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Brief Report

Estimating a meaningful reduction in menstrual blood loss for women with heavy menstrual bleeding

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Abstract

Objective:
A dichotomy exists within the treatment of heavy menstrual bleeding (HMB); guidelines and expert opinion recommend that clinical management be guided by subjective, patient-centered measures, yet clinical trials often describe treatment efficacy in terms of objective reductions in menstrual blood loss (MBL). The purpose of this investigation was to correlate subjective and objective aspects of HMB treatment by identifying the minimum change in MBL that would be considered meaningful to women.

Research design and methods:
Receiver operating characteristic (ROC) curve analyses were performed using data from a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of a novel, oral formulation of tranexamic acid (Lysteda*). The study enrolled women ages 18–49 years with a history of cyclic HMB. Menstrual blood loss was measured objectively using the alkaline hematin method and subjectively using the Menorrhagia Impact Questionnaire (MIQ), a patient-reported outcome instrument previously validated in an HMB population. Additional subgroup analyses were performed after stratification by low (80–160 mL/cycle) or high (>160 mL/cycle) baseline MBL.

Clinical trial registration:
NCT00401193 (NIH Clinical Trials Registry)

Results:
A total of 278 women were included in the ROC analyses. The best balance of sensitivity and specificity was achieved for predicting a patient-perceived meaningful improvement in MBL, at a cut point of 36 mL/cycle. Absolute reductions in MBL that were considered meaningful were more modest in women with lower baseline MBL (22 mL/cycle) and greater in women with higher baseline MBL (47 mL/cycle). However, an approximately 22% MBL reduction was meaningful to the majority of women in either the low or high baseline MBL subgroups.

Conclusions:
Reducing measurable MBL by 36 mL/cycle, or approximately 22%, was considered to be a meaningful improvement for the majority of women with HMB in this study population.

Introduction

The detrimental influence of heavy menstrual bleeding (HMB), or menorrhagia, on daily activities and health-related quality of life (HRQL) is often the trigger that prompts women to consult a physician regarding this condition[1,2].

*Lysteda is a registered trade name of Ferring Pharmaceuticals Inc., Parsippany, NJ, USA.

Additionally, subjective assessments are more often used in the clinical diagnosis of HMB than objective measurement of menstrual blood loss (MBL). Menstrual blood loss is not typically measured in clinical practice because (1) the process of collecting sanitary products and quantifying MBL is not feasible for the clinician or acceptable to the patient, and (2) an individual's perception of HMB does not always correspond with an abnormal amount of MBL (e.g., the ≥80 mL/cycle criterion often used in clinical trials)[3]. Evidence for therapeutic efficacy in clinical trials, however, is often based on objective measurements of MBL. A method is therefore needed to translate the objective measures of MBL used in clinical trials into metrics that are relevant to clinical practice and to women with HMB.

In this study, receiver operating characteristic (ROC) analyses were performed to determine the minimal reduction in MBL that would be considered meaningful or important to women with HMB. The ROC analyses provide a means to identify MBL values that balance sensitivity (i.e., true positive condition existence) and specificity (i.e., true negative condition existence) for the prediction of a patient-perceived meaningful improvement[4]. The objective measure of HMB was determined by quantifying MBL and the subjective measure of a meaningful or important response was assessed using a validated patient-reported outcome measure, the Menorrhagia Impact Questionnaire (MIQ)[5]. As the degree of MBL reduction that is considered meaningful may depend on baseline HMB severity, stratification by baseline MBL was also evaluated.

Patients and methods

The data for these analyses were derived from a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial of a novel, oral formulation of tranexamic acid (TA; Lysteda*). Women ages 18–49 years with a history of cyclic HMB were eligible to participate in the study if they met a minimum MBL requirement during two pretreatment cycles (average MBL ≥80 mL/cycle), had at least 6 months of regularly occurring menstrual cycles (21–35 days apart) with menstrual periods lasting no more than 10 days, and normal pelvic examinations, cervical cytology, and transvaginal ultrasonography. The presence of fibroids was not considered an abnormal finding unless they were of sufficient size or number to require surgical management. Women were randomized (2:2:1 allocation) to receive TA 1.3 g, TA 0.65 g, or placebo administered orally three times daily for up to 5 consecutive days (maximum of 15 doses) during three menstrual cycles. All 63 participating US study sites received Institutional Review Board approval before screening began. The study was conducted in accordance with the ethical principles set forth by the Declaration of Helsinki guidelines for good clinical practice.

