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The effects of blood cell salvage on transfusion requirements after decannulation from veno-venous extracorporeal membrane oxygenation: an emulated trial analysis

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Abstract

Background Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is a supportive therapy for acute respiratory failure with increased risk of packed red blood cells (PRBC) transfusion. Blood cell salvage (BCS) aims to reduce blood transfusion, but its efficacy is unclear. This study aimed to estimate the effect of BCS at the time of removal of the ECMO circuit (ECMO decannulation) on PRBC transfused.

Methods To compare BCS to non-blood cell salvage (n-BCS), we conducted an emulated trial of patients at two ECMO centres in the United Kingdom. We used inverse propensity of treatment weighting to control for confounding and estimated the average treatment effect of BCS on PRBC transfused within two days of decannulation, and on changes in haemoglobin (Hb).

Results We included 841 patients who underwent VV-ECMO decannulation. The estimated marginal mean number of PRBC transfused when using BCS was 0·2 (95%CI: 0·16, 0·25) units compared to 0·51 (95%CI: 0·44, 0·59) units with n-BCS; an average treatment effect of −0·31 (95%CI: −0·40, −0·22) units. BCS reduced the risk of receiving any PRBC transfusion by 17·1% (95%CI: 11·1%, 22·9%) equating to a number needed to treat for any PRBC transfusion of 6 (95%CI: 5, 9). The difference in expected Hb levels after decannulation between BCS and n-BCS was 5·0 (95%CI: 4·2, 5·8) g/L.

Conclusions The use of BCS during VV-ECMO decannulation may be an effective strategy to augment haemoglobin levels and reduce PRBC transfusions.

Keywords VV ECMO, ARDS, Blood cell salvage, PRBC, Transfusion

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Introduction

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is an established supportive therapy for severe and potentially reversible acute respiratory distress syndrome (ARDS) [1, 2]. Despite improving patient outcomes, including reducing mortality, VV-ECMO is associated with increased need for packed red blood cell (PRBC) transfusion. This includes following the removal of VV-ECMO cannulae and circuit (VV-ECMO decannulation), where large bore cannulae are removed from major veins and discarded along with the membrane lung and the circuit tubing containing the patient's blood [3, 4]. The administration of PRBC transfusion has a range of potential adverse effects and represents a scarce and expensive resource. Therefore, employing strategies that can reduce transfusion rates is a clinical priority.

One strategy to reduce PRBC transfusion for VV-ECMO patients involves salvaging blood loss at the time of decannulation. There is approximately 500–700 ml of blood within the VV-ECMO circuit which is commonly discarded. Some but not all VV-ECMO centres utilise blood cell salvage (BCS) systems during decannulation to conserve blood and minimise the risk of transfusion-related complications. The BCS systems collect blood from the VV-ECMO circuit and aspirates it into a reservoir. The red cells are isolated from other constituents of the salvaged blood by high-speed centrifugation. The separated erythrocytes are subsequently washed in normal saline fluid, resulting in a concentrated suspension of the patient's own red cells (approximately 60% haematocrit) ready for reinfusion [5].

It has been hypothesised that BCS could increase the haemoglobin (Hb) level at the time of decannulation, thereby reducing the need for PRBC transfusion. However, the evidence supporting BCS following ECMO decannulation is limited. Furthermore, conducting a prospective clinical trial is expensive and would take several years until data were available given the relatively low rate of patient enrolment. Therefore, we used routinely collected clinical data combined with causal inference methodologies [6], to emulate a target trial [7, 8]. We compared BCS during VV-ECMO decannulation versus decannulation without blood cell salvage (n-BCS) in adults with severe respiratory failure. Our primary objective was to estimate the effect of BCS on subsequent PRBC transfusions. Additionally, we examined changes in Hb levels, other routinely performed laboratory measurements, and other transfusion requirements.

