Activated Clotting Time and Cardiopulmonary Bypass, III. Effect of High Platelet Count on Heparin Management

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Abstract

Although standard methods of heparin management have proven adequate in routine cardiopulmonary bypass procedures there are, occasionally, extraordinary cases in which special management is necessary. When a patient's blood is introduced to the extracorporeal circuit the non-endothelial surface precipitates platelet adhesion and aggregation. One of the factors released at this time is Platelet Factor IV which acts to neutralize the anticoagulant effect of the heparin-antithrombin III complex. The purpose of this investigation was to relate platelet count to heparin requirement. Patients with thrombocytosis were studied. Heparin was managed as per usual except that additional heparin had to be given either before initiating bypass (after the three mg/kg loading dose failed to safely prolong the activated clotting time) or immediately after initiation of bypass due to a dangerously shortened coagulation time. Based upon the results of this study it is recommended that careful monitoring is necessary in thrombocytotic patients.

Methods

Patients undergoing open heart surgery at this institution receive a heparin loading dose of 300 units/kg. An additional 1500 units are added to the pump prime to achieve a total, on-pump heparin concentration of 2.5–3.5 units/ml. Manual activated clotting times (ACT) are obtained before and five minutes after the loading dose is administered to establish a dose-response curve. An ACT of greater than 300 seconds is presumed a safe level for the initiation of bypass. During bypass, ACT's are obtained as needed, usually every hour during hypothermia, to determine the adequacy of anticoagulation. Additional heparin is given, as needed, during each case to keep the ACT 3.5 to 4.5

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times the baseline. Another ACT is done just prior to the termination of bypass to estimate, by the dose-response curve, how much heparin is present and to determine a protamine dose.

At the beginning of this investigation, records of cardiopulmonary bypass cases from 1976 to 1980 were reviewed for unusual occurrences in thrombocytopenic patients. Only one case was found and it was carefully studied. As new patients with high platelet counts presented themselves, standard protocol was altered in order to more carefully monitor anticoagulation. ACT’s were done immediately after the initiation of bypass and every 15 to 30 minutes thereafter. Post-pump blood studies in these cases included platelet count, fibrinogen level, prothrombin time (PT) partial thromboplastin time (PTT), hemoglobin and hematocrit, plasma free hemoglobin, and fibrin split products.

**Results**

The case that prompted this investigation occurred five years ago. The patient, a 60 year-old woman, was admitted to this institution in August, 1976 with a diagnosis of aortic stenosis. She had a five-year history of angina pectoris, mild congestive heart failure, and her electrocardiogram showed evidence of an old anterior myocardial infarction and left ventricular hypertrophy. Cardiac catheterization revealed an aortic valve gradient of 100 mmHg. The day before surgery, an aortic valve replacement, blood work showed her clotting parameters to be within normal limits, a fibrinogen level of 390 mg/dl., and a platelet count of 725,000/mm³.

On the day of surgery, the patient was heparinized with 250 units/kg. (17,800 units), which was protocol at the time, but no pre- or post-heparin ACT’s were recorded. Ninety minutes after bypass was initiated the \( \text{paO}_2 \) dropped to 60 mmHg in spite of a normally adequate oxygen flow during hypothermia of four liters/minute, indicating oxygenator failure. The first ACT since initiating bypass was obtained and found to be 195 seconds, a dangerously low value. Thirty-five hundred units of heparin were given but 20 minutes later a clot was seen in the operative field. Another 3500 units were given but the subsequent clotting time of 600 seconds indicated probable clotting factor consumption. Within the next hour, the cardiotomy drain line clotted and the oxygenator began to foam and both were changed. The oxygenator was later opened and it was found that the defoamer was totally clotted off. Due to profuse bleeding, complicated by severe coagulopathy, the patient could not be sustained post-bypass and died on the operating table. Post-pump blood studies showed an ACT of 210 seconds, a fibrinogen level of 85 mg/dl., a PT of 20 seconds, a PTT of greater than 100 seconds, a thrombin time of greater than 120 seconds, and a fibrin split product level of between 10 and 40 mcg./dl. All of these values are consistent with clotting factor consumption. Another patient in which modified heparin management was used was a 64 year-old male who presented with three vessel coronary artery disease and plaque formation in his left carotid artery. On October 8, 1980 he underwent coronary artery bypass grafting and a left carotid endarterectomy. His preoperative blood work was within normal limits except for his platelet count, which was 603,000/mm³. During surgery the patient was heparinized with the standard 300 units/kg. (22,500 units) which prolonged the ACT from a baseline of 100 seconds to a presumably safe level of 350 seconds. However, a red coating and small aggregates were noted on the sides of the ACT tube as soon as it was first tilted. Ten minutes after bypass was initiated the ACT dropped to 280 seconds and 5,000 units of heparin were given. Every 30 minutes during the case additional heparin had to be given to keep the clotting time safely prolonged. A total of 23,000 units of additional heparin were given during the 159 minute pump run, doubling the loading dose. Post-bypass, a protamine dose of 150 mg brought the ACT back to 90 seconds or within normal limits. The patient’s post-pump platelet count was 170,000/mm³, his fibrinogen was 225 mg/dl., and his clotting parameters were also within normal limits.

