Neutralization of Heparin for Extracorporeal Membrane Oxygenation

ECMO Setinde Heparin Nötralizasyonu

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Extracorporeal membrane oxygenation (ECMO) uses adapted conventional cardiopulmonary bypass technology to provide prolonged respiratory or cardio-respiratory support for patients who failed conventional intensive care management (1). ECMO provides the very sick child with cardiac and/or respiratory support until the child’s own cardiac and/or respiratory system can provide the child’s needs. ECMO is fairly complicated. Morbidity and mortality has a high potential in this patient population.

The most common complications of ECMO are hemorrhagic, related to the systemic heparinization (2). 20% patients have clinically significant bleeding, including an intracranial hemorrhage (ICH) rate of 6% to 17.5% (3). Severe ICH is the most common cause of death in the neonatal ECMO patients and associated with poor outcome in survivors (4). Thromboembolic events leading to cerebrovascular accidents have also remained one of the major concerns with the use of ECMO (5).

Alternatives to systemic heparinization include heparin bounded circuits and epsilon-aminocaproic acid infusions (6). The available knowledge on clinical applications of heparin-coated perfusion is mainly based on short-term applications (7). Heparin bounded circuits do not completely eliminate the need for continuous heparin infusion. Also, aminocaproic acid has little value once bleeding has begun (6). In a recent study, either aprotinin or epsilon-aminocaproic acid administered in early postoperative period was shown to be ineffective in reducing postoperative bleeding (8). In this perspective, instead of lessening the heparin needed for the ECMO circuit, heparin blockage may theoretically be helpful, both for decreasing the risk of hemorrhage and for long term ECMO administration. Compartmentalizing the administration of heparin to the bypass circuit in Extracorporeal Membrane Oxygenation (ECMO) to prevent the bleeding complications without increasing the thrombosis risk may give a benefit. Protamine has been extensively used in the adult to reverse the effects of heparin after cardiopulmonary bypass surgery, but not in ECMO (9).

Like antibody antigen complexes, heparin-protamine complexes also activate the complement system. Heparin-protamine complexes must achieve a critical size in order to activate C1q. Heparin-protamine complexes secondarily initiate complement activation and eicosanoid generation, particularly thromboxane which may be responsible for many of the acute manifestations observed during protamine reversal of heparin anticoagulation. Complement activation is also related with the decrease in granulocyte count. Protamine reactions range from mild hypotension to severe cardiovascular collapse (10). Pulmonary hypertension and hemorrhagic pulmonary edema are other potential severe side effects of protamine (11). Peripheral platelet counts reduce 68% in animals receiving protamine. Also, there is a correlation between thrombocytopenia and development of hypotension (10). Anaphylactoid reactions due to protamine administration are mediated by complement activation leading to release of histamine, thromboxane and other vasoactive substances. These reactions may explain the pulmonary edema, pulmonary vasoconstriction, right ventricular failure and systemic hypotension following protamine administration (12).

Besides its primary action to increase the activity of antithrombin III, heparin has two other active sites, one for platelets and one for complement (9). Direct platelet activation by heparin reduces the benefit accrued from the use of this anticoagulant. Its effect on platelets is not uniform. Heparin increases the fibrinogen binding to platelets and stimulates aggregation (13). Rapid effects of heparin (5 min after 100 IU/kg) are; significant fall in platelet count, platelet aggregation and enhanced release of thromboxane A2 (14).

Von Willebrand factor is produced in megakaryocytes and endothelial cells, is stored in alpha granule of platelets and in Weibel-Palade body off endothelial calls and is present in plasma and vascular sub endothelium. VWF contributes to both...
platelet adhesion/aggregation and blood coagulation through its multiple adhesive functions for the platelet membrane receptors, glycoprotein Ib-IX-V complex, integrin alphalibbbeta3, heparin, various types of collagen and coagulation factor VIII. Among various functions, the most characteristic feature of vWF is its determinant role on platelet thrombus formation under high-shear rate conditions (15).

ECMO circuit itself acts as a continued thrombotic stimulus that in turn results in continued fibrinolytic activity, but it is the effect of the contact and fibrinolytic activity on platelet function that actually results in a haemostatic defect.

Compartmentalizing the administration of heparin to the bypass circuit should greatly impact on one of the significant causes of morbidity and mortality in the use of ECMO which is intraventricular hemorrhage secondary to systemic heparinization. Defining and proving the safety and reliability of heparin neutralization procedure for ECMO is crucial for further spread of ECMO technique and may lead to the removal of “hemorrhage” from ECMO contraindications list.

REFERENCES