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Prospective multicenter Observational study on Transfusion practice in vv-ECMO Patients: The PROTECMO Study

Study Protocol

CONTENT

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Summary

Background: Over the past decade, the use of extracorporeal membrane oxygenation (ECMO) for respiratory support in adults has increased. Several trials have highlighted how red blood cells transfusion can cause several negative effects and, currently, a restrictive transfusion trigger in critically ill patients is widely accepted.

The optimal management of anticoagulation targets and transfusion practice in veno-venous-ECMO (VV-ECMO) patients is still under debate. Traditionally, the threshold for transfusions of packed red blood cells (PRBC) in ECMO is aimed at keeping hemoglobin (Hb) values in the normal range (12-14 g/dL), but some case series have shown how the Hb target can be lower, and with comparable clinical outcomes.

While there are extensive reviews on predicted ECMO survival, and management (even with many debated issues), there is a significant knowledge gap in understanding the benefits and risks of transfusions during VV-ECMO

Methods/Design: Prospective observational multicenter study. The principal aim is to describe current effective blood product usage, during VV-ECMO. The secondary aim is to describe in a large cohort of ECMO patients the current anticoagulation strategy and bleeding episodes occurrence.

The study will be conducted at a multicenter level including in each center all consecutive adult vv-ECMO patients during one year. The data collection will include pre-ECMO characteristics, transfusion strategies and blood test results during the first twenty-eight days after ECMO cannulation or until the end of ECMO support if the length is shorter, and clinical outcomes up to the end of ICU stay.

The descriptive variable end points for the primary aim will be the daily and the total amount of PRBC and other blood products (Plasma, Platelets, Fibrinogen, Antithrombin III).

The descriptive variable end points for the secondary aim will be the type and dose of anticoagulation, and episodes of bleeding according to site and severity.

Expected Results: A collaborative combination of ECMO centers will evaluate prospective data of transfusion practices during ECMO. The investigators would be able to describe the currently strategy for administration of blood products, anticoagulation and the effective incidence of bleeding episodes worldwide.

Background

Over the past decade, the use of extracorporeal Membrane Oxygnation (ECMO) for respiratory support in adults has vastly increased [1]. Veno-venous ECMO (VV-ECMO) can be initiated in case of Acute Respiratory Distress Syndrome (ARDS) as salvage therapy for patients with profound gas exchange abnormalities despite protective lung ventilation and other rescue therapies [2, 3].

Many aspects of ECMO management are still under debate despite the increasing number of cases [4, 5]. Among these debated topics there is certainly the optimal management of transfusion practice [6].

Several trials in the last decade have recognized how red blood cells transfusion can cause several negative effects, including transfusion related immune reactions, the potential transmission of diseases, the development of transfusion-related complications (such as transfusion-related acute lung injury – TRALI – or transfusion-associated circulatory overload – TACO) and immunosuppression. [7, 8] The Anemia and Blood transfusion in critical Care (ABC) study, an epidemiological survey of 3534 patients conducted in 146 ICUs of western Europe, confirmed an increased mortality rate in transfused patients [9]. On the other hand, the Sepsis Occurrence in Acutely Ill Patients (SOAP) database (n=3147) found that although there was a direct relationship between the number of blood transfusions and the mortality rate, blood transfusion was not significantly associated with a worse mortality rate [10].

Hebert and colleagues randomized 838 critically ill patients to either a liberal protocol in which transfusions were administered to maintain hemoglobin levels above 9 g/dl, or a restrictive strategy in which hemoglobin levels were kept between 7 and 9 g/dl. Overall, the 30-day mortality rate was 19 % in the restrictive group and 23 % in the liberal transfusion group (p=NS). [11]

On the other hand, anemia can also cause a potential increase in morbidity and mortality in critically ill patients, and in ECMO is an even greater critical issue in reducing delivery of oxygen (DO2). [12, 13] Moreover, despite improvement in technology and care, complications related to ECMO are still high, and frequently involve an imbalance in the coagulation status due to anticoagulant use in the presence of coagulopathy [14-16]. Consequently, the risk of thrombosis (presumably microthrombosis) and hemorrhage remain to be high [17-20]. In the case of ongoing bleeding, transfusion of Packed Red Blood Cell (PRBC) is required to support desired haemoglobin levels [21, 22].

Traditionally, the threshold for PRBC transfusions in ECMO is aimed to maintain hemoglobin (Hb) values in the normal range (12-14 g/dL) [23]. Despite this, there is considerable uncertainty regarding the optimal haemoglobin threshold for the use of PRBC transfusions in anemic patients during ECMO support.