The second patient in which the relationship between high platelet count and additional heparin requirements was observed was a 71 year-old man with three vessel coronary artery disease and a left ventricular aneurysm. The patient’s preoperative blood work showed a platelet count of 895,000/mm³, a fibrinogen level of 348 mg/dl., a prolonged PT of 17.6 seconds, and a PTT of 29.4 seconds. On the day of surgery, October 16, 1980, the baseline ACT was 140 seconds. The 300 unit/kg. (17,500 units) heparin loading dose increased the subsequent ACT to only 150 seconds, indicating heparin resistance. Another 8,000 units of heparin were administered and the ACT was prolonged to 440 seconds. However, aggregates and a red coating immediately appeared on the sides of the ACT tube. Ten
minutes after bypass was initiated another ACT was done and the aggregates again appeared, in spite of the fact that the clotting time was greater than 720 seconds. Another 10,000 units of heparin were added to the bypass circuit and all subsequent on-pump ACT's were greater than 720 seconds and without aggregates.

Immediately post-bypass this patient's platelet count was 153,000/mm³ and his fibrinogen level had dropped to 156 mg/dl. A protamine dose of 150 mg., determined by a protamine titration, brought the clotting time back to 120 seconds. Twenty-four hours later the platelet count had risen to 459,000/mm³, the PT was 21.9 seconds, and the PTT was 30.1 seconds.

Discussion

When a patient undergoes cardiopulmonary bypass adequate anticoagulation must be maintained to prevent device failure, factor consumption, and the generation of thromboemboli. Heparin, a strongly acidic mucopolysaccharide, achieves this effect by acting as an antithrombin. A naturally occurring anticoagulant, Antithrombin III (AT III), inhibits thrombin activation by complexing with it. The highly negatively charged heparin molecule forms reversible bonds with AT III and dramatically accelerates the thrombin-AT III complex. Under normal circumstances this effectively blocks coagulation. The cases reported indicate that increased heparin is needed to maintain anticoagulation when a high platelet count is present, suggesting that some platelet factors may be the cause.

Platelets are the blood's main component for preserving vascular integrity and play a major role in hemostasis. When platelets come in contact with any nonendothelial surface they adhere to that surface and release their intracellular granules. Several substances are contained in these granules, including ADP, serotonin, and epinephrine, all of which induce platelet aggregation and plug formation. Fibrinogen and Platelet Factor 3 are also secreted. Platelet Factor 3 is the phospholipid component that catalyzes several steps of the coagulation sequence. Another substance secreted by the platelet granules is Platelet Factor 4, the anti-heparin. This factor consists of several low molecular weight polypeptides bound, non-covalently, to a carrier proteoglycan core. Its ability to neutralize anticoagulation is due to the direct action of free amino groups on the heparin-activated AT III complex rather than by an acid-base reaction. If Platelet Factor 4 is added to heparin-AT III-thrombin assay, the thrombin inactivation ceases as if no heparin had been present.

Conclusions

Because the occurrence of thrombocytosis in cardiopulmonary bypass patients is so rare, not enough patients were studied to provide statistical evidence as to the relationship between high platelet counts and increased heparin requirement. However, since one death occurred and, in two other cases, modified heparin management was needed, it is felt that a relationship does exist and should be reported. It may be concluded that the first patient's high platelet count and subsequently increased platelet factor release, combined with poor heparin management, was the cause of oxygenator failure and a contributory factor in her death. Concerning the other two cases, it can be stated that knowledge of the danger of high platelet counts may have saved their lives. It is recommended that the platelet count be checked before every cardiopulmonary bypass case. If, during a case, a red coating with aggregates, which may be platelets, is noted on the post-heparin ACT tube, it is recommended that ACT be done as soon as bypass is initiated and frequently thereafter so that heparin management can be closely monitored.

References