Review Article

Blood product transfusions on extracorporeal membrane oxygenation: a narrative review

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Background and Objective: Extracorporeal membrane oxygenation (ECMO) remains amongst the most invasive measures to treat organ dysfunctions, such as refractory cardiogenic shock and/or respiratory failure, in many cases being considered a last resort. Hemodilution, hemolysis and coagulation disorders are very common during ECMO therapy, necessitating blood and blood products transfusions virtually in every patient undergoing ECMO. There exist no randomized data on blood product transfusion protocols in the ECMO population. The only evidence comes from observational studies and cardiopulmonary bypass experiences in patients undergoing cardiac surgery which should not be extrapolated to ECMO patients because of substantial differences in circuit composition, support duration, heparinization and access.

Methods: The current review attempts to summarize the existing evidence on blood product transfusions in patients undergoing ECMO therapy. We screened PubMed and Google Scholar for all reports on blood product transfusion in ECMO patients up until December 2020. The review summarizes separately available data on red blood cells, platelets, fresh frozen plasma and coagulation factors.

Key Content and Findings: There is a significant variability in-between centers regarding hemoglobin or hematocrit threshold for red blood cells transfusion in ECMO patients. Data from observational studies suggest that lower thresholds for red blood cell transfusion may not adversely influence survival while being more cost-effective. A gap in knowledge persists regarding the indications for platelet transfusions with some experienced centers adopting relatively low thresholds in non-bleeding patients.

Conclusions: Randomized controlled trials accessing restrictive or liberal strategies in blood product transfusions are necessary. Reported worse prognosis in patients with multiple transfusions should be associated with their worse baseline status rather than transfusions themselves.

Keywords: Extracorporeal membrane oxygenation (ECMO); transfusions; red blood cells; fresh frozen plasma; platelets

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Introduction

Extracorporeal membrane oxygenation (ECMO) can be a life-saving procedure providing temporal support for insufficient lungs, heart or both. While effective in restoring blood flow to vital organs, at the same time adequately oxygenating the blood, it also provokes a cascade of hematological and inflammatory repercussions. Its implementation is associated with various complications influencing patients' survival (1). Some of these are inherent to the device—exposure of blood to the artificial surface and high mechanical shear stress generated with centrifugal pumps can result in the development of an acquired coagulopathy (2,3). Others are a result of anticoagulation therapy, necessary to prevent circuit thrombosis, which puts patients at risk for serious bleeding, which occurs commonly (4-6).

These adverse events can be ameliorated with blood products transfusion. Unfortunately, there are no specific recommendations to guide the treatment of patients on ECMO in terms of blood products management (7). Randomized controlled trials focusing on transfusion requirements in the ICU or after cardiac surgery did not include ECMO patients (8,9). Lack of established guidelines for blood products administration in this population is the cause of high variability between centers.

This analysis aims to review studies evaluating transfusion management on ECMO and explore the current outcomes associated with it. We present the following article in accordance with the Narrative Review reporting checklist (available at https://aob.amegroups.com/article/view/10.21037/aob-21-30/rc).

Methods

We searched online databases, PubMed and Google Scholar, with keywords: "ECMO", "transfusions", "blood products", "red blood cells", "platelets", "fresh frozen plasma", "cryoprecipitate". Retrospective and observational studies were considered with no restriction on the date of publication, up to December 31, 2020. Search strategy is summarized in *Table 1*. We excluded publications with no information about blood products management on ECMO therapy and those about pediatric patients. There were no restrictions regarding ECMO modality. In the tables some studies are mentioned twice if they contained data of two separate subgroups (e.g., veno-arterial (VA) and veno-venous (VV) patients).

Red blood cells

Transfusion of red blood cells is frequently required over the course of therapy (5,10), which is predictable because bleeding represents the most common complication in patients on ECMO, especially on veno-arterial (VA) modality (11,12). Red blood cells are routinely transfused when bleeding occurs to improve oxygen delivery to tissues. Nonetheless, red blood cell (RBC) supply has some drawbacks. A study by Shorr *et al.* (13) reported that transfusion of packed RBCs increases the risk of ventilator-associated pneumonia, suggesting that fewer transfusions can improve patient's outcomes. Also, transfusion, in general, is associated with immunomodulation, which may increase infection risk (14,15). There is a positive association between transfused RBC units and mortality in ECMO patients (6). This association, however, is probably confounded by the relationship between patients with more comorbidities requiring more RBC transfusions. These conditions demand more aggressive treatment, which is correlated with poor survival as demonstrated in the study by Omar *et al.* (16) wherein non-survivors needed more RBC units than survivors. High mortality observed in included studies evokes the question about transfusion triggers which could help optimize patients' care. Such a trigger is the hemoglobin (Hb) threshold. There are two strategies in RBC transfusion depending on Hb level—restrictive when transfusion is performed at a Hb level of 7–9 g/dL, and liberal with a Hb level between 10–12 g/dL. Doyle *et al.* (17) compared these strategies and suggested that the restrictive approach to RBC transfusion during ECMO has similar survival outcomes as the liberal approach and is more cost-effective. A recent meta-analysis reported that adopting a lower transfusion threshold in ECMO settings was associated with a lower rate of transfusion and lower risks of mortality (18) which can also be observed in the studies included herein. However, the authors noted that the results

