ORIGINAL ARTICLE

Prehospital Resuscitation with Type O Whole Blood for Trauma and Hemorrhage

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ABSTRACT

BACKGROUND

Blood transfusion before arrival at a hospital reduces mortality from traumatic hemorrhage and shock. Whether transfusion with whole blood is more beneficial than transfusion with blood components is uncertain, as are the effects of the length of time that blood products are in storage between donation and transfusion.

METHODS

In this pragmatic, multicenter, phase 3, cluster-randomized trial, we assigned 44 air medical bases in a 2:1 ratio to the use of up to 2 units of whole blood or as-indicated blood components (plasma, red cells, or both) for prehospital transfusion in trauma patients during 1-month blocks. The primary outcome was death from any cause within 30 days after randomization. An observational substudy assessed outcomes according to the storage age of whole blood.

RESULTS

Of 1020 eligible patients transported to hospitals by the air bases, 715 were assigned to receive whole blood and 305 to receive blood components; 695 and 298, respectively, were included in the primary analysis. Mortality at 30 days was 25.9% in the whole-blood group and 20.5% in the component group (adjusted odds ratio, 1.24; 95% confidence interval [CI], 0.87 to 1.76; P=0.24). No substantial between-group differences in adverse events were observed. In the observational substudy, 30-day mortality was 27.1% among 210 patients who received whole blood with a storage age of 15 to 21 days and 26.4% among 443 patients who received whole blood with a storage age of 1 to 14 days (adjusted odds ratio, 0.99; 95% CI, 0.74 to 1.32).

CONCLUSIONS

In injured patients with hemorrhagic shock, the use of whole blood for prehospital transfusion did not result in lower 30-day mortality than the use of blood components. (Funded by the Congressionally Directed Medical Research Programs and the U.S. Army Medical Research Acquisition Activity; TOWAR ClinicalTrials.gov number, NCT04684719.)

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*A complete list of members of the Type O Whole Blood and Assessment of Age during Prehospital Resuscitation (TOWAR) Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Contemporary management of severe injury focuses on the early transfusion of blood products.[1-3] Despite advances in resuscitation, hemorrhage remains a leading cause of preventable death.[4] The transfusion of blood components (red cells, plasma, or both) in the prehospital environment, before arrival to definitive care, is associated with higher survival than delayed transfusion or no transfusion.[2,3]

Treatment with low-titer group O whole blood (which has low anti-A and anti-B antibody titers) is increasingly used in both military and civilian settings because the logistics of transfusion are simpler than those with blood components and the blood is widely available from donors.[5,6] Whole blood can provide rapid, balanced volume resuscitation and concomitant reversal of coagulopathy. Multiple observational studies have shown that resuscitation with whole blood is safe and is associated with better outcomes than resuscitation with blood components.[5,7] Despite benefits in the early hospital setting, high-level evidence is limited with regard to the efficacy and safety of transfusion with whole blood in the prehospital phase of care. In addition, knowledge of whether any diminution of hemostatic potential occurs during storage of whole blood remains limited.[8-11]

The Type O Whole Blood and Assessment of Age during Prehospital Resuscitation (TOWAR) trial was designed to evaluate the safety and efficacy of prehospital transfusion with low-titer group O whole blood as compared with blood components, as well as to characterize differences in outcome associated with the storage age of whole blood, in patients with severe injuries that warranted transfusion owing to risk of hemorrhagic shock. We hypothesized that prehospital transfusion with low-titer group O whole blood would lead to lower 30-day mortality than transfusion with blood components.

Methods

Trial Design

In this pragmatic, multicenter, phase 3, cluster-randomized clinical trial, we compared outcomes for patients who received up to 2 units of low-titer group O whole blood (the whole-blood group) with those for patients who received red cells, plasma, or both (the component group) during prehospital resuscitation. Other than the blood product administered, no other aspect of care was altered during the prehospital phase or after hospital arrival.

The first, second, and last authors were responsible for designing the trial, gathering the data, performing the analyses, and writing the manuscript with help from the other authors. All the authors agreed to submit the manuscript for publication. The first, second, and last authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). No agreements between the sponsors and the authors restricted access to the data, limited the authors' ability to analyze the data independently, or constrained the preparation or submission of the manuscript.

Trial Oversight

The Food and Drug Administration (FDA), the Office of Human Research Oversight of the U.S. Department of Defense, and the Human Research Protection Office at the University of Pittsburgh approved the trial (FDA Investigational New Drug number, 26968). An external data and safety monitoring board oversaw the trial. The single institutional review board at the University of Pittsburgh, with review and acknowledgment from local site institutional review boards, approved an exception from informed consent to enroll patients. This approval included community consultation and public disclosure. We notified enrolled patients, their legally authorized representatives, or both as soon as feasible and obtained consent for continued participation. The data are reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[12]

