Original Report

An Open-Label, Single-Arm, Efficacy Study of Tranexamic Acid in Adolescents with Heavy Menstrual Bleeding

Sarah H. O'Brien MD [1,2,*], Surbhi Saini MD [3], Heidi Ziegler RN, BSN, CCRP [1], Myra Christian-Rancy BS [1], Sanjay Ahuja MD [4], Kerry Hege MD [5], Stephanie L. Savelli MD [6], Sara K. Vesely PhD [7]

[1] Division of Pediatric Hematology/Oncology, Nationwide Children's Hospital/The Ohio State University College of Medicine, Columbus, Ohio
[2] Center for Innovation in Pediatric Practice, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio
[3] Division of Pediatric Hematology/Oncology, Penn State Hershey Children's Hospital, Hershey, Pennsylvania
[4] Division of Pediatric Hematology/Oncology, Rainbow Babies & Children's Hospitals, Cleveland, Ohio
[5] Division of Pediatric Hematology/Oncology, Riley Hospital for Children at Indiana University Health, Indianapolis, Indiana
[6] Division of Pediatric Hematology/Oncology, Akron Children's Hospital, Akron, Ohio
[7] Department of Biostatistics and Epidemiology, Hudson College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

A B S T R A C T

Study Objective: Heavy menstrual bleeding (HMB) occurs in up to 40% of adolescent girls, significantly affecting their daily activities. Identifying alternative treatment strategies for HMB is particularly important for adolescents who prefer not to take hormonal contraception. Our objective was to determine whether use of tranexamic acid (TA) would increase health-related quality of life and decrease menstrual blood loss (MBL) in adolescents with HMB.

Design, Setting, Participants, Interventions, and Main Outcome Measures: In an open-label, multi-institutional, single-arm, efficacy study, patients 18 years of age or younger with HMB were treated with oral TA 1300 mg 3 times daily during the first 5 days of menses and monitored over the course of 4 menstrual cycles (1 baseline; 3 treatment cycles). Assessment of MBL was performed using the Menorrhagia Impact Questionnaire (MIQ) and the Pictorial Blood Assessment Chart. The MIQ includes Likert scale items, validated to assess the influence of HMB on quality of life. In previous studies, a 1-point decrease or more in score correlated with clinically significant improvement.

Results: Thirty-two patients enrolled in the study, and 25 had sufficient follow-up data to be deemed evaluable. The mean age of the participants was 14.7 years (range, 11-18 years). There was an overall improvement in all items of the MIQ, with a greater than 1-point improvement in the MIQ perceived blood loss scale. When using TA, mean Pictorial Blood Assessment Chart score improved by 100 points. There were no medication-related serious adverse events.

Conclusion: Use of TA in female adolescents with HMB is well tolerated and leads to clinically meaningful reduction in MBL.

Key Words: Heavy menstrual bleeding, Menorrhagia, Tranexamic acid, Menorrhagia Impact Questionnaire

Introduction

Heavy menstrual bleeding (HMB) is commonly encountered in adolescents.[1] In population-based studies, 1 in 4 women experience HMB at some point during their reproductive years[2] and HMB has a significant detrimental effect on their quality of life.[3–5] HMB has a multifactorial etiology, with up to 20% of patients having an underlying bleeding disorder.[6,7] Commonly used treatment approaches include the use of combined oral contraceptives, levonorgestrel-releasing intrauterine devices, and cyclical progestin.[8,9]

Tranexamic acid (TA), a competitive plasminogen inhibitor (antifibrinolytic), has been used for the treatment of HMB outside of the United States for decades,[10] and has established efficacy in reducing menstrual blood loss (MBL) in adults. A new oral formulation of TA with increased absorption time (Lysteda; Ferring Pharmaceuticals) was approved by the US Food and Drug Administration in 2009 for women 18 years of age and older with cyclic HMB. In a study of adult women, those receiving 3900 mg/d of TA for up to 5 days per menstrual cycle had significantly greater reduction in MBL compared with the placebo group. Similar safety and efficacy data are lacking for adolescents, for whom identifying alternative treatment strategies is particularly important. Although oral contraceptives are often the first-line treatment for HMB, barriers to effective use of oral contraceptives in young adolescents include difficulties with compliance, concerns about side effect profile, hesitancy to commit to a daily medication in an otherwise healthy young woman, as well as religious and cultural influences on willingness to use a "birth control pill." For these patients, TA is a potential alternative to oral contraceptives.

