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Age of Transfused Blood in Critically Ill Adults

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ABSTRACT

BACKGROUND

Fresh red cells may improve outcomes in critically ill patients by enhancing oxygen delivery while minimizing the risks of toxic effects from cellular changes and the accumulation of bioactive materials in blood components during prolonged storage.

METHODS

In this multicenter, randomized, blinded trial, we assigned critically ill adults to receive either red cells that had been stored for less than 8 days or standard-issue red cells (the oldest compatible units available in the blood bank). The primary outcome measure was 90-day mortality.

RESULTS

Between March 2009 and May 2014, at 64 centers in Canada and Europe, 1211 patients were assigned to receive fresh red cells (fresh-blood group) and 1219 patients were assigned to receive standard-issue red cells (standard-blood group). Red cells were stored a mean (±SD) of 6.1±4.9 days in the fresh-blood group as compared with 22.0±8.4 days in the standard-blood group (P<0.001). At 90 days, 448 patients (37.0%) in the fresh-blood group and 430 patients (35.3%) in the standard-blood group had died (absolute risk difference, 1.7 percentage points; 95% confidence interval [CI], −2.1 to 5.5). In the survival analysis, the hazard ratio for death in the fresh-blood group, as compared with the standard-blood group, was 1.1 (95% CI, 0.9 to 1.2; P=0.38). There were no significant between-group differences in any of the secondary outcomes (major illnesses; duration of respiratory, hemodynamic, or renal support; length of stay in the hospital; and transfusion reactions) or in the subgroup analyses.

CONCLUSIONS

Transfusion of fresh red cells, as compared with standard-issue red cells, did not decrease the 90-day mortality among critically ill adults. (Funded by the Canadian Institutes of Health Research and others; Current Controlled Trials number, ISRCTN44878718.)

BLOOD TRANSFUSIONS ARE ADMINIS-tered frequently and may have unintended consequences in critically ill patients.[1-4] Current regulations permit the storage of red cells for up to 42 days, but prolonged storage has been associated with changes that may render red cells ineffective as oxygen carriers and that lead to the accumulation of substances that have untoward biologic effects.[5-8]

A systematic review of 18 observational studies involving a total of 409,840 patients and three randomized, controlled trials involving a total of 126 patients suggested that the transfusion of older red cells, as compared with newer red cells, was associated with a 16% increase in the risk of death.[9] However, a recent randomized trial did not document adverse consequences on oxygenation, immunologic, or coagulation variables in 50 patients undergoing mechanical ventilation who received red-cell units that had been stored for a median of 4.0 days, as compared with 50 patients who received blood that had been stored for 26.5 days.[10] In the Age of Blood Evaluation (ABLE) pilot trial involving 66 patients, 27% of the patients who received fresh blood, as compared with 13% assigned to standard-issue blood, died or had a life-threatening complication (P=0.31).[11]

Blood-transfusion services typically provide the oldest compatible red cells as an inventory-management approach ("first in, first out") to minimize waste of blood components. This practice is amplified at large centers, because suppliers send fresh red cells to small centers or remote locations where usage is low. Frequently, unused older red cells are returned from these centers for redistribution to larger centers, thus exposing some of the sickest patients in any system to the oldest available blood. We hypothesized that among critically ill adults, fresh red cells stored for less than 8 days would be superior to standard-issue red cells, resulting in lower mortality at 90 days.

METHODS

STUDY DESIGN AND OVERSIGHT

The ABLE trial was a multicenter, randomized, blinded trial comparing red cells stored for less than 8 days with standard-issue red cells. Randomization was performed with the use of a centralized computer-generated assignment sequence, with stratification according to study site. Critically ill patients were assigned in a 1:1 ratio to one of the two study groups, with the use of permuted blocks of varying sizes of 6, 8, or 10. Randomization was initiated by blood-transfusion personnel when the first red-cell transfusion was requested. Only the study statistician at the coordinating center had knowledge of the randomization codes. An opaque sticker was affixed over the expiration and collection dates on the blood units, or the labels were changed, so that the medical team would be unaware of the treatment-group assignments. Blood-transfusion technologists refrained from releasing information on storage duration to all clinical and research personnel.

The conduct of the trial and the safety of participants were overseen by the data and safety monitoring committee, whose members reviewed interim analyses after each consecutive group of 500 patients had been followed for 90 days. We adopted O'Brien–Fleming group-sequential stopping rules for the four interim analyses. All data management and statistical analyses were performed by the Methods Centre at the Ottawa Hospital Research Institute in Ottawa. Clinical coordination was conducted by the Research Center of Sainte-Justine Hospital in Montreal. The trial was conducted with the support of the Canadian Critical Care Trials Group.