The primary efficacy endpoint of the study was change from baseline in objectively measured MBL; subjective improvement during treatment was an important secondary endpoint. Menstrual blood loss was measured during all study menstrual cycles using a validated alkaline hematin method. HRQL was assessed via the MIQ administered 1–4 days after each baseline and on-treatment menstrual cycle. The MIQ consists of six specific measures (or items) related to the patient's most recent menses (or period). One measure related to the patient's perceptions of the amount of MBL (on a scale from 1 [light] to 4 [very heavy]). Three measures related to limitations in activities, i.e. limitations of physical activities (LPA), social or leisure activities (LSLA), and on work outside or inside the home (LWH) (on a scale from 1 [not at all limiting] to 5 [extremely limiting]). One measure delineated the actual activities impacted, and one measure was a global impact (and meaningfulness) assessment of the change in MBL. For this last measure, a woman was considered to have experienced a meaningful reduction in MBL if she indicated 'improved' MBL compared with the previous menstrual period (rather than no change or worsening), and that this change was 'meaningful or important' to her (Yes or No). 'How much' or the degree of change in MBL was also assessed in this global measure (i.e., bleeding either improved or worsened, on a scale from 1 [almost the same, hardly better at all] to 7 [a very great deal better]).

Statistical analyses were performed on the modified intent-to-treat population (mITT) – all randomized women who had received at least one dose of study drug, provided adequate baseline and on-treatment MBL data, and completed the MIQ for at least the first menstrual cycle. Construction of the curve for the ROC analysis was based on MBL values and MIQ global assessment measure data acquired at baseline and during the first on-treatment menstrual cycle. All women who participated in the study and had evaluable study data were included in the blinded ROC analysis. For the sensitivity and specificity determinations, subjective MBL reductions were dichotomized to either above or below incrementally increasing objective MBL reduction set-point threshold values. Two-by-two contingency tables (increased by 1 mL increments) were then constructed to determine the fraction of true positive (sensitivity), true negative (specificity), false positive, and false negative responses.

A true positive was defined as a meaningful response on the MIQ paired with an objective MBL change from baseline (reduction) above each threshold. A true negative was defined as a non-meaningful response on the MIQ paired with an objective MBL reduction below each threshold.

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A false positive was defined as meaningful response on the MIQ paired with an objective MBL reduction that was below each threshold. A false negative occurred if a woman did not consider the change in her MBL meaningful, but the quantitative measurement was above the threshold. The optimal operating point, or MBL cut point, in the ROC curve was identified as the best balance between sensitivity and specificity; this value was determined by the intersection of the ROC curve and a diagonal line drawn from the upper left corner of the graph down to the bottom right corner ([0% 100-specificity, 100% sensitivity] to [100% 100-specificity, 0% sensitivity]). The optimal operating point was interpreted as the MBL threshold for defining a responder.

Additional exploratory, post hoc analyses were performed to evaluate the effect of baseline MBL on perception of MBL improvement and to correlate the degree of MBL improvement with reductions in activity limitations, specifically limitations in physical activities (LPA) and limitations in social or leisure activities (LSLA). For the baseline MBL analyses, women were stratified into two groups: 'low' baseline MBL (80–160 mL/cycle) and 'high' baseline MBL (>160 mL/cycle; equivalent to twice the MBL volume required for study entry). Thresholds for a meaningful improvement according to baseline MBL strata were determined using change from baseline MBL and percentage change from baseline MBL data. In addition, MBL thresholds for patient perception of an at least 'somewhat better' MBL result (score of 3 or higher on the MIQ global assessment of the degree of MBL change) were calculated using baseline MBL stratification. The magnitude of improvement in this global measure that was considered meaningful was also determined.

Results

A total of 304 women were enrolled in the study and 297 received at least one dose of study medication. The mean age was 39 years and two-thirds of the study population were white (Table 1). Mean baseline duration of HMB for the overall study population exceeded 10 years. Differences in baseline parameters among treatment groups were not statistically significant. The mITT population consisted of 294 women (TA 3.9 g/day, $n = 115$; TA 1.95 g/day, $n = 112$; placebo, $n = 67$). Sufficient MIQ data for the ROC analyses were available for 278 women: 168 (60.4%) women were categorized within the low baseline MBL subgroup and 110 (39.6%) women in the high baseline MBL subgroup.

