Evaluation of adolescents with heavy menstrual bleeding using the International Society of Thrombosis Haemostasis-Bleeding Assessment Tool and The Pediatric Bleeding Questionnaire scores

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ABSTRACT

Background. Heavy menstrual bleeding (HMB) is a common condition in adolescents. However, bleeding disorders are known to be one of the causes of HMB in adolescent girls, so they should be considered. Simple methods that can be used in primary health care are needed to determine whether patients have bleeding disorders.

The aim of this study was to evaluate the bleeding score of patients admitted with HMB and to determine the diagnostic value of patients who were symptomatic but whose initial hemostatic tests were normal.

Methods. A total of 113 adolescents with HMB and 20 healthy adolescent girls were included in the study. The Pediatric Bleeding Questionnaire (PBQ) and the International Society of Thrombosis Haemostasis-Bleeding Assessment Tool (ISTH-BAT) were used for evaluation.

Results. Overall, approximately 18% (n= 20) of the adolescents in the study were diagnosed with a bleeding disorder. The cut off value for the 'clinically significant bleeding score' was found to be 3.5.

Conclusions. The PBQ and ISTH-BAT can help distinguish a significant bleeding history from an otherwise trivial bleeding and can be included in the algorithm for the primary care of adolescents with HMB with suspected bleeding disorders.

Key words: heavy menstrual bleeding, bleeding disorder, Bleeding Score, Türkiye.

Heavy menstrual bleeding (HMB) is a common condition in adolescent girls, with an incidence ranging from 12.1% to 37%.[1-3] HMB affects patients' quality of life and may lead to symptoms of anemia and iron deficiency. As a result, these patients may require transfusions.[3] A hematology consultation is often requested to evaluate for recurrent iron deficiency anemia and underlying inherited bleeding disorders.

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The main cause of HMB is the immaturity of the hypothalamic-pituitary-ovarian axis. However, bleeding disorders are known to be one of the causes of adolescent HMB, and their complaints should be considered. The number of hemorrhagic symptoms is higher in adolescents when a more severe bleeding phenotype or disorder is present. In the literature, an underlying bleeding disorder has been found in 10% to 62% of patients with HMB.[4-7] The most common inherited bleeding disorder is von Willebrand disease (vWd), whose rate of which is 1% in the normal population but 5-36% in patients with HMB.[8-13]

To determine whether patients have bleeding disorders, simple methods that can be used in primary health care are needed. Standardized bleeding scores have been developed for the diagnosis of bleeding disorders, in which a detailed and accurate bleeding history is obtained. However, there are only a few comprehensive studies in adolescents with HMB. With this study, we aimed to prospectively evaluate the ability of the International Society of Thrombosis Haemostasis - Bleeding Assessment Tool (ISTH-BAT) and Pediatric Bleeding Questionnaire (PBQ) to predict the presence of a previously undiagnosed bleeding disorder in adolescent girls admitted with HMB.

Material and Methods

Patient Study Population

The study was conducted prospectively between October 2020 and March 2021. This study included adolescent girls (age < 18 years) with HMB who were consulted in the Pediatric Hematology Unit of the Dr. Sami Ulus Maternity and Children Research and Training Hospital. The control group (n=20) consisted of adolescent girls admitted to the general pediatric outpatient clinic for preoperative evaluation.

Clinical data, including age at first bleeding event, age at menarche, age at examination, age at diagnosis, time to development of HMB, medical and family history, laboratory test results, final diagnoses and hospitalizations, iron deficiency anemia, need for blood transfusions, and therapeutic modalities, were recorded.

According to the 2018 FIGO diagnostic criteria, HMB was defined as "excessive menstrual blood loss affecting a woman's physical, social, emotional, and/or material quality of life.". Excessive menstrual blood loss was defined as persistent heavy bleeding > 7 days, flooding or gushing sensation, shedding of clots, change of protection every 1-2 hours. Anovulatory bleeding was defined as a menstrual duration < 21 or > 45 days.[14,15]

Patients were divided into 3 groups: HMB with a bleeding disorder (group 1), HMB without a bleeding disorder (group 2), and the healthy control group (group 3).