Table 1 The search strategy summary

Items	Specification
Date of search	5–7 January 2021
Databases and other sources searched	PubMed, Google Scholar
Search terms used	"ECMO", "transfusions", "blood products", "red blood cells", "platelets", "fresh frozen plasma", "cryoprecipitate"
Timeframe	Up to 31 December 2020
Inclusion	Retrospective and observational studies, expert opinions, guidelines in English regarding adult population
Selection process	Two authors (EO, MP) independently screened databases. Discrepancies were resolved by discussion

might be influenced by studies' bias and their heterogeneity. Nevertheless, such information can be valuable for medical teams. The international survey performed by Martucci *et al.* (19) demonstrated that the majority of participants do not set the pre-specified threshold Hb level as a trigger for transfusions. The study also showed an inverse relationship between center's volume and Hb threshold for RBC transfusion. Here, we present an overview of recent studies regarding transfusion of red blood in ECMO patients (*Table 2*) along with hemoglobin thresholds used (*Table 3*). In ECMO settings, the decision about the type of cannulation is crucial in terms of bleeding prevention and possible transfusion. The study by Kanji *et al.* (20) showed that the percentage of patients cannulated peripherally experiencing bleeding was much lower than those cannulated centrally. Moreover, the peripheral cannulation group needed fewer RBC units. This is consistent with the fact that central cannulation is proven to put patients at higher risk of bleeding (27). Therefore, peripheral cannulation should be chosen when possible.

Coagulation disorders

Another significant aspect of ECMO management is anticoagulation. The most widely used anticoagulant is unfractionated heparin (UFH) (28), which carries a risk of heparin-induced thrombocytopenia (HIT). In addition, systemic anticoagulation may favor severe bleeding (29). Notwithstanding, the introduction of heparin-bonded circuits and new generations of oxygenators enables performing ECMO therapy without or with minimal heparin administration (30,31). A systematic review by Fina *et al.* (32) confirmed the feasibility of ECMO without systemic anticoagulation in selected circumstances, mostly in post-cardiotomy treatment and during active bleeding. However, further investigation is needed to evaluate the benefits of such management.

Thrombocytopenia is a common finding among patients on EMCO, occurring in up to 21% of cases (33). Although the underlying pathophysiology is not completely understood, an interplay between a primary disease process causing increased platelet consumption, platelet aggregation due to interaction with an artificial surface and effects of pharmacological agents, likely takes place (34). Contact with artificial surfaces and high shear stress during ECMO run lead to enhanced platelet aggregation and consumption. Platelet receptor shredding (35,36) and a loss of von Willebrand factor, which is necessary for platelet adequate function (36), both occur in the ECMO setting. Balle *et al.* showed impaired platelet aggregation and decreased activation on day 1 of ECMO support compared to control individuals, however, the difference disappeared when adjusted for platelet count, opposing the functional impairment of platelets during ECMO (37). Mandatory anticoagulation, usually achieved with unfractionated heparin, creates a risk of HIT, which is estimated to occur in 3.7% (33) of ECMO patients. Undeniably, the patient's primary disease often leads to increased platelet consumption with or without sepsis and disseminated intravascular coagulation. In fact, several studies showed that thrombocytopenia in patients on ECMO was not associated with duration of support, but rather with platelet count at initiation of ECMO and severity of disease process, assessed with Acute Physiology and Chronic Health Evaluation (APACHE) II score (38,39). Finally, VA- ECMO patients specifically could be exposed to factors contributing