Patient Population

Patients transferred from the scene of injury or a referring emergency department to a participating trauma center were eligible for enrollment in the trial if they had had at least one episode of hypotension (defined as a systolic blood pressure of ≤90 mm Hg) and tachycardia (defined as a heart rate of ≥108 beats per minute) or if they had had severe hypotension (defined as a systolic blood pressure of ≤70 mm Hg) without tachycardia. Eligible patients were enrolled and underwent randomization during transport to the participating trauma center regardless of whether

transfer originated at the scene of trauma or a referring emergency department. Key exclusion criteria were an age of less than 18 years or more than 90 years; injury associated with isolated falls from a standing position, drowning, or hanging; burn injuries; pregnancy; legal detention; traumatic cardiac arrest; penetrating brain injury; inability to obtain intravenous or intraosseous access; objection to enrollment by the patient or a family member; or the presence of a medical bracelet indicating the desire to opt out of the trial. Additional exclusion criteria are listed in Table S1 in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND MASKING

We used a single-stage cluster randomization scheme in which participating air medical bases were assigned in a 2:1 ratio to use whole blood or component therapy for transfusion for fixed 1-month blocks; the assignment for the initial block was randomly determined. This randomization scheme was chosen to minimize blood waste, simplify delivery logistics, and ensure adequate power for an observational substudy involving whole blood. The assigned intervention was open label to allow for required regulatory procedures. The personnel who assessed trial outcomes were unaware of the trial-group assignments. Two

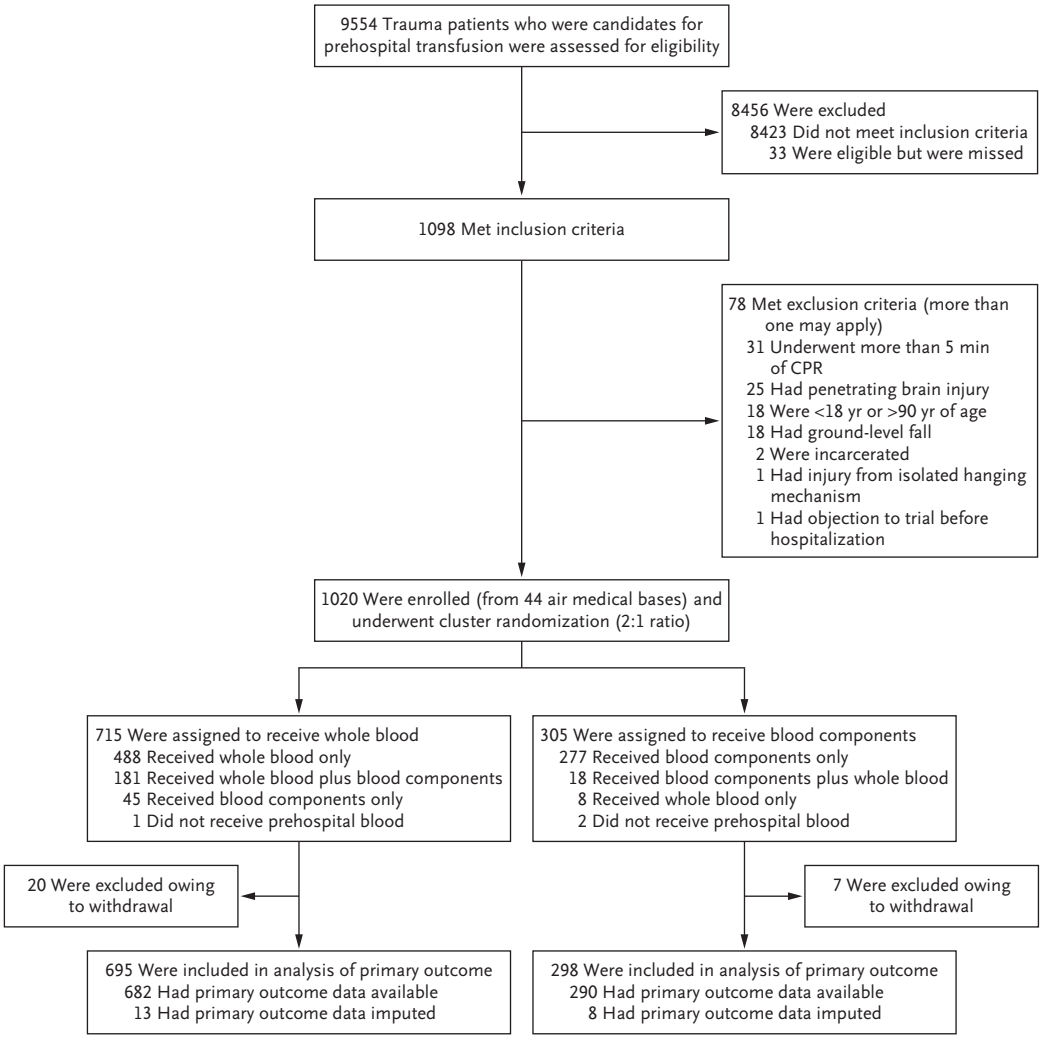


Figure 1. Screening, Randomization, and Analysis.
CPR denotes cardiopulmonary resuscitation.

participating sites used whole blood as their standard prehospital practice at the initiation of the trial. These sites followed the appropriate randomization assignment.

