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EXPERT REVIEW

Reducing Heavy Menstrual Bleeding: Safety and Efficacy of Tranexamic Acid

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Abstract: Menorrhagia or Heavy Menstrual Bleeding (HMB) remains a public health challenge among women in the reproductive age group. Anti-fibrinolytics such as tranexamic acid and epsilon aminocaproic acid, play an important role in the medical management of HMB, as HMB is associated with an increase in local fibrinolysis. Lysteda is a novel oral formulation of tranexamic acid which has recently been approved by the US FDA for treatment of HMB. Efficacy of tranexamic acid in the general gynecologic population as well as in women with bleeding disorders is discussed in this review. Safety and adverse effect profile is also addressed for both these populations.

Keywords: heavy menstrual bleeding, menorrhagia, anti-fibrinolytics, tranexamic acid

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Introduction

Menorrhagia is a public health challenge with over 18 million women affected worldwide.[1] Menorrhagia can be defined as heavy menstrual bleeding lasting for more than 7 days or resulting in the loss of more than 80 mL per menstrual cycle.[2] A pictorial blood assessment chart or PBAC score is a pictorial method of assessment of menstrual blood loss.[3] The PBAC score has been validated in adult women with greater than 80% sensitivity and specificity for scores greater than 100 for a diagnosis of menorrhagia.[3] One study found that variables that predicted a blood loss of greater than 80 mL per menses were clots greater than 1 inch, low ferritin levels or changing a pad or tampon more than hourly (flooding).[4] The etiology of menorrhagia could be either gynecologic and endocrinologic conditions, or disorders of hemostatic imbalance. The American College of Obstetricians and Gynecologists (ACOG) committee on gynecologic practice recommends screening for common bleeding disorders such as von Willebrand disease (VWD) for adolescents with menorrhagia, adult women with menorrhagia, and women undergoing hysterectomy for the sole indication of menorrhagia.[5] While there is limited data on the prevalence of bleeding disorders among adolescents with menorrhagia, the available data suggest the prevalence of VWD to be 5%–36%; the prevalence of platelet dysfunction to be 2%–44%, the presence of a clotting factor deficiency to be 8%–9% and the presence of thrombocytopenia to be 13% to 20%.[6] Gynecologic and endocrinologic causes of menorrhagia include anovulatory bleeding, anatomic causes such as polyps and fibroids, and very rarely endometrial cancers. The most common anatomic cause of menorrhagia in premenopausal women is uterine polyps and submucous fibroids.[7] The most common endocrinologic cause of menorrhagia is anovulatory bleeding usually seen in adolescent and perimenopausal populations. Polycystic ovary syndrome (PCOS) is a syndrome of anovulation, irregular and heavy menses, obesity, hirsutism, and insulin resistance. Both hypo and hyperthyroidism can cause menorrhagia. Rarely, prolactin-producing tumors can cause menorrhagia. Choice of treatments often depend on the patient's age, future fertility wishes, and in some cases, individual treatment preferences. Medical management includes medications containing estrogen, progestins, or a combination of the two, the insertion of progestin containing intrauterine devices, antifibrinolytics such as tranexamic acid (Lysteda) or epsilon amino caproic acid (Amicar), 1-desamino-8-D-arginine vasopressin (DDAVP), and in some cases non-steroidal aniti-inflammatory drugs (NSAIDS). Surgical options include endometrial ablation and hysterectomy. Tranexamic acid is an attractive option for medical management of menorrhagia in all age groups as it is safe, effective, and non-hormonal method of treatment with very few reports of adverse events.

Role of Anti-Fibrinolytics in Treatment of Menorrhagia

Heavy menstrual bleeding (HMB) is associated with an increase in local fibrinolysis.[8] Plasminogen activators are a group of enzymes that cause fibrinolysis (the dissolution of clots). An increase in the levels of plasminogen activators has been found in the endometrium of women with heavy menstrual bleeding compared to those with normal menstrual loss.[9] Plasminogen activator inhibitors (antifibrinolytic agents) have therefore been promoted as a treatment for heavy menstrual bleeding. Most of the studies in literature are with tranexamic acid as the anti-fibrinolytic agent. The effect of tranexamic acid on lowering endometrial tPA activity and menstrual fluid fibrinolysis has been reported in women with heavy menstrual bleeding.[10]

Only two medications are approved by the US FDA for treatment of HMB—tranexamic acid and levonorgestrel-release intrauterine system (LNG-IUS [Mirena]). As an oral formulation of tranexamic acid was only recently approved in the US, epsilon aminocaproic acid (Amicar), a lysine analogue with similar mechanism of action as tranexamic acid has been clinically used. Studies using Amicar are lacking in women with HMB. Amicar is also reported to be 10 fold less potent than Lysteda.[11]