Table 2 Baseline patient characteristics

Study	Study type	No. of patients	Reasons for ECMO	Age (years)	VA/VV ECMO (%)
Ang 2009 (4)	Retrospective	42	CS	46.8±12.7	88% *vs.* 12%
Kanji 2010 (20) Central cannulation	Retrospective	28	CS, HF with hypoxia	52±14	100% *vs.* 0%
Kanji 2010 (20) Peripheral cannulation	Retrospective	22	CS, HF with hypoxia	46±16	100% *vs.* 0%
Agerstrand 2015 (21)	Retrospective	38	ARDS	33±21	10.6% *vs.* 89.4%
Omar 2015 (16)	Retrospective	154	cardiac and pulmonary	51	82% *vs.* 12%
Voelker 2015 (22)	Retrospective	18	ARDS	37.1±15.6	0% *vs.* 100%
Mazzeffi 2016 (6) VA ECMO	Retrospective	54	PCS and other	50±21.1	100% *vs.* 0%
Mazzeffi 2016 (6) VV ECMO	Retrospective	64	ARDS and other	50±21.1	0% *vs.* 100%
Buscher 2017 (23) VA ECMO	Retrospective	32	CS	48±16	100% *vs.* 0%
Buscher 2017 (23) VV ECMO	Retrospective	16	ARDS	35±13	0% *vs.* 100%
Cahill 2018 (24)	Retrospective	30	CS, cardiomyopathy	60.7±12.4	100 *vs.* 0%
Swol 2018 (25)	Retrospective	32	lung failure, sepsis	54	6.2% *vs.* 93.8%
Guimbretiere 2019 (5) VA ECMO	Observational prospective	410	CS, post-cardiotomy	54.6±14.1	100% *vs.* 0%
Guimbretiere 2019 (5) VV ECMO	Observational prospective	99	N/R	48.2±16.9	0% *vs.* 100%
Martucci 2019 (10)	Observational prospective	82	ARDS	42±11	0% *vs.* 100%
Esper 2021 (26)	Retrospective	676	PCS, CS, respiratory shock and other	50.3	100% *vs.* 0%

No, number; VA, veno-arterial; ECMO, extracorporeal membrane oxygenation; VV, veno-venous; CS, cardiogenic shock; HF, heart failure; ARDS, acute respiratory distress syndrome; PCS, post-cardiotomy cardiogenic shock; N/R, not reported.

to thrombocytopenia such as open-heart surgery and prolonged resuscitation for cardiac arrest.

Platelets

The literature on platelet transfusion among patients on ECMO is sparse. In a meta-analysis by Jiritano *et al.*, only 3 of 21 studies reported rates of platelet transfusion which varied between 0–50% of patients (33). Other studies, not included in this meta-analysis, reported even higher rates of platelet transfusion (5,10). No guidelines currently exist on platelet transfusion thresholds in patients on ECMO. ELSO 2017 guidelines only state that in a bleeding patient, platelets should be transfused to reach a level of 100,000/μL (40). More recent COVID-specific guidelines suggest a platelet threshold of 50,000/μL, while allowing for lower thresholds if no clinically significant bleeding is present (41). However, they emphasize that not enough evidence exists to guide transfusion thresholds. The usual practice is to transfuse platelets when counts fall below 80,000/μL (40), although several experienced centers use a more conservative approach and transfuse platelets only when they fall below 40,000–50,000/μL (5,10), or even as low as 20,000 in non-bleeding patients (38). Recent Canadian expert consensus suggests a platelet transfusion threshold at 50,000/μL with consideration of a higher threshold in patients undergoing cannulation, decannulation, high-risk procedures or those deemed to be at high-risk of bleeding. They also discourage

