POST CARDIOPULMONARY BYPASS: EXCESSIVE BLEEDING AND ITS MANAGEMENT

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Excessive post operative bleeding after cardiopulmonary bypass is a complex process and the causes are multifactorial. In the modern era of medicine with the increased fear of contracting transfusion related problems, it is vital that a complete haemostasis is achieved at the end of surgical procedure and the bleeding stops within a reasonable time after transfer of the patient to the intensive care unit. In the last several years of blood and blood products usage during open heart procedure has decreased phenomenally. In the 1950's twenty to thirty units of blood were used in cardiac operations, but now in the 1990's the rate is down to almost none in most of the operative procedures. If the trend of blood transfusion had not decreased than the number of operations performed today would not have been possible as it would have required enormous number of blood units available. Bleeding following cardiopulmonary bypass can be a major contributor of morbidity and mortality. The incidence of reexploration in post cardiopulmonary bypass is less than 3%. However, reexploration by itself may increase the morbidity which may include renal failures, sepsis and added risks of blood and blood product transfusions. Proper anticoagulation of the patient is of utmost importance in patients undergoing cardiopulmonary bypass. Heparin which is used for its anticoagulant effect was discovered by Mcleen when working to find a procoagulant. A fortunate discovery because without it the cardiac surgery would not have been possible. At the end of CPB the heparin is neutralized with protamine, developed by Chargoff and Olson in 1938. The causes of excessive post CPB bleeding are complex and improperly understood. However, it is important to diagnose the medical cause using laboratory tests and if they are all negative or unhelpful, then surgical reexploration becomes mandatory. The definition of excessive bleeding is not clearly delineated. Blood loss of 150 ml/hour/sq meter of body surface area is considered excessive. Another study defined excessive blood loss of greater than 400 ml during the first two hours after surgery. However, Saleem et al. defined it to be greater than 100 ml in any one hour. The causes of perioperative bleeding are many and can be classified as below.

1. ***Known patient conditions***
2. ***Residual heparin***
3. ***Decrease in plasma factors***
4. ***Decrease in platelets; number of function***
5. ***Fibrinolysis***
6. ***Surgical***

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KNOWN PATIENT CONDITIONS

Apart from known conditions inherited or acquired which can cause excessive bleeding, several therapeutic agents may disturb the coagulation pathway. The drugs which can affect the platelet function they include aspirin, anti-inflammatory agents especially nonsteroidal anti-inflammatory drugs, and dextrans to name a few.

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RESIDUAL HEPARIN

At the end of CPB appropriate dose of protamine is given to neutralize heparin and this is confirmed with ACT which comes to base line value. However, in some cases protamine seems to be eliminated leaving the heparin to be active again to cause excessive bleeding and increase in ACT. In patient with excessive bleeding this should be kept in mind and the ACT be repeated to confirm or refute the diagnosis.

FIBRINOLYSIS

Cardiopulmonary bypass leads to decrease in level of all coagulation factors due to

hemodilution and subclinical fibrinolysis. Dilution of plasma factors occur from priming fluids of the pump. Levels of all coagulation factors are reduced by 40-60%. However factor V is reduced by almost 70%. Interestingly though concentration of factor VIII which is involved in the inflammatory response is increased during CPB. During CPB because of the contact of blood with CPB pump circuit which is devoid of endothelium and surgical trauma there is activation of coagulation, platelets and white blood cells. There are also changes in the homeostasis mechanism. This is now commonly referred to whole body inflammatory response. Heparin is given for anticoagulation which protects the bypass machine but many of the functions of platelets, coagulation and fibrinolysis remains in the deranged functional state. The reason is that heparin acts near the end of the coagulation cascade by the inhibition of factor X and accelerates antithrombin III binding of thrombin. As heparin does not inhibit the early reaction of coagulation cascade, CPB activates platelets and plasma proteins involved in the contact and the fibrinolytic system. Finbrinolysis was a common occurrence in the first twenty years of cardiac surgery. Recently due to improvement in equipment, oxygenator and the proper use of heparin has reduced the fibrinolysis to a great extent. Yet some degree of fibrinolysis does occur as evidenced by substantial reduction in blood loss by antifibrinolytic therapy. During CPB there is an increased fibrinolytic activity. Along with it there is decrease in the inhibitor activity that is responsible to control fibrinolysis. There is increase in plasma levels of D-dimer or other fibrin degradation products (FDP's). The decrease of D-dimer levels last for two days post CPB and then the increase occurs up to seven days.

