The Bleeding Time: Review of Basic Principle, Clinical Applications, and Laboratory Pitfalls

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ABSTRACT

The bleeding time is one of the oldest tests for primary hemostasis which is still performed nowadays.This test evaluates mainly the primary hemostatic function. Some preanalytical variables including patients' physiology and hematological status may impact test results. Various protocols of bleeding time are performed. Each method has pros and cons, although the template bleeding time is currently preferred over other methods because it is well-standardized. Interpretation of the results according to a well-established reference range is important. At the moment, indications of bleeding time are very limited due to its poor sensitivity and reproducibility. More sensitive and specific assays have been developed for the diagnosis of specific conditions. However bleeding time is still useful in uremic patients. A cautionary note - this test should not be used as a screening test for prediction of bleeding preoperatively.

Keywords: Bleeding time, Clinical applications, Pitfalls

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INTRODUCTION

The bleeding time (BT) is one of the oldest tests for primary hemostasis which is still performed nowadays.[1] This test evaluates the interaction between platelets and the small blood vessel wall at the skin. Therefore, it is considered as an in vivo platelet function study.[2-4] The BT provides information for the diagnosis and prediction of bleeding in certain settings, although many variables must be considered prior to performing testing. Inappropriate use of this test not only misleads the patient management, but it also leads to unnecessary complications and costs to the patients.[5,6] In this article, the history, basic principles, clinical applications, and pitfalls of the BT are reviewed.

Development of the bleeding time

The skin BT was firstly described by Milian as a coagulation test.[7] In 1910, Duke reported three patients who had hemorrhagic diathesis directly due to decreased platelets.[8] In this outstanding article, Duke proposed a simple technique to explain hemorrhagic phenomena which he called the "bleeding time". He demonstrated that the degree of prolongation of BT was related to the severity of bleeding symptom and platelet count. Moreover, the BT could be shortened when patients received whole blood transfusions. His finding had great impact on the development of knowledge in the hemostasis field in the early 1900s.[9]

In 1935, Ivy reported that the BT performed by Duke's technique could not predict bleeding in a number of patients with jaundice.[10] The hypothesis about the defect of Duke's BT was the variation of capillary tone. Therefore, Ivy improved the technique by standardizing the capillary tone with uniform pressure applied proximal to the BT wound. This method was used along with Duke's method for a period of time. However, poor reproducibility of BT still occurred and many attempts were made to improve the technique.[11,12] In 1969, Mielke et al improved the Ivy's BT in order to study the effect of aspirin.[13] They proposed the template system which made control of the incision more precise than using only a blade. This template BT which is modified from Ivy's method has become popular and accepted as a standard method for the BT.[14-16] Many devices were then developed for commercial aims.[1,17]

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Principle of the bleeding time

The BT is usually done by making a small incision on the skin and then recording the time which is required for bleeding to stop. This period of time is called "bleeding time". It mainly reflects the physiologic interaction of the small blood vessel wall and platelets responding to vascular injury.[18] As a result, the BT is usually performed when primary hemostatic defect is suspected.

Preanalytical variables that affect the bleeding time

Many preanalytical variables such as physiology and hematological status of the patients may affect the BT result.[15] To prevent erroneous results, these factors must be considered and controlled.

Age

Macpherson et al reported that the template BT was significantly shorter in subjects who were older than 50 years as compared with those who were younger.[19] Gerrard et al also demonstrated the inverse relationship of the length of the BT and patient age.[20]

For the neonatal group, the BT is usually equivalent to or shorter than that of the adult group.[17] However, specific acquired factors such as antepartum maternal medication could influence the length of the BT in this group of patients.[21] Del Vecchio et al also reported that gestational age was an independent factor which affects the BT during first ten days of life.[22] Therefore, it may be difficult to interpret the BT in this group of patients.

Gender

It was believed that the female BT was usually longer than the male BT due to the differences of soft tissue, and hormonal effect on blood vessels.[23] However, many reports demonstrated conflicting data about the difference of the BT between sexes.[17,19,24] Although some investigators suggest sex-specific reference interval for interpretation[25], this policy is not suggested by the CLSI (Clinical Laboratory and Standards Institute).[15]

Skin characteristics

Abnormalities of skin can affect the BT result. The area of skin with heavy hairs, scars, tattoos, moles, bruises, superficial veins, infection, edema, or local hemorrhage should be avoided.[15] In elderly patients or patients with skin atrophy whose BT is difficult to interpret, so alternative testing for the diagnosis of bleeding disorders should be considered.

