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THE PERFUSION STRATAGY IN PATIENTS WORTH COAGULATION DISORDERS

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High dosage anticoagulation during cardiopulmonary bypass is mandatory in order to prevent life- threatening clot formation. Unfractionated heparin (UFH) is the gold standard for this purpose. However, in patients undergoing CPB operations, 25 - 50 % develop heparin dependent antibodies during the postoperative period. This is typically between day 5 - 10, if UFH is continued during the postoperative course. These antibodies activate platelets causing a pro-thrombotic disorder, known as heparin-induced thrombocytopenia (HIT type II), which can lead to life-threatening thrombo-embolic complications. If urgent cardiac operation with the use of CPB required in patients with positive antibody titre required, different anti-coagulatory approaches are available.

Lepirudin, a recombinant hirudin deriving from the salivary secretion of the leech forms a tight 1:1 stochiometric complex with thrombin. It acts by occupying the putative fibronogen-binding site and the catalytic site of thrombin is blocked. As a result, all of the thrombin-catalyzed procoagulant reactions, such as conversion of fibrinogen to fibrin, activation of coagulation factor V, VIII and XIII, and thrombin-induced platelet activation, are inhibited. The protocol used in all patients with HIT II consist of an initial intravenous lepirudin bolus of 0.25 mcg/kg body weight, and additional lepirudin to the priming solution (0.2 mg/kg bw) to achieve plasma levels > 2.5 mcg/ml at the start of CPB. If a lepirudin plasma level is < 2.5 mcg/ml, an additional bolus of 10 mg lepirudin is given. A continuous iv infusion of 30 ml/h (0.5 mg/min) is administered during CPB. Every 30 min, ECT is measured. If lepirudin plasma level is between 3.5 - 4.5 mcg/ml, no change in infusion rate is performed. If lepirudin plasma level is > 4.5 mcg/ml, the rate of infusion is reduced by 10 ml/h, and if plasma level is < 3.5 mcg/ml the rate of infusion is increased by 10 ml/h.

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Several in-vitro and in-vivo experiments have shown that the ACT and the APTT were not sufficiently sensitive in monitoring r-hirudin plasma levels. However, whole blood ecarin clotting time (ECT) has been demonstrated to be a reliable monitoring system using citrate anticoagulation whole blood, standard normal human plasma, and ecarin solution. The ECT is determined using a coagulometer and r-hirudin concentration can be estimated using a calibration curve, which has been constructed by using citrate-anticoagulated whole blood spiked with r-hirudin to achieve different final concentrations.

As there is no antidote available to reverse the anticoagulant effect of lepirudin, hemofiltration can be used successfully to remove lepirudin from the blood circulation. This can be of importance in case of impaired renal function, lepirudin overdosage and bleeding complications. However, in patients with normal kidney function, no antidote is necessary to reverse the anticoagulatory effect of lepirudin after the end of CPB. This is because the half-life of lepirudin is only approximately one hour and plasma levels decrease rapidly after the end of infusion.

In patients with HIT type II and a positive heparin-induced platelet aggregation (HIPA) test, patients are treated with lepirudin during CPB and during the postoperative course. However, in patients with history of HIT II but negative HIPA test, unfractionated heparin and standard protamine protocol can be used in combination with pre and postoperative treatment with lepirudin.

Bivalirudin, a recently introduced CPB alternative anticoagulant, can be used similarly to the lepirudin infusion protocol. An iv Bivalirudin bolus of 1.5 mg/kg and continuous infusion of 2.5 mg/kg/h (42 mcg/kg/min) are used. Moreover 50 mg are added to the pump circuit volume. The anti-coagulatory monitoring is performed using ECT. The half-life of Bivalirudin is only 25-36 min and it is predominantly (80%) eliminated through proteolytic cleavage within plasma. A minority (20%) is

excreted by the kidneys. This makes the drug favourable for patients with impaired renal function. Moreover less postoperative bleeding complications are observed using Bivalirudin in comparison to Lepirudin.

A number of congenital and acquired coagulation disorders are observed in patients undergoing cardiopulmonary bypass. Due to the high dosage anticoagulation (400 U/kg UFH) during cardiopulmonary bypass, the predominant risk of these patients are intra-operative and especially postoperative bleeding complications.

Hemophilia A and B, are congenital defects in the efficacy of Factor VIII and Factor IX. This coagulation disorder can result in postoperative bleeding complications. In case of prolonged bleeding, recombinant F IX and F VIII concentrates can be substituted to increase F IX and F VIII activity above 40%. Mild forms of hemophilia A can be treated by the systemic vasopressin analogue DDAVP.

Von Willebrand disease is a congenital disorder of the Willebrand factor synthesis and may result in postoperative bleeding due to the inability of platelets to fix to the subendothelial matrix. Recombinant Willebrand factor can be used in case of bleeding complications. In mild forms, DDAVP can be used.

Typical symptoms of F XIII deficiency are late postoperative bleeding and disorders of wound healing. These can be treated by F XIII concentrates.

As antithrombin (AT III) is a co-factor to heparin, its deficiency can result in an inadequate response to heparin anticoagulation. An antithrombin deficiency can be congenital or acquired (long-term heparin therapy). The therapy consists of a substitution of AT III concentrates. Other coagulation factor deficiencies are seldom seen. A deficiency of fibrinogen has to be treated in patients with a fibrinogen activity below 100 mg/dl.

Platelet disorders resulting in hemorrhagic diathesis are very seldom seen. In patients with platelet disorders, bleeding complications can occur despite a normal platelet count. Acquired coaguation disorders can occur in patients with liver dysfunction or previous therapy with coumarin derivates. This results in a deficiency of vitamin K dependent plasma coagulation factors (II, VII, IX, X, protein C and protein S). In the case of prolonged bleeding after cardiopulmonary bypass, fresh frozen plasma (FFP) can be transfused if the INR value is below 2.0. In patients with impaired liver function, FFP transfusion should be avoided and instead of this, PPSB precipitates can be used.

If patients are pre-treated with Acetylic acid or Clopidogrel, Aprotinin or Tranexemic acid can be administered during cardiopulmonary bypass in order to reduce the postoperative bleeding risk. In case of pre-treatment with Abciximab, a transfusion of platelets is necessary. If only low dosages of Abciximab have been administered, synthetic vasopression analogue DDAVP can be used successfully in order to prevent bleeding complications. In case of pre-treatment with fibrinolytics such as urokinase, streptokinase and t-PA transfusion, fresh frozen plasma can be transfused after the end of cardiopulmonary bypass in order to normalize coagulation.

In patients with congenital thrombophilic disorders, such as APC resistance or disorders of the protein C system, no special anticoagulation during CPB has to be performed. However, in these patients, sufficient postoperative anticoagulation using heparin or coumarin derivates has to be performed to prevent thrombo-embolic complications.

In patients with IdiopathicTthrombocytopenic Purpura (ITP), an increased intra-operative and postoperative bleeding risk is observed. Preoperative treatment with immunoglobulins in a dosage of 0.4 g/kg bw for 3 days, will lead to an increase of platelet count. Alternatively, these patients can be treated with gluco-corticoids in a dosage of 100 mg per day. In emergency operations, platelet transfusions may become necessary.

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