Prompted by the general reappraisal of PRBC transfusion use, some case series using lower target for Hb during vv-ECMO support have been published [24-26]. However, such protocols do not use/suggest a definitive trigger/target of Hb [27].

There is also some evidence that a higher number of transfusions in ECMO patients is associated with worse outcomes [28-30]. However, such a relationship is difficult to assess given the large

number of factors influencing transfusion practice in this setting: target of anticoagulation, frequent bleeding episodes, the peculiar characteristics of the circuits that can cause mechanical damage, activation of inflammation, and consumption of platelet and coagulation factors, to name but a few [31].

Moreover, most of the available data on transfusions during ECMO are heterogeneous, usually including VV-ECMO and veno-arterial-ECMO (VA-ECMO) configuration, and mixing adults with neonatal and pediatric cohorts, which are historically more represented. Recently, a meta-analysis including 1042 patients presenting refractory ARDS and focusing on complication rate and hospital mortality associated with VV-ECMO showed a limited impact of bleeding and total number of haemo-derivates administrated on patient outcome. [32]

In this context, the decision of giving a transfusion during ECMO support is still a real challenge since several parameters have to be taken into account at the same time. A strict trigger has not yet been defined in this population, and the literature on critically ill patients suggests a relevant reduction in the amount of transfusion.

Rationale for the study

Providing adequate DO2 can be approached in several ways during vv-ECMO support, but the hemoglobin target is always a critical point, and a relevant piece of the puzzle of assuring the best oxygenation in patients affected with acute respiratory failure (ARF). There may be important variations between hospitals and countries in the use of PRBC transfusions, which may impact patient outcome. Large scale, national, and international studies are currently lacking.

While there are extensive reviews on predicted ECMO survival, and management (even with many debated issues), there is a significant knowledge gap in understanding the benefits and risks of transfusion during VV-ECMO. [30, 33, 34]
An international multicenter study will evaluate prospective observational data of transfusion practices during VV-ECMO for ARF, analyzing it in light of anticoagulation and bleeding episodes.

Aim of the study

The PROTECMO study is aimed at being a collaborative study including a large number of ECMO centers worldwide, describing, in real practice,

1) Incidence of major bleeding events and amount of blood product transfused
2) Type, trigger and level of anticoagulation adopted

The descriptive variable end points for the primary aim will be the daily and the total amount of PRBC and other blood products (Plasma, Platelets, Fibrinogen, Antithrombin III).

The descriptive variable end points for the secondary aim will be the type and dose of anticoagulation, and episodes of bleeding according to site and severity.

Study Design: international multicenter prospective observational cohort study.

For the primary outcome PRBC will be evaluated as total amount during the ECMO run and for the first 28 days as daily amount. The total amount of PRBC, adjusted for the ECMO length of stay, will be evaluated in light of pre-ECMO parameters (age, comorbidities, postoperative state and severity scores) and of daily data (bleeding episodes, ECMO blood flow, dieresis, CRRT, Hb, major events). Daily occurrence of PRBC transfusion will be described according to pre-ECMO characteristics and daily parameters (Hb, bleeding, hemodynamics, renal function, circuit change).

Plasma, platelets, Fibrinogen, Antithrombin III administration will be evaluated according o pre-ECMO data and according to daily APTT level (or other coagulation monitoring adopted), bleeding episodes, sepsis.

For the secondary outcomes type of anticoagulant will be described as well as daily dose and daily target for the parameter targeted (APTT, ACT, r-TEG, anti-Xa according to local protocol). Anticoagulation will be described in relation to pre-ECMO parameters and daily episodes of bleeding and occurrence of sepsis.

Bleeding episodes will be described according to site (airway – including tracheotomy - oro-nasal, gastric, intrathoracic, abdominal, intestinal, retroperitoneal, urinary tract, other) and classified according to severity following 5 adjusted categories of the Bleeding Academic Research Consortium (BARC) score: Type 0, no bleeding; Type 1, Any overt bleeding that requires heparin infusion rate reduction or PRBC transfusion (provided Hb drop was related to bleeding); Type 2, any overt bleeding that requires heparin infusion rate reduction and packed red blood cells transfusion or non-surgical procedure to stop bleeding (provided Hb drop was related to bleeding); Type 3, Any life-threatening bleeding that required PRBC transfusion and surgical intervention for control of bleeding or ECMO discontinuation; Type 4: any fatal bleeding.

The study is prospective and, consequently, in each center all consecutive adult patients who are eligible according to inclusion and exclusion criteria should be included in the study up to 20 patients.