ASSIGNMENT OF INTERVENTION

Blood products were collected according to site blood-banking protocols and stored at air medical bases according to established procedures. Air medical bases assigned to use whole blood for a given month were stocked with 2 units of group O blood with anti-A and anti-B titers of less than 256 and a shelf life of up to 21 days. Eligible patients received up to 2 units of whole blood, with administration of the second unit guided by clinical status and site protocols. Bases assigned to the component group were stocked with red cells, plasma, or both; eligible patients received component therapy according to standard transfusion practices without protocol-defined minimums or limits. Air medical bases were not limited to carrying only investigational blood products during months in which they were assigned to use whole blood. All additional care,

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Whole Blood (N=715)	Blood Components (N=305)
Mean age — yr	44.8±18.9	45.5±19.3
Female sex — no./total no. (%)	193/706 (27.3)	77/304 (25.3)
Race or ethnic group — no./total no. (%)†		
Non-White	168/631 (26.6)	80/289 (27.7)
Hispanic	65/613 (10.6)	31/263 (11.8)
Type of injury — no./total no. (%)		
Blunt	564/707 (79.8)	233/305 (76.4)
Penetrating	143/707 (20.2)	72/305 (23.6)
Mechanism of injury — no./total no. (%)‡		
Fall	53/707 (7.5)	28/305 (9.2)
Machinery	6/707 (0.8)	3/305 (1.0)
Motor vehicle collision	478/707 (67.6)	190/305 (62.3)
Struck by or against object	16/707 (2.3)	5/305 (1.6)
Firearm	107/707 (15.1)	51/305 (16.7)
Impalement	2/707 (0.3)	1/305 (0.3)
Stabbing	27/707 (3.8)	16/305 (5.2)
Other	45/707 (6.4)	19/305 (6.2)
Abbreviated Injury Scale score >2 — no./total no. (%)§		
Head and neck	260/661 (39.3)	106/290 (36.6)
Face	26/661 (3.9)	16/290 (5.5)
Chest	386/661 (58.4)	155/290 (53.4)
Abdomen	222/661 (33.6)	112/290 (38.6)
Limbs	268/661 (40.5)	120/290 (41.4)
External	11/661 (1.7)	3/290 (1.0)
Injury Severity Score — median (IQR)¶	25.0 (16.0–34.0)	23.0 (14.0–34.0)
Glasgow Coma Scale score — median (IQR)‖	11.0 (3.0–15.0)	13.0 (3.0–15.0)
Traumatic brain injury — no. (%)	296 (41.4)	109 (35.7)
Transfer site — no. (%)		
Scene of injury	507 (70.9)	215 (70.5)
Other hospital	208 (29.1)	90 (29.5)

Table 1. (Continued.)

Characteristic	Whole Blood (N=715)	Blood Components (N=305)
Prehospital intervention — no./total no. (%)		
Intubation	389/715 (54.4)	147/304 (48.4)
Cardiopulmonary resuscitation	74/714 (10.4)	22/303 (7.3)
Defibrillation	12/714 (1.7)	3/302 (1.0)
Use of a tourniquet	94/715 (13.1)	49/305 (16.1)
Use of a pelvic binder	155/715 (21.7)	67/305 (22.0)
Treatment with tranexamic acid	298/713 (41.8)	114/304 (37.5)
Treatment with crystalloids or colloids	446/713 (62.6)	192/303 (63.4)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Data on age were available for 710 patients in the whole-blood group and 303 patients in the component group; Injury Severity Scores were available for 661 and 290, respectively; and scores on the Glasgow Coma Scale were available for 696 and 287. IQR denotes interquartile range.
† Race and ethnic group were reported by the patients or family members.
‡ More than one mechanism may apply.
§ Scores on the Abbreviated Injury Scale range from 1 to 6, with higher scores indicating more-severe injury (1, minor; 2, moderate; 3, serious; 4, severe; 5, critical; and 6, maximal [untreatable]). Scores are assigned within each region of the body (head and neck, face, chest, abdomen, limbs, and external [skin]).
¶ The Injury Severity Score ranges from 1 to 75, with higher scores indicating more-severe injury. It is calculated as the sum of the squares of the highest Abbreviated Injury Scale scores in the three most severely injured body regions; any injury with an Abbreviated Injury Scale score of 6 is assigned an Injury Severity Score of 75.
‖ Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating decreased level of consciousness. Scores are calculated as the sum of scores for eye opening (on a scale of 1 to 4), verbal response (on a scale of 1 to 5), and motor response (on a scale of 1 to 6).

including that received on arrival at the receiving hospital, was at the discretion of the treating clinicians, without further trial requirements.

TRIAL OUTCOMES

The primary outcome was death from any cause within 30 days after randomization. Additional prespecified secondary outcomes included death within 3, 6, and 24 hours after arrival at the participating trauma center; death in the hospital; death attributable to hemorrhage or brain injury; the amount of blood products transfused during the first 24 hours after arrival; multiple organ failure; nosocomial infection; acute respiratory distress syndrome; allergic or transfusion-related reactions; time to hemostasis; and coagulation measurements. Platelet function was assessed in a convenience sample of patients at three sites with measurement capabilities. We analyzed the effects of treatment in prespecified subgroups (Table S2).