Temperature

Romlin et al found that the BT was significantly prolonged when the skin temperature was lowered from 32 degrees C to 28 degrees C, irrespective of the body core temperature.[26] Therefore, the BT should be performed at ambient temperature.[15]

Anemia

The relationship between the BT and anemia was observed and cited in Duke's original paper. He found that the BT in anemic patients was prolonged more than in normal subjects and this relationship was independent of the platelet count.[8] Correction of anemia can shorten the previously prolonged BT in most patients.[27,28] Because anemia can affect the BT result, the hematocrit of patient must be raised to more than 30 percent prior to the testing process in order to avoid this impact.[15, 29]

$$\text{Expected bleeding time (minutes)} = 30 - \frac{\text{Platelet count (/mm}^3\text{)}}{4{,}000}$$

Fig 1. The Harker and Slichter equation for "expected bleeding time".

Thrombocytopenia

Negative correlation between the BT and number of circulating platelets between 10,000/mm^3 to 100,000/mm^3 has been reported.[30] Harker and Slichter proposed the "expected bleeding time" equation for patients with platelet counts in this range (Fig 1). The benefit of this equation is to identify the additional effect of platelet dysfunction when the actual BT exceeds the expected BT by more than five minutes. However, the user must follow the same protocol as the original paper when using this equation to reproduce an accurate result. Moreover, the result must be interpreted cautiously because in some conditions, such as immune thrombocytopenia (ITP) and leukemia, the BT and platelet numbers may not be directly related.[17] Because of this, the BT is usually not generally indicated when the patient has platelet counts lower than 100,000/mm^3.

Medications

Many medications can affect platelet function and prolong the BT via various mechanisms. These drugs include aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), anti-platelet drugs, antibiotics (especially for beta lactam group), and herbal medications.[31] Commonly used anticoagulants such as heparin and warfarin at therapeutic doses do not affect the platelet function.[15] The optimal timing of testing after cessation of these drugs is very important. Aspirin irreversibly inhibits the aggregation of platelets throughout their lifespan, i.e. 7 to 10 days. The duration of platelet inhibition by NSAIDs is mainly determined by the half-life of each drug. Clopidogrel and ticlopidine are anti-platelet drugs which inhibit platelets for about 7 days after ingestion. For herbal medicines, including spices, the significance of the effect on platelet function remains controversial.[32-34]

Procedures for the bleeding time

Currently, there are three methods for measuring the BT: Duke method, Ivy method, and template (or modified Ivy) method.

The Duke Method[8]

A small cut is made by a lancet at the earlobe. Then the blood from this cut is blotted on absorbent paper every 30 second intervals. The size of the incision is controlled by making the size of the first blot of 1 cm to 2 cm in diameter. The rate of decrease in size of blot on paper was described to be related to the decrease of hemorrhagic tendency. The total time for bleeding required to stop is recorded and called the BT. In general, no repeated testing is performed due to restricted space.

As compared with other methods, the advantages of the Duke method include the simple procedure without a need for special equipment, relatively low cost, and minimal scar formation. However, this procedure is

very difficult to standardize and has poor precision and accuracy, so it is less popular nowadays.

The Ivy Method[10]

The skin at the forearm is usually chosen to be tested by this method. Before testing, patients should be informed about the possibility of scarring, keloid formation, and skin infection. The appropriate site is located at lateral one-third and 2 to 3 cm distal to the antecubital crease.[15] The pressure at 40 mmHg is applied and maintained on the upper arm using an appropriate size of blood pressure cuff. This process is needed for controlling capillary tone and improving sensitivity of the test. Two punctures are made with the distance of 5 to 10 cm apart in quick succession by a disposable lancet. Any lancet which makes a puncture size of 2.5 mm depth and more than 1 mm width is suitable.[35] The time between the cuff inflation and incision making should be 30 to 60 seconds. Timing starts right after the punctures are made by employing a recorder device. The drops of blood are then wicked, not blotted, with the filter paper every 30 seconds until bleeding ceases. The filter paper must not contact with the puncture sites. Frequent wicking may be required if the bleeding is excessive. The BT is measured as in the Duke method. The procedure should be discontinued if the bleeding does not cease within 20 minutes. A single measurement is acceptable in some centers, although the test should be repeated when the result is abnormal.[16]

The Ivy BT is superior to the previous Duke method in that it provides much more sensitivity and reproducibility of the result by standardizing the capillary tone.[10] However, poor reproducibility still occurs because of the variation of the size of punctures performed by different operators.