The primary objective of this study was to assess the efficacy of TA in decreasing MBL and increasing health-related quality of life (HRQoL) in adolescents with HMB.

Materials and Methods

The presented study was a prospective, multicenter, single-arm, efficacy study of TA for the treatment of HMB in

The authors indicate no conflicts of interest.

* *Address correspondence to:* Sarah H. O'Brien, MD, Division of Pediatric Hematology/Oncology, Nationwide Children's Hospital, 700 Children's Drive, Office FB3444, Columbus, OH 43205; Phone: (614) 722-3070
E-mail address: sarah.obrien@nationwidechildrens.org (S.H. O'Brien).

1083-3188/$ - see front matter
https://doi.org/10.1016/j.jpag.2019.01.009

Table 1
Study Inclusion and Exclusion Criteria

Study inclusion criteria
• Menstruating and between 10 and 19 years of age • Nonsmoker • Negative pregnancy test • Menstrual cycles occur every 21-60 days • Either sexually inactive or agree to use a barrier method with spermicide throughout the study period
Study exclusion criteria
• Severe anemia (hemoglobin <8 g/dL) • Active thromboembolic disease, history of thromboembolic disease, known inherited thrombophilia, or family history of thrombosis in a first-degree relative • Severe medical or psychiatric illness • Severe bleeding disorder (patients with mild bleeding disorders such as von Willebrand disease type 1, platelet storage pool or release defects, and bleeding tendency due to Ehlers-Danlos syndrome were included in the study) • Pregnancy in the past 6 months or breastfeeding • Use of estrogen- and/or progesterone-containing hormonal contraception within 3 months of study entry • Use of systemic steroids within 1 month of study entry • History of subarachnoid hemorrhage • History of hepatitis B, C, or HIV • Baseline creatinine >20% above the upper limit of normal for age

female adolescents. Its primary goal was to assess whether the use of TA during the first 5 days of menses decreased MBL and improved HRQoL defined by a 1 point or more improvement in the Menorrhagia Impact Questionnaire (MIQ) score.[11]

Patients

Young women aged 10-19 years were eligible to be enrolled during regularly scheduled visits to pediatric hematology clinics for evaluation or management of HMB. Four children's hospitals participated in the study (Nationwide Children's Hospital, Columbus, OH; Akron Children's Hospital, Akron, OH; Rainbow Babies and Children's Hospital, Cleveland, OH; Riley Hospital for Children at Indiana University Health, Indianapolis, IN). At Nationwide Children's Hospital (primary study site), a system-wide electronic mail message to employees and the publication of the study advertisement on an online, publicly available, searchable database of clinical trials was also used to augment recruitment. For study inclusion, the diagnosis of HMB was on the basis of the medical judgement of the principal or the site investigator, although patients did need to have baseline cycles occurring every 21-60 days to be eligible (Table 1). Participants with and without previously diagnosed bleeding disorders were eligible for inclusion. Participants were excluded if they had used hormonal contraception (estrogen or progestin) within 3 months of study entry or had an anticipated need to initiate hormonal contraception during the study period. The study was approved by the institutional review board of each participating site. Written informed consent was obtained from the legal guardian of each participant and written informed assent was obtained from each participant.

Study Protocol and Data Collection

Upon enrollment, participants underwent a study entrance medical history, physical examination, and baseline laboratory testing (Table 2). The study period consisted of 1 pretreatment baseline menstrual cycle, 3 on-treatment menstrual cycles (cycles 1, 2, and 3), and a study exit visit. Study staff kept in contact with families via phone, e-mail, or text messaging reminders (on the basis of the selected patient preference at time of enrollment). At the end of each cycle, participants returned a completed Pictorial Blood Assessment Chart (PBAC) and medication administration log. Study staff administered the MIQ to each participant over the phone within 7 days of completion of each menses. Adverse event data were collected for each participant throughout the 4-month study period at clinic visits and during follow-up phone calls. Participants were considered evaluable if at least 2 of the 3 treatment cycles, in addition to the baseline cycle, were completed.

Upon successful completion of data collection for the first and third treatment cycle and study exit visit, each participant received a small monetary compensation. There was an additional small monetary incentive for returning PBACs, subject diaries, and unused medication.

