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Role of ISTH Bleeding Assessment Tool in Diagnosing Patients with Suspected Bleeding Disorders

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Abstract

Objective: To compare the ISTH-BAT score with the results of light transmission aggregometry in patients suspected of having bleeding disorders, particularly those with platelet function disorders.
Methodology: This study was conducted at the Chughtai Institute of Pathology, Lahore, from January 2022 to March 2023. A total of 183 patients with suspected bleeding disorders, aged between 3 months and 18 years, were enrolled. The ISTH-BAT questionnaire was administered, and scores were calculated and compared with the results of light transmission aggregometry. Data were analyzed using SPSS-23, with the p-value calculated using the chi-square test.
Results: The study comprised 183 patients, including 97 (53%) males and 86 (47%) females, with ages ranging from 1 to 16 years and a median age of 6 years. The BAT score was calculated for each patient using the ISTH questionnaire. A score below 3 was considered normal, while a score above 3 was considered abnormal. Among the patients, 73 (39.8%) had a normal ISTH-BAT score, while 110 (60.1%) had an abnormal score. Of the 110 patients with an abnormal ISTH-BAT score, 90 (81.8%) were diagnosed with a bleeding disorder, while 20 (18.1%) did not have a bleeding disorder.
Conclusion: In conclusion, the ISTH-BAT score is an effective tool for assessing patients with suspected bleeding disorders, particularly for those with suspected platelet function disorders, which can be rare and challenging to diagnose.
Keywords: Bleeding disorder, ISTH BAT score, Light transmission aggregometry.

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Introduction

Bleeding disorders are a group of disorders in which the clotting system of the body becomes defective. These disorders are mostly inherited and rarely acquired. These disorders can lead to heavy and prolonged bleeding after an injury or surgery. Bleeding can also begin spontaneously and may be difficult to stop.[1] Normal physiological interaction of platelets, endothelial cells, von Willibrand factor and coagulation factors maintain the integrity of the vascular system in case of any trauma but if any one of these interactions becomes impaired, massive bleeding occurs.[2] Different bleeding disorders that can occur include platelet function disorders, von Willibrand disease and coagulation factor deficiencies. In Pakistan, Hemophilia is the most common bleeding disorder followed by von Willibrand disease and Glanzmann Thrombasthenia.[3]

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Deficiencies in Factor VIII and Factor IX result in X-linked hemorrhagic diseases known as hemophilia A and hemophilia B, respectively.[4] Hemophilia patients experience spontaneous and post-traumatic bleeds, typically occurring in muscles and joints, although life-threatening intracranial bleeds can also manifest.[5] Rare inherited bleeding disorders encompass deficiencies in fibrinogen, factor II, V, VII, X, XI, XIII, and combined V and VIII deficiencies.[6]

Von Willibrand disease is a common inherited bleeding disorder caused by deficient or defective von Willebrand factor effecting almost 1% of the world population.[7] It leads to massive mucocutaneous bleeding often making life a misery for the patients if not diagnosed and treated promptly.

Platelets play an integral role in hemostasis and any structural or functional defect in platelets can lead to catastrophic bleeding which is a nightmare for both patients and physicians. Platelet function disorders (PFD) include defects of platelet adhesion, activation or aggregation which may be due to defective receptors, granules or cytoskeleton.[8] Diagnosing patients with

suspected PFD is a challenge as these disorders are rare and are present in regions where consanguinity is common and secondly due to variable presentation of these patients with bleeding symptoms ranging from mild bruising to life threatening hemorrhages.[9]

International Society on Thrombosis and Hemostasis Bleeding assessment tool (ISTH-BAT) is an internationally used questionnaire covering 14 important bleeding sites to establish the severity of bleeding in patients with suspected bleeding disorders. It is used as an initial screening tool to differentiate between physiological and pathological bleeding. The normal reference ranges of ISTH-BAT score were established in 2014 with normal range of for males being 0-3, for females 0-5 and pediatric age group (less than 18 years) 0-2.[10] It has also been established that patients with bleeding disorders tend to have higher ISTH-BAT score as compared to normal population.[11] The diagnostic utility of ISTH-BAT score has been extensively validated in patients of suspected von Willebrand disease but its role in diagnosing suspected PFD is still unclear.[12]

Light transmission aggregometry (LTA) is a widely used test to diagnose bleeding disorders but this test has several limitations. It is an expensive, time consuming and specialized test which is often not available in tertiary care hospitals or laboratories.[13] Therefore, the purpose of this study is to screen patients with bleeding history using ISTH-BAT score and to predict the outcome of LTA based on the ISTH-BAT score. By this we will be able to establish ISTH-BAT score as a cost-effective screening tool for patients with suspected bleeding disorder specially platelet function disorders and refer only those patients who have high ISTH-BAT score for LTA and other tests like factor assays.