Table 3 Outcomes

Study	Transfusion thresholds (g/dL)	RBC count (units)	PLT count (units)	FFP count (units)	Cryoprecipitate count (units)	Mortality	Time on ECMO (days)	Bleeding	Thrombosis
Ang 2009 (4)	10	10	3	4	4.5	73.2%	11	64.3%	0%
Kanji 2010 (20) Central cannulation	N/R	15.9	9.8	3	6.1	50%	2.5	64%	11%
Kanji 2010 (20) Peripheral cannulation	N/R	7.9	4.4	1.2	0.5	46%	3	18%	9%
Agerstrand (21) 2015	7	1	N/R	N/R	N/R	26.3%	9±3.3	26.3%	21.1%
Omar 2015 (16)	N/R	Survivors: 23	35	12.1	27.5	66%	4.4	39.6%	N/R
		Non-survivors: 34.7	55.2	13.9	25.7				
Voelker 2015 (22)	7	29.6±39	N/R	N/R	N/R	38.9%	21.7±30	N/R	N/R
Mazzeffi 2016 (6) VA ECMO	10	21	3	7	N/R	59.3%	7±6.6	68.5%	16.7%
Mazzeffi 2016 (6) VV ECMO	10	15	1	2	N/R	34.4%	7±6.6	39.1%	9.4%
Buscher 2017 (23) VA ECMO	8	2 per day (p.d.)	0.4 p.d.	1 p.d.	0.9 p.d.	31%	N/R	N/R	N/R
Buscher 2017 (23) VV ECMO	8	0.7 p.d.	0.1 p.d.	0.1 p.d.	0.1 p.d.	31%	N/R	N/R	N/R
Cahill 2018 (24)	8	15.3	2.5	4.2	0.9	63.3%	7.4±8.2	43.3%	N/R
Swol 2018 (25)	8	N/R	N/R	N/R	N/R	34.4%	10.3±12	N/R	N/R
Guimbretiere 2019 (5) VA ECMO	8	11.9	3	10	N/R	43.9%	7.4±6.1	59.8%	59.8%
Guimbretiere 2019 (5) VV ECMO	8	9.4	3	9.8	N.R	40.4%	10.5±10.2	34.3%	34.3%
Martucci 2019 (10)	8	8	6	10.9	N/R	23.2%	14±10.4	41.5%	N/R
Esper 2021 (26)	7	12	2	4	0	42.3%	7.2	N/R	N/R

RBC, red blood cells; PLT, platelets; FFP, fresh frozen plasma; ECMO, extracorporeal membrane oxygenation; VA, veno-arterial; VV, veno-venous; N/R, not reported.

platelet transfusion when platelet dysfunction is suspected without thrombocytopenia, unless objective evidence, such as aggregometry and cytometry, is available (34). A study by Esper *et al.* assessed survival prognosis associated with platelet transfusions for patients on VA-ECMO. They reported increased mortality associated with platelet transfusion at 90 days and 1 year. This may be explained by the systemic inflammatory response to platelets, which usually come from multiple donors, as well as by functional and biochemical changes occurring in stored platelets (26). However, several important factors (such as age, cannulation type, and creatinine levels on ECMO) remained unadjusted in their analysis. Since no randomized controlled trial has ever addressed this issue, no conclusion can be made whether platelet transfusion worsens the prognosis, or if patients with the more severe underlying disease have more profound thrombocytopenia and consequently are given more platelet transfusions.

Fresh Frozen plasma and coagulation factors

Evidence on fresh frozen plasma, or plasma factors

transfusion in ECMO-supported patients is almost non-existent, with only a handful of studies published on the subject. ELSO 2017 guidelines recommend daily fibrinogen measurements with the intention to maintain a range between 250 to 300 mg/dL with infusion of fresh frozen plasma or fibrinogen (40). The most feared complication during ECMO treatment is uncontrolled bleeding. ELSO 2017 guidelines allow for fresh frozen plasma or specific clotting factors transfusion in this scenario if there is evidence for these deficiencies (40). Patients on VA-ECMO for PCS may be especially vulnerable to bleeding due to the surgical wound and often long CPB times (11). 2020 ELSO guidelines pay extra attention to this issue, underscoring the importance of determining the presence of underlying factor deficiency with ACT, aPTT, factor Xa activity, fibrinogen levels and thromboelastography. In cases of massive bleeding, ELSO 2020 guidelines recommend administering packed cells, fresh frozen plasma and platelets in a 6:1:1 ratio to avoid a further dilution of coagulation factors (28).

An important factor contributing to coagulation disorders among patients on ECMO is acquired von Willebrand factor disorder (AVWD). Large-molecule von Willebrand factor (vWF) unfolds in ECMO circuits, making it more vulnerable to cleavage with proteinases (42). Kalbhenn *et al.* observed diminished levels of vWF in all 100 investigated patients as soon as one hour after implantation. They recommend routine monitoring of vWF, and prophylactic desmopressin administration to those with AVWD without apparent bleeding and VWF- containing-factor VIII concentrate if bleeding does occur (36). It is essential to keep in mind that, during ECMO, an interplay between bleeding and coagulation takes place, as plasma anticoagulants are also depleted. Therefore, the ELSO 2017 guidelines state that if clotting in the circuit occurs despite normal or high doses of heparin, and if antithrombin 3 assay is not available, fresh frozen plasma should be given until the clotting is controlled (40).

Conclusions

This review focusing on transfusion in ECMO patients has shown large variability in blood products management between centers which might be a result of a lack of specific recommendations. Worse outcomes in patients with a larger number of transfusions should be viewed as a reflection of patients' deteriorating condition rather than be associated with the transfusion themselves.

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Footnote

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