The template (or modified Ivy) method[15]

The same procedure as described for the Ivy BT is applied except for using a standard instrument for incision making instead of using a lancet manually. The device usually comprises of a plastic template unit containing a steel blade which can protract and retract automatically by using spring-activated system. When used properly, it can provide a uniform incision size which improves the reproducibility of the test. Because of this reason, this method is the most preferred method at present. The incision size depends on the types of templates. For adults, the recommendation of incision size is 5 mm length and 1 mm depth. The direction of incision should be parallel to the length of forearm.

Using the standardized incision by template makes this assay more reliable compared with other methods. Moreover, the result from the incision may correlate with hemostatic response to surgical wound more than that of the puncture method performed in the Duke or Ivy BT. However the scar formation may occur more frequently compared with the puncture method. The cost of testing is increased because of the template use. The availability of the template is also problematic in some areas. In unpublished data about BT testing in Thailand surveyed from the Thailand National External Quality Assurance Scheme (NEQAS) participants revealed that the device is not widely available in Thailand. An example of an existing commercial template in Thailand is the Triplett® Bleeding Time Device (Helena Laboratories, USA, Fig 2).

Fig 2. The Triplett® Bleeding Time Device.

The modified procedure for special situations

Pediatric cases

The BT performed in pediatric patients is different from that in adult cases. The criteria for this group are generally the patient with an age lower than 16 years old and/or body weight lower than 40 kg.[15] For this group, the pediatric sphygmomanometer with appropriate cuff should be used. Maintained pressure should be adjusted according to the patient's age and body weight.[17] The appropriate pressures for infants are 20 mmHg for those with body weight less than 1,000 g, 25 mmHg for those with body weight between 1,000 to 2,000 g, and 30 mmHg for those with body weight above 2,000 g. The specific template which generates a small incision size should be used in order to reduce scar formation. The incision length of 3 mm or less and depth between 0.5 to 1 mm is acceptable.[17,36]

Patients with contraindication for using forearm as a site of testing

The BT should not be done at the skin with inappropriate characteristics as described earlier or at the site with intravenous infusion and catheterization. When both upper extremities are contraindicated, the leg may be used as alternate site of testing.[15,37] The patient should be in a supine position. The appropriate cuff for the thigh should be applied for maintaining the pressure. The medial aspect of the calf at 6 to 8 cm below the knee is the suitable site for incision making. The procedure is then similar to that performed at the forearm. However, a separate reference interval for the leg BT should be used for interpretation.

Measures for the prevention of errors

A number of preventive measures should be employed in order to obtain accurate results and avoid harm to patients.

- The stopwatch should be regularly checked for the good calibration.
- When the sphygmomanometer is used, it should be regularly checked to make sure that the device does not have air leaking and the pressure can be maintained at the desired level.

- Alcohol at the testing site must be completely dried before making the puncture or incision because the residual alcohol may prolong the result.
- The puncture or incision making should be followed strictly to the instruction because variation of puncture or incision size can cause the inconsistent results.
- During the blood wicking, the filter paper must not contact with the wound because this will remove the clot and prolong the result.
- The wound should be properly managed after the procedure is complete. It should not have direct contact with alcohol, because this can cause recurrent bleeding and increase scarring. In the case of excessive bleeding, the wound must be pressured until the bleeding ceases. The bandage should remain for at least 1 day.

Interpretation of the bleeding time

The reference interval of the BT has been reported varying according to the method and device used. Therefore, the "local" reference interval of BT should be established by each laboratory.[15-17] Separate reference intervals are needed for the special group of patients, such as, pediatric patients or patients using leg BT.

The BT which exceeds the upper limit usually indicates the abnormalities in primary hemostatic system. However, the BT may also be prolonged in patients with severe coagulation deficiencies. The examples are deficiencies of coagulation factor V, factor VIII, factor IX, and fibrinogen.[15,16,38] Overdose of oral anticoagulants may also prolong the BT.[39]

Clinical utilities of the bleeding time

Diagnosis of primary hemostatic defects

The BT is usually indicated when moderate to severe defects in the platelet-vessel interaction are suspected. These conditions include vascular defects and platelet dysfunction, which can be caused by either hereditary or acquired etiologies.[15,16] Vascular disorders with bleeding are rare conditions and the BT is the only hemostatic testing which is used for the demonstration of abnormality. However, a careful history taking and physical examination are considered as the most useful diagnostic tools because these patients usually have normal BT.[40] Therefore the BT is infrequently indicated in these settings.[35]