Methodology

This study was conducted at Chughtai Institute of Pathology in Lahore, following approval from the institute's IRB committee. The study spanned from January 2022 to March 2023. A total of 183 patients suspected of having a bleeding disorder were enrolled after providing informed consent. Both male and female patients between 3 months and 18 years of age were eligible for inclusion. Patients with a platelet count of less than 80 x 10^9/L and those who had received a blood transfusion within the last 15 days were excluded from the study.

The ISTH-BAT questionnaire was filled by Resident hematologist prior to testing and score was calculated. Then blood was collected by venipuncture into an EDTA vial for platelet count and in 4 vials of buffered trisodium citrate anticoagulant vials for LTA. The platelet count was run on automated hematology analyzer Sysmex XN 9000 and verified by microscopy. If platelet count was above 80 x 10^9/L, bleeding time was also performed using IVY's method under aseptic conditions. PT and APTT were run on automated Sysmex CS 1600 and Sysmex CS2500 instrument.

Visual inspection of samples was done and icteric, lipemic and hemolyzed samples were rejected. LTA was performed using Helena-AGGRAM at 37 degrees centigrade within 2 hours of sample collection. Platelet poor plasma (PPP) was formed by centrifuging one citrate vial at 6000 rpm for 6 minutes and platelet rich plasma (PRP) was formed by centrifuging the other 3 citrate vials at 900 rpm for 7 minutes. The PRP were left for at least 30 minutes prior to testing. The aggregometer was calibrated by a cuvette containing PRP which equates 0% light transmission and a second cuvette containing PPP which equates 100% light transmission. 250ul of PPP was taken in a glass tube and was run as a blank in all 4 wells of instrument. Then 3 other glass tubes with 225ul of PRP were put in each of the other wells of the instrument and 25ul of ADP was put in first tube, collagen in second and Ristocetin in the third tube. Then the channel button was pressed and the time to reach the final reaction was noted. When an agonist is added to the platelets, they aggregate and absorb less light and so the transmission increases and is detected by the photocell and recorded as a function of time. The instrument calculates the result in percentage.

The diagnosis, based from the results of LTA and ISTH-BAT scores, was recorded in an Excel spreadsheet. The data were analyzed using SPSS-23. Frequencies and percentages were computed for categorical variables, while means and standard deviations were calculated for quantitative variables. The chi-square test was employed to determine the significance level (p-value).

Results

The study comprised 183 patients, with 97 (53%) being male and 86 (47%) female, aged between 1-16 years, with a median age of 6 years.

BAT scores were determined for each patient using the ISTH questionnaire. A score below 3 was considered normal, while a score above 3 was deemed abnormal. Among the patients, 73 (39.8%) had a normal ISTH-BAT score, while 110 (60.1%) had an abnormal score.

Of the 110 patients with an abnormal ISTH-BAT score, 90 (81.8%) were diagnosed with a bleeding disorder, while 20 (18.2%) did not exhibit any bleeding disorder. The frequencies of different bleeding disorders among patients with abnormal ISTH-BAT scores are presented in Table I.

Table I: Different bleeding disorders diagnosed in patients with abnormal ISTH-BAT score.

Diagnosis	N	%
Normal	73	100
No bleed disorder	20	18.2
Glanzmann Thrombasthenia (GT)	63	57.3
Von Willebrand Disease (VWD)	19	17.3
Factor Deficiency	8	7.3
Total	110	100

The relationship between ISTH-BAT score and consanguinity, as well as family history, is presented in Table II. Out of 110 patients with abnormal BAT scores, 91 (82.7%) had a history of consanguinity, while 41 (37.3%) had a family history of a bleeding disorder. Conversely, among the patients with normal BAT scores, only 32 (43.8%) had a history of consanguinity, and a family history of a bleeding disorder was present in only 3 (4.1%) patients.

Table II: Relationship of ISTH-BAT score with consanguinity and family history.

BAT score	Consanguinity	N (%)	Family History	N (%)
Normal	Absent	41 (56.2%)	Absent	70 (95.9%)
	Present	32 (43.8%)	Present	3 (4.1%)
Abnormal	Absent	19 (17.3%)	Absent	69 (62.7%)
	Present	91 (82.7%)	Present	41 (37.3%)

A receiver operating characteristic (ROC) curve was performed to evaluate the ISTH-BAT score as a discriminating tool between patients with or without a bleeding disorder on platelet function studies. Area under the curve (AUC) was 0.909 (95% confidence interval, 0.865, 0.954).

Sensitivity, specificity, positive predictive value and negative predictive value of ISTH-BAT were calculated as 78.5%, 100%, 100% and 81% respectively, shown in table III.