The protocol, including details of trial conduct and the statistical analysis plan, has been published previously[12] and is available with the full text of this article at NEJM.org. The study protocol was approved by the local or regional research ethics board for each participating institution. The study was designed by the authors, who vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol. No one who is not an author contributed to the writing of the paper. There was no support from a commercial entity for this study. At sites where deferred consent was permitted, written informed consent was obtained from the patient or surrogate decision maker as soon as possible after enrollment. If consent was declined, the study intervention was stopped, but we explicitly requested to keep all information on patients who had been enrolled in the trial and ascertain 90-day follow-up data.

STUDY POPULATION

We enrolled critically ill adults from tertiary care intensive care units (ICUs) at 64 centers (26 in

Canada, 20 in the United Kingdom, 10 in France, 7 in the Netherlands, and 1 in Belgium) (see the Supplementary Appendix, available at NEJM.org). We selected study sites at which all red-cell units were leukoreduced before storage and suspended in saline–adenine–glucose–mannitol (SAGM) additive solutions.

We screened patients 18 years of age or older who were admitted to participating ICUs. Patients were eligible if a first red-cell transfusion was prescribed within 7 days after admission to the ICU and if they were expected to require invasive or noninvasive mechanical ventilation for at least 48 hours. Reasons for exclusion of patients are listed in Figure S1 in the Supplementary Appendix.

INTERVENTION

We compared the use of fresh red cells that had been stored for less than 8 days with the usual transfusion practice, whereby blood-transfusion services issue the oldest available compatible blood. Participating blood-transfusion services in collaboration with blood centers agreed to maintain an inventory of fresh red cells for patients assigned to the fresh-blood group. We anticipated that compatible red cells stored for less than 8 days might not always be available to patients assigned to receive fresh red cells. In such instances, the protocol specified that patients assigned to the fresh-blood group receive the freshest compatible red cells (i.e., not the oldest compatible, as issued in the standard-blood group). For this clinical trial, we defined adherence to the transfusion protocol for the fresh-blood group as the transfusion of red-cell units that had been stored for less than 8 days and for the standard-blood group as the transfusion of the oldest compatible red cells. We administered the study interventions until hospital discharge, death, or up to 90 days after randomization, whichever occurred first. There were no other trial interventions related to red cells or other blood products. We did not mandate or monitor any bedside transfusion guidelines. All decisions regarding patient care were at the discretion of the attending physicians and the clinical team.

OUTCOMES

The primary outcome measure was 90-day all-cause mortality. We ascertained survival status by direct contact with clinical teams, patients, or families and occasionally by contact with primary care physicians or by review of vital-statistics registries.

We also collected information on several secondary outcomes, including organ dysfunction.[13] We recorded infections, including nosocomial pneumonia, deep-tissue infections (peritonitis and mediastinitis), and bacteremia, which we categorized according to Centers for Disease Control criteria.[14] We examined the length of stay in the ICU and in the hospital as well as the duration of respiratory, hemodynamic, or renal support. Adverse events and transfusion reactions were recorded daily. Patient data were abstracted from hospital charts. Information on the duration of red-cell storage was provided by blood-bank technologists.

STATISTICAL ANALYSIS

We estimated that a total sample of 2266 patients would be needed for the study to have 90% power to detect an absolute difference in risk of 5 percentage points from a baseline mortality of at least 25%, at a type I error rate of 5% (two-sided alpha). With an anticipated rate of loss to follow-up at 90 days of 5%, we calculated that 2510 patients would have to undergo randomization.[15]

All the statistical analyses were based on the intention-to-treat principle. We also performed two prespecified analyses of 90-day mortality: first, we performed a per-protocol analysis that was limited to patients who received at least one red-cell transfusion after randomization; second, as a sensitivity analysis, we restricted our analysis to patients in the fresh-blood group who received only units stored for less than 8 days versus patients in the standard-blood group who received only units stored for more than 7 days. We calculated the absolute risk difference (risk in the fresh-blood group minus risk in the standard-blood group) with 95% confidence intervals for all mortality analyses, including 90-day mortality. A positive value suggested increased mortality or number of events in the fresh-blood group, whereas a negative value suggested a greater number of events in the standard-blood group. We compared continuous measures, including length of stay in the hospital or ICU and duration of respiratory, hemodynamic, or renal support, using the Wilcoxon rank-sum test.

