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Evaluation of Normal Range of Bleeding Scores in Healthy Iranian Adults using the International Society on Thrombosis and Hemostasis Bleeding Assessment Tool

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ABSTRACT

Background: Bleeding assessment tools are key components in the evaluation of patients suspicious for bleeding disorders. The exact determination of the normal ranges of ISTH-BAT (International Society on Thrombosis and Hemostasis –Bleeding Assessment Tool) in the healthy population is a crucial step for determining who needs to be referred for further coagulation laboratory examinations. We aimed to determine the normal range of ISTH-BAT and simultaneously evaluate the Von Willebrand disease (VWD) diagnostic panel tests in a healthy Iranian group.
Methods: ISTH-BAT as well as prothrombin time, activated partial thromboplastin time, factor VIII clotting assay, von Willebrand factor (VWF) antigen, VWF ristocetin cofactor assay, ristocetin induced platelet agglutination, and blood group typing were assessed for 25 normal adults without any bleeding symptoms or a known coagulation disorder.
Results: In the 25 studied subjects (13 men, 12 women), the range of bleeding score was 0-6 in women and 0-5 in men; however, since the scores were lower than 2 in most (68%) cases, the interquartile range (IQR) was used for normalizing the data. The ISTH-BAT normal range was found to be 1-4 in women and 0–2 in men.
Conclusion: According to this result, the ISTH-BAT cut-off for abnormal bleeding score was ≥5 in adult women and ≥3 in adult men. These data may be valuable in the routine practice of clinicians and adult hematologists in our country for the assessment of individuals with suspected bleeding disorders.

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Introduction

Von Willebrand disease (VWD) is the most common inherited bleeding disorder with a prevalence of 1% in the general population.[1,2] VWD is caused by quantitative or qualitative defects in the von Willebrand factor (VWF). Based on the last classification of the international society on thrombosis and hemostasis (ISTH), VWD includes three main types. Type 1 and 3 VWD are caused by either partial or virtually total quantitative defects of VWF and type 2 as qualitative defects, which comprised of four subgroups (2A, 2B, 2M, 2N).[3] People with VWD experience frequent nosebleeds, easy bruising, and excessive bleeding during and after invasive procedures, such as tooth extractions and surgery. Women depending on the VWD subtype may experience heavy menstrual bleeding and postpartum hemorrhages.[4,5]

The laboratory diagnosis of VWD is quite challenging and requires a battery of complex tests including screening, diagnostic, and specialized panels.[6] The current diagnostic tests suggested by the VWF ISTH-subcommittee include VWF antigen (VWF:Ag), Factor VIII clotting assay (FVIII:C), and ristocetin cofactor

activity of VWF (VWF:RCo).[3]

Clinical understanding of the presence and severity of bleeding symptoms is an essential step in evaluating suspected patients with a bleeding disorder since laboratory assessment will only be performed in suspicious cases.[7] The lack of a standardized assessment of bleeding symptoms led specialists to try to develop bleeding assessment tools (BATs). The two initially designed bleeding questionnaires (BQ); Vicenza and MCMDM-1VWD BQ developed by Rodeghiero and colleeagues and Tosetto and co-workers, respectively, have been validated by many studies.[8,9] Since the above BATs were established first only for the identification of patients affected by VWD, the ISTH/SSC Joint Working Group in 2010 provided a single bleeding assessment tool to standardize the reporting of bleeding symptoms for all coagulation disorders and was intended to be used in pediatric and adult patients.[10]

The exact determination of normal ranges of bleeding scores in healthy subjects in both men and women is crucial in differentiating healthy people from patients with VWD and other bleeding disorders. To our knowledge, there has been no study to determine the normal range of bleeding scores in Iran. We aimed to determine the normal range of bleeding scores and simultaneously evaluate the VWD diagnostic panel tests in a healthy group for further clinical application and research studies on VWD in Iran.

