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How to Manage Thrombocytopenia with ECLS: A Proposal of Clinical Reasoning Tools

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Abstract: Extracorporeal life support (ECLS) is increasingly used as a rescue therapy in patients with refractory cardiac/respiratory failure for temporary support or bridge to decision-making in both adult and pediatric patients. Complications such as bleeding and thrombosis remain major causes of morbidity and mortality in patients treated with ECLS. Hemostatic complications related to ECLS are multifactorial in patients with multiple organ dysfunctions and are incompletely characterized. Persisting thrombocytopenia and/or platelet dysfunction is the most frequent one. Herein, we report the case of a patient who developed severe thrombocytopenia after 5 days of ECLS associated with thrombi deposition in the circuit and oxygenator. After ECLS circuit and membrane change, we observed an increase and normalization in platelet count in 3 days. We propose a case-based reasoning to manage thrombocytopenia with ECLS.
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OVERVIEW

Extracorporeal life support (ECLS) is increasingly used as a rescue therapy in patients with refractory cardiac/respiratory failure for temporary support or bridge to decision-making in both adult and pediatric patients. Complications such as bleeding and thrombosis remain major causes of morbidity and mortality in patients treated with ECLS (1). Hemostatic complications related to ECLS are multifactorial in patients with multiple organ dysfunctions and are often incompletely characterized. Persistent thrombocytopenia and/or platelet dysfunction is the most frequent factor affecting hemostasis (2). Moreover, persisting thrombocytopenia in critically ill patients is associated with increased mortality (3). As in any setting, identification of underlying causes and mechanisms is important to make the appropriate therapeutic decisions. Evaluation of causes and mechanisms of platelet abnormalities are based on clinical and biological criteria. Daily inspection of the membrane oxygenator and all other parts of the ECLS circuit is mandatory to detect thrombi deposition that could alter oxygenator function and be a source of thrombo-embolic complications (4). Thrombi deposition may reveal inadequate anticoagulation or consumption coagulopathy. Thrombocytopenia is an alarm sign for both situations, even if other causes of thrombocytopenia must be investigated (3). Adequate function of the oxygenator is assessed by monitoring the pre-oxygenator and post-oxygenator oxygen partial pressure and the oxygenator ability to remove CO_2. If oxygenator dysfunction is not recognized early, oxygenator failure may occur and require urgent circuit/oxygenator replacement (5). Herein, we report the case of a patient who developed severe thrombocytopenia after 5 days of ECLS associated with thrombi deposition in the circuit and oxygenator. After an ECLS circuit and oxygenator change, we observed a spontaneous increase in the patient's platelet count within 3 days.