We used multivariable logistic-regression models to calculate absolute risk differences while adjusting for possible independent confounding

variables, including center, patient age, sex, co-existing illnesses, illness-severity score on the Acute Physiology and Chronic Health Evaluation II (APACHE II; range, 0 to 71, with higher scores indicating a greater risk of death),[16] and the Multiple Organ Dysfunction Score (range, 0 to 24, with higher scores indicating more severe organ dysfunction).[17] We also compared Kaplan–Meier survival curves, with time to death censored at 90 days as the outcome. We compared treatment effects using a log-rank test, followed by Cox proportional-hazards modeling with the same explanatory variables used in the logistic-regression models. This approach was used for the secondary outcomes of all-cause mortality at 28 days, as well as mortality in the hospital or ICU.

Prespecified subgroup analyses of 90-day all-cause mortality were performed according to age (<40 years, 40 to <50 years, 50 to <60 years, or ≥60 years), APACHE II score (<20 vs. ≥20), number of red-cell units transfused (1 to 3 vs. >3), and admission category (medical, surgical, or trauma). The same multivariable logistic-regression models were used in each subgroup stratum.

Dichotomous data are presented as numbers and percentages, whereas continuous data are expressed as means and standard deviations or medians and interquartile ranges, as appropriate. We report 95% confidence intervals. P values have not been adjusted for multiple comparisons. Data were analyzed with the use of SAS software, version 9.1 (SAS Institute).

Table 1. Baseline Characteristics.*

Characteristic	Fresh Blood (N = 1206)	Standard Blood (N = 1206)	Total (N = 2412)
Age — yr	61.3±16.7	61±16.7	61.2±16.7
Male sex — no. (%)	682 (56.6)	643 (53.3)	1325 (54.9)
Coexisting illness — no. (%)	512 (42.5)	514 (42.6)	1026 (42.5)
APACHE II score†	21.9±7.7	21.6±7.6	21.8±7.6
Length of stay in ICU — days	2.4±2.0	2.4±2.1	2.4±2.1
Time from hospitalization to ICU admission — days	2.6±6.6	2.7±6.5	2.6±6.5
Organ injury and support			
MODS‡	5.0±3.1	4.7±3.1	4.9±3.1
Invasive mechanical ventilation — no. (%)	1176 (97.5)	1174 (97.3)	2350 (97.4)
Renal-replacement therapy — no. (%)§	324 (26.9)	354 (29.4)	678 (28.1)
Vasoactive support — no. (%)¶	750 (62.2)	765 (63.4)	1515 (62.8)
Type of admission — no. (%)			
Emergency	1164 (96.5)	1169 (96.9)	2333 (96.7)
Elective	42 (3.5)	37 (3.1)	79 (3.3)
Major admission category — no. (%)‖			
Medical	845 (70.1)	867 (71.9)	1712 (71.0)
Surgical	175 (14.5)	152 (12.6)	327 (13.6)
Trauma			
Brain injury	110 (9.1)	106 (8.8)	216 (9.0)
No brain injury	76 (6.3)	80 (6.6)	156 (6.5)

* Plus–minus values are means ±SD. ICU denotes intensive care unit.
† Scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) range from 0 to 71, with higher scores indicating a higher risk of death.[16]
‡ The Multiple Organ Dysfunction Score (MODS) ranges from 0 to 24, with higher scores indicating more severe organ dysfunction.[17]
§ Renal-replacement therapy included continuous renal-replacement therapy, peritoneal dialysis, or hemodialysis.
¶ Vasoactive support was defined as continuous vasoactive drug infusion for hemodynamic support (excluding dopamine infusion at a dose of ≤5 μg per kilogram of body weight per minute).
‖ Major admission category was missing for one patient in the standard-blood group.

RESULTS

PATIENTS

From March 2009 through May 2014, a total of 19,196 patients were eligible for inclusion. Of these, 16,605 patients (86.5%) met at least one exclusion criterion; the patient or a surrogate decision maker declined consent in 81 instances. Therefore, 2510 patients underwent randomization; 80 (3.2%) were withdrawn after randomization because we were unable to obtain primary outcome data, leaving 2430 patients (1211 in the fresh-blood group and 1219 in the standard-blood group) in the intention-to-treat analysis (Fig. S1 in the Supplementary Appendix). Baseline data were available for 1412 of the 1430 patients with primary outcome data. Of these 2430 patients, 94 (3.9%) did not receive any red-cell transfusions. The two study groups had similar characteristics at baseline (Table 1). The overall rate of loss to follow-up was 3.2% at 90 days.