OBSERVATIONAL SUBSTUDY

To assess the potential association between the storage age of whole blood and trial outcomes, we prespecified an observational substudy limited to patients in the whole-blood group. In this study, death within 30 days and secondary outcomes were assessed according to the length of time the blood was in storage between donation and transfusion (15 to 21 days vs. 1 to 14 days).

STATISTICAL ANALYSIS

Baseline characteristics are summarized according to trial group. The primary outcome was compared between groups with a two-sided Donner–Klar test for proportions. A mixed-effects logistic-regression model was used to estimate the association between transfusion with whole blood and death within 30 days, with a random intercept for the air medical base and adjustment for trial month and for variables that were imbalanced at baseline — traumatic brain injury (yes or no) and prehospital intubation (yes or no). Imbalanced variables were prespecified as those for which the P value for the between-group comparison was less than 0.1.

Prespecified subgroup analyses assessed the heterogeneity of the treatment effect with models that were consistent with that used for the primary analysis, with inclusion of a treatment-by-subgroup interaction term. The analysis of

Table 2. Primary and Secondary Outcomes.*

Outcome	Whole Blood (N=695)	Blood Components (N=298)	Effect Estimate (95% CI)†
Primary outcome			
Death within 30 days — no. (%)	180 (25.9)	61 (20.5)	1.24 (0.87 to 1.76)‡
Secondary outcomes			
Death within 3 hr — no./total no. (%)	64/679 (9.4)	16/298 (5.4)	1.72 (0.96 to 3.08)
Death within 6 hr — no./total no. (%)	76/679 (11.2)	21/298 (7.0)	1.55 (0.92 to 2.62)
Death within 24 hr — no./total no. (%)	98/679 (14.4)	33/298 (11.1)	1.25 (0.81 to 1.93)
In-hospital death — no./total no. (%)	171/689 (24.8)	58/298 (19.5)	1.25 (0.87 to 1.78)
Death from hemorrhage or exsanguination — no./total no. (%)§	61/677 (9.0)	23/295 (7.8)	1.08 (0.65 to 1.81)
Death from traumatic brain injury or herniation — no./total no. (%)§	61/677 (9.0)	23/295 (7.8)	0.98 (0.56 to 1.71)
Units transfused within 24 hr after arrival — median (IQR)			
Whole blood	0.0 (0.0 to 1.0)	0.0 (0.0 to 1.0)	0.91 (0.69 to 1.21)
Plasma	1.0 (0.0 to 4.0)	1.0 (0.0 to 5.0)	0.85 (0.66 to 1.11)
Platelets	0.0 (0.0 to 1.0)	0.0 (0.0 to 1.0)	0.86 (0.63 to 1.17)
Red cells	1.0 (0.0 to 4.0)	2.0 (0.0 to 5.0)	0.86 (0.67 to 1.09)
Cryoprecipitate	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.81 (0.49 to 1.32)
Hemostasis¶			
No. of patients/total no. (%)	619/694 (89.2)	277/296 (93.6)	0.61 (0.35 to 1.04)
Median time to hemostasis — min (IQR)	60.0 (60.0 to 78.0)	60.0 (60.0 to 80.0)	0.98 (0.88 to 1.09)
Multiple organ failure — no. (%)‖	98 (14.1)	37 (12.4)	1.12 (0.74 to 1.69)
Nosocomial infection — no. (%)	57 (8.2)	26 (8.7)	0.92 (0.55 to 1.54)
Acute respiratory distress syndrome — no. (%)‖	273 (39.3)	121 (40.6)	0.87 (0.66 to 1.17)
Coagulation measurements			
INR >1.5 within 1 hr after arrival — no./total no. (%)**	109/538 (20.3)	57/216 (26.4)	0.69 (0.46 to 1.02)
Median prothrombin time within 1 hr after arrival — sec (IQR)	14.2 (12.3 to 16.4)	14.5 (12.2 to 16.5)	0.05 (–0.68 to 0.78)

* All models were adjusted for traumatic brain injury, prehospital intubation, and month of enrollment as fixed effects, with random intercepts and random slopes for the participating air medical base. The widths of the confidence intervals for secondary outcomes have not been adjusted for multiplicity and should not be used in place of hypothesis tests. The number of units of blood products transfused and the time to hemostasis were available for 694 patients in the whole-blood group and 296 in the component group; data on prothrombin time were available for 538 and 216, respectively. INR denotes international normalized ratio.

† Effect estimates are reported as adjusted odds ratios, except those for units transfused (reported as adjusted incidence rate ratios), time to hemostasis (reported as an adjusted odds ratio), and prothrombin time (reported as the adjusted β).

‡ P=0.24.

§ Data are shown for patients for whom the indicated outcome was listed as one of up to two causes of death.

¶ Hemostasis was considered to have been reached in patients who received no more than 1 unit of whole blood or red cells in any 60-minute interval within 4 hours after arrival at the trauma center.