Medication Acquisition and Administration

Ferring Pharmaceuticals supplied 3600 Lysteda tablets (650 mg) for the purpose of this study. In 2013, Ferring Pharmaceuticals stopped the production of Lysteda and after October 2014, all patients enrolled on this study received generic TA. Participants were instructed to take 2

Table 2
Study Schema

	Study Entry	Baseline (Pretreatment)	Cycle 1	Cycle 2	Cycle 3	Study Exit*
			Treatment with TA			
History and physical	×					×
MIQ and PBAC		×	×	×	×	
Complete blood count	×†					×
Ferritin	×†					×
Creatinine	×†					
Urine pregnancy test	×					
Phone call		×‡	×‡	×‡	×‡	

MIQ, Menorrhagia Impact Questionnaire; PBAC, Pictorial Blood Assessment Chart; TA, tranexamic acid.
* Study exit visit to occur within 30 days of the end of the fourth menses.
† Study laboratory tests completed at study entry or within 60 days before initiation of study medication treatment.
‡ Study phone call to occur within 7 days of the end of the menses (MIQ administered).

tablets (1300 mg) of TA 3 times a day (3900 mg/d) for a maximum of 5 days during monthly menstruation (15 total doses). If menses lasted less than 5 days, participants were instructed to stop the medication when menses ended.

Compliance was defined as adhering to prescribed therapy two-thirds of the time or more. To meet this definition, participants who completed 2 treatment cycles had to use 40 or more of the 60 expected tablets and participants who completed 3 treatment cycles had to use 60 or more of the 90 expected tablets. Compliance was assessed by study personnel, who reviewed participant study diaries and counted returned tablets.

Study End Points

The primary study end point was predetermined to be an improvement in HRQoL as defined by a 1 point or more decrease (improvement) in the individual items of the MIQ score.

The MIQ is a validated, disease-specific patient-reported outcome measurement tool used in patients with HMB for subjective assessment of blood loss, limitations in work (school attendance in the case of adolescents), limitations in social/leisure and physical activities, as well as an overall assessment of the meaningfulness of any observed changes in quality of life (Table 3).[11] The overall respondent burden, as noted in the validation study, is an average of 2 minutes. A change in the MBL measured according to PBAC scores, as well as change in hemoglobin and ferritin concentrations, were defined as secondary end points for this study. Investigators have shown that a PBAC score of 150-185 or more correlates with 80 mL or more of MBL measured using the alkaline hematin test.[12,13] The PBAC has not been well studied in adolescents with HMB, but one study reported a correlation between PBAC scores and self-identification among adolescents as having heavy, normal, or light menses.[14]

Statistical Considerations

An efficacy analysis was conducted using data from a modified intent-to-treat population, defined as participants with sufficient data from the pretreatment phase and 2 or more treatment cycles. Changes in the MIQ scores were measured across the treatment cycles using a Friedman test. As hypothesized, no differences were observed across treatment cycles so the average MIQ scores during treatment cycles were compared with the pretreatment value for each MIQ item using paired *t* tests. Sample size calculation was on the basis of the assumption of a 25% dropout rate and greater than 90% power to detect an improvement in MIQ score of 1 or more point using an α of 0.05 and assuming that the SD of the difference would be 1.4 or less. If the data were not normally distributed, a Wilcoxon signed rank test was used with resulting power of 89%. A paired *t* test was used to analyze intraparticipant changes in PBAC scores, hemoglobin, and ferritin. A McNemar χ^2 test was used to compare the change in the percentage of patients who reported heavy/very heavy bleeding from baseline to treatment cycle 3 (MIQ-1). Demographic and safety data are described using summary statistics.

Table 3
Menorrhagia Impact Questionnaire[8]

MIQ Question	Response Scale
1. During your most recent menstrual period, your blood loss was:	1. Light 2. Moderate 3. Heavy 4. Very heavy
2. How much did your bleeding limit your school attendance?	1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely
3. How much did your bleeding limit you in your physical activities?	
4. How much did your bleeding limit your social or leisure activities?	
5/5a/5b. Compared with your previous menstrual period, would you say your blood loss during this period was:	0. About the Same 1. Better 2. Worse (if better or worse, patient given 7-point response scale): 1. Almost the same, hardly better/worse at all 2. A little better/worse 3. Somewhat better/worse 4. An average amount better/worse 5. A good deal better/worse 6. A great deal better/worse 7. A very great deal better/worse
6. Was this a meaningful or important change for you?	0. No 1. Yes

MIQ, Menorrhagia Impact Questionnaire.

