

Effect of Fresh vs Standard-issue Red Blood Cell Transfusions on Multiple Organ Dysfunction Syndrome in Critically Ill Pediatric Patients

A Randomized Clinical Trial

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IMPORTANCE The clinical consequences of red blood cell storage age for critically ill pediatric patients have not been examined in a large, randomized clinical trial.

OBJECTIVE To determine if the transfusion of fresh red blood cells (stored ≤ 7 days) reduced new or progressive multiple organ dysfunction syndrome compared with the use of standard-issue red blood cells in critically ill children.

DESIGN, SETTING, AND PARTICIPANTS The Age of Transfused Blood in Critically-Ill Children trial was an international, multicenter, blinded, randomized clinical trial, performed between February 2014 and November 2018 in 50 tertiary care centers. Pediatric patients between the ages of 3 days and 16 years were eligible if the first red blood cell transfusion was administered within 7 days of intensive care unit admission. A total of 15 568 patients were screened, and 13 308 were excluded.

INTERVENTIONS Patients were randomized to receive either fresh or standard-issue red blood cells. A total of 1538 patients were randomized with 768 patients in the fresh red blood cell group and 770 in the standard-issue group.

MAIN OUTCOMES AND MEASURES The primary outcome measure was new or progressive multiple organ dysfunction syndrome, measured for 28 days or to discharge or death.

RESULTS Among 1538 patients who were randomized, 1461 patients (95%) were included in the primary analysis (median age, 1.8 years; 47.3% girls), in which there were 728 patients randomized to the fresh red blood cell group and 733 to the standard-issue group. The median storage duration was 5 days (interquartile range [IQR], 4-6 days) in the fresh group vs 18 days (IQR, 12-25 days) in the standard-issue group ($P < .001$). There were no significant differences in new or progressive multiple organ dysfunction syndrome between fresh (147 of 728 [20.2%]) and standard-issue red blood cell groups (133 of 732 [18.2%]), with an unadjusted absolute risk difference of 2.0% (95% CI, -2.0% to 6.1%; $P = .33$). The prevalence of sepsis was 25.8% (160 of 619) in the fresh group and 25.3% (154 of 608) in the standard-issue group. The prevalence of acute respiratory distress syndrome was 6.6% (41 of 619) in the fresh group and 4.8% (29 of 608) in the standard-issue group. Intensive care unit mortality was 4.5% (33 of 728) in the fresh group vs 3.5% (26 of 732) in the standard-issue group ($P = .34$).

CONCLUSIONS AND RELEVANCE Among critically ill pediatric patients, the use of fresh red blood cells did not reduce the incidence of new or progressive multiple organ dysfunction syndrome (including mortality) compared with standard-issue red blood cells.

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Transfusion is frequent in critically ill children, as reported in a 2009-2010 single-center study in which 10% to 20% of critically ill children received a red blood cell transfusion.¹ Red blood cell transfusion is associated with higher mortality, as reported in a cohort of children admitted to intensive care between 2009 and 2012 and who received a red blood cell transfusion, the reported 30-day mortality rate was 8%.² Transfusions in critically ill patients are primarily used to improve oxygen delivery and to prevent shock, organ failure, and death. Red blood cell units can be stored for up to 42 days. In vitro and ex vivo studies suggest that increased storage duration may impair red blood cell oxygen delivery as well as adversely affect immune, endothelial, and hemostatic function.³ Through one or several of these mechanisms, transfusion of older red blood cells may increase the risk of organ failure or death in critically ill patients. Observational studies and exploratory analyses of randomized clinical trials also suggest that for patients who receive larger volumes of older red blood cells, there is an association with poor outcomes.⁴⁻⁷

Randomized clinical trials examining the effect of red blood cell storage age have been performed in critically ill premature neonates,⁸ severely anemic children with malaria and thalassemia,⁹ and hospitalized and critically ill adults.¹⁰⁻¹³ None of these trials have demonstrated that fresh red blood cells improve clinical outcomes. However, these trials may not be generalizable to critically ill pediatric patients, for the physiology and etiologies of critical illness differ from that of neonates and adults. Furthermore, despite these trials, there is still wide variation in policies and practices on the use of fresh red blood cells (≤ 7 days of storage), particularly among neonates and those undergoing cardiac surgery, based on the expectation that they will improve outcomes.¹⁴ We therefore performed a randomized clinical trial to determine the effect of red blood cell storage age on new or progressive organ failure in critically ill pediatric patients.

Methods

Study Design and Oversight

The Age of Blood in Children in Pediatric Intensive Care Unit (ABC-PICU) trial protocol was approved by institutional research boards at each clinical site. Written informed consent was obtained from a legal guardian for all study patients prior to study enrollment; trained research coordinators or medical practitioners at all study sites obtained consent. The trial was a multicenter, randomized, double-blind, superiority trial comparing red blood cells stored for no more than 7 days with standard-issue red blood cells (oldest in the inventory at time of the transfusion order). Blinding was accomplished by applying an opaque sticker over the expiration and collection dates in the blood bank prior to allocation to the patient care area or this information was deleted on the label of individual red blood cell units and associated documents to mask group allocation. Data management was shared between the Division of Biostatistics at Washington University in St Louis and the Methods Centre at the Ottawa

Key Points

Question What is the effect of fresh red blood cells on organ dysfunction in critically ill pediatric patients?

Findings In a randomized clinical trial involving 1538 critically ill pediatric patients, there were no significant differences in organ dysfunction between fresh (20.2%) and standard-issue red blood cell groups (18.2%).