‖ The occurrence of multiple organ failure and of acute respiratory distress syndrome was assessed among patients who were admitted to the intensive care unit for at least 2 days and was not assessed beyond 7 days after randomization.

** Because the distribution was bimodal, the INR was dichotomized (>1.5 vs. ≤1.5).

secondary outcomes varied according to outcome distribution and otherwise followed the same approach as the primary analysis. Binary outcomes were analyzed with mixed-effects logistic regression, continuous outcomes with mixed-effects linear regression, and count outcomes with negative binomial regression. Death within 30 days was assessed in a time-to-event analysis with Kaplan–Meier curves, whereas time to hemostasis was analyzed with a Cox proportional-hazards frailty model to estimate hazard ratios.

Baseline demographic and clinical characteristics were stratified according to the storage age of whole blood among patients assigned to

the whole-blood group with available storage-age data. When 2 units of whole blood were used in a single transfusion, the average storage age was used for analyses. A generalized boosted regression model was used to estimate propensity scores for receipt of older whole blood (storage age, 15 to 21 days), with incorporation of prerandomization variables known to be associated with the primary outcome. A mixed-effects log-binomial regression model with inverse probability weighting based on the propensity score was used to estimate the association between the storage age of whole blood and death within 30 days. Prespecified subgroup analyses included interaction terms for storage age and subgroup. Analyses of other outcomes followed the same distribution-based approaches described above. Sensitivity analyses were performed with multiple approaches for missing survival status at 30 days, including categorizing all the patients with unknown survival status as alive, excluding those with missing outcomes, and categorizing all those with unknown survival status as deceased.

Sample-size calculations were carried out before the start of the trial. We determined that a sample of 1020 patients from 40 participating sites, with patients assigned in a 2:1 ratio to receive whole blood (680 patients) or blood components (340 patients), would provide the trial with 80% power to detect a difference in 30-day mortality of 10 percentage points (26% vs. 16%)[3] with a two-sided type I error rate of 0.05 and an intraclass correlation coefficient of 0.02.[3] Analyses were carried out according to a modified intention-to-treat approach. Patients who had undergone randomization under an exception from standard procedures for informed consent were able to opt out of continued participation and have their data excluded from analyses. Patients who opted to withdraw after randomization were excluded from the modified intention-to-treat population.

RESULTS

PATIENTS

From May 2022 through June 2025, a total of 9554 patients who were transported by 44 prehospital bases to 11 trauma centers were assessed for eligibility. A total of 1098 patients were eligible for enrollment, and of these, 1020 met all the inclusion criteria and no exclusion criteria and were included in the intention-to-treat population. Of those patients, 715 were transported by air bases that had been randomly assigned to the whole-blood group, and 305 were transported by bases assigned to the component group (Fig. 1).

The majority of the patients were men (73.5%) and had injury from a blunt mechanism, with a median Injury Severity Score of 25 (interquartile range, 14 to 34; scores range from 1 to 75, with higher scores indicating greater severity and a score of >15 indicating major trauma). Traumatic brain injury was present in 405 patients (39.7%), and prehospital intubation occurred in 536 patients (52.5%). Operative intervention during the first 24 hours occurred in 634 patients (62.2%). Most patients (70.8%) were transported from the scene of injury, and the remaining patients were transported from a referring emergency department (Table S3). The demographic and injury characteristics of the patients and the prehospital vital signs were similar in the two trial groups (Table 1).

PROTOCOL ADHERENCE

Prehospital teams performed transfusion with the assigned blood products in 964 (94.5%) of 1020 patients enrolled in the trial. In the whole-blood group, 343 patients (48.0%) received 1 unit of whole blood, 326 (45.6%) received 2 units of whole blood, and 46 (6.4%) received no whole blood. Of the patients assigned to the whole-blood group, 226 (31.6%) received blood components, either alone or in addition to whole blood.

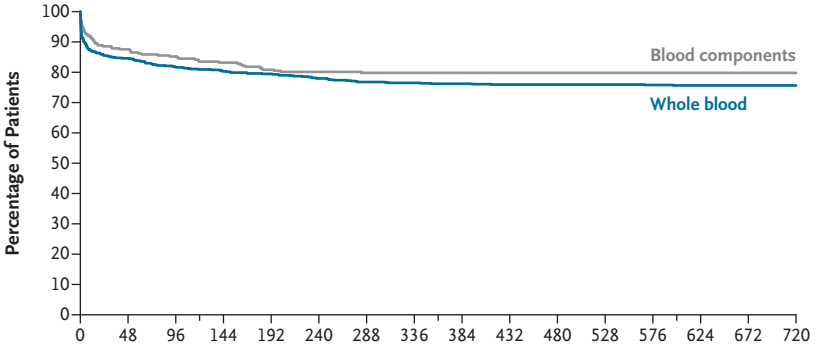
In the component group, 136 patients (44.6%) received 1 unit of red cells, 129 (42.3%) received 2 units of red cells, 117 (38.4%) received 1 unit of plasma, and 93 (30.5%) received 2 units of plasma; 175 patients (57.4%) received both red cells and plasma. Of the patients assigned to the component group, 15 (4.9%) received 1 unit of whole blood and 11 (3.6%) received 2 units of whole blood.

