ORIGINAL ARTICLE

Prehospital Whole Blood in Traumatic Hemorrhage — a Randomized Controlled Trial

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ABSTRACT

BACKGROUND

Whole-blood transfusion has recently gained favor in the management of severe hemorrhage; however, data from large clinical trials evaluating its clinical effectiveness and safety are lacking.

METHODS

We conducted a pragmatic, phase 3, multicenter, unblinded, randomized, superiority trial across 10 air ambulance services in England. Patients with major traumatic hemorrhage who were attended by a participating air ambulance service were randomly assigned to receive either whole-blood transfusion (up to 2 units) or standard care with blood components (up to 2 units each of red cells and plasma) before arrival at the hospital. The primary outcome was a composite of death from any cause or massive transfusion (≥10 units of blood components or products) within 24 hours after randomization.

RESULTS

A total of 942 patients underwent randomization. After the exclusion of participants with nontraumatic hemorrhage or traumatic cardiac arrest, 616 were included in the analysis (314 in the whole-blood group and 302 in the standard-care group). A primary-outcome event occurred in 48.7% of the participants in the whole-blood group and in 47.7% of those in the standard-care group (relative risk, 1.02; 95% confidence interval, 0.80 to 1.31; P=0.84). The incidence of death from any cause at all time points, massive transfusion, and other secondary outcomes appeared to be similar in the two groups. Prothrombin times were above the normal range in 40.7% of the participants in the whole-blood group and in 30.5% of those in the standard-care group. More serious adverse events occurred in the standard-care group than in the whole-blood group (37 and 31, respectively). The incidence of thrombotic events appeared to be similar in the two groups.

CONCLUSIONS

Among participants with life-threatening hemorrhage, prehospital transfusion of 2 units of whole blood was not superior to standard care in reducing the risk of death or massive transfusion within 24 hours. (Funded by NHS Blood and Transplant and others; ISRCTN Registry number, ISRCTN23657907.)

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Blood transfusion is a lifesaving treatment in the management of severe traumatic hemorrhage. The debate surrounding the relative benefits of transfusing individual blood components (red cells, plasma, or platelets) as compared with whole blood is ongoing, with a growing emphasis on early prehospital transfusion, which is performed as close to the time of injury as possible before arrival at the hospital.[1,2]

Whole blood combines red cells, plasma, and platelets, although its composition and specifications vary between countries.[3-5] Several countries have implemented whole-blood transfusion into clinical practice, and international randomized trials are ongoing; however, robust evidence comparing the clinical effectiveness and safety of whole-blood transfusion with blood-component therapy is limited.[6-8]

In the United Kingdom, prehospital transfusion by air ambulance teams usually involves the administration of red cells alone, or red cells and plasma as separate components.[9] Recently, leukocyte-depleted platelet-rich whole blood, containing red cells, plasma, and platelets, has become available and can be stored at 4°C (±2°C) for up to 21 days.[3,10] The use of a single bag streamlines logistics, shortens administration time, aids limited circulatory access, and decreases the risk of transfusion errors.[11]

As part of a national program in England, the Study of Whole Blood in Frontline Trauma (SWiFT)[12] trial aimed to determine whether prehospital transfusion of up to 2 units of whole blood was superior to standard blood components in reducing the risk of death or massive transfusion (defined as the administration of ≥10 units of blood components or products) within 24 hours in patients with life-threatening traumatic hemorrhage.

METHODS

TRIAL DESIGN

The SWiFT trial was a pragmatic, phase 3, multicenter, unblinded, randomized, controlled, superiority trial involving trauma patients with life-threatening bleeding across 10 air ambulance services (comprising physician–paramedic clinical teams[1]), who were received by 19 hospitals. We compared the outcomes in participants who were randomly assigned to receive leukocyte-depleted whole blood (group O, with low levels of anti-A and anti-B antibodies)[13,14] with outcomes in participants who received red cells and plasma (the standard-care group) in the prehospital setting (Table S26 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[12] No other aspects of patient care during transport or after hospital arrival were altered.