Meaning This study did not demonstrate a benefit in the use of fresh red blood cell transfusions for critically ill children.

Hospital Research Institute. The clinical trial protocol has been published.¹⁵ The original trial protocol and its amendments are in [Supplement 1](#), and the statistical analysis plan is provided in [Supplement 2](#).

Study Population

Critically ill patients from pediatric intensive care units (PICUs) were enrolled at 50 centers (29 in the United States, 10 in Canada, 8 in France, 2 in Italy, and 1 in Israel; [Table 1](#)). Patients admitted to participating PICUs or in the process of being admitted from the operating room, aged 3 days to 16 years, were screened for eligibility. Patients were eligible if the first transfusion was administered within 7 days of PICU admission,¹⁶ and if they were expected by the attending physician to stay in the PICU for at least 24 hours. Exclusion criteria are listed in [Figure 1](#).

Randomization

Critically ill patients were randomly allocated by means of a centralized computer-generated assignment sequence using variable permuted block sizes of 2, 4, and 6 and were stratified according to patient age group (< 29 days, 29-365 days, > 365 days) and study site. The randomization process was initiated by study site blood bank personnel after the first transfusion was requested by treating clinicians or ordered to be on hold for a surgical procedure. Only the independent study statistician at the data coordinating center had knowledge of randomization codes.

Interventions

Fresh red blood cells (stored ≤ 7 days) were compared with standard-issue red blood cells (delivery of the oldest compatible units available). The intervention continued for 28 days after randomization or until hospital discharge or death, whichever occurred first. All red blood cells used in the trial were prestorage leukocyte-reduced. Although the transfusion guidelines were provided to all study sites (see [Supplement 3](#)), adherence to these guidelines was not monitored. All decisions about transfusions were at the discretion of the clinical team.

Outcomes

The primary outcome was the development of new or progressive multiple organ dysfunction (referred to as organ dysfunction herein). Organ dysfunction was measured as the proportion of patients who developed a new multiple organ dysfunction syndrome (new MODS) or among those whose multiple organ dysfunction worsened (progressive MODS) by

Table 1. Baseline Patient Characteristics

| Characteristic | Red Blood Cell Group, No. (%) | |
|--|-------------------------------|---------------------------------------|
| | Fresh (n = 728) | Standard-issue (n = 733) ^a |
| Age, median (IQR), y | 1.8 (0.5-6.9) | 1.9 (0.5-7.0) |
| Weight at admission to ICU, median (IQR), kg | 11.0 (6.8-21.9) | 11.6 (6.5-24.0) |
| Sex | | |
| Girl | 352 (48.4) | 339 (46.3) |
| Boy | 376 (51.6) | 394 (53.7) |
| Time between hospital admission and ICU admission, median (IQR), d | 0.8 (0.6-1.6) | 0.8 (0.6-1.5) |
| Recruitment per country, sites | | |
| United States, 29 | 415 (57.0) | 423 (57.7) |
| Canada, 10 | 196 (26.9) | 194 (26.5) |
| France, 8 | 92 (12.6) | 89 (12.1) |
| Italy, 2 | 19 (2.6) | 18 (2.5) |
| Israel, 1 | 6 (0.8) | 9 (1.2) |
| Type of ICU admission | | |
| General medical | 429 (58.9) | 440 (60.0) |
| Medical, cardiac | 20 (2.7) | 24 (3.3) |
| Surgical, noncardiac | 125 (17.2) | 112 (15.3) |
| Surgical, cardiac | 104 (14.3) | 107 (14.6) |
| Trauma | 50 (6.9) | 50 (6.8) |
| Admission to randomization, median (IQR), h | 23.0 (4.5-56.0) | 33.0 (7.0-65.5) |
| Location of first transfusion | | |
| No. of patients | 726 | 733 |
| Operating room | 140 (19.3) | 132 (18.0) |
| ICU | 582 (80.2) | 600 (81.9) |
| Other | 4 (0.5) | 1 (0.1) |
| Hemoglobin level before first transfusion, median (IQR), g/dL | 7.20 (6.70-8.50) | 7.30 (6.60-8.30) |
| PRISM III score at randomization, median (IQR) ^b | 5.0 (2.0-9.0) | 5.0 (1.0-9.0) |
| No. of patients | 725 | 728 |
| PELOD-2 score at randomization, median (IQR) ^c | 5 (3-7) | 5 (3-7) |
| No. | 726 | 731 |
| MODS at randomization ^d | 257 (35.4) | 265 (36.2) |

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MODS, multiple organ dysfunction syndrome; PELOD-2, Pediatric Logistic Organ Dysfunction 2 score; PRISM III, Pediatric Risk of Mortality III score.

^a The total number of participants was 1461. One patient who was randomized to the standard-issue group died in the operating room during cardiac surgery and had no data available for the primary outcome and some secondary outcomes. This patient was not included in the primary outcome but was included in some baseline analyses and in mortality analyses.

^b Score ranges from 0 to 71; with higher scores indicating higher risk of death.²²

^c The score ranges from 0 to 33; a higher score indicates greater severity of multiple organ dysfunction syndrome.¹⁸ The score can be estimated over the entire stay in the ICU or over 1 day (daily PELOD-2).

^d Defined by Proulx et al,¹⁶ which is explained further in the Methods section.

experiencing another organ dysfunction as defined by Proulx et al.¹⁶ We categorized patients with no organ dysfunction at randomization as having new MODS if they developed 2 or more concurrent organ dysfunctions; patients with 1 organ dysfunction that progressed to 1 or more, new MODS; patients with 2 or more organ dysfunctions that progressed to more, progressive MODS; and patients who died, progressive MODS.