Methods

Study design

We included routinely collected data on patients from two nationally commissioned UK severe respiratory failure and VV-ECMO centres within Guy's & St Thomas' NHS Foundation Trust, London (UK). from January 2015 to August 2022 (7.5 years). The two centres adhere to the same nationally specified [9] acceptance and admission criteria for patients requiring VV-ECMO, have common local practice and treatment guidelines, and share a proportion of clinicians who work cross-site. This makes the management of patients on VV-ECMO comparable. The notable difference in practice between these two centres was the routine use of BCS with VV-ECMO decannulation at one centre, with the other routinely discarding blood within the VV-ECMO circuit, i.e. no BCS. This difference was primarily due to separate perfusionist teams and practices but did not affect other aspects of care such as transfusion decisions and thresholds. We extracted data on the included patients from the electronic health records (ICIP, Philips Netherlands) of the participating centres. This included demographics and admission characteristics, laboratory results before and after VV-ECMO decannulation, use of BCS at decannulation, and blood products subsequently transfused.

We characterised a hypothetical target trial using the trial emulation framework described by Hernán and Robins.[8] We used the process of specifying and emulating an ideal experimental trial to clarify the decisions and assumptions required for the analysis of the available observational data. A comparison of target and emulated trials is presented fully in Table S1 of the supplemental material, with the emulated trial protocol described below by domain of the trial emulation framework.

Eligibility criteria

Inclusion criteria

We included adults undergoing VV-ECMO decannulation who had received VV-ECMO for > 24 h at time of decannulation. We included data from the first episode of VV-ECMO and decannulation only.

Exclusion criteria

We excluded patients with ongoing significant haemorrhage preceding decannulation (defined as > 1 PRBC transfused in the preceding 24 h), sickle cell trait, pregnant women, and those patients non-accepting of blood transfusions.

Treatment strategies

The BCS was performed using a cell salvage system (Sorin Xtra® autotransfusion device, LivaNova, London, UK) separating whole blood remaining in the VV-ECMO circuit after decannulation, into its separate constituents. Red blood cells were washed and returned to the patient as a high haematocrit suspension in saline [10]. Where BCS was not used, the residual blood in the VV-ECMO circuit was discarded.

Assignment procedures

Treatment allocation in the emulated trial was determined by the routine use of BCS at one centre and n-BCS at the other, contrasting with the randomisation of the target trial.

We could not control directly for centre but instead controlled for patient characteristics which differed in distribution between the two centres (and hence treatment assignment) and were suspected to affect outcomes (see Estimands and statistical analysis section below).

Study outcomes

The primary outcome was the total number of PRBC units transfused within the two calendar days following VV-ECMO decannulation. A priori, we considered this a pragmatic time interval during which any blood loss at the time of decannulation might trigger PRBC transfusion. Secondary outcomes included 1) changes in pre-specified haematological (i.e. Hb, platelets, and fibrinogen), inflammatory (i.e., C-reactive protein (CRP), white cell count (WCC)), and coagulation (activated partial thromboplastin time (APTT), international normalised ratio (INR)) laboratory measurements before and after decannulation; and 2) transfusion of other blood products in the same time interval.

Estimands and statistical analysis

All analyses were conducted at the individual patient level. Descriptive statistics are presented for continuous variables as means and standard deviations (SDs), categorical variables as frequencies and proportions, and count variables as observed counts and estimated marginal means. We chose to estimate the treatment effect of BCS on each outcome (primary and secondary) across the entire study population, i.e. the estimand of interest was the average treatment effect (ATE), measured using a mean difference for continuous outcomes, relative risk and risk differences of blood product transfusions, and mean difference in transfusion counts.