PRIMARY OUTCOME

Data for the primary outcome were available for 972 patients (95.3%), with data imputed for 13 patients in the whole-blood group and 8 patients in the component group. The primary analysis included 695 patients in the whole-blood group

and 298 patients in the component group (the modified intention-to-treat population). A total of 27 patients (20 in the whole-blood group and 7 in the component group) were excluded from the primary analysis owing to withdrawal from the trial.

A Overall Survival According to Treatment Group



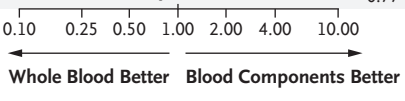
Log-rank test: χ^2=2.18; P=0.13

No. at Risk

Blood components	297	249	239	238	237	237	237
Whole blood	681	552	532	520	518	516	516

B Subgroup Analysis of 30-Day Mortality

Subgroup	No. of Patients	Whole Blood	Blood Components	Odds Ratio (95% CI)
		no. of deaths/no. of patients (%)		
Overall	992	180/695 (25.9)	61/297 (20.5)	1.24 (0.87–1.76)
Head or neck AIS score >2				
Yes	359	81/254 (31.9)	35/105 (33.3)	0.92 (0.55–1.54)
No	566	70/388 (18.0)	25/178 (14.0)	1.20 (0.71–2.04)
Transfer site				
Scene of injury	703	133/491 (27.1)	47/212 (22.2)	1.26 (0.84–1.89)
Other hospital	290	47/204 (23.0)	14/86 (16.3)	1.21 (0.60–2.46)
Severe hypotension (≤70 mm Hg)				
Yes	543	130/377 (34.5)	40/166 (24.1)	1.59 (1.02–2.47)
No	450	50/318 (15.7)	21/132 (15.9)	0.84 (0.47–1.51)
Age				
18–55 yr	679	90/481 (18.7)	25/198 (12.6)	1.50 (0.86–2.61)
≥56 yr	307	85/209 (40.7)	35/98 (35.7)	1.31 (0.78–2.17)
Sex				
Male	720	130/498 (26.1)	46/222 (20.7)	1.23 (0.82–1.86)
Female	263	46/188 (24.5)	15/75 (20.0)	1.11 (0.54–2.26)
Race or ethnic group				
White	654	117/450 (26.0)	43/204 (21.1)	1.28 (0.84–1.95)
Non-White	244	29/165 (17.6)	13/79 (16.5)	0.79 (0.37–1.68)
Trauma center				
A	150	27/107 (25.2)	6/43 (14.0)	1.91 (0.68–5.31)
B	248	35/155 (22.6)	17/93 (18.3)	1.05 (0.52–2.10)
C	68	16/44 (36.4)	7/24 (29.2)	1.22 (0.38–3.95)
D, E, or K	64	11/54 (20.4)	4/10 (40.0)	0.40 (0.09–1.89)
F	39	7/30 (23.3)	3/9 (33.3)	1.04 (0.18–5.96)
G	116	19/88 (21.6)	4/28 (14.3)	1.50 (0.45–5.00)
H	62	14/42 (33.3)	4/20 (20.0)	2.15 (0.55–8.37)
I	113	32/85 (37.6)	6/28 (21.4)	2.33 (0.78–6.91)
J	133	19/90 (21.1)	10/43 (23.3)	0.77 (0.31–1.91)



At 30 days after randomization, overall mortality was 24.3%, with 180 deaths in the whole-blood group and 61 deaths in the component group. Mortality at 30 days was 25.9% in the whole-blood group and 20.5% in the component group after imputation and adjustment for clustering and imbalance (adjusted odds ratio, 1.24; 95% confidence interval [CI], 0.87 to 1.76; P=0.24) (Table 2). The intraclass correlation coefficient was 0.01 (95% CI, −0.02 to 0.04), which indicates negligible clustering and no statistically meaningful site-level variation. The Donner–Klar test showed a between-group difference of 0.082 (P=0.08), which indicates no significant difference after accounting for clustering. The results of sensitivity analyses that addressed missing data with respect to vital status at 30 days were similar (Table S4). The Kaplan–Meier survival curves were similar in the two groups (χ^2=2.18 by a log-rank test; P=0.13) (Fig. 2A). Mortality at 30 days did not appear to differ substantially among the seven prespecified subgroups (Fig. 2B). A per-protocol analysis involving patients who received prehospital whole blood (regardless of whether they also received blood components) or who received blood components alone is shown in Tables S5 and S6.

Figure 2 (facing page). Overall Survival and Subgroup Analysis of Mortality at 30 Days According to Treatment Group.