We chose new or progressive MODS as the primary outcome because data indicating that it correlates with mortality and quality of life in critically ill pediatric patients was clinically relevant.¹⁷ Organ dysfunction was monitored for up to 28 days or until death or discharge, whichever came first. Secondary outcomes included PICU and hospital mortality, 28- and 90-day all-cause mortality, highest number of organ dysfunctions, Pediatric Logistic Organ Dysfunction 2 (PELOD-2) score,¹⁸ nosocomial infections (pneumonia, blood stream infection, urinary tract infections, sepsis), acute lung injury, acute respiratory distress syndrome (ARDS), mechanical ventilation-free and PICU-free days, use of hemodynamic support (vasoactive drugs or extracorporeal support), renal support (renal re-

placement therapy), symptomatic deep vein thrombosis, reported transfusion reactions, and other adverse events.

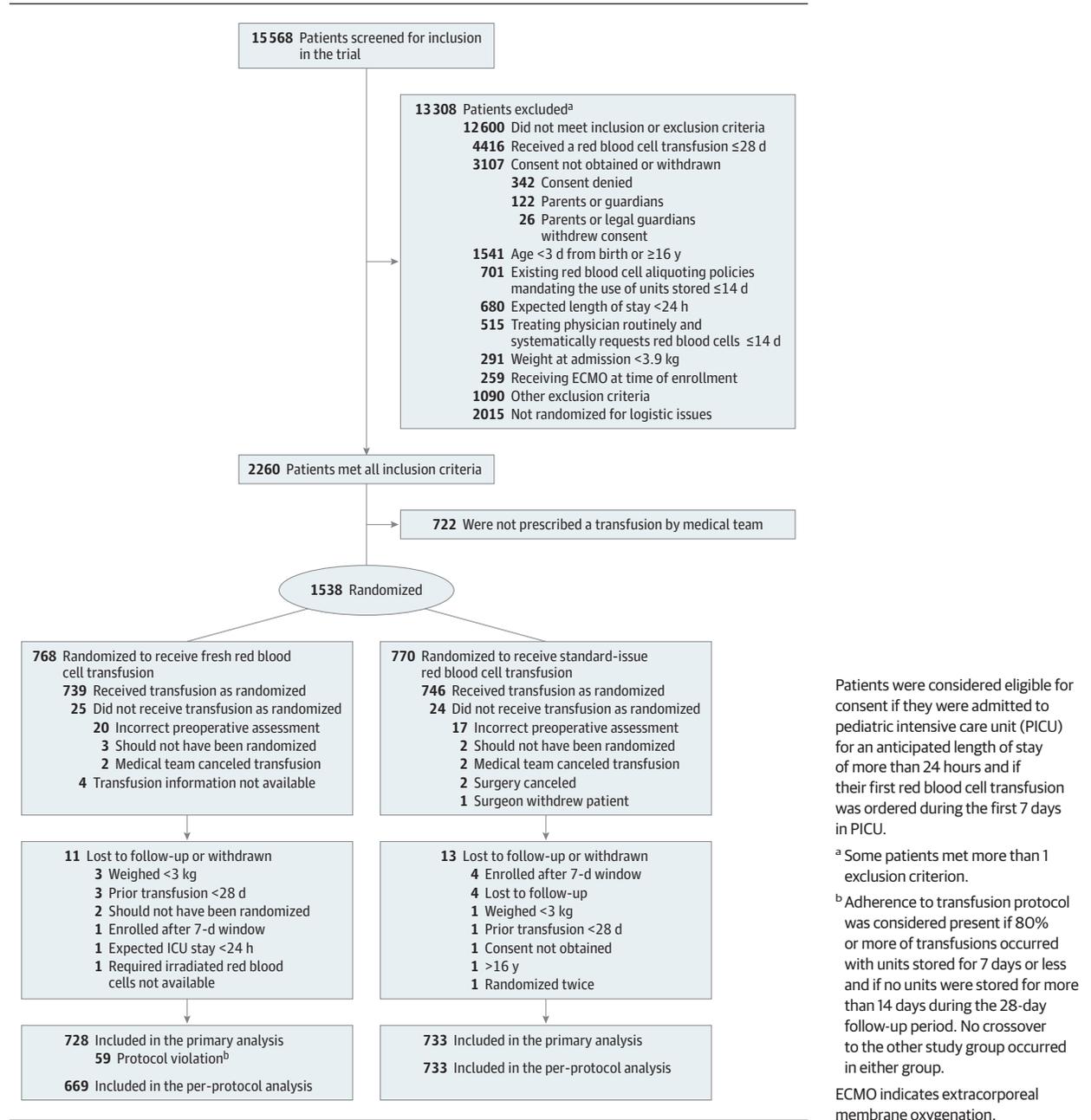
Power Analysis and Sample Size

The primary objective of the trial was to determine whether fresh red blood cells were superior to standard-issue red blood cells. Based on observational studies,^{19,20} the incidence of organ dysfunction in the trial population was expected to be 18% in the standard-issue group and 12% in the fresh red blood cell group, representing an expected relative risk reduction of 33%. The sample size of 1538 (769 per group) was based on the formula for 2 independent proportions with an outcome incidence of 18% in the standard-issue and 12% in the fresh red blood cell groups, a 2-tailed α of .05, a power of 0.90, and an anticipated loss to follow-up rate of 1.7% based on results of the Transfusion Requirements in Pediatric ICU study.²¹

Statistical Analysis

Baseline characteristics in both study groups were assessed using frequency distributions and univariate descriptive

Figure 1. Screening, Randomization, and Follow-up in a Study of the Effect of Fresh vs Standard-issue Red Blood Cell Transfusions in Critically Ill Pediatric Patients



statistics including measures of central tendency and dispersion. Dichotomous data are presented as numbers and percentages; continuous data are expressed as mean (SDs) or medians (interquartile ranges [IQRs]), as appropriate. Any clinically relevant and statistically significant imbalances were considered for adjusted analyses of primary and secondary outcomes. Postrandomization characteristics of interventions and cointerventions are presented using frequency distributions with measures of central tendency and dispersion and analyzed using relative risks and 95% CIs for dichotomous data and either independent *t* tests or Wilcoxon rank-sum tests for continuous data as appropriate.