Table III: Sensitivity and Specificity of ISTH-BAT score

BAT score	Diagnosis	
	Normal	Abnormal
Normal	73	0
Abnormal	20	90

*Sensitivity= TP/(TP+FN)= 73/(73+20)*100=78.5%*
*Specificity= TN/(TN+FP)= 90/(90+0)*100=100%*
*Positive Predictive Value= TP/(TP+FP)*100= 73/(73+0)= 100%*
*Negative Predictive Value= TN/(TN+FN)*100=90/(90+20)= 81%*
TP: True positive, TN: True negative, FN: False negative, FP: False positive

Discussion

Diagnosing and treating patients with bleeding disorders is a huge challenge specially in developing countries like Pakistan, where many patients die without ever being diagnosed. Unavailability of diagnostic facilities and sparsity of medical funds remain the major hurdle in early detection of bleeding disorders. Furthermore, incomplete bleeding evaluation or misinterpretation of laboratory results can lead to delay in diagnosis that ultimately affect patient's prognosis.[14]

Bleeding disorders are predominantly inherited and exhibit a higher prevalence in regions where consanguinity is widespread. Similar to our findings, studies in Saudi Arabia have also reported a higher prevalence of bleeding disorders among individuals with consanguineous relationships.[15] Additionally, research conducted in Pakistan has highlighted the increased occurrence of platelet function disorders, such as Glanzmann thrombasthenia, within populations with high rates of consanguinity. [16]

Saqlain et al. have made similar observations to ours, noting that patients with Glanzmann thrombasthenia exhibit higher ISTH-BAT scores compared to normal controls.[17] Gresele and colleagues found that the ISTH-BAT score efficiently differentiated between patients with platelet function defects and healthy individuals. However, they also noted that distinguishing between von Willebrand disease and platelet function defects was challenging.[18] Apak et al. similarly observed that patients with von Willebrand disease had higher ISTH-BAT scores and suggested that the severity of the disease could be assessed based on this score.[19]

Contrary to this a study conducted by Ambaglio et al assessed ISTH-BAT score in perioperative patients and

found out that ISTH-BAT score does not correctly identifies patient with mild bleeding disorders.[20] Likewise, another study states that ISTH-BAT score has limited diagnostic value in clinical evaluation.[21] Another study conducted in USA analyzed the role of ISTH-BAT score in identifying any bleeding disorder in adolescent female presenting with heavy menstrual bleeding. They proposed that the scoring needs modification as the diagnostic accuracy of ISTH-BAT score was not up to the mark. [22]

Conclusion

We conclude that the ISTH-BAT score is an effective tool for assessing patients with suspected bleeding disorders, especially those with suspected platelet function disorders, which are rare and difficult to diagnose. We recommend widespread use of the ISTH-BAT score by physicians, particularly those working in rural areas of Pakistan, as it is cost-effective and easy to use. Utilizing the ISTH-BAT score will aid in identifying patients who require further advanced testing, thereby reducing the workload on laboratories and providing economic benefits to financially disadvantaged patients. Incorporating the ISTH-BAT score into diagnostic protocols can lead to a more precise approach in diagnosing patients with bleeding disorders.

Limitations: The limitation of this study was that only three agonist reagents were used to perform LTA. Arachidonic acid and epinephrine were not used due to their unavailability. Therefore, important diagnosis like Bernard-Soulier syndrome and storage pool disorder were not detected.