INTERVENTION

A total of 5198 red-cell units were given to patients in the fresh-blood group and 5210 to patients in the standard-blood group (Table 2). The average duration of storage was 6.1±4.9 days in the fresh-blood group versus 22.0±8.4 days in the standard-blood group (P<0.001). The rate of adherence to the transfusion protocol was 95.4% for all red cells transfused, with 100% of patients in the standard-blood group receiving only standard-issue red cells and 84.0% of patients in the fresh-blood group receiving only red cells stored for less than 8 days (Table 2, and Fig. S2 in the Supplementary Appendix). In the fresh-blood group, all the patients received the freshest red cells available (i.e., there were no protocol violations). Only 6.6% of the patients in the fresh-blood group received more than 1 red-cell unit that had been stored for more than 7 days, and only 4.6% received more than 2 units that had been stored for more than 7 days. Most patients in the fresh-blood group (238 of 249 patients [95.6%]) who received only 1 red-cell transfusion received exclusively red-cell units that had been stored for less than 8 days (Table S2 in the Supplementary Appendix). Cointerventions were similar in the two groups before and after randomization (Table 1, and Table S3 in the Supplementary Appendix).

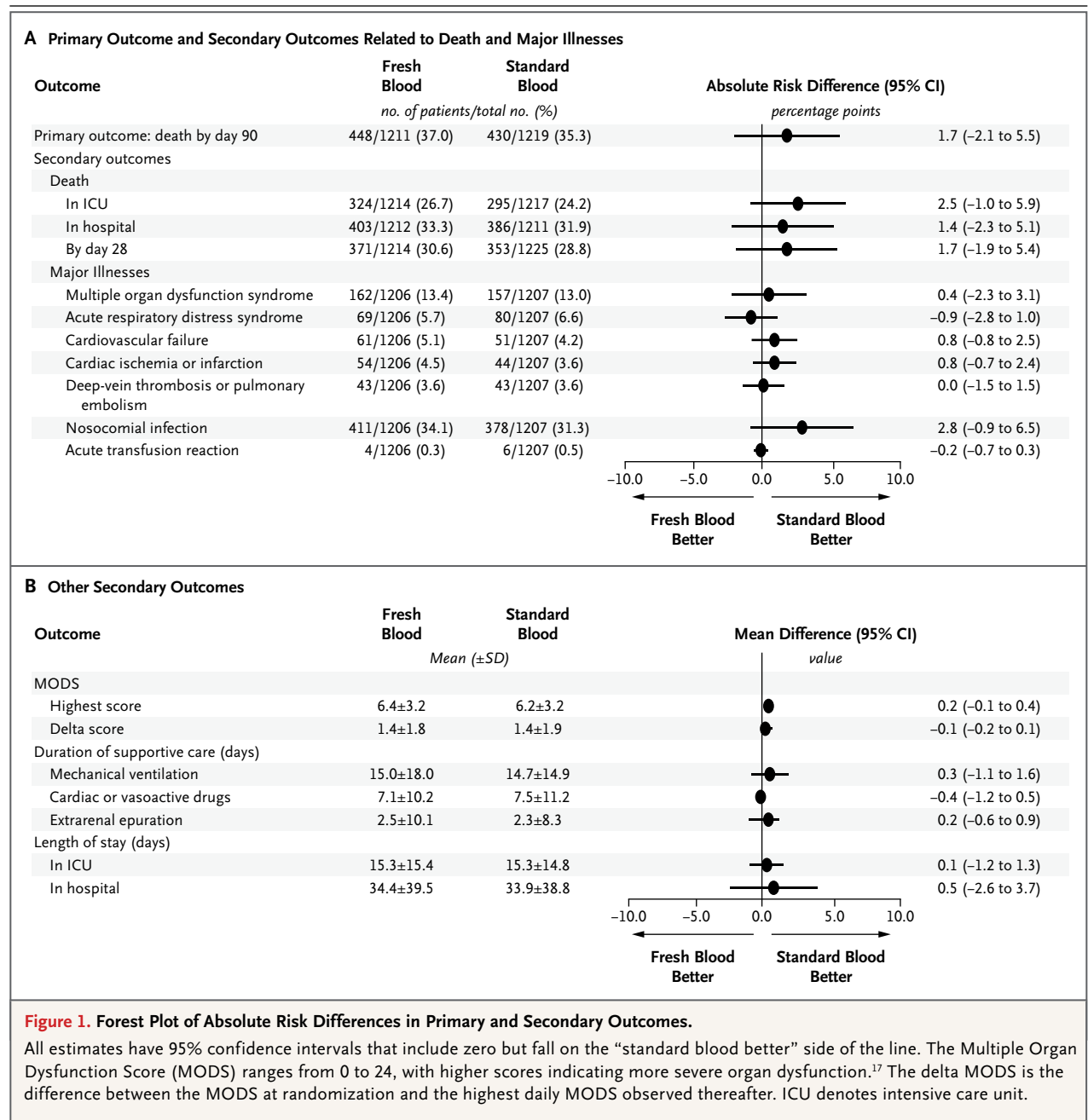| Table 2. Anemia and Red-Cell Transfusions.*			
Variable	Fresh Blood	Standard Blood	P Value
Hemoglobin level in ICU			
No. of patients evaluated	1207	1206	
Level before first transfusion — g/dl	7.69±1.28	7.64±1.09	0.27
Lowest level after randomization — g/dl	7.34±1.46	7.31±1.41	0.61
Red-cell transfusions after randomization			
Patients who received at least one transfusion — no./total no. (%)†	1163/1207 (96.4)	1173/1208 (97.1)	0.30
Time from randomization to first transfusion — hr	10.3±16.2	9.7±16.2	0.43
No. of red-cell units per patient who received at least one transfusion	4.3±5.2	4.3±5.5	0.98
Duration of storage of all red-cell units — days	6.1±4.9	22.0±8.4	<0.001
Adherence to transfusion protocol — no./total no. (%)			
Patients‡	977/1163 (84.0)	1206/1206 (100)	<0.001
Red-cell units§	4723/5198 (90.9)	5210/5210 (100)	<0.001