The prespecified primary analysis of the primary outcome included patients according to their randomization group and excluded patients who were lost to follow-up, patients whose parents or guardians withdrew consent, and patients who did not receive a transfusion if after randomization a transfusion was not performed. The primary analysis was performed using an unadjusted χ^2 comparing the proportion of patients who acquired organ dysfunction up to 28 days after randomization. The principal measure of effect was an unadjusted absolute risk reduction with 95% CIs. We also planned to report an unadjusted relative risk reduction as is reflected in Section 4.15.4 of the protocol (Supplement 1); however,

Table 2. Anemia and Red Blood Cell Transfusions: Intervention and Cointerventions^a

| | Red Blood Cell Group, No. (%) | | P Value |
|---|-------------------------------|---------------------------------------|---------|
| | Fresh (n = 728) | Standard-issue (n = 733) ^b | |
| Transfusions after randomization | | | |
| No. of transfusions | 1630 | 1533 | |
| Duration of storage, median (IQR), d | 5 (4-6) | 18 (12-25) | <.001 |
| Volume of units transfused per patient, median (IQR), mL/kg | 17.5 (12.9-32.8) | 16.6 (12.3-30.6) | .19 |
| No. of patients | 723 | 731 | |
| Time from randomization to first transfusion, median (IQR), h | 2.0 (1.0-3.0) | 2.0 (1.0-3.0) | |
| No. of patients | 726 | 733 | |
| Donor exposure to red blood cell units in patients transfused, No. of exposures per patient, median (IQR) | 1 (1-2) | 1 (1-2) | .24 |
| No. of patients | 727 | 733 | |
| Adherence, No./Total (%) | | | |
| Adherence to study protocol ^c | 679/727 (93.4) | 733/733 (100) | <.001 |
| Adherence to transfusion protocol instructions ^d | 1520/1630 (93.3) | 1533/1533 (100) | <.001 |
| Cointerventions after randomization | | | |
| Received other blood products | 323 (44.4) | 303 (41.3) | .24 |
| Frozen or fresh frozen plasma | 160 (22.0) | 149 (20.3) | .44 |
| Apheresis platelets | 109 (15.0) | 113 (15.4) | .81 |
| Random donor platelets | 63 (8.6) | 53 (7.2) | .31 |
| Cryoprecipitate | 87 (11.9) | 75 (10.2) | .30 |
| Albumin 5% | 116 (15.9) | 95 (13.0) | .11 |
| Albumin 25% | 204 (28.0) | 187 (25.5) | .28 |
| Systemic corticosteroids | 268 (36.8) | 251 (34.2) | .30 |

Abbreviation: IQR, interquartile range.

^a In all comparisons, the fresh group was used as the reference.

Postrandomization characteristics of interventions and cointerventions are presented using frequency distributions with measures of central tendency and dispersion, and analyzed using relative risks and 95% CIs for dichotomous data and either independent *t* tests or Wilcoxon rank-sum tests for continuous data depending on their distribution.

^b Total number of participants was 1461. One patient who was randomized to the standard-issue group died in the operating room during cardiac surgery and had no data available for the primary outcome, some secondary

outcomes, and some cointerventions. This patient was not included in the primary outcome but was included in mortality analyses.

^c For the purpose of this study, patients in the fresh group were considered adherent to protocol if 80% of the units were stored for for 7 days or less and if no units were stored for more than 14 days during the 28-day follow-up period.

^d Adherence to transfusion protocol instructions was defined as (number of transfusions with units stored for ≤ 7 days)/(total number of transfusions) for fresh group and as (number of standard-issue transfusions)/(total number of transfusions) for the standard-issue group.

section 4.15.5 of the protocol omitted relative risk reduction as a measure of effect, which was an oversight. The decision to calculate and present both measures of effect (absolute risk and relative risk reduction) was made in advance of all analyses. All secondary outcomes were analyzed in the same manner as the primary outcome.

Secondary analyses of the primary outcome included a risk difference adjusted for center, age, sex, comorbid illnesses, and severity of illness scores. Post hoc, the adjusted measure of effect was the adjusted relative risk as the model, for the adjusted risk difference did not converge largely due to a number of centers with a small number of randomized patients. Thus, the primary outcome was analyzed using Poisson regression with robust standard errors, adjusting for age, sex, and PELOD-2 score at randomization and adjusting for all comorbidities at ICU admission. We performed mixed-effect modeling with each center treated as a random effect. Clustering by center was accounted for using an exchangeable correlation. The treatment effect was expressed as an adjusted relative risk with 95% CIs. Unadjusted and adjusted Cox proportional-hazards models were developed with the same variables used in the Poisson regression model. The treatment effects

were expressed as a hazard ratio with 95% CIs. To assess proportionality, we added the time-dependent function of treatment by including the interaction of treatment and log function of time to the model. The interaction was not significant ($P = .32$); thus, the proportionality assumption was not violated. In addition to the primary analysis, the above analyses were repeated using per-protocol populations consisting of patients who exclusively received red blood cells within 7 days in the fresh group and consisting of all the patients in the standard-issue group. We also compared patients who exclusively received fresh red blood cells (≤ 7 days) in the fresh group with patients who only received red blood cells stored for more than 7 days.