Informed consent was obtained from the parents/guardians of all patients according to the latest version of the Declaration of Helsinki, and the study was approved by the Ethics Committee of Health Sciences University, Dr. Sami Ulus Maternity and Children Research and Training Hospital (date 10/23/2020, number: E-20/10-011).

Pediatric Bleeding Questionnaire Administration

PBQ and ISTH-BAT were used for assessment.[16-19] The PBQ and ISTH-BAT assess the presence and severity of bleeding symptoms including epistaxis, easy bruising, bleeding from minor wounds, oral cavity bleeding, bleeding after dental or surgical procedures, bleeding from the gastrointestinal tract, menorrhagia, and an 'Other' category that includes venipuncture bleeding, hematuria, and pediatric specific symptoms (umbilical cord hemorrhage, cephalohematoma, and post- circumcision bleeding). The scoring is based on a scale ranging from 0 to 4 in most categories and from -1 to 4 in some categories, with 4 representing the most severe symptoms. Menstrual blood loss was described by a pictorial blood loss assessment chart (PBAC) using the scoring system of Higham et al.[20] A PBAC value of ≥ 100 was used as a cut-off value based on its diagnostic value as described in the original publication.

ISTH-BAT and PBQ were administered face-to-face by a pediatric hematologist to 113 adolescents with HMB and control groups. After obtaining the written consent of the outpatient control persons, bleeding scores were recorded by study doctor and the bleeding history was documented. The time to complete ISTH-BAT and PBQ was 20-25 minutes.

Laboratory Methods and Diagnostic Criteria

The initial evaluation of children with HMB consists of documentation of a detailed personal and family history of bleeding, physical examination, hemoglobin (Hgb), ferritin levels, and an initial hemostasis screening panel, comprising platelet count and morphology, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, clot lysis test and bleeding time (bleeding time was determined by Ivy method). Tests for von Willebrand factor antigen (vWf:Ag), von Willebrand factor ristocetin cofactor activity (vWf:Rco) and FII, FV, FVII, FVIII, FIX, FX, FXI, FXIII levels were included in the screening panel cases with HMB. The bleeding time was used as a test to screen for functional platelet disorders. The Platelet Function Analyzer (PFA-100) test was planned for patients with prolonged bleeding time. The diagnosis of platelet function disorders (PFD) was made using a complete blood count, a blood smear, PFA-100 (including 10 mcg collagen/epinephrine and 50 mcg collagen/adenosine diphosphate as aggregates) and a platelet aggregometer (Chronolog Corporation, Havertown, PA, USA). A PFD was defined as a decrease in platelet aggregation to one or more agonists below 2 standard deviations of the normal laboratory range and/or a prolonged closure time with ADP or epinephrine without exposure to aspirin and other antiplatelet drugs.

In cases of confirmed factor deficiency, the factor assay was repeated within 2–4 weeks. The cut-off values for the diagnosis of clotting factor deficiencies were <0.50 IU/mL for FII, FV, FVII, FVIII, FIX and FX, XIII, <0.70 IU/mL for FXI and <150 mg/mL for fibrinogen.

The diagnosis of vWd depended on low vWf:Ag and vWf:Rco and FVIII:C levels. The lower limits of the normal range for vWf:Ag and vWf:Rco were <0.50 IU/mL.[21] The diagnosis of mild factor deficiency was based on at least two separate measurements of the level of the relevant clotting factor.

Anemia was defined as Hgb <11g/dL and iron deficiency or low ferritin levels were defined as serum ferritin levels ≤ 20 ng/mL. Iron deficiency anemia was defined when both anemia and ferritin levels ≤ 20 ng/mL were present.