Panel A shows Kaplan–Meier estimates of survival among patients who underwent volume resuscitation with whole blood or blood components in the prehospital setting. Time zero was defined as the time of arrival at a participating trauma center. Panel B shows the odds ratio for death within 30 days in seven prespecified subgroups. The dashed vertical line represents an odds ratio of 1.0, which indicates no difference in mortality between the whole-blood group and the component group. Estimates were derived from logistic-regression models with death within 30 days as the outcome and with treatment-by-subgroup interaction terms. All models were adjusted for traumatic brain injury, prehospital intubation, and month of enrollment as fixed effects, with random intercepts and random slopes for the participating air medical base. Scores on the Abbreviated Injury Scale (AIS) range from 1 to 6, with higher scores indicating more-severe injury. Race and ethnic group were reported by the patients or family members. Non-White race or ethnic group included Asian, Black, American Indian or Alaska Native, and other. Owing to small numbers of patients or events and model convergence limitations, some trial sites were combined for analyses.

SECONDARY OUTCOMES

Mortality at 3, 6, and 24 hours and in-hospital mortality appeared to be similar in the whole-blood and component groups. No apparent differences between groups were noted with respect to the number of units of blood products transfused within 24 hours or the incidence of multiple organ failure, nosocomial infection, or acute respiratory distress syndrome (Table 2). Coagulation measurements and a convenience sample of platelet function measures are shown in Table S7.

OBSERVATIONAL STUDY OF WHOLE-BLOOD STORAGE AGE

Of the 668 patients in the whole-blood group for whom the storage age of the transfused whole blood was known, 216 (32.3%) received whole blood with a storage age of 15 to 21 days and 452 (67.7%) received whole blood with a storage age of 1 to 14 days. Of these patients, 210 and 443, respectively, were included in the analysis of the primary outcome (Fig. S1 and Table S8). The storage age of whole blood did not appear to be associated with substantial differences in 30-day mortality between the two groups (27.1% vs. 26.4%; adjusted odds ratio, 0.99; 95% CI, 0.74 to 1.32) or in other secondary outcomes (Table S9). The Kaplan–Meier survival curves appeared to be similar in the two groups (χ^2=0.01 by a log-rank test) (Fig. 3A). The results of the analysis of 30-day mortality according to the storage age of whole blood in the seven prespecified subgroups suggested no apparent differences (Fig. 3B).

SAFETY

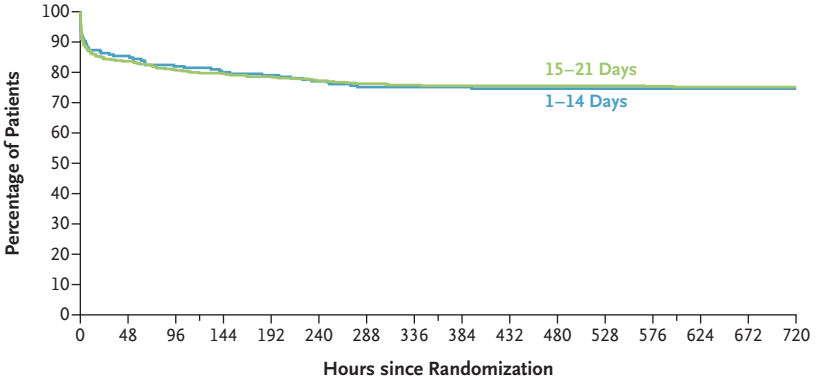
In the intention-to-treat population, the incidence of adverse events, including serious adverse events, was similar in the two trial groups (Table S10). The incidence of adverse events was also similar in the two groups stratified according to the storage age of whole blood in the observational substudy (Table S11).

DISCUSSION

Prehospital blood transfusion for patients at risk for hemorrhagic shock is increasingly common and is associated with higher survival than delayed transfusion or no transfusion.[1-3,13-15] Volume resuscitation with whole blood has now been widely adopted in military and civilian trauma centers because of the logistic and potential

hemostatic benefits.[16-21] Despite these changes, high-level evidence showing benefit from the use of prehospital whole blood as compared with blood components remains limited.[22,23] In this trial involving 1020 patients with severe injury who were enrolled during the prehospital phase of care, 30-day mortality did not differ significantly between the trial groups, nor were apparent between-group differences observed with respect to secondary outcomes, including units of blood products transfused within 24 hours after arrival at the hospital, multiple organ failure,

