrual blood loss, and its sample size was inadequate to provide a precise estimate of the effect (relative risk [RR] 2.5; 95% CI, 0.9-7.3).[11]

An extended-release option. Oral extended-release (ER) tranexamic acid (Lysteda), approved by the US Food and Drug Administration in 2009,[12] reduces blood loss with fewer GI effects than immediate-release tranexamic acid. In the RCT detailed below, Lukes et al assessed the efficacy and safety of this new formulation.

STUDY SUMMARY

ER formulation reduces blood loss, boosts quality of life

The researchers conducted a multicenter, randomized, double-blind placebo-controlled study comparing the effect of ER tranexamic acid on reduction of menstrual blood flow compared with placebo.[1] Reduction in menstrual blood loss >50 mL and a reduction in menstrual blood loss ≥36 mL (an amount previously established to be perceived as meaningful to women) were related primary outcomes. Improvements in limitations in social or leisure and physical activities and in self-perceived menstrual blood loss were secondary outcomes.

Study participants were women ages 18 to 49 years who had heavy menstrual bleeding, a normal pelvic exam, and a normal transvaginal ultrasound; current use of a nonhormonal birth control method was also required. Women with fibroids were not excluded unless surgery was planned. Exclusion criteria included significant coagulation issues, endocrinopathy, ocular disease, pregnancy or lactation, endometrial abnormalities, cervical cancer, anovulatory dysfunctional uterine bleeding, metrorrhagia, menometrorrhagia, and polymenorrhea.

Participants were randomized to receive either tranexamic acid 1.3 g by mouth 3 times a day for 5 days per menstrual cycle, beginning with the onset of heavy bleeding, or a matched placebo. The use of anticoagulants or NSAIDs during the menstrual period was not permitted.

Heavy bleeding was defined as ≥60 mL of blood loss in one measured cycle and an average ≥80 mL of blood loss over 2 measured cycles.

Mean reduction in blood loss per cycle over 6 cycles was 70 mL (a 40.4% reduction) in the active treatment group vs 13 mL (an 8.2% reduction) in the placebo group ($P<.001$). The proportion of women with a ≥50% reduction from baseline in blood loss was greater in the tranexamic acid group compared with the placebo group (35% vs 7%; $P<.001$), yielding a number needed to treat of 4. The mean reduction in *perceived* blood loss was also greater in the treatment group, but the difference was not statistically significant.

The researchers used a validated menstrual quality-of-life scale that measured social and physical quality of life using a 5-point Likert scale. Women treated with tranexamic acid had a mean reduction of 0.89 points from baseline on the social and leisure activity question, compared with a mean reduction of 0.38 points for those in the placebo group. On the physical activity question, those in the tranexamic acid group had a mean reduction of 0.90 points from baseline, vs a mean decline of 0.35 points in the placebo group.

These findings indicate that the women who received tranexamic acid experienced significantly fewer limitations in social and physical activities. Responses to a question about limitations in work activities showed that the treatment group had significant improvements there, as well. The ER form of tranexamic acid used in the study was well tolerated, with no significant differences in adverse effects between the intervention and control groups.

WHAT'S NEW

Women with heavy menstrual bleeding have a new option

The ER formulation of tranexamic acid used in the study does not appear to have the GI side effects associated with the immediate-release formula.

Tranexamic acid is taken only during the menstrual cycle and does not interfere with ovulation. Thus, it can be used by women

Extended-release tranexamic acid is better tolerated than the immediate-release formulation, with fewer GI adverse effects.

who desire fertility but are troubled by heavy bleeding.

CAVEATS

Questions about related conditions, use with hormones remain

The study included women with regular heavy menstrual periods (menorrhagia) and therefore may not be applicable to those with irregular heavy periods or anovulatory, dysfunctional uterine bleeding. In clinical practice, these conditions may overlap, but the safety and efficacy of tranexamic acid in such cases is unclear.

Another caveat, at least theoretically, is that research to date has neither identified nor excluded the possibility that tranexamic acid with concomitant use of hormonal agents might increase the risk of thrombotic events.[13] This risk is low based on evidence to date, but the theoretical uncertainty leads us to be cautious about the combination of tranexamic acid and hormonal therapy for long-term use.

Xanodyne Pharmaceuticals (which manufactured Lysteda) and Ferring Pharmaceuticals (its current owner) were major sponsors of this study. While we cannot recognize any source of bias as a result of sponsorship, the independence of the investigators in publishing the findings was not clearly stated, so it is possible that future independent studies would contradict these findings.

CHALLENGES TO IMPLEMENTATION

The treatment is costly

Lysteda is expensive, costing about $170 for 30 tablets of 650 mg each.[14] Cost aside, ER tranexamic acid appears to be safe, with no major barriers to its use. JFP

Women who took tranexamic acid were 5 times more likely to have a ≥50% reduction in blood loss from baseline compared with those receiving placebo.

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