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DESCRIPTION

We report the case of a 61-year-old male patient with a past medical history significant for type 2 diabetes mellitus, arterial hypertension, and chronic tobacco use. Drug-eluting stent was placed in the right coronary after his first acute myocardial infarction in 2006. The patient received dual-antiplatelet therapy with aspirin and clopidogrel, but with poor adherence. In April 2016, the patient presented with a new occlusion of the left circumflex, the left ramus intermedius, and stent occlusion of the right coronary artery. A drug-eluting stent was implanted in the circumflex and in the ramus intermedius. At that time, transthoracic echocardiogram revealed a moderately altered left ventricular (LV) ejection fraction (45%) and moderate mitral regurgitation. He was admitted to the emergency department of Bichat hospital in August 2016 because of asthenia and diarrhea. Occlusion of the left anterior descending artery was diagnosed and treated with a drug-eluting stent. Nevertheless, the patient developed cardiogenic shock. Positive inotropic therapy (dobutamine, then levosimendan) improved LV systolic function. Hemodynamic status quickly worsened with atrial and ventricular arrhythmias ultimately leading to cardiac arrest. Veno-arterial femoro-femoral ECLS was inserted percutaneously at the bedside during cardiopulmonary resuscitation. Extracorporeal membrane oxygenation (ECMO) systems were Quadrox Permanent Life Support System and Rotaflow centrifugal blodd pump from Maquet©, Rastatt, Germany. All components of the set, including the tubing and cannulas, were heparin coated. Improvement of clinical state was obtained. Unfractionated heparin (UFH) was used and titrated on anti-factor Xa values with the goal (.3–.4 U/mL). After five days of ECLS, he developed severe thrombocytopenia (51 G/L vs. 261 G/L before ECLS) (Figure 1) with thrombus deposition in the circuit and oxygenator. Activation of coagulation was documented by decreased fibrinogen (Fg) concentration (1.25 g/L vs. 5.34 g/L before ECLS). Prothrombin time (PT) and factor *V* remained within the normal range and were stable. We first suspected heparin-induced thrombocytopenia (HIT) as the patient was receiving UFH. On day 5, immunoglobulin G anti-PF4/heparin (PF4/H) antibodies were reported positive by enzyme-linked immunosorbent assay (optical density .763; expected values for absence of HIT are .5 or more). Subsequently, a heparin-induced platelet-activation assay did not show heparin-dependent platelet-activating antibodies and allowed us to excluded HIT as a diagnosis. Mild hemolysis was observed with lactate dehydrogenase (LDH) at 381 UI/L. On day 7, the circuit and oxygenator of the ECLS were changed. Forty-eight hours later, the platelet count had increased significantly to 100 G/L and reached 271 G/L 6 days after the circuit change. No platelet concentrates were transfused during this period, but he received four red blood cell units immediately after ECLS's start because of low hemoglobin concentration. LV assist device (Heartmate II; Abbott, Chicago, IL) was implanted after initial ECLS; then, a few months later, the patient had heart transplantation. Both interventions were uneventful.

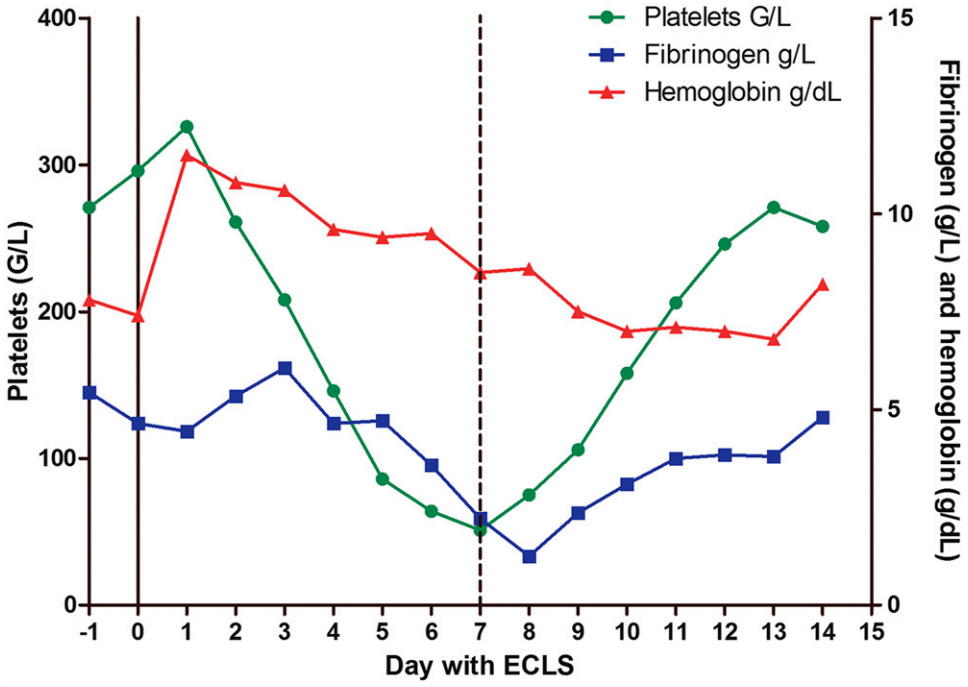

Figure 1. Time sequence of platelets count, fibrinogen and hemoglobin before and during ECLS. The first line (day 0) indicates the implementation of ECLS and the second dotted line (day 7) the circuit and membrane changing.