Results

A total of 32 subjects were enrolled in this study from June 2013 to July 2016. Of these, 2 were screen failures. Of the remaining 30 patients, 25 patients completed at least 2 of the 3 treatment cycles and were included in the final analysis (16 subjects: 3 treatment cycles; 9 subjects: 2 treatment cycles). Patients were enrolled across all participating sites, with most (21/25) enrolled at Nationwide Children's Hospital.

The mean age of the participants was 14.7 years (range, 11-18 years). Most (78%) of enrolled subjects were 1-year or more postmenarche (and 63% ≥2 years) at the time of study enrollment. Ninety-one percent described their baseline cycles as “monthly” or between 24 and 35 days in duration. Ten participants (40%) had an identified bleeding disorder. Baseline demographic characteristics for the 25 patients included in the analysis are described in Table 4. Of these 25 patients, 21 patients met the study definition of therapy compliance, on the basis of the number of tablets left at study exit visit.

At baseline, 4 of the 25 patients (16%) had a hemoglobin concentration of less than 12 g/dL. However, 11 (44%) subjects had reduced bodily iron stores with ferritin concentration of less than 20 ng/dL. Twenty-one subjects (84%) noted heavy or very heavy MBL as measured by a MIQ-1 score of 3 or more. Four girls (16%) reported that heavy

Table 4
Description of the Study Population (n = 25)

Variable	Value
Mean age	14.7 years (range, 11-18 years)
Mean weight	71.5 kg (range, 45.9-110.4 kg)
Race, n (%)	
White non-Hispanic	13 (52)
White Hispanic	1 (4)
Black non-Hispanic	7 (28)
Biracial	3 (12)
Asian	1 (4)
Bleeding disorder, n (%)	
Platelet function defect	6 (24)
Joint hypermobility	3 (12)
von Willebrand disease type 1	1 (4)

MBL led to at least moderate limitations on school activities (MIQ-2 ≥ 3), 9 (36%) reported that it limited their physical activities (MIQ-3 ≥3) and similarly, 9 (36%) reported that heavy MBL led to at least moderate limitations on their social and leisure activities (MIQ-4 ≥3).

MIQ-1: Perceived Blood Loss

For the 25 patients analyzed in this study, the mean MIQ-1 score improved from 3.0 at baseline to 1.91 on average across the treatment cycles ($P < .001$; difference = 1.09; 95% confidence interval [CI], 0.76-1.42; Fig. 1), fulfilling the primary end point of a 1-point or more improvement (median MIQ-1 changed from 3 at baseline to 2 across treatment cycles; $P = <.001$). When evaluated individually, 17 patients (68%) had an average 1-point or more improvement in their MIQ-1 score during the treatment cycles compared with their baseline cycle. All 17 patients (17/17; 100%) reported that this change was clinically meaningful (MIQ-6 score 1). The number of patients reporting heavy/very heavy blood loss decreased from 84% at baseline to 23% with the use of TA ($P < .001$; Fig. 2). In a subanalysis of patients with and without identified bleeding disorders, we did not note a statistically significant difference in change in MIQ-1 scores between these 2 populations.

MIQ-2, 3, and 4: Limitations on School Attendance, Physical, Social, and Leisure Activities

At baseline, the mean MIQ-2 score (limitations on school attendance) was 1.64 (range, 1-5), with only 6 of the 25 (24%) patients reporting any limitations on school attendance during their monthly menses (MIQ-2 score ≥2). The mean score did not change significantly with use of TA ($P = .134$; difference = 0.37; 95% CI, −0.12 to 0.87). Pre- and post median MIQ-2 scores were 1 and 1, respectively ($P = .25$).

The MIQ-3 score, reflective of limitations on physical activities, changed from a mean of 2.08 at baseline to 1.40