The Compound, Adverse Effect and Safety Profile

Tranexamic acid is a negatively charged synthetic lysine derivative that competitively inhibits plasmin activity.[12] It forms a reversible complex with plasminogen. Plasminogen is still converted to plasmin via an activator, however, the plasmin/tranexamic

acid complex cannot bind to fibrin, and fibrinolysis is inhibited.[13] A formulation of immediate-release tranexamic acid has been used safely and effectively for more than decades in Asia, Europe, Canada, and Australia. It was often given as two 500 mg tablets every 6 hours for up to 5 days for HMB and longer for mucocutaneous bleeding in patients with bleeding disorders such as hemophilia and von Willebrand disease.[14,15] However, this formulation can be associated with a lot of gastrointestinal adverse effects.[16] More recently, a novel oral formulation, Lysteda, designed to maximize efficacy and minimize gastrointestinal adverse effects, was approved by the US FDA for treatment of HMB.

The bioavailability of oral immediate-release tranexamic acid is approximately 34%, when taken with or without food, in healthy male volunteers.[17] A dose reduction is recommended with severe renal impairment.[18] No drug-drug interaction studies have been conducted with Lysteda. During menstruation, the recommended dose of Lysteda is 1.3 gms (two 650 mg tablets) three times daily for a maximum of 5 days without food or drink restrictions.

The safety of Lysteda was assessed in eight clinical studies—four in healthy volunteers and four in women with HMB. The eight studies included four phase I studies,[19,20] three phase III studies,[21–24] and one nine-cycle, open-label extension study.[25] The adverse events (AE) reported by more than 5% of subjects treated with Lysteda in the above mentioned studies were headache (50%), nasal and sinus symptoms (25%), back pain (20%), abdominal pain (19%), musculoskeletal pain (11%), arthralgia (7%), muscle cramps and spasms (6.5%), migraine (6%), and fatigue (5%). The combined safety results indicate a favorable adverse event profile for Lysteda. A total of 1276 women have received Lysteda in the eight clinical trials that led to its approval, with treatment data lasting up to 27 menstrual cycles. No thrombotic or thromboembolic events were reported in any of these studies in women who received Lysteda. Similarly no increased risk of venous thromboembolism has been reported with the other oral formulation of tranexamic acid in the past.[26]

Efficacy Data in the General Gynecologic Population

Tranexamic acid has been marketed as an effective treatment for women with heavy menstrual bleeding. This marketing has been based on the results of one randomized, double-blind, placebo-controlled trial of tranexamic acid to treat women with heavy menstrual bleeding.[21] This study randomized 196 women aged 18–49 years old with quantitatively measured mean menstrual blood loss of 80 mL or greater over two menstrual cycles to receive tranexamic acid (123 women) or placebo (73 women) in a 5:3 ratio. Women were excluded from the study if they had a diagnosed coagulopathy, evidence of unopposed estrogen such as an endometrial lining $>$ 12 mm or more than 35 days between menstrual cycles, and uterine leiomyomas requiring surgery. They could not use NSAIDs during their menstrual cycle or hormonal contraceptive methods. These women were randomized to tranexamic acid 1.3 g orally three times per day up to five days or placebo. A known coagulopathy was part of the exclusion criteria, however a work-up for a coagulopathy was not required prior to enrolling women with menorrhagia in the study.

The primary efficacy endpoints were mean reduction in menstrual blood loss compared to baseline, 50 mL reduction in menstrual blood loss compared to baseline, and a reduction in blood loss perceived to be meaningful to women. There was a statistically significant difference ($P < 0.001$) in each of these primary efficacy measure in the tranexamic acid group compared to the placebo group. The treatment group had a 40.4% reduction in blood loss compared to an 8.2% reduction in the placebo group ($P < 0.001$). This is a reduction of 69.6 mL of menstrual blood in the treatment group compared with 12.6 mL of menstrual blood in the placebo group. The treatment group was statistically more likely to have a 50 mL reduction in blood loss than the placebo group with 56% noting this reduction compared to 19%, respectively ($P < 0.001$). A reduction in menstrual blood loss of 36 mL was found to be clinically meaningful to women. In this study population, 69% of tranexamic acid users had a clinically meaningful blood loss, compared to 29% in the placebo group ($P < 0.001$).

A secondary endpoint of this study was quality of life. Women completed the MIQ, a disease specific, validated, patient reported outcome instrument. This instrument measured how the menstrual cycle limited their social or leisure activities, physical activities, and work activities. There was a statistically significant improvement in the amount of time the menstrual

cycle limited social or leisure activities, physical activities, and work activities in the tranexamic acid group compared to the placebo group.