Materials and Methods

We enrolled 25 healthy subjects with no bleeding symptoms or any known coagulation disorder in our study. Exclusion criteria were abnormal laboratory tests and pregnancy. Participants were recruited voluntarily, including students and staff of the Iranian Blood Transfusion Organization (IBTO). The study was approved by the High Institute for Education and Research in Transfusion Medicine and informed consent was obtained from all subjects in accordance with the Declaration of Helsinki. All samples were collected in 0.105M buffered trisodium citrate solution (1:9 anticoagulant to whole blood) and centrifuged at 1500 g for 10 minutes at room temperature to obtain platelet-poor plasma (PPP). All subjects were identified for ABO blood typing and were divided into O or non-O blood groups.

VWF Testing and Determination of ISTH-BAT

FVIII: C (one-stage clotting assay), prothrombin time (PT), activated partial thromboplastin time (aPTT), VWF: Ag and VWF: RCo were measured in the IBTO reference coagulation laboratory by HemosIL AcuStar (Instrumentation Laboratory, IL, Bedford, Ma. USA). We used the ISTH-BAT questionnaire to assess each participant bleeding score. Ristocetin-induced platelet aggregation (RIPA) test was measured by CHRONO-LOG using ristocetin concentrations 0.5, 0.6, 1.0 and 1.5 mg/mL.

We used IBM SPSS Statistics Premium (Grad Pack 22," 2014) for data analysis. The distribution of bleeding score values was represented by box plots. Each box plot represented the interquartile range with a median value (horizontal line). Results were expressed as medians and interquartile ranges (IQR) or means and ranges in the parenthesis.

Results

In this study, 13 participants were men and 12 were women, with median ages of 38 (range: 26-56) years and 32 (range: 24-59) years, respectively, and ABO blood typing is shown in table 1.

The male group showed a higher mean for FVIII: C, VWF: Ag and VWF: RCo than the female group, but it was not statistically significant. The range of the VWF: RCo / VWF: Ag ratio in the male and female groups were

Table 1: Baseline characteristics of the study population

Subjects	N	Age [a] (y)	Blood group (O/non-O)
Male	13	38 (26-56)	3/10
Female	12	32 (24-59)	6/6

[a]Median values (range)

Table 2: Laboratory and clinical phenotype parameters in normal adult males and females

	PT	aPTT	FVIII:C (IU/dl)	VWF:Ag (IU/dl)	VWF:RCo (IU/dl)	VWF:RCo/Ag ratio	BS
Mean							
M	11.0	35.3	114	124	91.6	0.75	-
F	11.3	34	102.8	106.6	81.0	0.78	-
SD							
M	0.56	2.1	19.4	29	20.6	0.13	-
F	0.6	2.0	28.7	27.5	15.5	0.17	-
Median							
M	10.9	36	114	116	93	0.75	1
F	11.2	34	100.5	105.5	78	0.77	2
Range							
M	10.2-12	31-38.2	85-158	86-196	56-135	0.4-0.9	0-5
F	10.5-12.7	31-38	66-145	70-149	55-109	045-1.1	0-6

M, Male; F, Female; VWF, von Willebrand factor; VWF: Ag, von Willebrand factor antigen; VWF: RCo, von Willebrand factor ristocetin cofactor; FVIII: C, Factor VIII procoagulant activity; BS, Bleeding Score; SD, Standard Deviation

Table 3: Reference ranges for RIPA in the healthy population

Ristocetin (mg/mL)	Mean	SD	Median	Range
1.5	82	8.8	82	58-104
1.0	71	11.58	74	33-99
0.6	3	1.9	2.0	1-10
0.5	1	1.1	1.0	0-4