The primary ROC curve analysis determined that a 36 mL/cycle cut point for reduction from baseline in MBL provided the best balance of sensitivity (65.3%) and specificity (65.7%; Figure 1 and Table 2). For women with less severe HMB (i.e., a lower baseline MBL), a reduction in MBL of 22 mL/cycle was perceived as meaningful by the majority of women (Table 3). For women in the higher baseline MBL stratum, a greater reduction in MBL (47 mL/cycle) was needed to be considered meaningful. Regardless of baseline MBL, a percent reduction in MBL of at least 22–23% was perceived by the majority of women as meaningful (Table 4).

A reduction in MBL of 35 mL/cycle corresponded to an at least 'somewhat better' categorization of menstrual bleeding (i.e., a score of 3 or better on the 7-point scale for MIQ global degree of MBL change measure) compared

Table 1. Demographic and baseline characteristics, intent-to-treat population.

Parameter	TA 3.9 g/day ($n = 115$)	TA 1.95 g/day ($n = 115$)	Placebo* ($n = 67$)
Mean age, years (SD)	39.2 (6.2)	40.2 (6.3)	38.9 (6.1)
Range	20–50	20–49	19–48
Race, *n* (%)			
White	77 (67)	76 (66)	43 (64)
Black	34 (30)	31 (27)	22 (33)
Asian	0	3 (3)	0
Other	4 (3)	5 (4)	2 (3)
Mean duration of HMB, years (SD)	11.94 (8.89)	12.13 (9.40)	9.98 (8.44)
Mean baseline MBL, mL/cycle† (SD)	169.0 (83.0)	178.0 (112.2)	153.6 (67.9)

*Differences between groups were not statistically significant ($p > 0.05$). *P*-values calculated using two-sided *t*-test.
†Modified intent-to-treat population data used ($n = 115$,TA 3.9 g/day; $n = 112$,TA 1.95 g/day; and $n = 67$, placebo group).
TA, tranexamic acid; SD, standard deviation; HMB, heavy menstrual bleeding; MBL, menstrual blood loss.

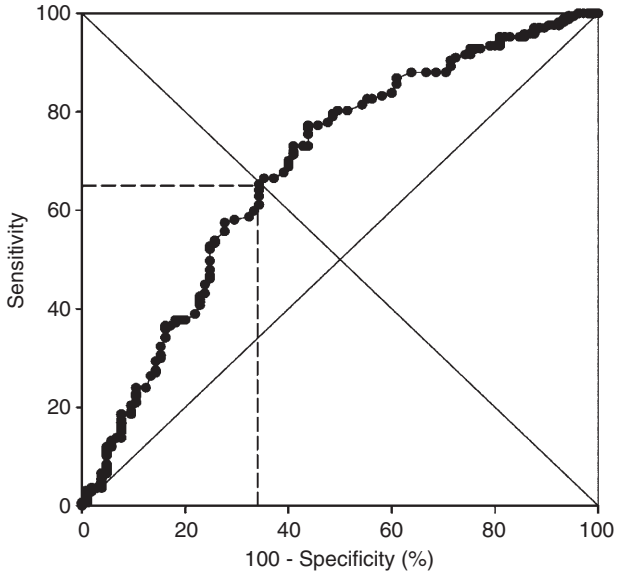

Figure 1. Receiver operating characteristic curve plot of sensitivity versus 100-specificity. Dashed lines indicate the sensitivity and 100-specificity at the menstrual blood loss reduction cut point of 36 mL/cycle.

with the previous menstrual cycle by women in the mITT population (Table 5). Reductions in MBL required to achieve this level of improvement were greater among women in the high baseline MBL subgroup (56 mL/cycle) compared with the low baseline MBL subgroup (20 mL/cycle). Improvement in patient-reported menstrual bleeding of at least 3 points predicted a self-described meaningful change with 100.0% sensitivity and 71.3% specificity.