Every patient included will be registered for baseline values, and will then be followed for ECMO management and transfusion management daily for the first two weeks and weekly during the following two weeks or until ECMO weaning if the ECMO run will be shorter than the observation time. During the first two weeks of observation, daily parameters will be recorded. Moreover, data will be recorded for every PRBC, Plasma, Platelets transfusion event. The patients will be observed for the clinical outcomes until they are discharged from the ICU and 6-months mortality will be recorded. Considering that according the Extracorporeal Life Support Organization summary, the average length of respiratory ECMO run is about 12 days we believe that the majority of ECMO run will be fully covered by the observation period and, at least, it will be paradigmatic of a center's actual practice and, at the same time, will assure a considerable sample size of transfusion events.

Data will be reported according to the STROBE (Strengthening the reporting of observational studies in epidemiology) statement checklist.

The knowledge about this topic may not be achieved differently by other study design like retrospective studies or surveys. In fact, in 2017, ESICM endorsed a survey on the topic (data presented at the ECISM congress 2018) that showed a strong variability among centers about blood products transfusions, but the level of evidence achieved by a survey is low. Moreover, to explore retrospectively datasets of published studies would not allow to highlight the current practice and the strength of the study rely on the length that is one year and will surely cover the current technological frame considering a rapidly evolving scenario.

Study population: inclusion criteria/patient selection

All patients who receive extracorporeal lung support (ECMO) for ARDS respiratory causes will be included. Of note, considering the observational design of our study, patients can be included in other studies concurrently (this will be noted on the CRF).

Exclusion criteria: refusal to include

Jehovah's witnesses and all patients refusing transfusions for personal reasons will not be excluded if a valid informed consent is acquired, but they will be analyzed separately.

Study conduction

The study will be conducted in compliance with the current Helsinki Declaration and the standards of good clinical practice.

The protocol will be entered into a public database (www.clinicaltrials.gov).

Given the explorative nature of this study, the required number of patients was not calculated, but considering at least 10 patients/year for each center (considered the worst prediction) we imagine that the included patients will be at least 100 in Italy and we presume to enroll at least a double number worldwide.

Study duration

- Transfusions decisions for each patient will be recorded daily during a two-week period after ECMO cannulation and weekly for the subsequent two weeks, or until the end of ECMO support if the length is < 28 days.
- Patients will be observed until ICU discharge with a follow up to sixth months for mortality
- The inclusion period will be 12 months for each center.

Data collection methods

Data will be recorded using pre-printed CRF by the principal investigator (PI) in each center or directly they will be recorded online. All data will be reported in a centralized online and Web-based fully encrypted database (REDCAP). The study coordinator will regularly contact the local PI to ensure data collection and reporting as well as completion of patient follow-up.

Moreover the study coordinator, available at ISMETT, will keep regularly updated the local investigators on the data recorded and will help in keeping in touch with local PI or if authorized will keep in touch with eventual hospitals or other sanitary residency where the patients are transferred. In the management of the study the data manager available at ISMETT will be dedicated to the goal of reducing to the minimal the loss of data also with the follow up.

The access to the REDCAP database will be regulated by personal credentials (username and password) so that each investigator will have granted specific levels of access (read-only, data entry, or full-administrative privileges).

Every participating center will have to ask the permission to their Ethic Committee or other relevant and competent authorities according to the local rules.

Data will include clinical characteristics: baseline demographics, basic biological values (e.g., blood gas, hemoglobin), primary diagnosis, comorbidities, underlying etiology of acute respiratory failure, severity of illness (e.g., SOFA, SAPS 2), type of ECMO, and the size of the cannulas.

ECMO management data will be collected daily for the first 28 days. Additionally, fluid balance, adverse events, Hb and all hematological data, anticoagulation management and monitoring will be collected every 24 hours.

Data will also be collected for the duration of mechanical ventilation, duration of ECMO, and ICU length of stay. Clinical outcome assessment will be made, with date of death, ICU discharge, hospital discharge, sixth month mortality.

Statistical Analysis

Descriptive statistics including frequency (percentage), median and interquartile range (IQR) will describe overall population and groups of survivors and non-survivors.

In order to describe current transfusion practice the amount of PRBC, Plasma and Platelets, will be described as units and ml and as a number of transfusions adjusted for ECMO length of stay and considering the concomitant bleeding episodes.

Fibrinogen and Antithrombin III will be described as mg or units respectively and as a number of administration.

Anticoagulation will be reported as type, mean dosage and the confidence interval (CI 95%).

Hb average level and the confidence interval (CI 95%) will be reported.

Baseline categorical and continuous variables will be compared for transfusion and ECMO weaning groups. In particular categorical variables will be compared with chi-square tests and continuous variables will be compared with Student's T-test, or Wilcoxon rank-sum tests, otherwise.