* Plus–minus values are means ±SD.
† Baseline data on 2 patients in the standard-blood group who received a transfusion were missing. Data on transfusion were missing for 36 patients (15 patients in the fresh-blood group and 21 patients in the standard-blood group).
‡ Patients assigned to the fresh-blood group were considered to be adherent to the transfusion protocol if they received red-cell transfusions only with units stored for less than 8 days; patients assigned to the standard-blood group were considered to be adherent if they received transfusions of the oldest available compatible red cells.
§ For red-cell units, adherence was defined as (number of red-cell units transfused that were stored ≤7 days) ÷ (total number of red-cell units transfused) among patients assigned to the fresh-blood group and as (number of standard-issue red-cell units transfused) ÷ (total number of red-cell units transfused) among patients assigned to the standard-blood group.

A Primary Outcome and Secondary Outcomes Related to Death and Major Illnesses

Outcome	Fresh Blood	Standard Blood	Absolute Risk Difference (95% CI)	
	no. of patients/total no. (%)		percentage points	
Primary outcome: death by day 90	448/1211 (37.0)	430/1219 (35.3)		1.7 (–2.1 to 5.5)
Secondary outcomes				
Death				
In ICU	324/1214 (26.7)	295/1217 (24.2)		2.5 (–1.0 to 5.9)
In hospital	403/1212 (33.3)	386/1211 (31.9)		1.4 (–2.3 to 5.1)
By day 28	371/1214 (30.6)	353/1225 (28.8)		1.7 (–1.9 to 5.4)
Major Illnesses				
Multiple organ dysfunction syndrome	162/1206 (13.4)	157/1207 (13.0)		0.4 (–2.3 to 3.1)
Acute respiratory distress syndrome	69/1206 (5.7)	80/1207 (6.6)		–0.9 (–2.8 to 1.0)
Cardiovascular failure	61/1206 (5.1)	51/1207 (4.2)		0.8 (–0.8 to 2.5)
Cardiac ischemia or infarction	54/1206 (4.5)	44/1207 (3.6)		0.8 (–0.7 to 2.4)
Deep-vein thrombosis or pulmonary embolism	43/1206 (3.6)	43/1207 (3.6)		0.0 (–1.5 to 1.5)
Nosocomial infection	411/1206 (34.1)	378/1207 (31.3)		2.8 (–0.9 to 6.5)
Acute transfusion reaction	4/1206 (0.3)	6/1207 (0.5)		–0.2 (–0.7 to 0.3)

