



Personalized blood products in neonatal extracorporeal membrane oxygenation: the path between protocols and mortality

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In recent decades, the use of neonatal extracorporeal membrane oxygenation (ECMO) has spread widely, with about 42,000 neonates who have undergone this modality as a life-saving support (1). The primary indication for neonatal ECMO is respiratory failure, most commonly caused by diaphragmatic hernia, meconium aspiration, or pulmonary hypertension (2). Cardiac indications for the use of neonatal ECMO represent a smaller part of cases overall, but are constantly growing (2,3). To date, congenital heart disease with hypoplastic left heart is the most common cause. Despite the fact that survival in neonatal ECMO population is high, with higher percentages in the pulmonary subpopulation than in the cardiac population (1), the side effects that are associated with the use of ECMO, such as bleeding and thrombosis, result in a worse outcome (4). In this context, blood transfusion is a frequent practice in neonatal ECMO due to frequent blood losses, and bleeding, and is done to support the oxygen delivery to tissues.

In the December 2019 issue of *Transfusion*, Keene and collaborators elegantly confirmed how both packed red blood cells (PRBC) and platelets (PLT) are associated with increased mortality. In a retrospective observational design, the authors highlighted the strong association between mortality and transfusions, adjusting the results for illness severity at ECMO initiation using the Neo-RESCUERS score (5). The relationship between greater volume transfusion and increased morbidity and mortality described by the authors is noted in many reports (6-8).

It is interesting to note that the primary diagnosis of neonates was considered one of the variables in the studied population, with a higher mortality among patients with congenital diaphragmatic hernia (5). Henríquez-Henríquez *et al.* have noted that pediatric patients and neonates undergoing ECMO due to respiratory disease received fewer transfusions than those undergoing ECMO due to congenital diaphragmatic hernia or cardiac disease (9). Moreover, through a historical cohort study of neonates treated with ECMO, Chevuru *et al.* reported that a higher number of PLT transfusions was required in neonates with meconium aspiration or sepsis, while a lower demand was observed in neonates undergoing veno-venous (VV) ECMO compared to those with veno-arterial (VA) ECMO (10).

After all, neonatal ECMO patients, given the severity of their organ dysfunction, have a particular predisposition to present transfusion-related adverse effects, such as infections and immune-mediated reactions. It has been observed that the increased risk of infection and thrombosis after transfusion of stored RBCs is due to structural change during storage, resulting in increased osmotic fragility, loss of deformability, and increased level of free hemoglobin (Hb). Moreover, a possible promotion of vasoconstriction is related to increased endothelial adhesion by stored RBCs (11). In Keene *et al.*'s retrospective study (5), RBCs used for ECMO are leukoreduced, leading to a reduction in the number of white blood cells (WBCs) in the blood products through centrifugation or filtration. Since several studies have shown that WBCs are associated with many complications of RBC

transfusions, the leukoreduction process could result in fewer immunomodulating reactions and endothelial adhesion of RBCs (12). Moreover, it is important to underline that while the primary goal of RBC transfusions is to increase oxygen-carrying capacity to support adequate tissue oxygenation, they can have very few benefits in treating mild anemia in ECMO patients. Even when there is a reduction in cardiac output due to acute bleeding or hypoxemia, VO₂ does not vary greatly until DO₂ falls below a critical point, and transfusions are rarely necessary to treat situations outside of hemorrhagic shock or severe anemia (13). In light of this, current data supports a restrictive blood transfusion strategy for ECMO patients, and the adoption of lower transfusion thresholds seems to be equally effective, though there is an indication from the Extracorporeal Life Support Organization (ELSO) to maintain Hb values within the normal range during ECMO (14).

In this context, as rightly expressed by the authors (5), the management of Hb levels and transfusion of blood products in patients receiving ECMO is still a matter of debate, with a transfusion threshold variability secondary to the paucity of clinical data.

During the study period, the authors chose to maintain traditional thresholds for transfusions: Hct >40%, PLT count >100,000/μL, fibrinogen level >100 mg/dL. In adults, though the actual triggers for transfusions are undetermined, many reports have illustrated a clear relation between transfusions and mortality, and centers with high volumes of ECMO management usually tolerate lower Hb levels during ECMO (15). Recently, Cahill *et al.* implemented a RBC transfusion protocol with a threshold of 8 g/dL in adult patients on cardiac ECMO, observing a reduction in the number of transfusions and associated complications, as well as improved survival (16). Likewise, other centers have initiated a restrictive transfusion strategy, with a threshold of 7 g/dL and low dosage of anticoagulants to obtain an activated partial thromboplastin time (aPTT) of 40 to 60 seconds in adults undergoing ECMO for ARDS, reporting a decrease in bleeding complications compared to what is reported in the literature (17). Considering these data, it can be deduced that a conservative transfusion strategy can be beneficial in the management of adult ECMO patients; unfortunately, to date the definition of an ideal transfusion threshold has not been the subject of many studies in the neonatal ECMO population. Therefore, it is not surprising that practice variability exists. In a neonatal ECMO cohort, a retrospective study of 72 neonates undergoing ECMO for hypoxic respiratory failure evaluated how the use of a

transfusion threshold of less than 35% hematocrits resulted in a lower RBC transfusion volume, without altering patient outcome (18), supporting the hypothesis that at least mild permissive anemia is likely safe in neonatal ECMO. This can also be applied to PLT transfusions considering that even intracerebral hemorrhage—the most severe complication during ECMO—may not be correlated with lower PLT levels (5).

