



Literature Reviews

Prevalence of heparin/platelet factor 4 antibodies before and after cardiac surgery.

Everett BM, Yeh R, Foo SY, Criss D, Van Cott EM, Laposata M, Avery EG, Hoffman WD, Walker J, Torchiana D, Jang IK. *Ann Thorac Surg.* 2007 Feb;83(2):592-7.

Reviewers

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Abstract

Heparin therapy carries a risk of thrombocytopenia and paradoxical thrombosis. An important mechanism is the formation of antibodies to complexes of heparin bound to platelet factor 4. Tests for antibodies that activate platelets are cumbersome. However, it is technically easy to measure antibody binding to immobilized heparin/platelet factor 4 complexes, and commercial ELISA kits are available for this purpose. The clinical usefulness of this frequently performed assay was examined in 299 cardiac surgical patients at Massachusetts General Hospital.

Platelet counts and antibody levels were measured just before surgery and 5 days later. For ethical reasons, clinicians were not blinded to the test results and were permitted to modify management accordingly. Patients were interviewed at 30 days for evidence of thromboembolic complications.

As expected from previous work, antibody presence (scored merely as positive or negative) increased significantly from a baseline incidence of 4% to a postoperative incidence of 22%. Criteria for postoperative thrombocytopenia criteria were met in about 17% of patients regardless of antibody status.

The frequency of thromboembolic events was 9% if antibody was negative postoperatively and 6% if positive. So, antibody alone did not help to predict events in this population. The frequencies were

7% if thrombocytopenia did not occur and 17% if it did occur. So, thrombocytopenia raised a red flag ($p = .06$). The frequency was 8% if one of the two factors did not occur and 25% if both occurred (antibody and thrombocytopenia). So, a positive antibody together with thrombocytopenia is more worrisome than thrombocytopenia alone (though $p = .13$).

Comments

The authors conclude that routine testing for postoperative antibody is not a clinically useful predictor of thromboembolic complications, but platelet counts are important to monitor.

The paper confirms that a lot of patients receiving heparin will develop ELISA-detectable antibodies against heparin/platelet factor 4 complex. Fewer will develop thrombocytopenia, and fewer still will manifest thromboembolic complications. So, routine postoperative screening for the antibody does not appear useful. However, interesting questions arise. For instance, suppose a postoperative patient acutely develops an indication for heparin or a heparin alternative. Is heparin OK if the antibody is negative? Is heparin absolutely contraindicated by a positive ELISA? It is difficult to ethically address such questions. After all, the ELISA is already an FDA-approved clinical tool, albeit one that has incompletely understood application. Many clinicians would not want to ignore a positive ELISA. Many researchers and their IRBs would be hardpressed to feel ethically secure in randomizing patients with antibodies to possibly receive heparin.

This problem will spur the development and adoption of novel anticoagulants. However, the introduction of every new heparin alternative carries risks. Who wants to be the first patient to try out a new anticoagulant for cardiopulmonary bypass? How will the researcher determine the target clotting time for that patient?

In any event, heparin-induced antibodies are unlikely to ever do a patient any good. After all, both heparin and platelet factor 4 are normally present in us all.