In women with moderate to extreme limitations in physical activities at baseline, a reduction in MBL of 31 mL/cycle was associated with a 1-point improvement in the 5-point LPA scale, with a sensitivity of 69.3% and a specificity of 56.6%. Similarly, an MBL reduction of 35 mL/cycle predicted an improvement in LSLA of 1 point with 65.3% sensitivity and 56.5% specificity in women with moderate to extreme baseline limitations in social and leisure activities.

Table 2. Primary ROC analysis for defining a meaningful improvement in MBL.

MBL cut point (mL/cycle)	Sensitivity (%)	Specificity (%)	100-Specificity (%)
−20	77.3	56.2	43.8
−25	73.1	57.1	42.9
−30	70.1	60.0	40.0
−35	66.5	64.8	35.2
−36	65.3	65.7	34.3
−37	64.1	65.7	34.3
−40	61.1	65.7	34.3
−45	55.7	72.4	27.6
−50	49.7	75.2	24.8

ROC, receiver operating characteristic; MBL, menstrual blood loss.

Discussion

In this population of women with HMB, a minimum change from baseline in MBL of 36 mL/cycle was considered meaningful by the majority of women. Throughout the analyses, a consistency was observed in this threshold, with a 35 mL/cycle MBL reduction indicating an at least 'somewhat better' perception of MBL during treatment and a 31–35 mL/cycle reduction correlating with a 1-point improvement in activity limitation scores. Although the threshold for a meaningful improvement did vary by baseline MBL, the percentage reduction did not, indicating that a 22–23% reduction in MBL during treatment would generally be considered a meaningful improvement for women with HMB.

Guidance for determining the magnitude of MBL reduction needed during HMB treatment to achieve a clinically relevant result has previously been lacking. One of the confounders for correlating MBL with HMB improvement is the variation in personal perceptions of MBL. For example, Hallberg and colleagues reported that nearly 80% of women who described their menstrual bleeding as heavy did not meet the volumetric criteria

Table 3. Optimal MBL reduction cut points for a meaningful improvement, stratified by baseline MBL.

Population	MBL cut point (mL/cycle)	ROC parameters			
		Sensitivity (%)	Specificity (%)	Total (%)	AUC
'Low' baseline	−22	75.8	60.6	136.4	0.703
'High' baseline	−47	73.5	61.5	135.0	0.680

Data are for the modified intent-to-treat population; MIQ global MBL 'meaningfulness' assessment measure.
MBL, menstrual blood loss; ROC, receiver operating characteristic; Total, sensitivity plus specificity; AUC, area under the receiver operating characteristic curve.
'Low' baseline MBL: (80–160 mL/cycle).
'High' baseline MBL: (>160 mL/cycle).

Table 4. Optimal MBL percent reduction cut points for a meaningful improvement, stratified by baseline MBL.

Population	MBL cut point (%)	ROC parameter			
		Sensitivity (%)	Specificity (%)	Total (%)	AUC
'Low' baseline	−23	69.7	63.6	133.3	0.691
'High' baseline	−22	73.5	61.6	135.1	0.664
Combined	−22	71.3	61.9	133.2	0.681

Data are for the modified intent-to-treat population; MIQ global MBL 'meaningfulness' assessment measure.
MBL, menstrual blood loss; ROC, receiver operating characteristic; Total, sensitivity plus specificity; AUC, area under the receiver operating characteristic curve.
'Low' baseline MBL: (80–160 mL/cycle).
'High' baseline MBL: (>160 mL/cycle).

Table 5. Optimal MBL reduction cut points for a 'somewhat better' or greater menstrual bleeding score, stratified by baseline MBL.

Population	MBL cut point (mL/cycle)	ROC parameter			
		Sensitivity (%)	Specificity (%)	Total (%)	AUC
'Low' baseline	−20	77.3	63.4	140.7	0.733
'High' baseline	−56	69.8	57.4	127.3	0.646
Combined	−35	67.5	62.7	130.2	0.677

Data are for the modified intent-to-treat population; MIQ global 'degree of MBL change' assessment measure.
MBL, menstrual blood loss; ROC, receiver operating characteristic; Total, sensitivity plus specificity; AUC, area under the receiver operating characteristic curve.
'Low' baseline MBL: (80–160 mL/cycle).
'High' baseline MBL: (>160 mL/cycle).

for HMB, whereas 40% of women with MBL greater than 80 mL/cycle considered their menstrual bleeding to be light or moderate[6]. In terms of clinical practice, guidelines and expert opinion have moved away from emphasizing quantitative assessment of HMB to a more patient-centric focus, encouraging physicians to address the issues that are concerning to patients, including the limitations imposed by excessive MBL on daily activities and HRQL[7,8]. Historically, patient-reported outcomes have not been the primary focus of HMB clinical trials[2]. Although modern trials are more apt to include patient-reported outcome measures, lack of a standard, disease-specific instrument makes interpretation of the results more challenging[9,10].