Estimation of the ATE required adjustment [11] for potential selection bias and confounding of treatment allocation and outcome, which we addressed using inverse propensity of treatment weighting (IPTW) for all fitted regression models. We developed a directed acyclic graph (DAG) [12, 13] (See Figure S1 in Supplemental Material) to represent the causal relationships between BCS and PRBC transfusion following decannulation. We a priori considered that Hb and patient age directly influence PRBC transfusion decisions. The DAG also included the hypothesised mechanism whereby BCS attenuates the reduction in Hb, with post-decannulation Hb dependent on pre-decannulation levels. These in turn depend on prior transfusion history and thus age. The admitting severe respiratory failure centre was hypothesised to influence both BCS use and potentially Hb management prior to decannulation. Inspection of the DAG indicated that an adjustment set including age and pre-decannulation Hb was required to estimate the ATE of BCS on the transfusion of PRBCs and Hb. An alternative adjustment set of covariates was selected with the method proposed by Belloni [14] et al., resulting in effect size estimates of similar magnitude and direction to IPTW estimates (See Supplementary Material for further details).

To estimate the ATE of BCS we fitted a weighted Poisson regression model on the count of PRBC units transfused and fitted a weighted logistic regression model for the binary occurrence of any PRBC transfusions. We used weighted linear regression adjusting for baseline, to estimate change scores in Hb levels before and after decannulation, and in the haematological, inflammatory and coagulation variables pre-specified as secondary outcomes. There were small amounts of missing data in the secondary outcome laboratory measurements only and we performed a complete case analysis for all outcomes (See Supplementary Material for further details with counts of missing data presented in Table S2).

To control for potential confounding, we applied IPTW to all fitted regression models using the *WeightIt* [15] package (v1.1) for R, with variance and confidence intervals (CIs) estimated via bootstrapping with 5000 repetitions. All statistical analyses were performed in R v4·3 [16].

Ethical considerations.

In compliance with UK Health Research Authority (HRA) regulations, this study was granted institutional approval (No. 13960) with the requirement for individual informed consent waived owing to the retrospective data collection of standard clinical care.

Results

Participants

A total of 917 patients were decannulated from VV-ECMO during the study period, of which 841 (91·7%) met the eligibility criteria for the emulated trial. Reasons for exclusion are shown in Fig. 1. BCS was used at decannulation for 367 (43.6%); 474 (56.4%) patients did