TRIAL OVERSIGHT

The trial was sponsored by National Health Service Blood and Transplant (NHSBT) and coordinated by the NHSBT Clinical Trials Unit. The authors designed the trial with input from the NHSBT Patient and Public Advisory Group during the design and funding stages. It was categorized as a Clinical Trial of Investigational Medicinal Product, with approvals from the Health Research Authority, South Central, Oxford C Research Ethics Committee, the Confidentiality Advisory Group, and local research and development departments at the participating sites (see the Supplementary Appendix).[12] Owing to the anticipated lack of capacity of the patients and the need for immediate treatment, obtaining consent before enrollment would have resulted in unsafe delays and was not feasible. Therefore, in accordance with regulations in the United Kingdom and the principles of the Declaration of Helsinki, enrollment occurred without the consent of patients. Written informed consent was obtained as soon as feasible after resuscitation from patients who survived and regained capacity or from a legal representative if the patient lacked capacity.

An independent trial steering committee and a data and safety monitoring committee provided trial oversight. All blood components were provided by NHSBT. The funders had no role in the design or conduct of the trial or in the analysis of the data. No commercial support was received. Apart from an increase in the sample size after a review by the data and safety monitoring committee, no substantive changes were made to the protocol (available at NEJM.org). The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol.

PATIENT POPULATION

Given the pragmatic nature of the trial, administration of whole blood and standard care was based on clinician judgment and the standard

criteria for initiation of blood transfusion for each air ambulance service. Patients of any age with a traumatic injury leading to prehospital transfusion for the treatment of major hemorrhage were eligible to participate. Patients were excluded if intravenous or intraosseous access could not be established, if they had a known objection to blood transfusion, or if they had received blood components or products before the arrival of the air ambulance service. Because the trial boxes contained the only blood products carried by most air ambulance services, it was prespecified that nontrauma patients would be enrolled in the trial but replaced in the sample size. It was also prespecified that patients who were in traumatic cardiac arrest (defined by the absence of a palpable pulse or signs of life) when the air ambulance service arrived would be enrolled but excluded from the primary analysis because survival was expected to be lower among these patients than among other patients with trauma[12]; the outcomes of these patients are reported separately (Tables S15, S38, and S39).

RANDOMIZATION AND TREATMENT

We randomly assigned blood boxes in a 1:1 ratio to be packed with either whole blood or standard blood components. Randomization was performed with the use of a centralized, Web-based service (Sealed Envelope). The randomization sequence was generated with randomly permuted blocks of varying undisclosed sizes and stratified according to air ambulance service.

Randomization was conducted by the transfusion laboratory teams who prepared the sealed, identical trial boxes according to the assigned treatment and dispatched them to air ambulance services to ensure that the clinical teams were unaware of the assignments. Participants were considered to be enrolled once the trial box was opened with an intent to transfuse. Once opened, the assigned treatment could not be concealed.

Participants received up to 2 units of whole blood in the whole-blood group or up to 2 units of red cells and 2 units of plasma (either thawed plasma or lyophilized plasma [used by four services] from the German Red Cross [DRK-Blutspendedienst West]) in the standard-care group; both whole blood and standard care could be administered by the intravenous or intraosseous route. After hospital admission, additional blood components were administered according to routine care.

OUTCOMES

The primary outcome was a composite of death from any cause or massive transfusion (defined as ≥10 units of any blood components in adults, and ≥40 ml per kilogram of body weight in pediatric participants [<16 years of age with a body weight of <50 kg]) within 24 hours after randomization.[15] Secondary outcomes included death from any cause at 6 hours, 24 hours, 30 days, and 90 days after randomization; massive transfusion; days free from organ failure (up to 30 days); days in critical care and hospital (up to 90 days); number of units of blood component or product and cell salvage received within 24 hours after randomization (including prehospital transfusions); use of additional hemostatic agents within 24 hours after randomization; a prothrombin time that was above the normal range; and an acid-base disturbance — the latter two secondary outcomes were measured in the first blood sample obtained on hospital arrival.[12]