Statistical analysis

All analyses were performed using IBM SPSS version 23 (SPSS IL, USA) software. The normality of variables was tested using a D'Agostino-Pearson omnibus normality test. The results are presented as means or medians (25–75% interquartile ranges [IQR]) unless stated otherwise. Comparisons were made between patients based on the diagnosis of bleeding disorders categorical variables were summarized using percentages and ratios and compared using the chi-square test, whereas continuous variables were summarized using appropriate measures of central tendency and dispersion. Parametric tests were used for variables that were distributed normally, while nonparametric tests were utilized for variables without normal distribution. The differences of two independent variables between groups were compared using the Student's t test and for comparison of more than two independent variables, ANOVA was used for the ones with a normal distribution. As a non-parametric test, the Mann-Whitney U test was used for the comparison of two independent variables and for comparison of more than two independent variables, Kruskal-Wallis test was used. The optimal cut off points of the bleeding score for discrimination of case and control groups from each other were evaluated by receiver–operator curve (ROC) analysis calculating the area under the curve (AUC) as giving the maximum sum of sensitivity and specificity (ie, Youden index) for the significant test. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated at the best cut off point. P value less than 0.05 was considered statistically significant.

Results

A total of 113 adolescents with HMB and 20 healthy adolescents were included in the study, all data were recorded during the study period and full results were collected. The characteristics of the patient and control groups are presented in Table I.

Overall, 18% (n=20) of the adolescents in the study were diagnosed with a bleeding disorder. Our results indicate that vWd is the most common disorder in adolescents with HMB (11.5%), followed by PFD (4.4%) and mild coagulation factor deficiency (FV and FVII, 1.8%). The platelet aggregometer identified platelet defects in 5/113 (4.4%) adolescents. The mean age of the patients was 14.29 ± 1.73 (10.8-17.5) years. The mean age at menarche for the entire cohort was 12.23 ± 1.03 (10-15) years and bleeding disorder evaluation occurred at a median of 2 years from menarche. Of the adolescents, 14% required hospitalization for evaluation and management of HMB. None

of the participants had a menstrual duration > 45 days. Forty-seven percent (n = 53) had iron deficiency anemia, 34% (n = 38) had only iron deficiency and overall iron deficiency was observed in 81% (n = 91). In adolescents diagnosed with bleeding disorders, mean hemoglobin (Hb) levels were reported to be similar to those without bleeding disorders (10.7 vs. 10.5). PFA-100 was administered to 8 patients with a prolonged bleeding time. A PFA-100 abnormality was found in 5 of these patients.

Sixteen patients had a history of tooth extraction, one patient twice and one patient with vWD had a history of bleeding after tooth extraction. Eight patients had a history of surgery in the past, one patient twice, and none of them had postoperative bleeding. None of the patients had muscle hematoma, hemarthrosis, or gastrointestinal (GI) system bleeding. The threshold value for ''clinically significant bleeding score'' was determined to be 3.5.

Table I. Characteristics of patient and control groups.

Symptom	Group-1 n=20	Group-2 n=93	Group-3 n=20	p
Age (yr), mean±SD (min-max)	14.77±1.72 (11-17.5)	13.9±1.59 (10.8-17.5)	15.45±1.84 (12-18)	<0.001
Age at menarche (yr), mean±SD (min-max)	12.37±0.74 (11-14)	12.02±1.01 (10-14)	13.10±0.96 (11-15)	<0.001
Hgb (g/dL), Median (IQR)	11.1 (8.2-12.9)	11.1 (8.1-12.6)	13.2 (12.6-13.6)	<0.001
IDA, n (%)	8 (40)	45 (48)	0 (0)	
ID, n (%)	12 (60)	79 (85)	0(0)	
PBAC at study entry, Mean ± SD*	380±145	320±139	61±23	<0.001
ISTH-BAT, Median (IQR)*	4 (4-5)	3 (2.5-3)	0 (0-0.75)	<0.001
PBQ, Median (IQR)*	4 (4-5)	3 (2.5-3)	0 (0-0.75)	<0.001
PBQ without menorrhagia, Median (IQR)	2 (1-3)	0 (0-0.75)	0 (0-0.75)	<0.001
Family history of bleeding, n (%)	N:8 (40)	N:4 (4.3)	N:0 (0)	<0.001
Blood transfusion, n (%)	N:2 (10)	N:14(15)	N:0	0.137
PT (s), mean±SD (min-max)	12.58±1.11 (11-14.5)	12.34±0.88 (9.4-14.4)	12.57±0.95 (10.8-13.8)	0.565
APTT (s), mean±SD (min-max)	27.1±2.51 (23.4-31.7)	25.38±3.06 (17.6-32.3)	26.85±2.02 (23.1-29.7)	0.048