COMMENT

Hemostatic complications, both bleeding and thrombosis, remain major causes of morbidity and mortality for patients treated with ECLS (6). Thrombosis pathophysiology is complex with the involvement of multifactorial mechanisms that include device-related, patient-related, or management-related thrombosis (1). Activation of the coagulation cascade is triggered by the exposure of plasma and blood cellular components to ECLS surfaces. This ultimately leads to a degree of hemolysis and thrombin generation, and consumptive loss of platelets, Fg, and coagulation factors (7). To our knowledge, this is the first case demonstrating a reversal of thrombocytopenia after

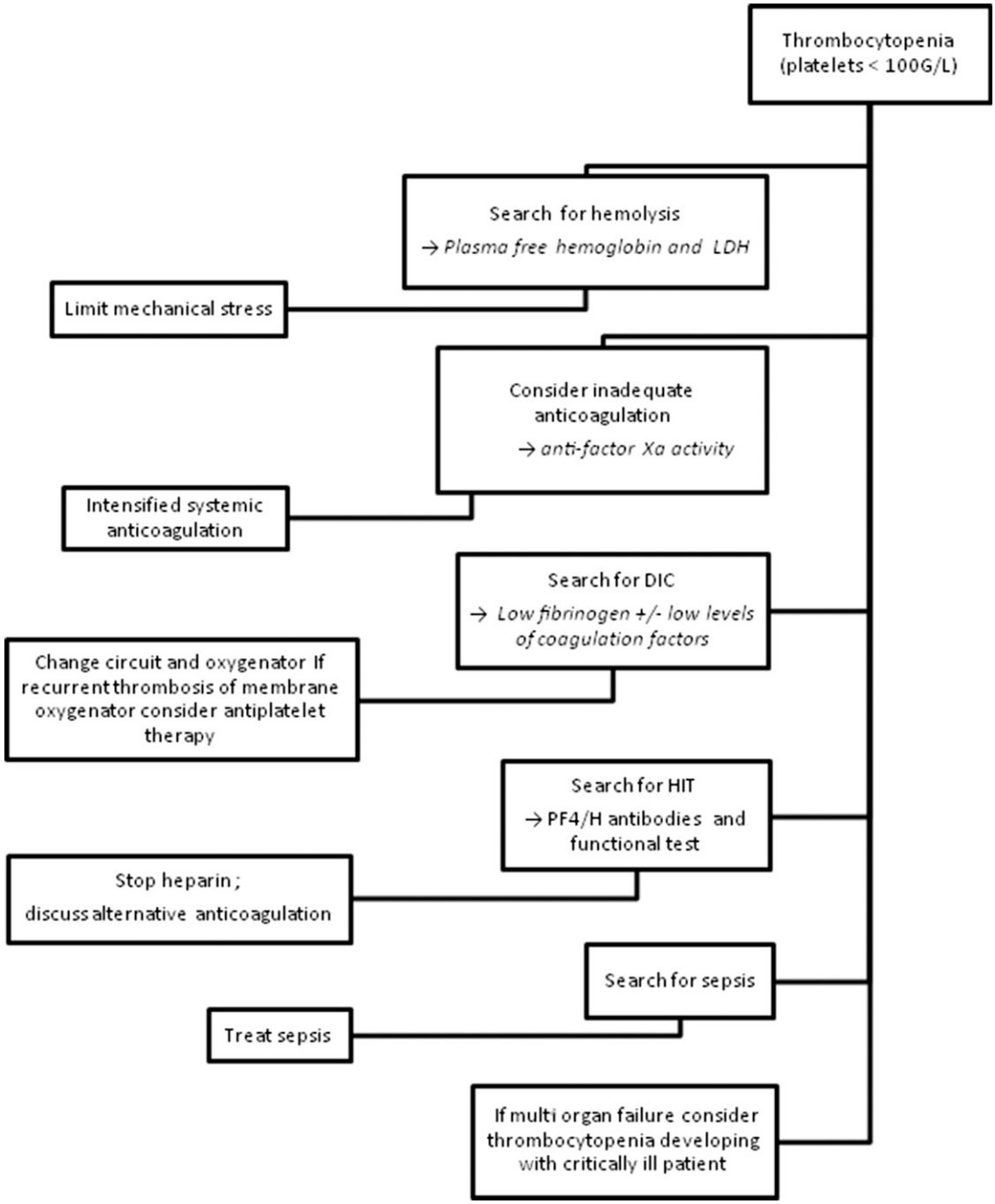

Figure 2. List of possible causes for the diagnosis and management of thrombocytopenia. LDH for lactate dehydrogenase, HIT for heparin-induced thrombocytopenia, PF4/H for antiplatelet factor 4/heparin, and DIC for disseminated intravascular coagulation.

changing a circuit and oxygenator. As in any setting of thrombocytopenia, it is important to identify all potential causes and mechanisms to take the appropriate therapeutic decisions, as shown in the algorithm (Figure 2). We listed below the six main causes of thrombocytopenia during ECLS. 1) Hemolysis is common in extracorporeal circuits, as evidenced by elevated plasma-free hemoglobin and LDH concentrations (8). A variety of factors, such as negative pressure generated by the pump during hypovolemia, clotting within the circuit or close to the cannula orifices, pump design, and excessive pump speed, may explain the occurrence of hemolysis. Furthermore, plasma hemoglobin may contribute to platelet adhesion, aggregation, and thrombosis (9), and increased LDH was associated with device thrombosis (10). 2) Inadequate anticoagulation by UFH may induce intravascular and pump thrombosis, which would result in coagulation factors and platelet consumption, and cause more bleeding, requiring larger transfusions. Under this case, consider intensifying the systemic anticoagulation by UFH with a higher anti-factor Xa activity. Furthermore, acquired antithrombin deficiency may contribute to the inefficacy of UFH. 3) Disseminated intravascular coagulation (DIC) or microcirculatory thrombosis could be hypothesized by the association of thrombocytopenia with low levels of coagulation factors is suggestive of its presence. Therefore, decreased Fg