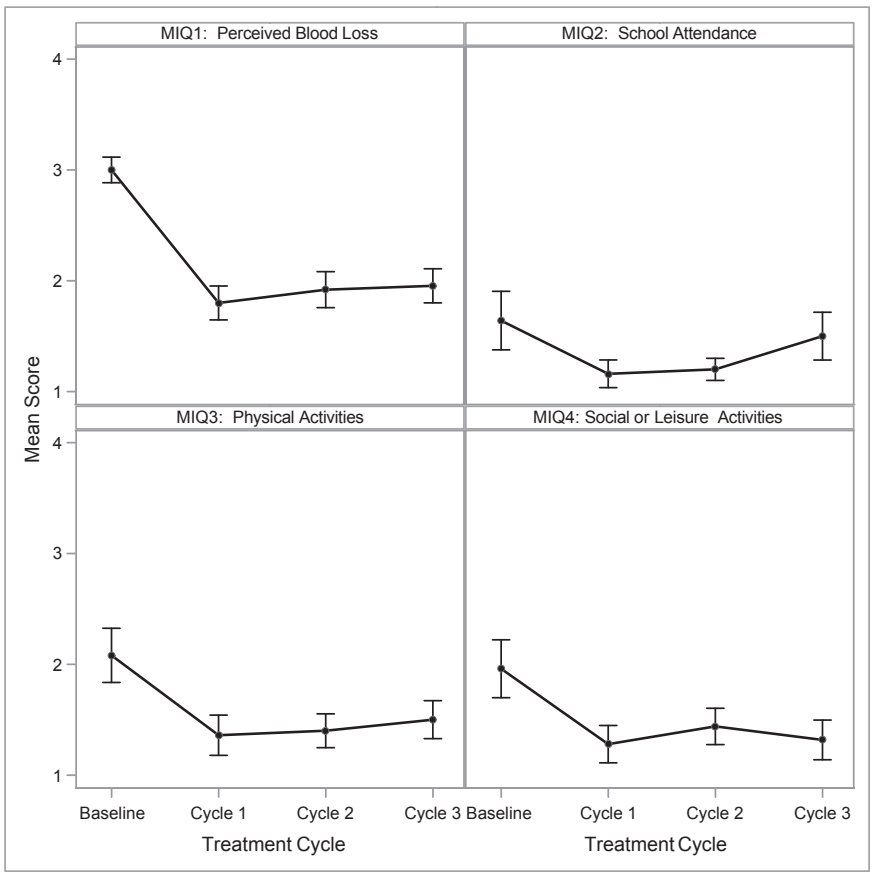

Fig. 1. Health-related quality of life scores at baseline and during treatment with tranexamic acid (TA) using the Menorrhagia Impact Questionnaire (MIQ) tool. For item 1 (MIQ1), there was a greater than 1 point improvement in the average score with the use of TA ($P < .001$). For items 2, 3, and 4 (MIQ2, 3, and 4), the change in average score was <1, however, the improvement in scores was statistically significant for MIQ3 ($P = .002$) and MIQ4 ($P = .009$).

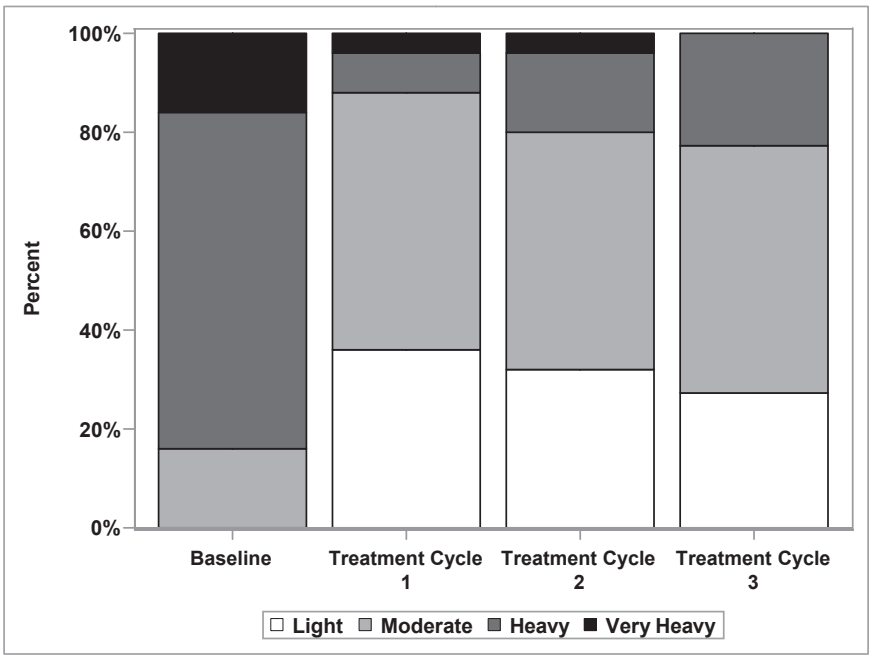

Fig. 2. Patient-reported reduction in menstrual blood loss (MBL) with use of tranexamic acid (TA), assessed according to responses to the first item of the Menorrhagia Impact Questionnaire (perceived blood loss). A 60% reduction in the number of patients reporting heavy/very heavy MBL was noted with the use of TA ($P < .001$).

averaged over 3 treatment cycles ($P = .002$; difference = 0.68; 95% CI, 0.28-1.08). Median MIQ-3 score changed from 2 to 1 ($P = .002$). Nine patients (36%) had a MIQ-3 score of 3 or more at baseline, indicating significant restrictions on physical activities because of HMB. For this subset of patients, the MIQ-3 score improved to an average of 1.74 over 3 treatment cycles, with a 1-point or more improvement in this item of the MIQ with the use of TA.