Determining minimally important changes in HMB has the most relevance for pharmacologic HMB therapies (e.g., hormonal therapies, competitive plasminogen inhibitors, anti-inflammatory drugs), as other treatment options such as hysterectomy or endometrial ablation eliminate or radically diminish MBL[11]. Pharmacologic agents are also highly heterogeneous in both mechanism of action and treatment efficacy. Interestingly, a reduction in MBL of 20% corresponds with the lower end of the efficacy spectrum for many of the pharmacologic agents that have been evaluated for the treatment of HMB. To the authors' knowledge, no pharmacologic therapy trials have established a volumetric threshold for a clinically relevant reduction in MBL; significance of MBL reduction is commonly based on statistical comparisons with baseline or placebo. One previous clinical trial of pharmacologic HMB treatment did report a high degree of correlation between MBL reduction and treatment satisfaction in women with HMB, but the MBL estimation was subjective rather than objective[12]. More recently, de Souza and colleagues found no correlation between MBL as measured by the Pictorial Blood Loss Assessment Chart and HRQL derived from the Short Form-36 (SF-36) questionnaire[13]. The SF-36 is a nonspecific HRQL measure that has been criticized for its lack of applicability in an HMB population, with some women reporting difficulty in answering SF-36 questions[9,14]. One of the strengths of the current study is use of a menorrhagia-specific patient-reported outcomes tool that addressed issues pertaining to MBL and the importance and meaningfulness of MBL changes to women.

This study provides a starting point and a methodology for correlating MBL reductions with meaningful improvement in HMB; however, confirmatory studies are needed to establish a minimally important change in MBL. Many women who consult physicians regarding HMB would not meet the volumetric MBL criteria used in this study[6]; therefore, performing a similar evaluation in women with lower baseline MBL may be of value. Furthermore, identifying patient characteristics that influence MBL perception (i.e., age, duration of HMB, etc.) may also be relevant to clinical practice. One potential criticism of this study is the use of the alkaline hematin methodology that, while accurate, only measures the blood component of menstrual loss and not the approximately 50% of menstrual fluid composed of tissue and fluids other than blood[15]. As alkaline hematin methodology is frequently employed in clinical trials, these data still provide a valid measure for assessing the strength of evidence for meaningful improvements in HMB.

Conclusion

Using data from a randomized, controlled clinical trial, a link between objective and subjective measures of MBL was established. A minimally important decrease from baseline in MBL of 36 mL/cycle, or approximately 22%, was determined to be meaningful for the majority of women with HMB in this study population. These findings provide a foundation for physicians to connect quantitative HMB clinical trial data with patient-centered care.

Transparency

Declaration of funding
Financial support for this study was provided by Xanodyne Pharmaceuticals, Inc. and Ferring Pharmaceuticals Inc.

Declaration of financial/other relationships

Dr Lukes receives or has received research support from Xanodyne, Ethicon, Merck, Bayer, Luitpold, Hologic, National Improvement for Women's Healthcare, Duramed, NIH, CDC/ATPR, Smith & Nephew, Trent Foundation, and AMS. She consults with and/or has served on speakers' bureaus for Ferring, Xanodyne, Hologic, AMS, Bayer, Interlace Medical, Microsulis, AMAG, Daichii, and Myriad. Dr Muse receives or has received research support from Amgen, Wyeth Research, Xanodyne, Merck, and CONRAD and has served as a consultant or on speakers' bureaus for Ferring, Lilly, Merck, and Wyeth. Dr Richter receives or has received research support or has acted as a consultant for Pfizer, Astellas Pharmaceuticals, Xanodyne, Uromedica, IDEO as well as receiving Pfizer and Warner Chilcott Education grants. Dr Moore is an employee of Xanodyne. Dr Patrick has acted as a consultant for Amgen, Meritage, Amylin, Pfizer, and Merck.

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