Subgroup analyses of the primary outcome were also performed for the following: illness category, severity of illness evaluated by the Pediatric Risk of Mortality III (PRISM III) score, stable vs unstable patients²¹ at the time of their first transfusion, ABO type, and volume of red blood cells transfused per kilogram. Interactions were assessed by adding the treatment, subgroup of interest, and interaction term in a multivariable logistic regression model. All analyses are presented without any adjustment for multiple comparisons. Missing data

Table 3. Clinical Trial Primary and Subset Outcomes^a

| Outcomes | Red Blood Cell Group, No./No. Evaluated (%) ^b | | Relative Risk (95% CI) | Absolute Risk Difference (95% CI) | P Value for Interaction Between Subgroups and Treatment |
|--|--|----------------|------------------------|-----------------------------------|---|
| | Fresh | Standard-issue | | | |
| Primary | | | | | |
| Organ dysfunction development ^{c,d} | 147/728 (20.2) | 133/732 (18.2) | 1.1 (0.9 to 1.4) | 2.0 (-2.0 to 6.1) | |
| Subset Outcomes | | | | | |
| Organ function development | | | | | |
| Age, d | | | | | |
| ≤28 | 9/30 (30.0) | 6/24 (25.0) | 1.2 (0.5 to 2.9) | 5.0 (-18.8 to 28.8) | .98 |
| 29-365 | 50/245 (20.4) | 48/261 (18.4) | 1.1 (0.8 to 1.6) | 2.0 (-4.9 to 8.9) | |
| >365 | 88/453 (19.4) | 79/447 (17.7) | 1.1 (0.8 to 1.5) | 1.7 (-3.3 to 6.8) | |
| ICU admission type | | | | | |
| Surgical, cardiac | 30/104 (28.5) | 22/106 (20.7) | 1.4 (0.9 to 2.2) | 8.1 (-3.5 to 19.7) | .71 |
| General, medical | 94/429 (21.9) | 86/440 (19.5) | 1.1 (0.9 to 1.5) | 2.4 (-3.0 to 7.8) | |
| Surgical, noncardiac | 10/125 (8.0) | 8/112 (7.1) | 1.1 (0.5 to 2.7) | 0.9 (-5.9 to 7.6) | |
| Trauma | 8/50 (16.0) | 8/50 (16.0) | 1.0 (0.4 to 2.4) | 0.0 (-14.4 to 14.4) | |
| Medical, cardiac | 5/20 (25.0) | 9/24 (37.5) | 0.7 (0.3 to 1.7) | -12.5 (-39.6 to 14.6) | |
| PRISM III score at ICU admission, quartile ^e | | | | | |
| 1 (0-1) | 24/164 (14.6) | 19/167 (11.4) | 1.3 (0.7 to 2.3) | 3.3 (-4.0 to 10.5) | .24 |
| 2 (2-5) | 37/209 (17.7) | 27/219 (12.3) | 1.4 (0.9 to 2.3) | 5.4 (-1.4 to 12.1) | |
| 3 (6-10) | 33/188 (17.5) | 39/174 (22.4) | 0.8 (0.5 to 1.2) | -4.9 (-13.1 to 3.4) | |
| 4 (11-40) | 53/167 (31.7) | 48/172 (27.9) | 1.1 (0.8 to 1.6) | 3.8 (-5.9 to 13.6) | |
| Exploratory Subset | | | | | |
| Organ dysfunction by red blood cell volume, quartile, mL/kg ^f | | | | | |
| No. of patients | | | | | |
| 1 (0.9-12.5) | 723 | 729 | | | .71 |
| 2 (12.6-16.97) | 26/175 (14.9) | 24/188 (12.8) | 1.2 (0.7 to 2.0) | 2.1 (-5.0 to 9.2) | |
| 3 (17.0-31.8) | 22/177 (12.4) | 28/187 (15.0) | 0.8 (0.5 to 1.4) | -2.5 (-9.6 to 4.5) | |
| 4 (31.9-920.0) | 36/183 (19.7) | 29/181 (16.0) | 1.2 (0.8 to 1.9) | 3.6 (-4.2 to 11.5) | |
| | 61/188 (32.4) | 52/174 (29.9) | 1.1 (0.8 to 1.5) | 2.6 (-7.0 to 12.1) | |

Abbreviations: ICU, intensive care unit; PRISM III, The Pediatric Risk of Mortality III score.

^a In all comparisons, the fresh red blood cell group was used as the reference. Superiority was checked for the primary outcome and for all secondary outcomes analyzing patients according to their randomization groups. The principal analysis was performed using an unadjusted χ^2 comparing the proportion of patients who acquire new or progressive multiple organ dysfunction syndrome after randomization. The principal measure of effect is an unadjusted absolute risk reduction with a 95% CI. Dichotomous secondary outcomes were analyzed using risk differences and 95% CIs followed by logistic regression procedures. Continuous outcomes were analyzed using independent t tests or Wilcoxon rank-sum tests depending on distribution of data.

^b No./No. evaluated (%) refers to No. with outcome/No. of patients evaluated (proportion). No. refers to number analyzed when it is less than the group total.