At study entry, 10 of 25 patients (40%) reported that HMB limited their social and leisure activities, of which 9 of 25 (36%) had an MIQ-4 score of 3 or more at baseline, indicating significant restrictions on social/leisure activities because of HMB. Overall, the MIQ-4 score changed from a mean of 1.96 to 1.33 ($P = .009$; difference = 0.63; 95% CI, 0.17-1.08), and pre- and post median MIQ-4 scores were 1 and 1, respectively ($P = .006$). However, for patients with significant restrictions on social/leisure activities, treatment with TA improved the MIQ-4 score from an average of 3.5 to 1.76 ($P = .002$; difference = 1.74; 95% CI, 0.86-2.62), showing a greater than 1-point improvement with treatment.

PBAC Scores

PBAC scores were available for 24 of the 25 subjects. Twenty (83%) subjects reported a PBAC score greater than 100 (abnormal) at baseline and 19 (79.2%) subjects reported an improvement in their PBAC scores during treatment with TA. Overall, the PBAC score improved from an average of 255.1 to 154.6 ($P < .001$; difference = 100.5; 95% CI, 46.3-154.7).

Hemoglobin and Ferritin Concentrations

No significant changes in hemoglobin or ferritin were observed over time. The average hemoglobin at study entry was 12.7 g/dL (n = 25; range, 10.4-15.3 g/dL) and during treatment with TA was 12.8 g/dL (n = 22; range, 10.6-14.7 g/dL; $P = .94$). The average ferritin concentration at baseline was 25.9 ng/dL (n = 25; range, 4-82 ng/dL). With TA treatment, the average ferritin was 26.3 ng/dL (n = 22; range, 5-59 ng/dL; $P = .61$).

Adverse Events

During the course of this study, a total of 2 serious adverse events were reported. These were 2 episodes of suicidal ideation (1 around the time of baseline assessment and 1 after TA initiation) that occurred in the same patient, who had a history of psychiatric illness. Neither event was thought to be related to the study drug. Most adverse events noted were known side effects of TA, and were mild to moderate in severity (Table 5). The most common adverse events reported were sinonasal symptoms (nasal

Table 5
Frequency of Adverse Events Reported with Tranexamic Acid Treatment

Event, n (%)
Sino-nasal symptoms: 17 (21)
Cough, sore throat, earache, mouth pain: 8 (10)
Fatigue: 8 (10)
Musculoskeletal pain: 7 (8.75)
Abdominal pain: 7 (8.75)
Headache: 7 (8.75)
Diarrhea, constipation, bloating, gastroenteritis: 5 (6.25)
Nausea, vomiting: 4 (5)
Menstrual discomfort and cramps: 3 (3.75)
Passage of blood clots with menses: 3 (3.75)
Prolonged bleeding: 3 (3.75)
Fever: 2 (2.5)
Anxiety: 2 (2.5)
Suicidal ideation: 2 (2.5)
Dizziness: 1 (1.25)
Urinary tract infection: 1 (1.25)
Yeast infection: 1 (1.25)

Total number of adverse events noted in 25 patients = 81.

congestion, headache, sinus pain). Other side effects noted during the study, notably musculoskeletal pain (back, abdomen), menstrual cramps, nausea, etc, were likely related to the underlying HMB. No thrombotic events were noted during the study period and none of the participants reported any ocular adverse effects.

Discussion

This prospective, open-label clinical study was designed to evaluate the usefulness of a newer formulation of TA in decreasing menstrual blood flow and improving HRQoL in adolescent girls with HMB. In our study cohort of 25 patients ranging in age from 11 to 18 years, the use of TA led to qualitative and quantitative improvement in MBL measured according to the MIQ and PBAC, respectively. Most of our subjects noted significant improvement in their MIQ-1 (perceived blood loss) and PBAC scores during treatment with TA. For most of these young girls, this improvement was noticeable during their first treatment cycle with TA, and was maintained over the course of the study period.