Inherited platelet dysfunction, such as Glanzmann-thrombasthenia, Bernard-Soulier syndrome, and storage pool disease, is a group of uncommon diseases. It involves the defects of platelet adhesion, aggregation, and granule secretion. Many experts suggest that the BT may not correlate with the bleeding symptom and so has a poor reproducible result. Therefore, the BT should not be used as a screening test in these settings.[41] The optional screening test for these patients is the platelet function analyzer (PFA-100®) assay. This study is an *in vitro* platelet function assay which simulates platelet adhesion and aggregation under high-shear conditions. Unfortunately, this machine is not available in Thailand. Therefore, the specific platelet function testing by light transmission aggregometry is usually considered as a next step for these patients.[31]

vonWillebrand disease (vWD) is one of the most common causes of hereditary bleeding disorders which is characterized by lack of von Willebrand factor (vWF) antigen or its function leading to the defect of platelet adhesion. Lind and Kurkjian reviewed ten studies about sensitivities of the BT for vWD diagnosis.[4] They found that the sensitivities of BT ranged from 17% to 75% with mean of 44% which is inferior to the PFA-100®. Because of its low sensitivity, normal BT cannot exclude the mild form of vWD and specific investigations are warranted if the patient has strong clinical suspicions of vWD. Another limitation of the BT for vWD diagnosis is the variation of the results which may differ from day to day even in the same patient.[42]

Acquired primary hemostatic defects, for examples, acquired storage pool disease, myelodysplastic syndrome, and myeloproliferative neoplasms may prolong the BT. However, the correlation between bleeding symptoms and BT in these settings is generally disappointing, so BT is not usually indicated in these settings.[15,43]

Prediction of bleeding in uremic patients

Bleeding diathesis may occur in the patients who have advanced deterioration of renal function or end-stage renal disease. The most important factor contributing to this phenomenon is the abnormalities of platelet functions due to uremic toxins.[44-47] Currently, the BT is considered as the most useful test for bleeding assessment in the patients with uremia.[46,48] Soyoral et al demonstrated that the skin BT of patients with chronic kidney disease was significant shorter after hemodialysis.[49] The authors also suggested that the skin BT may be used to predict bleeding prior to invasive procedure in uremic patients.

Treatment efficacy measurement after using hemostatic agents

Edlund et al investigated the efficacy of desmopressin in women who suffered from menorrhagia. All of these patients had prolonged BT but no common coagulation factor deficiency. It was found that no significant changes of BT occurred after treatment.[50] In this situation, clinical improvement, such as reduction of blood loss, is more useful than the laboratory assessment. The BT is also used to monitor vWD patients after cryoprecipitate or vWF-rich factor VIII concentrate infusion. However, plasma-based assays, such as vWF antigen assay and factor VIII activity, are more suitable for this setting because of their objective measurement.[15]

Pre-operative screening of bleeding

Many studies have demonstrated the poor ability of preoperative BT to predict bleeding risk of the patients from invasive procedures.[51-55] It was found that patients with normal BT may have excessive bleeding after surgical procedures. Furthermore, the BT is not a reliable testing to predict bleeding in patients who have recently ingested aspirin or NSAIDs. To assess the intra- or post-operative hemorrhage, clinical history about bleeding is considered the most useful screening tool.[53]

CONCLUSION

The BT is one of the oldest hemostatic testing methods which is currently used in various medical fields. This testing is used to explain bleeding phenomenon in patients with primary hemostatic defect. Nowadays, the indications of BT are very limited due to its poor sensitivity and reproducibility. More sensitive and specific assays are developed for the diagnosis of specific conditions. Many studies confirm that the BT should not be used as a screening test for prediction of bleeding preoperatively. However, the BT seems to be useful in uremic patients because it is the only testing which can predict bleeding. In the measurement of BT, care must be exercised, particularly regarding the influence of preanalytical variables and technical issues on the interpretation of results. Many correctable preanalytical factors especially the degrees of anemia and thrombocytopenia as well as certain medications could affect the BT result. To obtain the accurate result, an appropriate technique for BT should be performed. Currently, the template method is the most preferred method because it is a well-standardized procedure. In special situations, such as pediatric cases, the BT should be performed in an appropriate modified technique. The equipment, such as stopwatch and sphygmomanometer, must be calibrated regularly to ensure the good quality. To interpret the results, a local reference range should be applied. Abnormalities of coagulation factors could also prolong the BT, so clinical manifestations of the patients must be carefully reviewed along with the interpretation of the BT.

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