^c Primary outcome are listed in the Methods section.

^d Total number of participants was 1461. One patient who was randomized to the standard-issue group died in the operating room during cardiac surgery and had no data available for the primary outcome and some secondary outcomes. This patient was not included in the primary outcome but was included in mortality analyses.

^e The score ranges from 0 to 71; higher scores indicate higher risk of death.²²

^f Development of primary outcome in patients who exclusively received red blood cells stored for 7 days or less in the fresh group and all the patients in the standard-issue group.

were treated as missing, and the number of patients missing for each variable is reported. No imputation was done for missing outcomes. In coding and analyzing variables with missing data, we did not generate a separate category for missing. Rather, we excluded patients with missing data for a variable from the respective analysis. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary outcomes should be interpreted as exploratory. Data were analyzed with the SAS software version 9.1 (SAS Institute Inc). All statistical tests were 2-sided, and *P* values less than .05 were considered significant.

Results

Patients

From February 1, 2014, to August 15, 2018, a total of 15 568 patients were screened for inclusion. Of these, 13 308 met at least 1 exclusion criterion (Figure 1); the most frequent reasons for exclusion were having received a red blood cell transfusion within 28 days of eligibility, inability to obtain consent, and patient age being younger than 3 days or older than 16 years at time of the transfusion order. There were

2260 eligible patients who consented to participate; red blood cell transfusion was not administered to 722 patients. Therefore, a total of 1538 patients were randomized and received the intervention: 768 patients in the fresh red blood cell group and 770 in the standard-issue group. There were 40 patients in the fresh red blood cell group and 37 in the standard-issue group who were lost to follow up or withdrawn from the trial (Figure 1). The 2 study groups had similar characteristics at baseline (Table 1 and eTable 1 in Supplement 4).

Intervention

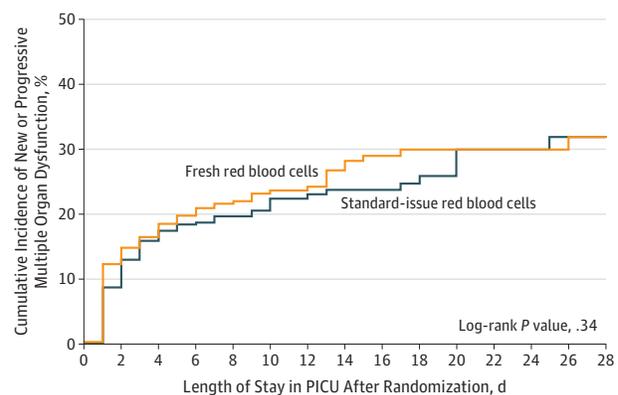
The median total volume of red blood cells transfused per patient in the fresh group was 17.5 mL/kg (IQR, 12.9-32.8 mL/kg) compared with 16.6 mL/kg (IQR, 12.3-30.6 mL/kg) in the standard-issue group ($P = .19$; Table 2). The median storage age in the fresh group was 5 days (IQR, 4-6 days) compared with a storage age of 18 days (IQR, 12-25 days) in the standard-issue group ($P < .001$). The median time from randomization to the first transfusion was 2.0 hours (IQR, 1.0-3.0 hours) in both study groups. In the fresh group, 679 of 727 patients (93.4%) exclusively received fresh red blood cells (Table 2; eFigure 1 in Supplement 4). Additional intervention data including adherence to the transfusion protocol instructions is provided in eTable 2 in Supplement 4.

Analysis of Primary Outcome

At 28 days after randomization, organ dysfunction occurred in 147 of 728 patients (20.2%) in the fresh red blood cell group and 133 of 732 (18.2%) in the standard-issue group (unadjusted absolute risk difference, 2.0%; 95% CI, -2.0% to 6.1%; $P = .33$; Table 3). The hazard ratio for the time to development of organ dysfunction in the fresh-blood group, compared with the standard-issue group, was 1.12 (95% CI, 0.88 to 1.41; $P = .34$; Figure 2).

The per-protocol analysis showed no significant differences in the primary outcome at 28 days between the patients in the fresh group who exclusively received red blood cells that had been stored for less than 7 days and the patients in the standard-issue group; organ dysfunction occurred in 129 of 699 patients (19.3%) in the fresh group and 133 of 732 (18.2%) in the standard-issue group, unadjusted absolute risk difference, 1.1 (95% CI, -3.0 to 5.2; $P = .59$; Table 4). Similarly, a sensitivity analysis showed no significant difference in the primary outcome between the patients in the fresh group who exclusively received red blood cells that had been stored for less than 7 days and patients in the standard-issue group who exclusively received red blood cells that had been stored for more than 7 days. Organ dysfunction occurred in 129 of 664 patients (19.3%) in the fresh group and in 114 of 671 patients (17%) in the standard issue group; with an unadjusted absolute risk difference of 2.3 (95% CI, -1.8 to 6.4; $P = .28$; Table 4). Multivariable analyses for the primary outcome also showed no significant differences for the fresh vs standard-issue groups with an unadjusted relative risk of 1.1 (95% CI, 0.9 to 1.4; $P = .33$) and adjusted relative risk of 1.2 (95% CI, 0.9 to 1.5; $P = .19$), respectively.