References

1. Hall JE, Hall ME. Hemostasis and blood coagulation. In: Guyton and Hall Textbook of Medical Physiology. 14th ed. Philadelphia: Elsevier; 2021.
2. Sang Y, Roest M, de Laat B, de Groot PG, Huskens D. Interplay between platelets and coagulation. Blood Rev. 2021 Mar;46:100733. https://doi.org/10.1016/j.blre.2020.100733
3. Sohaib Asghar M, Asghar A, Asghar F, Akram M. Spectrum of Bleeding Disorders In Pakistan: A Cross-Sectional Study. Fortune Journal of Health Sciences. 2020;03(02): https://doi.org/10.26502/fjhs012
4. Franchini M, Mannucci PM. Hemophilia A in the third millennium. Blood Rev. 2013;27(4):179-84. https://doi.org/10.1016/j.blre.2013.06.002
5. Zanon E, Pasca S. Intracranial haemorrhage in children and adults with haemophilia A and B: A literature review of the last 20 years. Vol. 17, Blood Transfusion. Edizioni SIMTI; 2019: 378-84.
6. PEYVANDI F, BOLTON-MAGGS PH, BATOROVA A, DE MOERLOOSE P. Rare bleeding disorders. Haemophilia. 2012 ;18(s4):148-53. https://doi.org/10.1111/j.1365-2516.2012.02841.x
7. James PD, Goodeve AC. von Willebrand disease. Genetics in Medicine. 2011 ;13(5):365-76. https://doi.org/10.1097/GIM.0b013e3182035931
8. Wagner M, Uzun G, Bakchoul T, Althaus K. Diagnosis of Platelet Function Disorders: A Challenge for Laboratories. Hamostaseologie.2022;42(01):036-45. https://doi.org/10.1055/a-1700-7036
9. SIMON D, KUNICKI T, NUGENT D. Platelet function defects. Haemophilia.2008;14(6):1240-9. https://doi.org/10.1111/j.1365-2516.2008.01898.x
10. Doherty D, Grabell J, Christopherson PA, Montgomery RR, Coller BS, Lavin M, et al. Variability in International Society on Thrombosis and Haemostasis-Scientific and Standardization Committee endorsed Bleeding Assessment Tool (ISTH-BAT) score with normal aging in healthy females: contributory factors and clinical significance. J Thromb Haemost. 2023;21(4):880-6. https://doi.org/10.1016/j.jtha.2022.11.045
11. BIDLINGMAIER C, GROTE V, BUDDE U, OLIVIERI M, KURNIK K. Prospective evaluation of a pediatric bleeding questionnaire and the ISTH bleeding assessment tool in children and parents in routine clinical practice. J Thromb Haemost. 2012;10(7):1335-41. https://doi.org/10.1111/j.1538-7836.2012.04775.x
12. Adler M, Kaufmann J, Alberio L, Nagler M. Diagnostic utility of the ISTH bleeding assessment tool in patients with suspected platelet function disorders. J Thromb Haemost. 2019 Jul;17(7):1104-12. https://doi.org/10.1111/jth.14454
13. Moenen FCJI, Vries MJA, Nelemans PJ, van Rooy KJM, Vranken JRRA, Verhezen PWM, et al. Screening for platelet function disorders with Multiplate and platelet function analyzer. Platelets.2019;30(1):81-7. https://doi.org/10.1080/09537104.2017.1371290
14. Batsuli G, Kouides P. Rare Coagulation Factor Deficiencies (Factors VII, X, V, and II). Hematol Oncol Clin North Am. 2021 ;35(6):1181-96. https://doi.org/10.1016/j.hoc.2021.07.010
15. Aljabry MS, Alabbas F, Elyamany G, Sedick Q, Alsuhaibani O, Elfaraidi H, et al. Clinicopathological features of rare bleeding disorders in high consanguinity population; A retrospective analysis from two tertiary hospitals in Saudi Arabia. J. Appl. Hematol. 2023 Apr 1;14(2):101-7.
16. Ali T, Gul S, Amar A, Shakoor M, Farhan S, Mohsin S, et al. Two homozygous missense mutations in ITGB3 gene as a cause of Glanzmann Thrombasthenia in four consanguineous Pakistani pedigrees. Int J Lab Hematol. 2020;42(5):628-35. https://doi.org/10.1111/ijlh.13266
17. Saqlain N, Fateen T, Tufail H, Mazher N. Utility of the ISTH bleeding assessment tool (BAT) in diagnosis of Glanzmann Thrombasthenia patients. Pak J Med Sci. 2022;38(4):791-5. https://doi.org/10.12669/pjms.38.4.5361

18. Gresele P, Orsini S, Noris P, Falcinelli E, Alessi MC, Bury L, et al. Validation of the ISTH/SSC bleeding assessment tool for inherited platelet disorders: A communication from the Platelet Physiology SSC. J Thromb Haemost. 2020 Mar;18(3):732-9.

19. Apak FBB, Ümit EG, Zengin Y, Evim MS, Ünal E, Özbaş HM, et al. Assessment of patients with von willebrand disease with ISTH/BAT and PBQ scores. Vol. 37, Turkish Journal of Hematology. Turkish Society of Hematology; 2020. p. 57-8.

20. Ambaglio C, Zane F, Russo MC, Preti PS, Scudeller L, Klersy C, et al. Preoperative bleeding risk assessment with ISTH-BAT and laboratory tests in patients undergoing elective surgery: A prospective cohort study. Haemophilia. 2021;27(5):717-23. https://doi.org/10.1111/hae.14376

21. Moenen FCJI, Nelemans PJ, Schols SEM, Schouten HC, Henskens YMC, Beckers EAM. The diagnostic accuracy of bleeding assessment tools for the identification of patients with mild bleeding disorders: A systematic review. Haemophilia. 2018;24(4):525-35. https://doi.org/10.1111/hae.13486

22. Jain S, Zhang S, Acosta M, Malone K, Kouides P, Zia A. Prospective evaluation of ISTH-BAT as a predictor of bleeding disorder in adolescents presenting with heavy menstrual bleeding in a multidisciplinary hematology clinic. J Thromb Haemost. 2020 ;18(10):2542-50. https://doi.org/10.1111/jth.14997