PLATELET ASSOCIATED BLEEDING

During the early post CPB period platelets play a major role as the cause of excessive bleeding. Platelets are essential and important for the homeostatic function. The bleeding related to platelets may be either due to decrease in the count or its function. Both the qualitative and quantitative deficiencies occur during CPB. Mechanical factors play a role. Loss of platelet occurs due to adherence to the pump circuit, shearing forces and turbulent flow. There is a wide variation in degree of thrombocytopenia reported in different studies. The reason for variation is due in part to differences in types of pumps, oxygenators, flow rates, degree of hypothermia, duration of bypass and suctioning technique. Hemodilution which invariably occurs also causes decrease in platelet count, reported to be not more than 30% and it then does not require any diuresis which occurs due to hemodilution, mannitol or by diuretic therapy would self correct it. Still the platelet count remains low up to second post operative day but returns to preoperative level in about seven days. Desegregation of aggregated platelet during CPB may in part contribute to the recovery too. Thrombocytopenia also occurs secondary to aggregation of platelets induced by heparin, ADP released from lysis of red blood cells, protamine, heparin protamin complex, and drugs like aspirin, some penicillins, nitrates and propronol to name a few. The studies show decrease in platelet count - which varies from 33% to 50%, a crucial number when excessive bleeding is manifested. Apart from quantitative dysfunction, qualitative dysfunction also occurs and may be of more importance. Platelet dysfunction also occurs not well established but possible mechanism may involve temporary depletion of functional platelet component, production of a labile inhibitor or membrane abnormality.

MANAGEMENT OF BLEEDING

Strategies to decrease bypass related hematological problems should be preventative. The focus should be on the activity of platelet reduction and inhibition of fibrinolysis. Management of bleeding should start from the preoperative planning stage. A complete history which include medications patient is taking e.g. Aspirin, Coumadin, bleeding diathesis. Tests include liver function, renal function (platelet dysfunction is associated with renal failure). All nonurgent / elective cases should be scheduled for surgery at optimum time so that drug effects are minimal and the tests for bleeding problems are normal. If a patient comes in for emergency cardiac operation and prothrombin time is increased due to Coumadin therapy, then fresh frozen plasma (FFP) should be given preoperatively. Similarly the patients

with thrombocytopenia be transfused with platelets and the count increased to above 70,000. One donor unit of platelets will increase the count by about 10,000. Patients coming to operating room shortly after streptokinase or urokinase infusion need to be treated with FFP or cryoprecipitate as they are liable to bleed profusely. The patients with bleeding diathesis should be treated with appropriate blood component and one should remember that post operatively these patients may need transfusions of deficient factors, as the delay will lead to increased blood loss and thereby loss of more of the coagulant factors and in addition will need treatment with FFP and platelets. Several different classes of drugs have been used to reduce blood loss and improve homeostasis. They include desmopressin acetate (DDAVP), epsilon amino-caproic acid (Amicar) and the serine protease inhibitor aprotinin (Tracylol).

APROTININ

Use of aprotinin therapy during surgical procedures is shown to have reduced the blood loss up to 50%. The therapy is expensive. Aprotinin is a natural protease inhibitor derived from bovine organs. It inhibits the plasma enzymes which are triggered during the CPB which reduces the inflammatory action of kallikrein and has effect on fibrinolysis. Several studies have proved the efficiency of reduced bleeding with the use of aprotinin during cardiac surgery. Hypersensitivity reactions have been reported in a small population especially if administered the second time and they may be classified as anaphylactic or anaphylactoid. Some concern is raised that use of aprotinin may cause the graft thrombosis because of the hypercoagulable state but that has not been proven. Two regimens have been used for aprotinin administration. When monitoring the activated clotting time for heparin efficacy along with the use of aprotinin it should be measured by cellite surface activation method.

EPSILON AMINO CAPROIC ACID (EACA)

In the past, use of EACA during cardiac surgery was quite common. However, there were conflicting results in the effectiveness as a routine therapy. But a recent study has suggested that EACA can reduce the blood transfusion requirement but this is a meta-analysis and should be proved with a clinical study. If its efficacy is proved then EACA may be a preferred medication as it is less expensive. In summary, a number of questions still have to be answered to understand the complete pathophysiology of the derangement caused by CPB; until then treatment of bleeding will remain with administration of antifibrinolytics of EACA or its analogs.

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