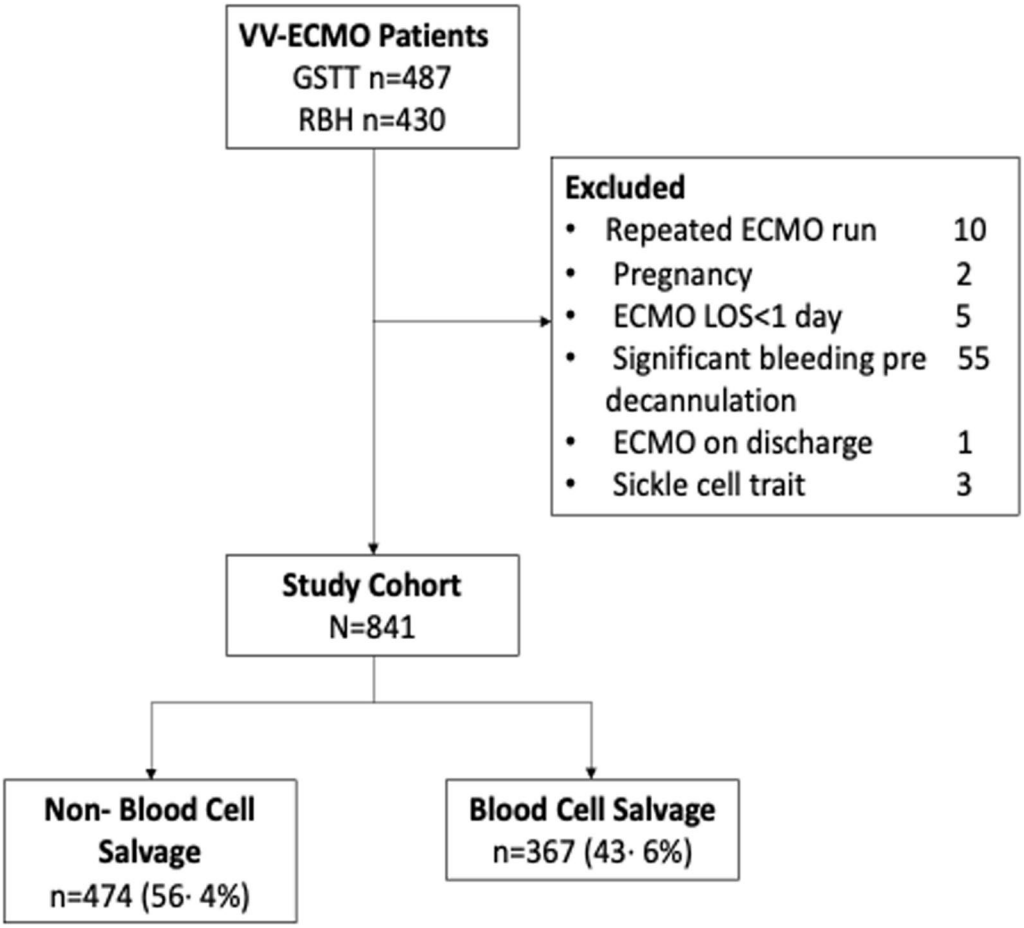

Fig. 1 Study recruitment, exclusion and treatment allocation flow diagram. Legend: Flow diagram illustrating the recruitment process, exclusion criteria, and treatment allocation. GSTT—Guy's & St Thomas' NHS Foundation Trust, RBH- Royal Brompton Hospital

not receive BCS. Admission characteristics and baseline variables before VV-ECMO decannulation are presented in Table 1. Patients had comparable mean (SD) length of stay in the ECMO unit of 27 (29) days in the n-BCS and 24 (18) days in the BCS ($p=0.1$).

Primary outcome—PRBC transfusion

We estimated that, if the entire study population had received BCS, the mean number of PRBC units transfused per patient in the two calendar days following decannulation would have been 0·20 (95%CI: 0·16, 0·25) units compared to 0·51 (95%CI: 0·44, 0·59) units if no patients had received BCS, an estimated reduction of 0·31 (95%CI: 0·22, 0·40) units.

The estimated marginal risk of receiving one or more PRBC transfusions in the two calendar days following decannulation was 17·5% (95%CI: 13·9%, 21·5%) if BCS were used across the entire study population, contrasting with 34.6% (95%CI: 30.3%, 39.2%) if n-BCS had been used for everyone, an absolute risk reduction of 17·1% (95%CI: 11·1%, 22·9%) (relative risk ratio of 0·51, 95%CI: 0·39, 0·66). This equated to a number needed to treat (NNT) for any blood transfusion of 6 (95%CI: 5, 9). Estimated population averaged counts are presented in Table 2, and observed counts of PRBC transfusions are presented in the supplemental information.

Secondary outcomes

Change in Hb

Decannulation with BCS was estimated to result in a marginal mean 1·2 (95%CI: 0·6, 1·8) g/L Hb increase compared to a mean Hb reduction of 3·8 (95%CI: 3·2, 4·3) g/L with n-BCS. The difference in expected Hb levels after decannulation between BCS and n-BCS was 5·0 (95%CI: 4·2, 5·8) g/L.

Transfusion of other blood products

Less than 5% of patients received transfusions of pooled platelets with no treatment effect of BCS observed. The estimated marginal mean risk of