–10.0   –5.0   0.0   5.0   10.0

Fresh Blood Better ← → Standard Blood Better

B Other Secondary Outcomes

Outcome	Fresh Blood	Standard Blood	Mean Difference (95% CI)	
	Mean (±SD)		value	
MODS				
Highest score	6.4±3.2	6.2±3.2		0.2 (–0.1 to 0.4)
Delta score	1.4±1.8	1.4±1.9		–0.1 (–0.2 to 0.1)
Duration of supportive care (days)				
Mechanical ventilation	15.0±18.0	14.7±14.9		0.3 (–1.1 to 1.6)
Cardiac or vasoactive drugs	7.1±10.2	7.5±11.2		–0.4 (–1.2 to 0.5)
Extrarenal epuration	2.5±10.1	2.3±8.3		0.2 (–0.6 to 0.9)
Length of stay (days)				
In ICU	15.3±15.4	15.3±14.8		0.1 (–1.2 to 1.3)
In hospital	34.4±39.5	33.9±38.8		0.5 (–2.6 to 3.7)

–10.0   –5.0   0.0   5.0   10.0

Fresh Blood Better ← → Standard Blood Better

**Figure 1. Forest Plot of Absolute Risk Differences in Primary and Secondary Outcomes.**

All estimates have 95% confidence intervals that include zero but fall on the "standard blood better" side of the line. The Multiple Organ Dysfunction Score (MODS) ranges from 0 to 24, with higher scores indicating more severe organ dysfunction.[17] The delta MODS is the difference between the MODS at randomization and the highest daily MODS observed thereafter. ICU denotes intensive care unit.

PRIMARY OUTCOME

At 90 days after randomization, 448 of 1211 patients (37.0%) in the fresh-blood group and 430 of 1219 patients (35.3%) in the standard-blood group had died. The unadjusted absolute risk difference was 1.7 percentage points (95% confidence interval [CI], –2.1 to 5.5), and the adjusted risk difference was also 1.7 percentage points (95% CI, –1.6 to 4.9) (Fig. 1).

SECONDARY ANALYSES

The survival analysis of the time to death showed a hazard ratio in the fresh-blood group, as compared with the standard-blood group, of 1.1 (95% CI, 0.9 to 1.2) (P=0.38) (Fig. 2). No significant difference in mortality was observed between the groups on the basis of age, number of units transfused, APACHE II score, or admission category (Fig. S3 in the Supplementary Appendix).
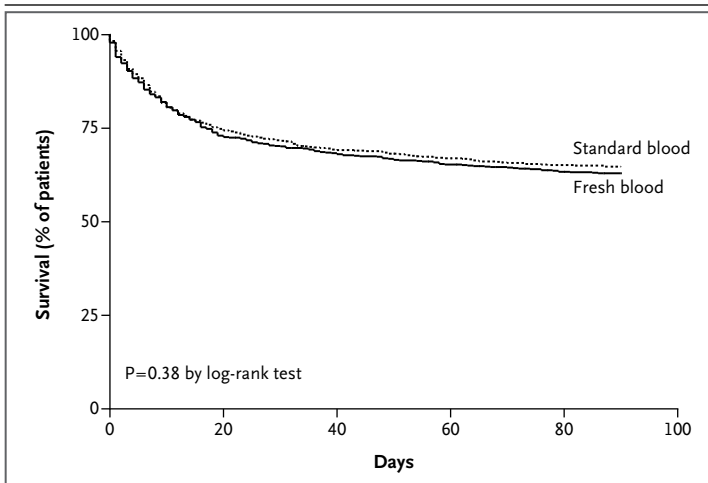
Figure 2. Kaplan–Meier Survival Analysis of Time to Death in the Intention-to-Treat Population.

The intention-to-treat population included 2430 patients. The hazard ratio in the fresh-blood group, as compared with the standard-blood group, was 1.1 (95% CI, 0.9 to 1.2).

No significant differences were observed with respect to major illnesses, duration of respiratory, hemodynamic, or renal support, or length of stay in the ICU or hospital. Acute transfusion reactions occurred in four patients in the fresh-blood group and six patients in the standard-blood group (Table S3 in the Supplementary Appendix).

We performed a per-protocol analysis of the primary outcome that included only patients who received a transfusion. At 90 days, 423 of 1153 patients (36.7%) in the fresh-blood group and 398 of 1163 patients (34.2%) in the standard-blood group had died (absolute risk difference, 2.5 percentage points; 95% CI, –1.4 to 6.4). We also performed a sensitivity analysis of the primary outcome in which we compared the outcomes of the 967 patients in the fresh-blood group who received only red cells that had been stored for less than 8 days versus the outcomes in the 1084 patients in the standard-blood group who received red cells that had been stored for more than 7 days. In this sensitivity analysis, the number of deaths at 90 days was 357 (36.9%) in the fresh-blood group and 370 (34.1%) in the standard-blood group (absolute risk difference, 2.8 percentage points; 95% CI, –1.4 to 6.9).