Multiple COX regression analysis will be used in order to explore the impact of confounding factors such as baseline patient severity, ECMO length of stay, bleeding episodes and possible others covariates and factors that will be observed and raised relevance during the first exploratory or univariate analysis. The impact of relevant confounding factors such as length of ECMO run, pre-ECMO severity scores, pre-ECMO administration of transfusions will be analyzed separately and together in multiple analyses.

In particular daily RBC transfusion will be studied according to the association to renal function, fluid balance, worst Hb level, episodes of bleeding, use of vasopressors, ECMO blood flow.

A p-value less of than 0.05 will be considered significant. Data handling and analyses will be done with SAS 9.4 software (SAS Institute Inc, Cary, NC, USA) and R 3.3 software (R Foundation for Statistical Computing).

Patient data Collection

For each included patient the investigators will collect the following data:

1. **Clinical data**

- Demographics: age, gender, weight, height, BMI
- Pre-existing pulmonary disease: asthma, cystic fibrosis, chronic obstructive pulmonary disease, pulmonary hypertension, pulmonary fibrosis, chronic restrictive lung disease
- Main co-morbidities: diabetes mellitus, chronic renal failure, ischemic heart disease, heart failure, chronic liver failure, neurological impairment
- Cause of ARF: bacterial pneumonia, viral pneumonia, trauma/burns, aspiration pneumonia, pancreatitis, pulmonary vasculitis, post lung transplantation
- Diagnosis: ARDS, Chronic end stage respiratory disease
- Postoperative period < 7 days. Pregnancy or peri-partum.
- Pre-ECMO hospital/ICU length of stay, mechanical ventilation days
- Patient characteristics at ICU admission: SAPS 2, SOFA score, PaO2/FiO2 ratio, hematocrit, platelets
- ECMO severity scores: PRESERVE score, RESP Score, ECMOnet if appropriate

2. **ECMO and daily management data**

- Type of circuit: heparin-bonded or not, type of oxygenator
- Type of anticoagulation: heparin, bivalirudin, argatroban, no anticoagulant

- Dose of anticoagulation
- Amount of PRBC, Plasma, platelets transfused (unit and ml) the day before
- Eventual Fibrinogen administration (mg)
- Antithrombin III level
- Antithrombin III administration (Type: human plasma-derived, recombinant) and dosage
- Episodes of bleeding classified according to site (airway – including tracheotomy - oro-nasal, gastric, intrathoracic, abdominal, intestinal, retroperitoneal, urinary tract, other) and severity according to 5 adjusted categories of the Bleeding Academic Research Consortium (BARC) score: Type 0, no bleeding; Type 1, Any overt bleeding that requires heparin infusion rate reduction or PRBC transfusion (provided Hb drop was related to bleeding); Type 2, any overt bleeding that requires heparin infusion rate reduction and packed red blood cells transfusion or non-surgical procedure to stop bleeding (provided Hb drop was related to bleeding); Type 3, Any life-threatening bleeding that required PRBC transfusion and surgical intervention for control of bleeding or ECMO discontinuation; Type 4: any fatal bleeding
- Daily blood and air flow, ECMO FiO2
- 24 hours diuresis and fluid balance
- Use of continuous renal replacement therapy
- Mean arterial pressure, use of vasopressors
- Septic shock
- Hemoglobin, hematocrit, platelet count, fibrinogen if available.
- Daily gas exchange: pH, PaO2, PaCO2, SaO2
- Daily parameter for anticoagulation value (APTT, ACT, r-TEG, anti-Xa according to local protocol).
- Major events (cardiac arrest)
- Cannulation site complications: (bleeding or thrombosis)
- Circuit change and main cause of change (thrombocytopenia, hypofibrinogenmia, evidence of clots, membrane dysfunction, hemolysis).

3. **PRBC Transfusion data** (only data available according to the center practice)

- Reason for transfusion: Low Hb, Hemodynamic impairment, Low ECMO blood flow
- Hb before transfusion
- First Hb checked after transfusion.
- Presence of bleeding, type of bleeding.
- SvO2, SaO2, lactates, ECMO blood flow, dose of vasopressor before and after (1 hour or best possible) transfusion

4. **Outcome data**

- ECMO weaning yes/not
- ICU discharge yes/not and date
- Days of mechanical ventilation after ECMO weaning. Date of death
- Type of discharge: ward, another ICU, rehabilitation center, home
- 6-months status: alive/deceased

Ethics: Informed Consent and Treatment of personal data

The study will be conducted in compliance with the current Helsinki Declaration and the standards of good clinical practice.