Table 1 Baseline demographic and clinical characteristics

	Overall[1] (N = 841)	Non-Blood Cell Salvage (n = 474)	Blood Cell Salvage (n = 367)	*p*-value
Age, years	43 (13)	42 (13)	43 (13)	0.06
Female, n (%)	349 (41)	200 (42)	149 (41)	0.6
Height, cm	171 (10)	171 (9)	171 (10)	0.7
Weight, kg	90 (26)	89 (25)	91 (27)	0.3
Body Mass Index (kg/m^2)	31 (8)	30 (8)	31 (9)	0.3
ECMO duration, days	16 (14)	15 (14)	17 (15)	< 0.001
Diagnostic Category, n (%)				
Pulmonary	623 (74)	325 (69)	298 (82)	
Extrapulmonary	57 (6.8)	35 (7.4)	22(6.0)	
Asthma	57 (6.8)	23 (4.9)	34 (9.3)	
Other	48 (5.7)	47 (9.9)	1 (0.3)	
Interstitial Lung Disease	37 (4.4)	28 (5.9)	9 (2.5)	
Trauma	16 (1.9)	16 (3.4)	0 (0)	
Haemoglobin, g/L	85 (10)	86 (11)	83 (9)	0.007
Platelets, × 10^9/L	164 (86)	165 (87)	163 (84)	0.7
Fibrinogen, g/L	3.69 (2.04)	4.01 (2.13)	3.28 (1.83)	< 0.001
White Cell Count, × 10^9/L	15 (7)	16 (7)	14 (8)	< 0.001
C Reactive Protein, mg/L	96 (84)	95 (82)	98 (87)	0.7
Bilirubin, µmol/L	19 (49)	20 (59)	18 (30)	< 0.001
Activated partial thromboplastin time ratio (APTTr)	1.49 (0.55)	1.53 (0.50)	1.45 (0.60)	< 0.001
Prothrombin time (INR)	1.08 (0.14)	1.09 (0.13)	1.06 (0.14)	0.001

Admission characteristics and baseline variables before VV-ECMO decannulation

All values are mean (SD) unless otherwise indicated

receiving a cryoprecipitate transfusion was 7·5% (95%CI: 5·1%, 10·6%) with BCS, and 4·6% (95%CI: 3·0%, 6·9%) if n-BCS was used, an absolute risk increase of 2·9% (95%CI: −0·4%, 6·4%), i.e., no effect of BCS on the risk of receiving a cryoprecipitate transfusion was observed.

Laboratory measurements

The mean fibrinogen levels were estimated to decrease by 0·2g/L following decannulation, irrespective of whether they received BCS (95%CI: 0·1, 0·2) or n-BCS (95%:0·2, 0·3). CRP level decreased by an estimated mean of 8·1 (95%CI: 4·8, 11·3) mg/L with BCS use, and decreased by 4·1 (95%CI: 0·4, 7·8) mg/L with n-BCS, although there was no evidence that these reductions were different. Bilirubin decreased with the use of BCS (−2·0 (95%CI: −2·6, −1·5) µmol/L) and n-BCS (−0·6 (95%CI: −1·3, 0·1) µmol/L), with the difference (1·3 (0·4, 2·2) µmol/L) greater with BCS. No changes following decannulation or effect of BCS were observed on white cell counts (WCC), platelets, APTTR, or INR measurements (See Supplementary Materials for further details).

Discussion

This emulated trial investigating the impact of BCS on PRBC transfusion requirements during VV-ECMO decannulation, provides evidence that BCS results in a small but important reduction in PRBC transfusion, and an increase in Hb when compared to n-BCS. This reduction in PRBC transfusion means that six patients need to receive BCS to save an additional patient from receiving PRBC transfusion (NNT of 6). We found no evidence for an effect of BCS on routinely collected inflammatory and coagulation markers, or transfusion of other blood cell products. These results are clinically relevant given the risks associated with PRBC transfusions, including alloimmunisation, transfusion-related immunomodulation, transfusion-related acute lung injury, and microcirculatory dysfunction [17, 18] and the general availability of BCS in all ECMO capable centres.