Figure 2. Kaplan-Meier Analysis of Time to Development of New or Progressive Multiple Organ Dysfunction Syndrome



The primary analysis set of patients included 1460 patients. The hazard ratio in the fresh-blood group compared with the standard-issue group, was 1.12 (95% CI, 0.88 to 1.44; $P = .34$). For a definition of new and progressive multiple organ dysfunction syndrome and how it is categorized for this study, see the Methods section. PICU indicates pediatric intensive care unit. The median observation time until new or progressive multiple organ dysfunction was 5.0 days (95% CI, 2.0-10.0 days) in each study group.

Analysis of Secondary and Subgroup Outcomes

No significant differences were observed in any of the secondary outcomes or subgroup analyses that were planned (Table 3, Table 4; eTable 3, and eFigures 2 and 3 in Supplement 3). Multiple exploratory analyses indicated that there was no statistically significant association between the red blood cell volume transfused and the primary outcome (Table 4, Table 5, and eTable 4 in Supplement 4). There were also no significant differences observed for individual organ failure after randomization (eTable 5 in Supplement 4). No significant differences were observed across countries (interaction effect between country and treatment: $P = .21$; eTable 3 in Supplement 4).

Discussion

In this trial involving critically ill children, the transfusion of fresh red blood cells did not affect the development of organ dysfunction or death compared with the use of standard issue red blood cells. Results in all subgroups and secondary outcomes analyses were consistent with the primary outcome. Current blood management policies that recommend fresh red blood cell units for certain populations of children, such as neonates and children requiring cardiac surgery,¹⁴ are not supported by the outcomes of this trial.

There are several potential explanations for the results of this trial indicating that fresh red blood cells did not reduce organ dysfunction in critically ill children. The first possibility is that study patients may not have needed a red blood cell transfusion to improve oxygen delivery; if there was no potential benefit for transfusion then there would be no additional relative benefit to detect as a function of red-cell storage duration. Another explanation for the results could be that while there are well-described changes that occur over time

Table 4. Clinical Trial Secondary Outcomes^a

| Secondary Outcomes | Red Blood Cell Group, No./No. Evaluated (%) ^b | | Relative Risk (95% CI) | Absolute Risk Difference (95% CI) | P Value |
|------------------------------------|--|----------------|------------------------|-----------------------------------|---------|
| | Fresh | Standard-issue | | | |
| Per-protocol analysis ^c | | | | | |
| Development of organ dysfunction | 129/669 (19.3) | 133/732 (18.2) | 1.1 (0.9 to 1.3) | 1.1 (-3.0 to 5.2) | .59 |
| Sensitivity analysis ^d | | | | | |
| Development of organ dysfunction | 129/669 (19.3) | 114/671 (17.0) | 1.1 (0.9 to 1.4) | 2.3 (-1.8 to 6.4) | .28 |
| Mortality | | | | | |
| In ICU | 33/728 (4.5) | 26/732 (3.5) | 1.3 (0.8 to 2.1) | 1.0 (-1.04 to 3.0) | .34 |
| In hospital | 36/728 (4.9) | 35/733 (4.8) | 1.0 (0.7 to 1.6) | 0.2 (-2.0 to 2.4) | .88 |
| ≤28 d | 33/716 (4.6) | 24/714 (3.4) | 1.4 (0.8 to 2.3) | 1.2 (-0.8 to 3.3) | .23 |
| ≤90 d | 49/716 (6.8) | 45/714 (6.3) | 1.1 (0.7 to 1.6) | 0.5 (-2.0 to 3.1) | .68 |
| Morbidity outcomes ^e | | | | | |
| Sepsis | 160/619 (25.8) | 154/608 (25.3) | 1.0 (0.8 to 1.2) | 0.5 (-4.4 to 5.4) | .83 |
| Severe sepsis | 63/619 (10.2) | 60/608 (9.9) | 1.0 (0.7 to 1.4) | 0.3 (-3.0 to 3.7) | .86 |
| Septic shock | 59/619 (9.5) | 57/608 (9.4) | 1.0 (0.7 to 1.4) | 0.2 (-3.1 to 3.4) | .93 |
| ARDS ^f | 41/619 (6.6) | 29/608 (4.8) | 1.4 (0.9 to 2.2) | 1.8 (-0.7 to 4.4) | .16 |
| Nosocomial infections ^g | 24/728 (3.3) | 23/732 (3.1) | 1.1 (0.6 to 1.8) | 0.1 (-1.6 to 2.0) | .86 |

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

^a See Table 3 footnotes for comparative explanations.

^b No./No. evaluated (%) refers to No. with outcome/No. of patients evaluated (proportion). No. refers to number analyzed when it is less than the group total.

^c Patients who exclusively received red blood cells 7 days or less in the fresh group and all patients in the standard-issue group.

^d Patients who exclusively received red blood cells within 7 days in the fresh group and exclusively received old red blood cells 7 days or older in the standard-issue group.

^e Sepsis, severe sepsis, and septic shock as defined by Goldstein et al.²³

^f Definition is drawn from Bernard et al and Thomas et al.^{24,25}

^g Nosocomial infection definitions by Lacroix et al,²⁶ Centers for Disease Control and Prevention,²⁷ and Calandra et al.²⁸