The study involves the enrollment of patients undergoing extracorporeal membrane oxygenation support and therefore unable to express a consent.

Every participating center will have to ask the permission to their Ethic Committee or other relevant and competent authorities according to the local rules.

At ISMETT, according the Italian rules (and we strongly suggest to follow the same at the other centers), the investigators will apply the following practice about informed consent as it was approved by the Ethic Committee. All the participating centers will be supported with approval by ISMETT Ethic Committee and providing materials and translated informed consent either for the participation in the study and for the data protection policy.

According to the Authorization N. 8 of the Italian Data protection Authority (hence named "Garante della Privacy"), data and biological samples relating to individuals that cannot provide their consent because they are incapable may be used for observational studies giving all the following caractheristics, as it is for our study: (i) no immediate beneficial for the patients in any case of results from the study (ii) the complete safety of procedures for the dignity and health of the enrolled patients, (iii) the lack of possibilities to perform a comparable study in an awake cohort, considering that ECMO is started in severely critically ill patients.
According to the art. 82 of the Codice Privacy the investigators will ask for a consent for the treatment of personal data of the patients that for the particular support of the ECMO are almost always sedated at least at the beginning of the ECMO running - so they have to be considered temporarily unable to express a consent - to those that have legal authority over them or to the immediate relatives or to a person cohabiting with them or – failing these – to the person in charge of the facility where the data subject is hosted. In case the patient is able to an informed consent it will be asked to himself.
In the case of following improvement of neurological condition of the patient a consent directly to the patient will be asked as soon as the patient will be considered again able to express a valid consent.
The investigators state that for the protection of privacy of the patients enrolled in the study, information and health data will be treated without identification elements and will be labeled with an alphanumeric code that will not allow to recognize the identity of the patients.
The list where there is the association between alphanumeric codes and identification data of the patients will be stored only by the principal investigator and will be used just in case of absolute necessity.
The results of the research will be diffused as aggregate data and in ways that will not allow in any case the identification of the enrolled patients.

Safety

The present study, giving its observational design, has a complete safety profile.
There will be no additional interventions or measurements other than those that are standard of care at the participating center. All clinical activity will follow the well established protocols for ECMO support at each participating center and consequently the patients are at no risk by in participating in the study.
Given the observational nature of the study, no insurance is required.

Predefined subgroup analyses

If the sample size will be adequate, as explorative analyses, we will perform some subgroup analyses according to the following predefined plan.

Exploratory analyses will stratify data for center workload (<10, 10-20, >20 ECMO run per year), according to geographical areas (we imagine a stratification among continents but we will verify if, giving the amount of data, will be reasonable a country stratification), and for pre-ECMO severity scores (Preserve score and Respscore) divided in quartiles.

Moreover, by the repeated measurements of hemoglobin and eventual transfusion event, for each center we will profile the actual and effective hemoglobin accepted as a trigger. The outcome weaning from ECMO and effective ICU discharge will be stratified also according to different hemoglobin values (<7, 7-10, >10, >12).

Another subgroups analysis will involve age, considered a major impacting factor in survival during ECMO. Patients will be divided in quartiles and patients > 60 years old will moreover evaluated.

Jehovah's witnesses and all patients refusing transfusions for personal reasons, as well as patients affected with hematological malignances will be analyzed separately.

Effective resources to implement the project

The study will be coordinated by IRCCS-ISMETT (Istituto Mediterraneo per I Trapianti e Terapie ad alta specializzazione).

Throught the REDCAP database, data will be collected and then analyzed at ISMETT.

The study has received the endorsement of the European Society of Intensive Care Medicine (ESICM) and the International ECMO network.

Professional statisticians and data manager at ISMETT will work on the project assuring proper data handling and performing the interim and final analyses.

No financial support is currently available.

Expected results, potential benefit of the study and publication program

A collaborative combination of ECMO centers will evaluate prospective data of transfusion practices during ECMO. The investigators would be able to describe the currently strategy for administration of blood products, anticoagulation and the effective incidence of bleeding episodes worldwide. Giving the lack of knowledge on the field, it will be valuable to attempt to find some evidence from actual clinical practice.

The promoter of the study, in accordance with the Note of the Italian Ministry of health n 6, 02 September 2002, will shortly publish the results of the Study, as soon as they are sent by every participating center, and anyway within 12 months after the completion of the study. Data will be published in a relevant journal in the field of intensive care medicine.

In each center two principal investigators will be involved, acknowledged as collaborators and listed in pubmed. The minimal number of patient recruited during one year will be 10 for each investigator. Some of the national coordinators, according to the entity of data and type of journal will be listed as authors.

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