concentration may indicate subclinical consumptive coagulopathy, so changing the ECLS circuit should be considered. We would consider a combination of antiplatelet treatment if there was no evidence of insufficient anticoagulation and/or heparin resistance and the thrombosis happened only in the oxygenator but not at other sites of the body. 4) Thrombocytopenia in patients with ECLS may also be due to HIT, which is caused by platelet-activating antibodies. Because of low positive predictive value of anti-PF4/H antibodies immunoassays, functional test as heparin-induced platelet assay is needed to rule out HIT diagnosis 5) The relevance of sepsis for the development of thrombocytopenia is well known. However, with ECLS, a diagnosis of sepsis is difficult because many sepsis criteria are not applicable while on ECLS. 6) Thrombocytopenia developing in critically ill patients is likely a marker of severe physiological stress. Platelet count less than 100 G/L occurs in up to 25% of patients in intensive care unit. The different time course of thrombocytopenia could merely reflect different duration of exposure to an artificial surface and mechanical stress. In our case, we suspected DIC because of a decrease in platelet count and Fg concentration. The PT did not decrease and remained stable around 12.8 seconds (11.3 seconds for control). Nevertheless, a decreased PT is not a sensitive sign of DIC. In addition, HIT was excluded and UFH treatment was continued. It is important to specify that we changed the ECLS circuit with a new one from the same brand with the same flow of 3.5 L/min. Thus, this did not change or increase hemocompatibility of its components (polyurethane and polymethylpentene) but solved a kind of "circuit's wear" and/or prothrombotic disorder. We cannot conclude on the exact mechanisms through which the change of the ECLS circuit corrected the activation (DIC-like) of the coagulation, but we can speculate that after several days, the circuit heparin coating is altered, thus exposing the artificial surfaces that become a trigger for the activation of the coagulation. The new circuit restores heparin coating, thus attenuating the activation of the coagulation.

CONCLUSION

Changing the ECLS circuit and oxygenator with the same device type and lot number disposables may reverse a thrombocytopenia and stop coagulation activation.

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