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REGULAR ARTICLE

The effect of uremia on platelet contractile force, clot elastic modulus and bleeding time in hemodialysis patients

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Abstract

Introduction: Uremic bleeding frequently occurs in dialysis patients. Although its mechanism is not well characterized, acquired platelet dysfunction has been implicated in its pathogenesis. Skin bleeding time has been used to characterize platelet dysfunction in this population. However, the bleeding time is prone to error. The goal of this study was to compare the bleeding time to the novel platelet function parameters platelet contractile force and clot elastic modulus as well as platelet aggregation studies in controls and patients receiving maintenance hemodialysis.

Materials and methods: Forty-five subjects completed this study (25 controls, 20 dialysis). All subjects had the Ivy skin bleeding time procedure performed, as well as the collection of whole blood samples for the determination of platelet contractile force, clot elastic modulus, % von Willebrand Factor antigen, and platelet aggregation studies. Pearson's correlation determined the relationships between

Abbreviations: ADP, adenosine diphosphate; BUN, blood urea nitrogen; CEM, clot elastic modulus; CKD, chronic kidney disease; Da, daltons; ESRD, end-stage renal disease; NS, not significant; PCF, platelet contractile force; PPP, platelet poor plasma; PRP, platelet rich plasma; SEM, standard error of the mean; vWF:Ag, von Willebrand factor antigen.

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skin bleeding time and platelet function and clot structure parameters and markers of renal dysfunction.
Results: Bleeding time was significantly prolonged in the dialysis group relative to controls. The platelet function parameters were not significantly different between groups. There was a significant relationship between bleeding time and creatinine concentration, however, no relationship existed between bleeding time and platelet function parameters.
Conclusions: Skin bleeding time poorly correlates with measurements of platelet function. There were no significant differences noted in platelet function between the groups despite the prolongations in bleeding time in the dialysis group. These data may suggest that the bleeding time reflects perturbations in platelet adhesion or secretion, and not aggregation. Further study is needed to characterize platelet function in dialysis patients.

It is widely known that patients with chronic kidney disease (CKD) are at increased risk for bleeding episodes [1,2]. This bleeding diathesis is commonly referred to as "uremic bleeding" [2]. The etiology of uremic bleeding is biochemically complex, and not completely understood. However, it is thought that uremic blood alters platelet function to result in abnormal platelet aggregation, secretion and adhesion to the vascular endothelium [1].

Several laboratory tests have been used to detect and quantify the level of hemostatic impairment in dialysis patients [3]. The bleeding time (also known as the Ivy bleeding time) has been the most commonly used test to assess platelet function in CKD patients [4]. The bleeding time is performed by making a standard incision on a patient's forearm, and measuring the time required for the bleeding to stop. Although seemingly straightforward, this test is hindered by several factors not related to hemostasis, such as operator technique, skin quality, skin temperature, and patient cooperation. Not surprisingly, the reproducibility and predictability of the bleeding time are limited [5—8]. In fact, some have called the bleeding time a "completely non-informative test" [8].

The bleeding time is used as a crude marker of platelet aggregation. Although previous studies have documented altered platelet aggregation in dialysis patients, there are few data that have assessed other mechanisms of clotting in dialysis patients such as clot retraction, clot rigidity, and platelet function.

Our research group has developed a novel whole blood coagulation monitoring system that provides a global evaluation of the integrity of the coagulation system by reporting the parameters platelet contractile force (PCF) and clot elastic modulus (CEM). PCF is the force produced by platelets during clot retraction, and is a novel measure of platelet function during clotting. This parameter is sensitive to platelet number and metabolic status, glycoprotein IIb/IIIa status, and the presence of antithrombin activities. CEM reflects the structural integrity of the blood clot [9]. It is sensitive to fibrinogen concentration, red blood cell flexibility, thrombin generation rate, platelet concentration and the forces produced by platelets during clot retraction. There have been no previous reports detailing the effect of uremia on platelet force development and clot structure using this novel system.

The goal of this study was to determine the effect of renal failure on PCF development and clot structure and to compare these results to those obtained from platelet aggregation studies and a bleeding time experiment.

Materials and methods

Study design and population

This was a single center, prospective study to assess bleeding time and platelet function in patients receiving hemodialysis. The Virginia Commonwealth University Institutional Review Board (Richmond, VA) approved this study prior to subject enrollment, and this study was conducted in compliance with the Declaration of Helsinki. Forty-five subjects completed this study: 25 controls and 20 end-stage renal disease (ESRD) subjects maintained on hemodialysis. All dialysis subjects were chosen at random, and had been receiving hemodialysis for at least 6 months. These subjects received hemodialysis 4 h in duration per session, 3 days/week. All subjects were anticoagulant naïve, non-thrombosed and otherwise healthy. Subjects were admitted into this study if they were older than 18 years and provided written informed