The improvements seen in items 3 (physical activity) and 4 (social activities) of the MIQ were statistically significant, but failed to meet our primary end point of a 1-point or more improvement in the average score during treatment with TA. For the one-third of patients who reported baseline severe restrictions on physical or social activities because of HMB, the use of TA did lead to significant improvement in their ability to participate.

In contrast to adult women, in whom a study of TA showed that most reported baseline moderate-severe limitations on work inside or outside of the home due to heavy menstrual blood flow,[15] only a small proportion of our study participants reported major restrictions on school attendance or participation due to heavy menses. This might reflect parental and societal pressure to attend school, despite significant physical discomfort, or it is possible that our study population had milder heavy menses at baseline.

Iron deficiency, with or without anemia, occurs commonly in young women with HMB.[16–18] None of our study participants were severely anemic at baseline, although nearly half of them had reduced bodily iron stores (serum ferritin <20 ng/dL), further substantiating that iron deficiency without anemia can be unrecognized if screening is performed with hemoglobin and red cell indices alone.[17] These participants were not routinely prescribed iron supplements, and because of the short duration of our study period, there was no significant change noted in the average hemoglobin or ferritin concentrations with the use of TA.

TA was generally well tolerated and most of the adverse events noted during the course of the study were mild to moderate in severity. The most common side effects reported were symptoms commonly reported with menses (headache, cramps) or otherwise unlikely to be study drug related (nasal congestion and other upper respiratory symptoms).

In a study of adult women, those who received 3900 mg TA per day for up to 5 days per menstrual cycle, showed clinically meaningful and significantly greater reduction in menstrual blood flow compared with women who received placebo.[15] Ferring Pharmaceuticals has also performed a pharmacokinetic study of Lysteda (Ferring Pharmaceuticals) in 20 female adolescents (12-16 years of age) with HMB (http://clinicaltrials.gov/ct2/show/results/NCT01190150), which showed that 3900 mg/d is also an appropriate dosage for this age group. Because our study population was similarly aged, we chose this dosing strategy. Because TA is sold as 650-mg tablets in the United States, this approach is suitable for all patients who weigh 40 kg or more.

Our study design was not without limitations, most notably the lack of a comparator (hormonal contraception, for example) or placebo-controlled arm. We selected a single-arm study design because of the numerous patient-level, parent-level, and cultural factors that affect decision-making regarding the use of hormonal contraception in young adolescents, and the ethical issues of the use of placebo in this setting. It was determined that a randomized design would be a major barrier to study feasibility. It is also true that dysfunctional bleeding due to anovulatory cycles will improve with time over the first 12-18 months after menarche. However, because of the relatively short duration of our study (4 months), and the fact that most enrolled subjects were 1 year or more post-menarche at the time of study enrollment, we do not believe natural history played a substantial role in the clinical improvements seen with use of TA.

Another limitation of our methodology is that the primary study end point was change in MIQ as opposed to a more objective change in measured blood loss.[19] However, a major factor that motivates patients with HMB to seek medical care is the negative effect of HMB on daily life.[20–22] Quality of life is an integral part of the National Institute for Health and Clinical Excellence definition of HMB, and HMB is defined by the International Federation of Gynecology and Obstetrics as excessive MBL that interferes with the woman's physical, emotional, social, and material quality of life.[23,24] The selection of change in MIQ as our primary outcome served to enhance the feasibility of our study (actual menstrual blood flow is quite burdensome to measure) and the clinical meaningfulness of our results. This study also included adolescents with and without an underlying bleeding disorder. However, none of the subjects with an identified bleeding disorder were treated with nasal desmopressin or replacement factor products during the study period, decreasing the heterogeneity of our study population.[25]

In conclusion, the use of TA in adolescent girls (with and without bleeding disorders) with cyclic HMB led to clinically meaningful reduction in the MBL and improvement in HRQoL. A small percentage of the patients reported mild/moderate side effects, and TA was generally well tolerated. TA offers a safe and efficacious first-line treatment option for young girls with cyclic HMB.

Acknowledgments

The authors thank Ferring pharmaceuticals (Parsippany, NJ) for the supply of 3600 Lysteda tablets that were provided to the patients as part of this study. This work was

supported by a grant from the Hemostasis and Thrombosis Research Society, United States (Clinical Research Award to S.H.O). S.S. was the recipient of the Joan Fellowship in Pediatric Hemostasis and Thrombosis at Nationwide Children's Hospital, 2016-2017.