DISCUSSION

The ABLE study did not show any benefit attributable to the transfusion of fresh red cells in critically ill patients. Not only were the primary outcomes similar in the two study groups, but the results were consistent in all per-protocol and subgroup analyses. These findings have important implications for the critical care and blood-transfusion communities. We surmise that the use of fresh red cells is not justified at this time. We might also infer that changes to red cells or the storage medium that have been documented in many laboratory studies[18] may have limited clinical consequences.

The results of our trial are consistent with those of seven randomized, controlled trials that compared various durations of red-cell storage. Five pilot trials did not detect clinically important clinical consequences of prolonged red-cell storage.[10,11,19-21] Moreover, in two larger trials, transfusion of fresh red cells, as compared with standard-issue red cells, did not reduce the complications of prematurity in very-low-birth-weight infants[22] or reduce the rates of organ failure or adverse events among 1098 patients undergoing elective cardiac surgical procedures.[23,24]

Our findings are not consistent with those of some previous observational studies that suggested that prolonged red-cell storage may be deleterious.[5,9,25-27] More than 40 observational studies have examined the effect of red-cell storage on various clinical outcomes, including mortality, rates of infection, and length of stay in the hospital. Although the initial studies showed an association between longer red-cell storage and adverse outcomes, these associations may have been spurious owing to sicker patients receiving more units with longer storage, the overlap between comparison groups in the age of the red cells transfused, and the inclusion of transfusions that occurred after the clinical events.[28] Results from more recent studies have been more balanced, with many studies showing no significant association between increased duration of red-cell storage and a worse outcome or showing worse outcomes with fresh red cells.[29-31]

Our trial has a number of strengths. It was sufficiently large to detect clinically important differences in 90-day mortality. In addition, we enrolled a wide spectrum of critically ill patients, ensuring broad applicability of our findings. Bias was minimized by concealed randomization, blinded study-group assignments, and a rate of loss to follow-up of less than 5%. The between-group difference in the duration of red-cell storage was statistically and clinically significant. The primary outcome

was clinically relevant and important to both patients and medical decision makers.

Limitations of this trial include the possibility that some groups of critically ill patients who are particularly vulnerable to the adverse consequences of prolonged red-cell storage were underrepresented in the trial. Overall, most patients received transfusions according to a restrictive transfusion strategy, with a mean pretransfusion hemoglobin level of 7.7 g per deciliter, even in the absence of guidelines or protocols. Thus, exposure to any red cells in this trial was much less than what would be the case at centers that are still opting for more liberal use of blood transfusions. Although the testing of shorter storage times might have led to different results, we selected a 7-day storage threshold for the fresh-blood group because blood-transfusion consultants suggested that post-trial implementation of a shorter storage period would not be feasible, especially given the requirement for infectious-disease testing (which takes up to 72 hours) and the finite number of blood donors.

We included only centers that used leukoreduced red cells; therefore, whether leukocytes worsen the degradation of red cells during storage or have other toxic effects that are enhanced by prolonged storage is uncertain. Only SAGM-suspended red cells were used in the trial, because this is the standard red-cell product that is supplied in Canada and Europe. Red cells suspended in additive solution 3 (AS-3), which are supplied in the United States, are similar. However, there are differences in the method of production and in storage solutions. The storage solutions result in similar, though not identical, in vitro red-cell defects,[32] suggesting that our results may be generalizable. Finally, we asked "Is fresh blood better than old blood?" rather than "Is old blood bad?"[33] Our trial does not address the issue of whether the use of red cells stored for very prolonged periods (35 to 42 days) results in harm.

In conclusion, we did not detect any clinically important improvements in primary or secondary outcomes among critically ill adults who received transfusions of fresh red cells.

