TRANSFUSION MEDICINE UPDATE

Institute For Transfusion Medicine JULY, 2000

Closure Time
Platelet Function Screening

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BACKGROUND

Platelet dysfunction may be acquired, inherited, or induced by platelet inhibiting agents. It is clinically important to assess platelet function as a potential cause of a bleeding diathesis, especially in critically ill patients who may develop life-threatening hemorrhages. The most common causes of platelet dysfunction are related to uremia, liver disease, von Willebrand's disease (vWD) and exposure to agents such as acetyl salicylic acid (ASA, aspirin). Current methods to assess platelet function include bleeding time (BT), aggregation studies and whole blood *in vitro* test systems such as the closure time (CT).

CLOSURE TIME TESTING

Closure times are performed on a PFA-100, an instrument and test cartridge system in which the process of platelet adhesion and aggregation following a vascular injury is simulated *in vitro*. This system allows for rapid evaluation of platelet function on samples of anticoagulated whole blood. Membranes consisting of Collagen/Epinephrine (CEPI) and Collagen/Adenosine-5'-diphosphate CADP and the high shear rates generated under standardized flow conditions, result in platelet attachment, activation and aggregation, building a stable platelet plug at the aperture. The time required to obtain full occlusion of the aperture is reported as the closure time (CT) in seconds. The test is sensitive to platelet adherence and aggregation abnormalities and allows the discrimination of aspirin-like defects and intrinsic platelet disorder. The CEPI membrane is used to detect platelet dysfunction induced by intrinsic platelet defects (vWD, drug effects etc.). Abnormalities result in prolongations of CT >175 seconds. Follow-up testing using the CADP membrane enables the discrimination of aspirin effects. The following table shows expected patterns observed with CT on normal subjects and subjects with various disorders.

	Normal	*ASA*	*vWD*	*Glanzmann's Thrombasthenia*
CEPI	normal	abnormal	abnormal	abnormal
CADP	normal	normal	abnormal	abnormal

CLOSURE TIMES vs. BLEEDING TIMES

While thrombocytopenias are accurately assessed by automated platelet counters, qualitative platelet defects are presently difficult to diagnose. The only global screening test for platelet and vascular functions is the BT. BT is a bedside procedure, is labor intensive, expensive and its accuracy is heavily dependent on operator skills. A critical review of BT concluded that the utility of BT is not enhanced by recent standardization attempts; that in individual patients there is no relationship between BT and platelet counts; that the BT is not a specific indicator of platelet function and that the BT is a poor indicator of surgical bleeding risk. As a consequence many clinicians no longer use BT. The noted deficiencies of BT lead to the development of an *in vitro* device that globally measures platelet-related primary hemostasis. Closure time is sensitive to platelet adherence and aggregation abnormalities and therefore has increased sensitivity for von Willebrand's screening when compared to bleeding time. Comparative studies at our facility support these findings: CT was abnormal in 64% of patients diagnosed with vWD as compared to 43% by BT.

INDICATIONS

Closure times are indicated when a disorder of platelet function is suspected by a personal or family history of easy bruising, nose bleeds, menorrhagia, or post-operative bleeding, especially following dental extractions or tonsillectomy. It is not recommended as a screen for potential bleeding risk. Closure times may be prolonged when the platelet count is < 100,000/mm^3 even if platelet function is normal. In addition the CT will be prolonged when hematocrit levels are < 35%, due to the contributory effect of red blood cells on platelet behavior. These restrictions should be considered prior to performing a closure time.

Suspected von Willebrand's disease, inherited platelet disorders and evaluation of acquired disorders of platelet function (hepatic disease, renal disease, drug effects) are appropriate clinical reasons for closure time screening. It may also be useful to monitor the response of therapeutics, such as DDAVP infusions, renal dialysis, platelet and antiplatelet drug therapy. Abnormal closure times, indicating possible defective platelet function, should be further investigated with standard platelet aggregation tests.

SUMMARY

Closure time is a test system to assess platelet-related primary hemostasis with improved accuracy and reliability in comparison to bleeding time. This assay is an important aid in the assessment of platelet dysfunction and bleeding risk caused by uremia, von Willebrand's disease, congenital platelet disorders and exposure to agents such as aspirin.

REFERENCES

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