Group 1, HMB with bleeding disorders; Group 2, HMB without bleeding disorders, Group 3, healthy control group.
*There is a statistical difference between the scores of the Groups 1-2 in comparison to Group 3.
APTT: activated partial thromboplastin time, Hgb: hemoglobin, HMB: heavy menstrual bleeding, ID: Iron deficiency, IDA: Iron Deficiency Anemia, IQR: 25–75 % interquartile range, ISTH-BAT: International Society of Thrombosis Haemostasis-Bleeding Assessment Tool, PBAC: pictorial blood loss assessment chart, PBQ: Pediatric Bleeding Questionnaire, PT: prothrombin time.

In our study, we found a bleeding score of 3.85 ± 1.63 (3-10) in HMB patients with existing bleeding disorders, 2.83 ± 1.07 (1-5) in HMB patients without bleeding disorders, and 0.25 ± 0.44 (0 – 1) in the healthy control group. There was no significant difference between the ISTH-BAT and PBQ scores. Without menorrhagia, the bleeding score was 0.95 ± 1.46 (0-6) in Group 1, 0.11 ± 0.35 (0-2) in Group 2, and 0.25 ± 0.44 (0-1) in the healthy control group. Regarding the performance of PBQ as a screening tool to identify bleeding disorders in adolescents with HMB, the ROC curve analysis showed good discrimination with an AUC of 0.90 (95% CI: 0.84; 0 ,96) (Fig. 1). At a threshold of bleeding score (BS)=3.5, the sensitivity was 95%, the specificity was 76.3%, the PPV was 46.3%, and the NPV was 98.6%.
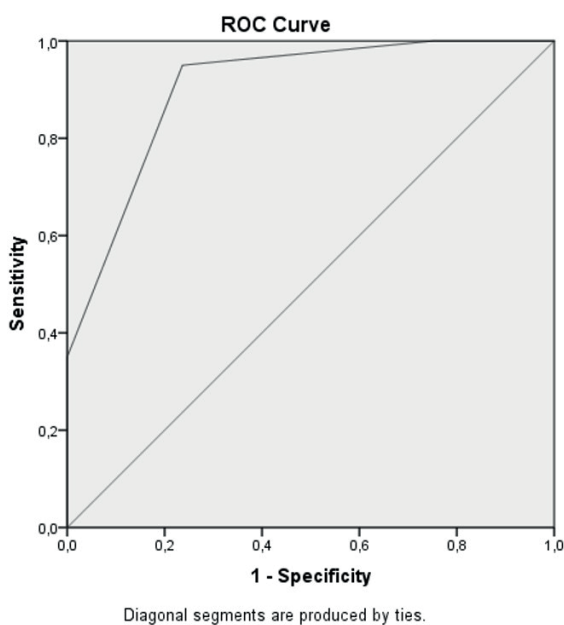

Fig. 1. Receiver operating characteristics (ROC) curve of PBQ to predict the presence of bleeding disorder in patients with HMB at BS=3.5. The ROC curve analysis demonstrated good discriminative ability having an area under the curve (AUC) of 0.90 (95% confidence interval: 0.84-0.96).
BS: bleeding score, HMB: heavy menstrual bleeding, PBQ: Pediatric Bleeding Questionnaire

Discussion

It is usually difficult to assess bleeding disorders in children with HMB. Previously, the use of the ISTH-BAT score in determining bleeding disorders has been studied and previous reports have found that the clinically significant bleeding score is 3-4 overall.[22-24]

In this study, we tried to find the cut-off point in patients with HMB. Our study shows that an ISTH-BAT score of ≥3.5 demonstrates diagnostic accuracy in excluding bleeding disorders in adolescents with HMB. In patients with HMB, an ISTH-BAT score can be used, which could reduce false-positive diagnoses of bleeding disorders and identify those adolescents who are unlikely to benefit from repeat testing.