REFERENCES

1. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409-17. [Erratum, N Engl J Med 1999;340:1056.]
2. Lacroix J, Hébert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med 2007;356:1609-19.
3. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371:1381-91.
4. The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014; 370:1683-93.
5. Tinmouth A, Fergusson D, Yee IC, Hébert PC. Clinical consequences of red cell storage in the critically ill. Transfusion 2006;46:2014-27.
6. Bennett-Guerrero E, Veldman TH, Doctor A, et al. Evolution of adverse changes in stored RBCs. Proc Natl Acad Sci U S A 2007;104:17063-8.
7. Spinella PC, Sparrow RL, Hess JR, Norris PJ. Properties of stored red blood cells: understanding immune and vascular reactivity. Transfusion 2011;51:894-900.
8. Aubron C, Nichol A, Cooper DJ, Bellomo R. Age of red blood cells and transfusion in critically ill patients. Ann Intensive Care 2013;3:2.
9. Wang D, Sun J, Solomon SB, Klein HG, Natanson C. Transfusion of older stored blood and risk of death: a meta-analysis. Transfusion 2012;52:1184-95.
10. Kor DJ, Kashyap R, Weiskopf RB, et al. Fresh red blood cell transfusion and short-term pulmonary, immunologic, and coagulation status: a randomized clinical trial. Am J Respir Crit Care Med 2012; 185:842-50.
11. Hébert PC, Chin-Yee I, Fergusson D, et al. A pilot trial evaluating the clinical effects of prolonged storage of red cells. Anesth Analg 2005;100:1433-8.
12. Lacroix J, Hébert PC, Fergusson D, et al. The Age of Blood Evaluation (ABLE) randomized controlled trial: study design. Transfus Med Rev 2011;25:197-205.
13. Marshall JC. A scoring system for multiple organ dysfunction syndrome. In: Vincent JL, Reinhart K, Eyrich K, Sprung C, eds. Sepsis: current perspectives in pathophysiology and therapy. Berlin: Springer-Verlag, 1994:38-49.
14. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128-40. [Erratum, Am J Infect Control 1988;16:177.]
15. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. Control Clin Trials 1981; 2:93-113.
16. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
17. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638-52.
18. Hess JR. Red cell changes during storage. Transfus Apher Sci 2010;43:51-9.
19. Walsh TS, McArdle F, McLellan SA, et al. Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? Crit Care Med 2004;32:364-71.

20. Heddle NM, Cook RJ, Arnold DM, et al. The effect of blood storage duration on in-hospital mortality: a randomized controlled pilot feasibility trial. Transfusion 2012;52:1203-12.

21. Aubron C, Syres G, Nichol A, et al. A pilot feasibility trial of allocation of freshest available red blood cells versus standard care in critically ill patients. Transfusion 2012;52:1196-202.

22. Fergusson DA, Hébert P, Hogan DL, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial. JAMA 2012;308:1443-51.

23. Steiner ME, Assmann SF, Levy JH, et al. Addressing the question of the effect of RBC storage on clinical outcomes: the Red Cell Storage Duration Study (RECESS) (Section 7). Transfus Apher Sci 2010;43:107-16.

24. Steiner ME, Triuzi DJ, Assinavy SY, et al. Randomized trial results: red cell stor-age age is not associated with a significant difference in multiple organ dysfunction score or mortality in transfused cardiac surgery patients. Transfusion 2014;54:Suppl:15A. abstract.

25. van de Watering L. Red cell storage and prognosis. Vox Sang 2011;100:36-45.

26. Vamvakas EC. Meta-analysis of clinical studies of the purported deleterious effects of "old" (versus "fresh") red blood cells: are we at equipoise? Transfusion 2010;50:600-10.

27. Lelubre C, Vincent JL. Relationship between red cell storage duration and outcomes in adults receiving red cell transfusions: a systematic review. Crit Care 2013;17:R66.

28. van de Watering L. Pitfalls in the current published observational literature on the effects of red blood cell storage. Transfusion 2011;51:1847-54.

29. Middelburg RA, van de Watering LM, Briët E, van der Bom JG. Storage time of red blood cells and mortality of transfu-sion recipients. Transfus Med Rev 2013;27:36-43.

30. Kaukonen KM, Vaara ST, Pettilä V, et al. Age of red blood cells and outcome in acute kidney injury. Crit Care 2013;17:R222.

31. Heddle NM, Eikelboom J, Liu Y, Barty R, Cook RJ. Exploratory studies on the age of transfused blood and in-hospital mortality in patients with cardiovascular diagnoses. Transfusion 2015;55:364-72.

32. Antonelou MH, Kriebardis AG, Stamoulis KE, Economou-Petersen E, Margaritis LH, Papassideri IS. Red blood cell aging markers during storage in citrate-phosphate-dextrose-saline-adenine-glucose-mannitol. Transfusion 2010;50:376-89.

33. Bennett-Guerrero E, Stafford-Smith M, Waweru PM, et al. A prospective, double-blind, randomized clinical feasibility trial of controlling the storage age of red blood cells for transfusion in cardiac surgical patients. Transfusion 2009;49:1375-83.

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