References

1. James AH, Ragni MV, Picozzi VJ: Bleeding disorders in premenopausal women: (another) public health crisis for hematology? Hematology Am Soc Hematol Educ Program 2006;474
2. Fraser IS, Mansour D, Breymann C, et al: Prevalence of heavy menstrual bleeding and experiences of affected women in a European patient survey. Int J Gynaecol Obstet 2015; 128:196
3. Cote I, Jacobs P, Cumming D: Work loss associated with increased menstrual loss in the United States. Obstet Gynecol 2002; 100:683
4. Pawar A, Krishnan R, Davis K, et al: Perceptions about quality of life in a school-based population of adolescents with menorrhagia: implications for adolescents with bleeding disorders. Haemophilia 2008; 14:579
5. Shankar M, Chi C, Kadir RA: Review of quality of life: menorrhagia in women with or without inherited bleeding disorders. Haemophilia 2008; 14:15
6. Zia A, Rajpurkar M: Challenges of diagnosing and managing the adolescent with heavy menstrual bleeding. Thromb Res 2016; 143:91
7. Vo KT, Grooms L, Klima J, et al: Menstrual bleeding patterns and prevalence of bleeding disorders in a multidisciplinary adolescent hematology clinic. Haemophilia 2013; 19:71
8. Pai M, Chan A, Barr R: How I manage heavy menstrual bleeding. Br J Haematol 2013; 162:721
9. Srivaths LV, Dietrich JE, Yee DL, et al: Oral tranexamic acid versus combined oral contraceptives for adolescent heavy menstrual bleeding: a pilot study. J Pediatr Adolesc Gynecol 2015; 28:254
10. Callender ST, Warner GT, Cope E: Treatment of menorrhagia with tranexamic acid. A double-blind trial. Br Med J 1970; 4:214
11. Bushnell DM, Martin ML, Moore KA, et al: Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life. Curr Med Res Opin 2010; 26:2745
12. Janssen CA, Scholten PC, Heintz AP: A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. Obstet Gynecol 1995; 85:977
13. Zakherah MS, Sayed GH, El-Nashar SA, et al: Pictorial blood loss assessment chart in the evaluation of heavy menstrual bleeding: diagnostic accuracy compared to alkaline hematin. Gynecol Obstet Invest 2011; 71:281
14. Sanchez J, Andrabi S, Bercaw JL, et al: Quantifying the PBAC in a pediatric and adolescent gynecology population. Pediatr Hematol Oncol 2012; 29:479
15. Lukes AS, Moore KA, Muse KN, et al: Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial. Obstet Gynecol 2010; 116: 865
16. Wang W, Bourgeois T, Klima J, et al: Iron deficiency and fatigue in adolescent females with heavy menstrual bleeding. Haemophilia 2013; 19:225
17. Johnson S, Lang A, Sturm M, et al: Iron deficiency without anemia: a common yet under-recognized diagnosis in young women with heavy menstrual bleeding. J Pediatr Adolesc Gynecol 2016; 29:628
18. Sharma R, Stanek JR, Koch TL, et al: Intravenous iron therapy in non-anemic iron-deficient menstruating adolescent females with fatigue. Am J Hematol 2016; 91:973
19. Lukes AS, Muse K, Richter HE, et al: Estimating a meaningful reduction in menstrual blood loss for women with heavy menstrual bleeding. Curr Med Res Opin 2010; 26:2673
20. Shapley M, Jordan K, Croft PR: Abnormal bleeding patterns associated with menorrhagia in women in the community and in women presenting to primary care. Fam Pract 2007; 24:532
21. Kulkarni R: Improving care and treatment options for women and girls with bleeding disorders. Eur J Haematol 2015; 95(Suppl 81):2
22. Shapley M, Jordan K, Croft PR: Why women consult with increased vaginal bleeding: a case-control study. Br J Gen Pract 2002; 52:108
23. National Institute for Health and Clinical Excellence: Heavy Menstrual Bleeding. London, England, National Institute for Health and Clinical Excellence, 2007
24. Munro MG, Critchley HO, Fraser IS: The FIGO systems for nomenclature and classification of causes of abnormal uterine bleeding in the reproductive years: who needs them? Am J Obstet Gynecol 2012; 207:259
25. Kouides PA, Byams VR, Philipp CS, et al: Multisite management study of menorrhagia with abnormal laboratory haemostasis: a prospective crossover study of intranasal desmopressin and oral tranexamic acid. Br J Haematol 2009; 145:212