Iron treatment and transfusion requirements may develop due to iron deficiency anemia caused by HMB. Hematology consultations are often requested to investigate recurrent iron deficiency anemia and underlying hereditary bleeding disorders. 12% of adolescents with HMB require hospitalization. In the literature, the rate of iron deficiency anemia in adolescents with HMB is given as 9-16% and the need for transfusions as 12%.[25-28] In our study, 47% of patients had anemia due to iron deficiency and 14% had at least one transfusion history. Our results were high compared to what has been reported in the literature. The rate of inherited bleeding disorders in adolescent girls with HMB ranges from 10% to 62%.[4-7] The most common inherited bleeding disorders are vWd, which are observed in 1% of the general population and 5-36% in patients with HMB.[8-13] In our study group, the rate of bleeding disorders was 18%. Our results indicate that vWd is the most common condition in adolescents with HMB (11.5%), followed by PFD (4.4%) and mild coagulation factor deficiency (1.8%). In the literature, it is assumed that the prevalence of bleeding disorders is high, but this does not necessarily reflect the general population,

as most subspecialty clinics treat bleeding diathesis more frequently as they are referred more complicated patients. This referral bias probably led to a higher incidence of bleeding disorders in this study compared to primary care settings.

PFD and coagulation factor deficiency are the rarest bleeding disorders seen in women with HMB. The frequency of PFD ranged from 3.2% to 7.0% in studies examining platelet function in women with HMB.[29-31] Our results were similar to those reported in the literature.

In various studies, PBQ has shown a sensitivity of 83% and a specificity of 79% for bleeding disorders in vWd patients.[19] Philipp et al. used an 8-item screening test in 217 adult patients (sensitivity 89%, specificity 72%, haemostatic abnormality was detected in 71% of patients (5% vWd).[32]

However, there are very few studies in adolescents presenting with HMB of ISTH-BAT in the diagnosis of bleeding disorders in HMB was investigated and the clinically significant bleeding score was found in previous reports.[22,23]

The cut-off level for ''clinically significant bleeding score'' was found to be 3.5 in our study, which was relatively lower than in the previous studies. The aim of this study was to assess adolescents with HMB using the pediatric bleeding score and to determine the diagnostic value in those patients who are symptomatic but with normal initial hemostatic tests. We recommend using the ISTH-BAT score because the PBQ and the ISTH-BAT score in our study was similar. In our study, we found a bleeding score of 3.85 ± 1.63 (3-10) in HMB patients with established bleeding disorders, 2.83 ± 1.07 (1-5) in HMB patients without bleeding disorders and 0.25 ± 0.44 (0-1) in the healthy control group. There was no significant difference between the ISTH-BAT and PBQ scores. Without menorrhagia, the bleeding score was 0.95 ± 1.46 (0-6) in group 1, 0.11 ± 0.35 (0-2) in group 2, and 0.25 ± 0.44 (0-1) in healthy controls. In a previous study conducted on vWd, the cut-off level of the pediatric bleeding score was 3.[24] Instead, we identified a score of ≥3.5 as predictive of bleeding disorders in adolescents with HMB. However, our study concludes that our bleeding scores were high due to the selection of a patient group of adolescent girls with HMB. The ISTH-BAT score of ≥3.5 in patients with bleeding disorders was mainly due to the presence of additional bleeding symptoms in HMB. Considering the scores other than HMB, the score was high in the bleeding disorder group, which was comparable to the literature.[19]

The high rates of bleeding disorders could be due to referral bias, as patients needing specialized care were more likely to be referred. This is a limitation of this study.

This study showed that bleeding scores can be used in patients with HMB admitted to primary health care settings and we believe patients with high scores should be referred to the hematologist for further evaluation.

Ethical approval

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: NÖ; data collection: contribution of all authors, analysis and interpretation of results: NÖ; draft manuscript preparation: NÖ, GŞ. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

Conflict of interest

The authors declare that there is no conflict of interest.

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