SD, Standard Deviation

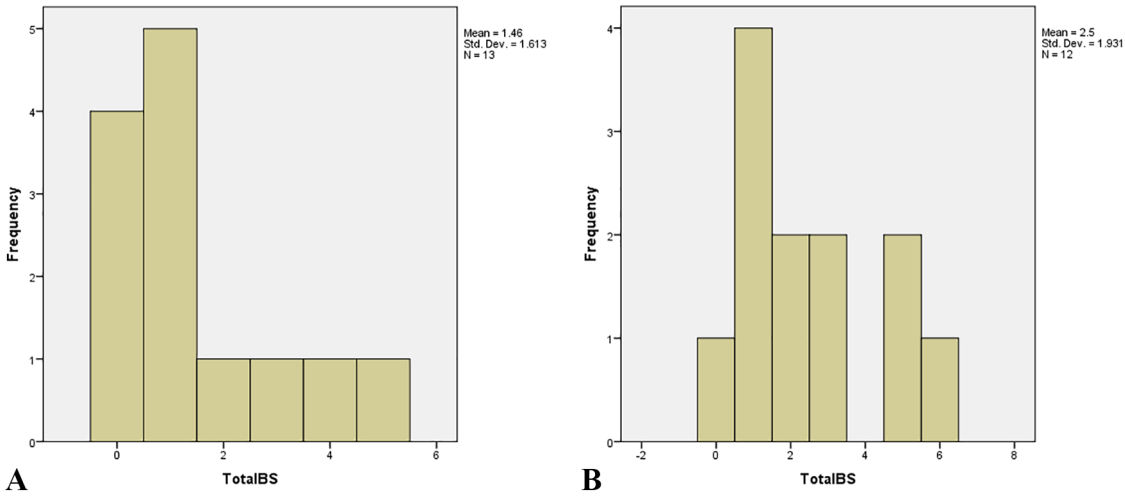

Figure 1: Bleeding score data for males (A) and females (B)

0.4-0.9 and 0.45-1.1, respectively (table 2).

The mean RIPA for ristocetin concentrations 0.5, 0.6, 1.0, and 1.5 mg/ml were 1%, 3%, 74% and 82%, respectively. The results of the RIPA test are summarized in table 3.

There was a wide range of bleeding scores (0-6 in women and 0-5 in men); however, the scores were lower than 2 in 68% of participants. There was no correlation between age and bleeding score (figure 1).

Since the data were not normally distributed (most subjects had a bleeding score <2 and there was only one man with bleeding score 5 and one woman with bleeding score of 6. We used the interquartile range (IQR) for normalizing the data to ensure the correct determination of bleeding score normal ranges for healthy control. Using the above-mentioned methodology, the normal bleeding score range was found to be 0–2 in men and 1-4 in women (figure 2).

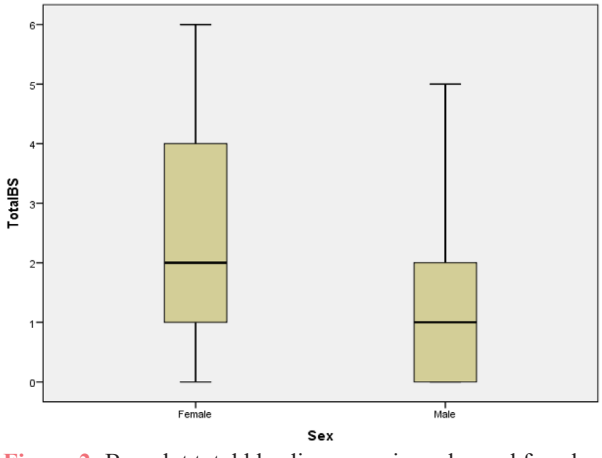

Figure 2: Box plot total bleeding score in males and females. Line: Median

Discussion

Bleeding assessment tools are key components in the evaluation of patients who are suspected of having bleeding disorders.[7] The exact determination of normal ranges of bleeding score in the healthy population is a crucial step for differentiating healthy people from patients with VWD and other bleeding disorders. The current study was designed to determine the normal range of bleeding score and simultaneously evaluation of the VWD diagnostic panel tests in a limited number of healthy subjects.