Blood cell salvage is commonly used during and following cardiopulmonary bypass to reduce the need for transfusion [19]. Yet the evidence of the efficacy of this technique in VV-ECMO patients during decannulation is limited. A small observational study in seven patients demonstrated reduced PRBC transfusion requirements with the use of an autotransfusion device, without

Table 2 Adjusted and unadjusted estimates of primary and secondary outcomes with use of BCS and n-BCS at decannulation

	Non-Blood Cell Salvage* (n = 474)	Blood Cell Salvage* (n = 367)	Mean Difference*
PRBC transfused, units			
Adjusted	0.51 (0.44, 0.59)	0.20 (0.16, 0.25)	0.31 (0.22, 0.40)
Unadjusted	0.48 (0.41, 0.56)	0.22 (0.17, 0.27)	0.26 (0.17, 0.35)
PRBC transfusion risk, %			
Adjusted	34.6 (30.3, 39.4)	17.5 (13.9, 21.5)	17.1 (11.1, 22.9)
Unadjusted	32.3 (28.0, 36.5)	19.1 (15.3, 23.4)	13.2 (7.3, 18.9)
Platelets transfused, units			
Adjusted	0.05 (0.03, 0.08)	0.04 (0.02, 0.06)	−0.02 (−0.04, 0.01)
Unadjusted	0.05 (0.03, 0.07)	0.04 (0.02, 0.06)	−0.02 (−0.04, 0.01)
Platelet transfusion risk, %			
Adjusted	5.1 (3.4, 7.5)	3.5 (1.9, 5.8)	−1.6 (−4.3, 1.2)
Unadjusted	5.1 (3.4, 7.4)	3.5 (2.0, 5.9)	−1.5 (−4.2, 1.3) Risk ratio 0.7 (0.357, 1.408)
Cryoprecipitate transfused, units			
Adjusted	0.09 (0.06, 0.14)	0.11 (0.08, 0.17)	0.02 (−0.04, 0.09)
Unadjusted	0.09 (0.05, 0.14)	0.11 (0.08, 0.17)	0.03 (−0.03, 0.09)
Cryoprecipitate transfusion risk, %			
Adjusted	4.6 (3.0, 6.9)	7.5 (5.1, 10.6)	2.9 (−0.4, 6.4)
Unadjusted	4.4 (2.8, 6.6)	7.6 (5.3, 10.8)	3.2 (0.0, 6.8)
ΔHaemoglobin, g/L			
Adjusted	−3.8(−4.3, −3.2)	1.2 (0.6, 1.8)	5.0 (4.2, 5.8)
Unadjusted	−3.9 (−4.5, −3.4)	1.4 (0.8, 2.0)	5.3 (4.5, 6.1)
ΔPlatelets, $\times 10^9$/L			
Adjusted	4.2 (1.1, 7.3)	3.7 (0.1, 7.2)	−0.7 (−5.4, 3.9)
Unadjusted	4.2 (1.0, 7.4)	3.7 (0.0, 7.3)	−0.5 (−5.4, 4.3)
ΔFibrinogen, g/L			
Adjusted	−0.2 (−0.3, −0.2)	−0.2 (−0.3, −0.1)	−0.1 (−0.2, 0.0)
Unadjusted	−0.2 (−0.3, −0.2)	−0.2 (−0.3, −0.1)	0.0 (−0.1, 0.1)

PRBC, Packed Red Blood Cells; APTTr, Activated partial thromboplastin time ratio; INR, Prothrombin time

* Estimate (95%Confidence Interval); Δ—Estimated change pre to post decannulation

harmful effects [20]. A case report has described the use of BCS during decannulation from VV-ECMO in a Jehovah's Witness patient [21]. BCS has been also shown to reduce PRBC transfusion requirements during ECMO if used during circuit changes for membrane lung dysfunction, which can occur in ~ 27% of patients receiving VV ECMO [22].

Our study found no difference in platelets or coagulation factors comparing BCS to n-BCS. Concerns regarding BCS during VV-ECMO decannulation relate to the potential coagulopathy due to removal of platelets and coagulation factors when auto-transfusing large volumes. [23, 24] Yet our data suggest these concerns are not warranted. Studies in the cardiopulmonary bypass patient population report conflicting findings, with some indicating no difference in coagulopathy and others reporting increased need for blood products transfusion [19, 25, 26]. Furthermore, we found no evidence of an effect of BCS on markers of inflammation despite concerns that BCS can trigger an inflammatory response. Previous studies investigating the effects of BCS on inflammatory markers including cytokines during CPB report conflicting results [27–29]. Another strategy used to reduce the need for blood transfusion is returning the blood within the ECMO circuit using a crystalloid solution while the circuit is still connected [30]. However, this technique requires tolerance of rapid transfusion of a large volume of fluid and increases the risk of air embolism.

