Thesis Title STUDIES OF PLATELET ABNORMALITIES IN THALASSEMIA

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ABSTRACT

Bleeding and thrombotic complications have been commonly found in thalassemia. The disorders could be attributed to the abnormalities of platelet function. The regulation of platelet responses has been known to be rather complicated. Thus the assessment of platelet function *in vitro* is subjected to minute changes in the platelet environment.

This study was designed to define those functional ab-

normalities in thalassemic platelets and also to characterize those variables that contribute to these abnormalities. The aggregation methods used in this study include optical, electrical and particle counting techniques. A number of "mediators" that are likely to be related to the pathological changes such as ATP, MDA, vitamin E and thromboxane were monitored by chemiluminescence, spectrophotometer, high performance liquid chromatography and radioimmunoassay, respectively. Tests of platelet function were performed in the whole blood (WB), platelet-rich plasma (PRP) and washed platelet suspension (WPS).

It was found that the platelets in thalassemia were very fragile as a significant fraction of platelets in the WB were lost during preparation. Platelet yields in PRP and WPS obtained from WB of the thalassemia were 30-60% and 10-20%, respectively, as contrast to 90-100% (PRP) and 75-85% (WPS) in the normal individuals. The assessment of platelet function could be best presented with the impedance method in the whole blood. Increased platelet aggregation and decreased lag time were observed in this whole blood model. On the contrary with the assessment of platelet function by the optical method, thalassemic platelets were apparently found to be hyporesponsive to high-dose stimuli and hyperresponsive to low-dose stimuli.

The results suggest that within the population of

thalassemic platelets, especially in the PRP, some were highly susceptible to activation while the other failed to respond. This wide range of heterogeneity provides a spectrum of platelet responses contributed by hyper- and hyporesponsive platelets. Preexposure of normal platelets to subthreshold levels of various agonists before the subsequent maximum stimulation showed "amplification" or "desensitization" process. Blood-borne components from thalassemic red cells and iron overload were shown to influence the platelet responses. These factors may be partly responsible for the heterogeneity of platelets in thalassemia.

Thalassemic platelets also seem to be under continuous stress as antioxidative vitamin E in plasma, RBC and platelets were exhausted and associated with the increased MDA, an indicative marker of lipid peroxides. Supplementation of vitamin E, 300-600 mg/day by oral route, could correct the vitamin E deficiency state and decrease the overload of lipid peroxides. These stressed platelets generate more proaggregatory prostaglandin (thromboxane A2) under minimum manipulation as detected levels of thromboxane in the serum and the washing medium of thalassemic platelets were elevated. The released "mediator" may provide an "amplification" loop for enhancing platelet aggregation following agonist stimulation <u>in vitro</u>. Production of thromboxane in serum was found to be suppressed with low dose aspirin, 20-60 mg/day. Administration with low dose dipyridamole, 75 mg/day, resulted in the stabilized in-

tegrity of arachidonate pathway during platelet washing.

It is concluded that circulating thalassemic platelets are fragile and susceptible to activation. They are exposed to many blood-borne components *in vivo* and to various stimuli *in vitro*. The extent and characteristic of the exposure may determine the responsiveness of the platelets, either hyper- or hypoaggregatory state. The chemical defect found to occur in the arachidonate metabolism of thalassemic platelets has provided a rational approach for further therapeutic intervention.