Table 5. Patient Intensive Care Unit Secondary Outcomes

| | Red Blood Cell Group ^a | | Difference, Mean (95%CI) | P Value |
|--|-----------------------------------|--------------------|--------------------------|---------|
| | Fresh | Standard-issue | | |
| 28-d ICU-free days ^b | | | | |
| Median (IQR) | 21.9 (14.5-25.3) | 22.0 (16.1-25.6) | | .33 |
| Mean (SD) [No.] | 18.6 (8.8) [716] | 19.1 (8.4) [712] | -0.6 (-1.5 to 0.3) | .21 |
| 28-d Mechanical ventilation-free days ^c | | | | |
| Median (IQR) | 25.4 (19.6-27.9) | 25.8 (20.2-28.0) | | .27 |
| Mean (SD) [No.] | 21.7 (8.6) [710] | 22.3 (8.0) [707] | -0.5 (-1.4 to 0.3) | .21 |
| Worst PELOD-2 score ^d | | | | |
| Median (IQR) | 5 (2-7) | 5 (2-7) | | .41 |
| Mean (SD) [No.] | 5.9 (6.4) [709] | 5.5 (5.7) [713] | 0.4 (-0.2 to 1.0) | .21 |
| Δ PELOD-2 score, change from randomization to worst ^e | | | | |
| Median (IQR) | 0 (-2 to 1) | 0 (-2 to 1) | | .26 |
| Mean (SD) [No.] | 0.5 (5.8) [707] | -0.05 (4.7) [712] | 0.5 (-0.003 to 1.1) | .051 |
| Length of hospital stay, d | | | | |
| Median (IQR) | 12.7 (5.7 to 27.2) | 13.1 (6.3 to 25.5) | | .83 |
| Mean (SD) | 21.2 (23.5) | 20.7 (23.4) | 0.5 (-1.9 to 2.9) | .66 |

Abbreviations: ICU, intensive care unit; IQR, interquartile range; PELOD-2, Pediatric Logistic Organ Dysfunction-2 score.

^a Values in square brackets indicate number of patients analyzed among all participants.

^b Calculated by subtracting the actual ICU length of stay in days from 28. If a patient died within 28 days or stayed in ICU for more than 28 days after randomization, 28-day ICU-free days were reported as 0.

^c Calculated by subtracting from 28 the number of days spent receiving mechanical ventilation. If the patient died within 28 days or required

mechanical ventilation for more than 28 days after randomization, 28-day mechanical ventilation-free days were reported as 0.

^d The score ranges from 0 to 33; higher scores indicate greater severity of multiple organ dysfunction syndrome.¹⁸ The score can be estimated over the entire stay in the ICU or over 1 day (daily PELOD-2).

^e The change in the score is the difference between the daily PELOD-2 score at study entry and the worst daily PELOD-2 score thereafter. Patients whose score did not change or decreased after randomization were considered to have a change of 0.

in red blood cell units, these changes are not clinically relevant and there are no benefits of transfusing fresh red blood cells in a heterogeneous group of critically ill children. It is possible that the current use of prestorage leukoreduction for red blood cell units has mitigated most of the storage lesion effects, which were predominantly described prior to its use.²⁹ Another theory is that any potential benefit from fresh red blood cells was mitigated by increased risk of adverse effects as a result of immune dysregulation or other mechanisms.^{30,31} There is mounting evidence that the so called “chronological” age of a stored red blood cell unit does not equate to its “biological age.” Metabolomic data indicate that there is wide variation in red blood cell unit quality upon donation and, moreover, that rate of change of red blood cell metabolic activity over time is also highly variable between donors.³² This explanation may account for discordance between in vitro and animal data demonstrating adverse red blood cell storage lesion effects and the lack of effect of storage age on clinical outcomes in all large clinical trials performed.

The results of this trial were consistent with previously published randomized clinical trials examining the effect of fresh vs older red blood cells in critically ill neonates, severely anemic children, and adult patients. In these 6 trials there were no significant differences in clinical outcomes.⁸⁻¹³ All point estimates, overall and in major subgroups, favored standard-issue red blood cells. These same observations were noted in 3 of 5 previously published randomized trials.¹⁰⁻¹² Therefore, it is highly improbable that fresh red blood cells were superior to standard-issue red blood cells in all the patient populations studied. This concept is supported in a recently published meta-analysis.³³

This trial has several strengths. A wide spectrum of critically ill pediatric patients were included and the study population was representative of PICUs in developed countries, enhancing applicability of these findings. Adherence to the trial protocol was excellent. The trial was also large enough to detect a reduction in organ dysfunction from 18% to 12%,

a clinically important difference. Ascertainment bias was minimized by concealed randomization and blinded study group assignments.

Limitations

This study has several limitations. First, similar to prior randomized clinical trials addressing the question of red blood cell storage, it is possible that some subgroups of critically ill children more vulnerable to the adverse effects of prolonged red blood cell storage were underrepresented. Second, this trial, as well as all prior trials examining red blood cell storage age, have predominantly enrolled patients who did not require large volumes. The mean or median total volume transfused in adult trials was 2 to 4 units per participant.^{10,12,13} In this trial, there was no effect of storage duration on outcomes even in the highest quartile of volume transfused (>30 mL/kg), which equates to approximately 2 to 3 transfusion events per patient over the study period. A dose effect with larger amounts of older red blood cells transfused over short periods of time adversely affecting outcomes is possible and has been reported in retrospective studies and secondary analyses of 2 randomized clinical trials.⁴⁻⁷ Third, as a result of using standard delivery of red blood cells, the median storage age was low at 18 days. This did not allow for the examination of the effect of older red blood cells in the trial. This limitation also occurred in the majority of the other randomized clinical trials examining the clinical effects of red blood cell storage.^{8,10-13} Thus this trial, as well as others, cannot address relative safety of transfusing red blood cells stored for 35 to 42 days.

Conclusions

In critically ill pediatric patients, the use of fresh red blood cells did not reduce the incidence of new or progressive multiple organ dysfunction syndrome (including mortality) compared with standard-issue red blood cells.

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Data Sharing Statement: See Supplement 5

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