There were very few adverse events in the study population. The most commonly reported adverse events in the tranexamic acid group compared to the placebo group were menstrual discomfort (61.5% vs. 50%, respectively), headache (55.6% vs. 50%, respectively), back pain (23.9% vs. 19.4%, respectively), nausea (14.5% vs. 15.3%, respectively), and anemia (10.3% vs. 5.6%, respectively). None of these adverse events were statistically significant. There were also very few serious adverse events in the study. In the tranexamic acid group there was one case each of tachycardia, urticaria, post-traumatic stress disorder, and hypoglycemia. In the placebo group on subject had a deep vein thrombosis.

Efficacy Data in Women with Bleeding Disorders

Antifibrinolytics have been successfully used to manage menorrhagia in women with bleeding disorders. Tranexamic acid reduced menstrual blood flow in 40% of 38 women with bleeding disorders as measured by a PBAC score $<$ 100 or to the woman's satisfaction.[27] A US multisite crossover design study randomized 116 women with menorrhagia (PBAC $>$ 100), negative gynecological evaluation, and abnormal laboratory hemostasis, to receive either tranexamic acid or intranasal 1-desamino-8-D-arginine vasopressin (IN-DDAVP) for two menstrual cycles.[28] The subjects then crossed over to the second study drug for two additional cycles. IN-DDAVP, 300 µg, was administered on days two and three of menstrual bleeding, and tranexamic acid (Cyclokapron) was administered in tablet form at a dosage of 1 g four times a day for the first 5 days of menstrual bleeding. The primary outcome measures for this study were change in menstrual blood loss (MBL), measured by the PBAC score, and quality of life (QOL). The estimated decrease in the PBAC from baseline was −64.1 [95% confidence interval (CI) = −88.0, −40.3] for IN-DDAVP and −105.7 (95% CI = −130.5, −81.0) for tranexamic acid. The decrease in PBAC was greater for tranexamic acid than IN-DDAVP (P-value = 0.0002, 95% CI = 19.6, 63.6). The test for treatment-type effect was significant ($P < 0.0001$) suggesting a greater reduction in PBAC score with tranexamic acid. This study is the only one to examine the effect of tranexamic acid on QOL using validated instruments. In this study, there was a greater improvement in QOL with tranexamic acid as compared to IN-DDAVP use. It was unclear though, whether the difference was because of a difference in the schedule of administration (2 days with IN-DDAVP versus 5 days with tranexamic acid) or a more efficacious mechanism for improving hemostasis. Another randomized, double-blind crossover study using 300 µg IN-DDAVP in combination with tranexamic acid or placebo in women with menorrhagia and a prolonged bleeding time, during two days of the menstrual bleeding demonstrated a significant reduction of MBL in the cycles treated with combined IN-DDAVP and tranexamic acid compared to placebo.[29] As DDAVP is known to stimulate the release of plasminogen activator from vascular endothelium,[30] thus increasing fibrinolytic activity, concomitant treatment with an anti-fibrinolytic such as tranexamic acid makes sense.

Conclusion

Menorrhagia is a problem experienced by many reproductive age women. Whether menorrhagia is caused by structural malformations of the uterus such as fibroids, endocrinologic causes such as polycystic ovarian syndrome, or a coagulopathy such as von Willebrand's Disease, tranexamic acid appears to be a very safe and effective medical treatment. There are very few adverse events reported, and the evidence suggests that there is no increased risk of thrombosis in women using tranexamic acid.[25–30] The recommended dosing is 1300 mg three times per day up to 5 days. Women should initiate the medication on the heaviest day of the menstrual cycle and continue until bleeding has improved, or up to 5 days. There are no studies evaluating the use of tranexamic acid in combination with other medical therapies for the treatment of heavy menstrual bleeding. Additional research is definitely warranted to determine if combining tranexamic acid with NSAIDs and/or hormonal contraceptive methods would further improve blood loss and quality of life for women with menorrhagia, and if there would be any increase in adverse events if these

medications are used together. Tranexamic acid is a well-tolerated and very effective non-hormonal, non-surgical treatment option for women with menorrhagia, and should be used as a first-line alternative to other medical and surgical treatments.

Author Contributions

Conceived and designed the experiments: LP, JM, SA. Analysed the data: LP, JM, SA. Wrote the first draft of the manuscript: LP, JM, SA. Contributed to the writing of the manuscript: LP, JM, SA. Agree with manuscript results and conclusions: LP, JM, SA. Jointly developed the structure and arguments for the paper: LP, JM, SA. Made critical revisions and approved final version: LP, JM, SA. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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