To date, several studies have been conducted to determine the normal range of BATs in different bleeding disorders. In the Vicenza Bleeding Questionnaire (BQ), which uses a 0 to +3 scoring system for each bleeding symptom, the cut-off value for a positive "bleeding score" was >3 in adult men and >5 in adult women. In the MCMDM-1VWD BQ, which uses a -1 to +4 scoring system for bleeding symptoms, an association between VWD and a bleeding score >3 in both men and women is proposed.[8,9] A comprehensive study by Elbatarny and co-workers developed a bioinformatics system to allow for the merging of the data collected from four different BATs (the MCMDM-1VWD BQ, the Condensed MCMDM-1VWD BQ, the Pediatric BQ and the ISTH-BAT). Consistent with our findings, their final analysis showed that the normal ranges for bleeding score were 0–3 and 0–5 for adult men and women, respectively.[11]

In a study by Shahriari and co-workers, the mean bleeding score of the healthy subjects was 5.35±4.48, compared to our population which showed a mean scores of 1.9±1.8.[12] In other words, the range of bleeding score in their study was 1-10. We believe that the difference in

the figures may be a consequence of the implementation of different statistical methods. Elbatarny and colleagues normalized the data by using IQR, excluding outlier values.[11,12] We also did the same in our analysis.

Different studies indicated that ISTH-BAT is clinically applicable for deciding whether extended laboratory work-up is reasonable of patients suspicious for bleeding disorders or not.[13-16]

The results of our study are in agreement with the findings reported by Lowe and colleagues.[13] They evaluated the utility of the ISTH-BAT in predicting platelet defects. They recruited 21 healthy subjects along with 79 subjects suspicious for inherited platelet function disorders. Their findings revealed that the 95th percentile for the ISTH-BAT score was 4 in healthy control subjects (using IQR).[13]

Recently, Rashid et al. investigated the use of ISTH-BAT to predict correctly inherited platelet dysfunction disorders (on 100 healthy volunteers and 161 cases suspected with inherited platelet function disorders). They demonstrated that the 95th percentile of bleeding score based on ISTH-BAT in their study was remarkably low (BS<1).[17] They concluded that it might be the result of enrolling younger age group as healthy subjects (28 % of their studied participants were younger than 18 years old), in comparison to Lowe GC's and our study who recruited healthy subjects older than 24 and 18 years old, respectively.[13,17] It should be pointed out that young adults and children might face less hemostatic challenges (like pregnancy, tooth extraction, postoperative bleeding, or menorrhagia) which might have an effect on the interpretation of bleeding scoring systems.[18]

In this study, we found 56% of subjects reported no bleeding symptoms or just had one. Rodeghiero and colleagues mentioned that about 92% of normal subjects had never suffered from bleeding or had experienced just one episode.[8] Multiple studies attempted to calculate the frequency of hemorrhagic symptoms in different groups of patients and normal populations.[4,12,19,20] In two different studies, Rodeghiero et al. and Mittal et al. reported mucocutaneous bleedings as common manifestations in healthy populations.[19,21] A study by Mittal et al. claimed that symptoms of epistaxis and oral bleeding among healthy children had the highest mean scores.[21]

Our study had some obvious limitations. The small number of the samples certainly affects the statistical power of the study which needs further studies with large normal control samples in order to be able to interpret the bleeding scores more precisely in normal and patient groups. The second limitation of our study was the lack of a predefined pediatric control group for establishing

In conclusion, we found a normal range of bleeding score 0-2 for males and 1-4 for females; therefore, the cut-off for a positive or abnormal BS was ≥3 and ≥5 in adult males and females, respectively. This ascertained that ISTH-BAT normal range may be valuable in the routine practice of clinicians and adult hematologists in our country for assessment of individuals with suspected bleeding disorders and determining who need to be referred for further laboratory examinations.

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Conflict of Interest: None declared

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