Turning attention to the results obtained by the authors, the ECMO complications described in the study, including mechanical clot and bleeding, were correlated with different coagulation profiles in neonatal primary diagnoses. Indeed, the underlying disease can lead to a state of hypo- or hyper-coagulation associated with a general inflammatory response. Bleeding and thrombotic complications are related to many underlying factors in the neonatal ECMO population, including the germinal matrix underdevelopment of prematurely born infants, the sepsis-related disseminated intravascular coagulopathy (DIC), and the surgical procedures performed. In the neonatal population, the number of PLTs is in the normal range or slightly increased, but at the same time a platelet hyporeactivity is well reported, as well as a reduction of protein C, protein S, and antithrombin (AT) levels (3). While hemostasis in the healthy neonatal population manages to be well-balanced, the same cannot be said for neonatal ECMO patients. In addition, while the challenging management of anticoagulation, due to developing hemostasis, on the one hand helps to prevent thrombotic complications, on the other, it increases the risk of bleeding. When the contact between the blood and the ECMO circuit surfaces occurs, coagulation and inflammatory cascade are triggered. The platelet adhesion to the surfaces of the circuit favors thrombotic complications, even if ECMO-induced thrombocytopenia is reported more frequently in neonates than in older children. In this context, though there are no standardized protocols for the management of anticoagulation in neonatal ECMO, it would be appropriate to investigate this aspect in order to optimize it. Unfractionated heparin (UFH) is commonly used in the management of anticoagulation of neonates undergoing ECMO, but in the neonatal population the effectiveness of UFH may be affected by reduced levels of AT, and some studies have shown that the implementation of AT has allowed a reduction in the dosage of UFH used. However, the real benefit of this practice is not yet clear (3). An alternative to the use of UFH are direct thrombin inhibitors, of which bivalirudin is the most widely used. This

choice could be advantageous because it does not require an adequate level of AT; however, the absence of reversibility makes it less safe (3). Anticoagulation management should also be supported by optimal anticoagulative monitoring in neonatal ECMO. Of a particular interest is the study of the coagulative profile of the patients with thromboelastography (TEG) and thromboelastometry (ROTEM), associated with standard tests such as activated clotting time (ACT), aPTT, and unfractionated heparin assay (UFH assay) (19).

The restrictive approach to transfusions during ECMO should be considered the more globally possible in patient blood management care, and also adequate general support. In fact, during ECMO the reduction of transfusions starts with a lower blood sampling, a reduction in blood losses through a more balanced anticoagulation, and a circuit configuration and component use able to reduce the need for transfusions and hemodilution. Modern ECMO systems have a greater biocompatibility, which results in fewer adverse effects and, therefore, in fewer transfusions. The heparin-coated circuits induce a lower activation of the coagulative and inflammatory cascade, while in the development phase it is the nitric oxide embedded surfaces, associated with antiplatelet properties (19). The use of shorter tubes of the circuit ECMO is associated with a lower use of blood products, as they decrease the priming volume of the circuit and prevent hemodilution compared with larger circuits, increasing the effectiveness of transfusions in treating the present deficiency (20,21).

The reduction of the transfusion volume is also possible through the adoption of a protective approach to ECMO management, for example by shortening the duration of ECMO and standardized transfusion protocol through education of medical personnel.

The adoption of a restrictive transfusion strategy associated with a protective approach in the management of ECMO might reduce the adverse effects of a more liberal transfusion strategy in ECMO-supported patients, but the general treatment of the patients is not secondary, and the adequate administration of micro- and macro-nutrients as well as vitamin support has to be administered to support hemopoietic function.

On the basis of the above, it would be appropriate to design well-controlled studies that can validate the benefits of the above-mentioned strategies, taking into account the several variables of the neonatal population. The sample size to be studied should be large enough to allow a stratification of transfusion risks/benefits among the different subpopulations of neonatal ECMO. In particular,

future studies should focus attention on the relationship between liberal *vs.* restrictive transfusion practices and the outcome of neonatal patients, assessing the duration of the primary disease, the number of days of ECMO support, and the outcomes of neurological development (6). The requirements for the transfusion strategy of neonatal and pediatric ECMO patients vary according to the pathology, age, and type of ECMO. To avoid unnecessary transfusions, different parameters, and not only the goal of a normal Hb value as a trigger for the transfusions, should be considered. In this regard, it would be appropriate to know the volemic assessment of neonates in order to study their cardiopulmonary status by means of appropriate parameters, and to elaborate one that reflects the relationship between oxygen consumption and extraction in order to use it as a transfusion target value (21). Given the importance of transfusions during ECMO support, the establishment of optimal transfusion thresholds and well-defined strategies for a protective approach to neonatal and pediatric patients should be a priority for future research.

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