A Overall Survival According to Blood Storage Age



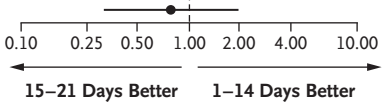
Log-rank test: χ^2=0.01; P=0.93

No. at Risk

15–21 Days	205	168	159	155	153	153	153
1–14 Days	434	347	336	329	329	327	327

B Subgroup Analysis of 30-Day Mortality According to Blood Storage Age

Subgroup	No. of Patients	15–21 Days	1–14 Days	Odds Ratio (95% CI)
		no. of deaths/no. of patients (%)		
Overall	653	57/210 (27.1)	117/443 (26.4)	0.99 (0.74–1.32)
Head or neck AIS score >2				
Yes	241	25/81 (30.9)	52/160 (32.5)	0.98 (0.50–1.94)
No	365	24/118 (20.3)	44/247 (17.8)	1.43 (0.78–2.61)
Transfer site				
Scene of injury	471	39/149 (26.2)	90/322 (28.0)	1.18 (0.69–2.02)
Other hospital	182	18/61 (29.5)	27/121 (22.3)	1.32 (0.57–3.08)
Severe hypotension (≤70 mm Hg)				
Yes	354	42/114 (36.8)	84/240 (35.0)	1.31 (0.75–2.30)
No	299	15/96 (15.6)	33/203 (16.3)	1.14 (0.52–2.49)
Age				
18–55 yr	452	26/140 (18.6)	61/312 (19.6)	1.41 (0.70–2.84)
≥56 yr	196	31/70 (44.3)	51/126 (40.5)	1.08 (0.56–2.08)
Sex				
Male	468	41/157 (26.1)	84/311 (27.0)	1.11 (0.65–1.91)
Female	176	15/50 (30.0)	30/126 (23.8)	1.63 (0.71–3.76)
Race or ethnic group				
White	425	38/127 (29.9)	75/298 (25.2)	1.29 (0.77–2.17)
Non-White	154	11/61 (18.0)	18/93 (19.4)	1.01 (0.39–2.63)
Trauma center				
A	98	13/37 (35.1)	14/61 (23.0)	1.18 (0.37–3.74)
B	153	5/37 (13.5)	30/116 (25.9)	0.90 (0.26–3.11)
C or H	75	6/15 (40.0)	20/60 (33.3)	0.67 (0.15–3.06)
D, E, F, or K	76	6/33 (18.2)	11/43 (25.6)	1.95 (0.50–7.57)
G or J	167	11/41 (26.8)	27/126 (21.4)	1.72 (0.64–4.62)
I	84	16/47 (34.0)	15/37 (40.5)	0.78 (0.31–1.96)



nosocomial infection, acute respiratory distress syndrome, coagulation measurements, and platelet function measurements. These results have important implications for both civilian prehospital resuscitation and military blood-supply planning.

Hemostatic resuscitation with blood components in austere, far-forward military settings may not be feasible.[16-18] Whole blood combines the benefits of all three blood components (red cells, plasma, and platelets), has a long shelf life, and reduces the need to monitor multiple units of blood products outside the blood bank.[24] The results of the current observational substudy provide insights into the associations of patient outcomes and hemostatic function with the storage age of whole blood.

Prehospital care for patients with severe injuries has evolved over time. In a previous trial involving prehospital transfusion in patients at risk for hemorrhagic shock, which completed enrollment nearly a decade ago, overall mortality was 33.0% in the group receiving standard care.[3] In the current trial involving a similar patient population, the overall mortality among all enrolled patients was 24.3%. A recent randomized trial involving prehospital use of whole blood showed similar 30-day mortality.[23] Improvements such as the use of reduced crystalloid resuscitation, early blood transfusion, and an emphasis on control of hemorrhage and use of resuscitation adjuncts may contribute to lower mortality.[1-3,25-29]

The strengths of the current trial include the pragmatic design with generalizability, pragmatic inclusion criteria, and the large sample size. The randomization block design with a 2:1 ratio between the whole-blood group and the component group allowed for a robust observational whole-blood substudy.

Limitations of the trial include the cluster-randomized design, which was essential because of the logistics of prehospital care. Several variables may have increased the potential risk of type II error in the primary analysis. Blood-product crossover between trial groups occurred. Blood transfusion before randomization was not a criterion for trial exclusion, which potentially limited differences between the trial groups. The overall transfusion volume provided in the prehospital phase of care was low as compared with the volume of products provided in the hospital. Some patients in the component group received both plasma and red cells, which may have resulted in similar resuscitation characteristics in the two trial groups. Similarly, some patients in the whole-blood group received additional transfusion with blood components. The number of units of blood products transfused in the prehospital environment was not addressed in the protocol. The intervention could not be masked, which leaves the potential for treatment bias. Measurements of coagulation and platelet function were limited by missing data and potential spectrum bias. The analyses of primary and secondary outcomes may be limited by unmeasured or unknown confounders.

In patients at risk for hemorrhagic shock who underwent blood transfusion, the use of whole blood did not result in lower 30-day mortality than the use of blood components. The storage age of whole blood through 21 days from donation was not associated with apparent differences in outcomes.

Figure 3 (facing page). Overall Survival and Subgroup Analysis of Mortality at 30 Days According to Storage Age of Whole Blood.

Panel A shows Kaplan–Meier estimates of survival among patients in the whole-blood group according to the storage age of the blood (the amount of time from donation to transfusion). Time zero was defined as the time of arrival at a participating trauma center. Panel B shows the odds ratio for death within 30 days in seven prespecified subgroups. The dashed vertical line represents an odds ratio of 1.0, which indicates no difference in mortality between the group receiving older blood (storage age, 15 to 21 days) and the group receiving newer blood (storage age, 1 to 14 days). Estimates were derived from logistic-regression models with death within 30 days as the outcome and with treatment-by-subgroup interaction terms. All models were adjusted for month of enrollment (fixed effect), the participating air medical base (random effect to account for clustering), and inverse probability of treatment weighting. Owing to small numbers of patients or events and model convergence limitations, some trial sites were combined for analyses.

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