Our study has several strengths. A distinctive feature is the emulation of a target trial framework, allowing us to bridge the gap between observational data and the ideal experimental conditions of a randomised clinical trial. The protocol for our emulated trial provided a clear framework for investigating the research question, framing the analyses and providing transparent prespecified definitions of our study population, intervention and outcomes. Emulation of inclusion/exclusion criteria identified the study population removing sources of confounding and heterogeneity. There was a consistently applied treatment where we found no endogenous reasons that the included population could not receive BCS, albeit some participants did not receive BCS for exogenous reasons such as equipment failure. Trial emulation was particularly helpful in addressing the inherent confounding in this observational study, attempting to ensure conditional exchangeability and informing the statistical estimation of treatment effects. These results are important as no prospective clinical trial addressing this question is currently expected and any future study will take several years until data were available given the relatively low rate of patient enrolment.

Our study has limitations. Treatment allocation was dictated by the admitting centre rather than random allocation; therefore, the presence of unobserved confounding cannot be definitively excluded. This implies that the estimated treatment effects encompass the hypothesised mechanism of BCS on PRBC transfusion *and* any dependence of transfusion policy on centre. There is a possibility that the decreased PRBC transfusion rate with the use of BCS may be partially attributable to variations in transfusion thresholds or local preferences. However, both centres share common practices and treatment guidelines, with some clinicians working across both sites, reducing bias from physician preference. Additionally, the haemoglobin levels and the proportion of

patients above and below the transfusion threshold were similar between the sites (See Online Supplement Fig S6). Consistent with the primary results, the Hb level increased post-decannulation in the BCS group. Finally, the time of the day when the decannulation took place was comparable across sites, making the time window selected for the primary outcome consistent.

A key limitation of our study is the two-day post-decannulation period used to assess transfusion requirements. This timeframe was incorporated into the trial design and analysis plan to capture the immediate effects of BCS on transfusion needs. Additionally, most patients are transferred back to their referring ICU 48 h after decannulation, which complicates data collection and interpretation beyond this point due to variability in transfusion practices across centres.

A longer follow-up period (e.g., 3–5 days) might have provided additional insights into the longer-term effects of BCS and allowed for quantification of the average treatment effect of BCS on delayed PRBC transfusion and changes in haemoglobin (Hb), potentially due to delayed bleeding episodes or the impact of BCS on red blood cell lifespan [31].

Future research is also needed to evaluate the economic implications of implementing a BCS protocol in comparison n-BCS and to provide a more comprehensive understanding of the feasibility and sustainability of integrating BCS into widespread clinical practice.

Conclusion

In this emulated trial of patients undergoing decannulation from VV-ECMO we found that BCS decreased PRBC transfusion with no changes in inflammatory and coagulation markers, and no difference in the transfusion of other blood products, in the two calendar days following VV-ECMO decannulation. These findings suggest BCS should be considered when patients are decannulated from VV-ECMO. The reduction in PRBC transfusion using BCS found in our emulated trial is important considering local, national, and international demands in blood product supplies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05177-7.

Additional file1

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Author contributions
VC and BS are joint first authors; LR and LC are joint senior authors. Study concept and design: VC, BS, LC, LR. Acquisition, analysis or interpretation of data: BS, RHK, BG. First drafting of manuscript: VC, BS, LC, LR. Critical revision for important intellectual content and final approval of manuscript: NB, PC, BG, LG, LG, TWH, CL, FM, BP, AR, ET, DFM. Study supervision: LC, LR.

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Availability of data and materials
Data and study documents can be requested by contacting the corresponding author and will be made available in accordance with local data sharing policies.

Declarations

Competing interests
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