Safety outcomes included thrombotic events occurring up to 30 days after randomization, as well as transfusion reactions or adverse events considered to be related to prehospital blood components or serious adverse events occurring within the 14 days after transfusion, up to the time of hospital discharge, or up to the time of death, whichever occurred first. Among the participants who received whole blood, those who were in traumatic cardiac arrest, had nontraumatic hemorrhage, or did not undergo randomization received follow-up evaluations to obtain safety data. Adverse events that occurred in these participants are reported separately from the adverse events that occurred in the modified intention-to-treat population (Table S20). Cost-effectiveness analyses including quality-of-life outcomes were also planned (results not reported here).[12]

STATISTICAL ANALYSIS

Using data from a previous study,[1] we estimated that the percentage of participants with a primary-outcome event in the first 24 hours after randomization would be 68%. The sample size was calculated with the use of SAS Enterprise Guide software, version 7.13 (SAS Institute). The trial was powered to detect an absolute differ-

ence of 12 percentage points (relative difference, 38%) in the risk of death from any cause or massive transfusion (the composite primary outcome) between the two groups (68% in the standard-care group vs. 56% in the whole-blood group). Assuming a two-sided test with 85% power, a 5% significance level, and one interim analysis (performed with the use of O'Brien–Fleming boundaries to inform early stopping for harm or benefit), we calculated that the trial would require a sample of 602 participants; after allowing for the occurrence of traumatic cardiac arrest at the time of arrival of the air ambulance service in 25% of the participants (the data for whom would be excluded from the analysis) and an additional dropout of 5%, we determined that the total number of participants required for this trial would be 848.

After the first 300 participants underwent randomization, the data and safety monitoring committee conducted a preplanned blinded review of the sample size with the use of overall event rate data (not analyzed according to trial group) and increased the sample size to 900 participants (excluding those with nontraumatic hemorrhage). One preplanned interim analysis of the primary outcome was performed after 400 participants (excluding those who were in traumatic cardiac arrest) underwent randomization; the results of this analysis were reviewed by the data and safety monitoring committee only, and the trial continued as planned.

Analyses followed the statistical analysis plan (available with the protocol). Summary statistics for all outcomes and marginal effects from modeling analyses are reported. The primary modified intention-to-treat analysis of death from any cause or massive transfusion excluded participants with nontraumatic hemorrhage and those who were in traumatic cardiac arrest on arrival of the air ambulance service. For the purposes of analysis, 2 units of whole blood (approximately 940 ml) were prespecified as equivalent to 4 units of total units of red-cell and plasma components (approximately 1104 ml) to account for volume differences. The composite primary outcome was analyzed with the use of a marginal mixed logistic-regression model, with air ambulance services fitted as a random effect and treatment group fitted as a fixed effect, to test a two-sided superiority hypothesis. A sensitivity analysis of the primary outcome was also performed with the use of a conditional model (Table S36). The statistical analysis plan specified that between-group differences would be reported as odds ratios; however, at the request of the *Journal*, these are reported as relative risks.

Secondary outcomes were analyzed in accordance with the statistical analysis plan (see the Supplementary Appendix). The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

Missing data for the primary outcome were assumed to be missing completely at random and were not imputed in the main analysis. However, we performed a sensitivity analysis to explore imputation of data reflecting extreme scenarios for participants with missing primary-outcome data (as described in the statistical analysis plan).

The analysis of the primary outcome was replicated across four predefined subgroups: presence of traumatic brain injury (defined by a score of ≥3 on the Abbreviated Injury Scale for the head; scores range from 0 to 6, with a score of 0 indicating no injury and a score of 6 indicating an unsurvivable injury), population of patients (adults or pediatric patients <16 years),[16] injury type (blunt or penetrating), and Injury Severity Score (≤15, 16–25, or ≥26; scores range from 0 to 75, with higher scores indicating greater injury severity; an Injury Severity Score of >15 indicates major trauma).[17] We also explored the treatment effect on the primary outcome of several post-intervention factors, including prehospital anesthesia (yes or no), prehospital transport time (≤20 or >20 minutes), and, for participants in the whole-blood group, the age of the whole-blood units (1–14 or >14 days).

Safety outcomes were also summarized according to trial group. Thrombotic events were summarized according to trial group; a marginal logistic-regression model, with adjustment for air ambulance service as a random effect, was used to analyze the occurrence of at least one thrombotic event.

RESULTS

PARTICIPANTS

From December 2022 through September 2024, we enrolled a total of 942 participants (470 in the

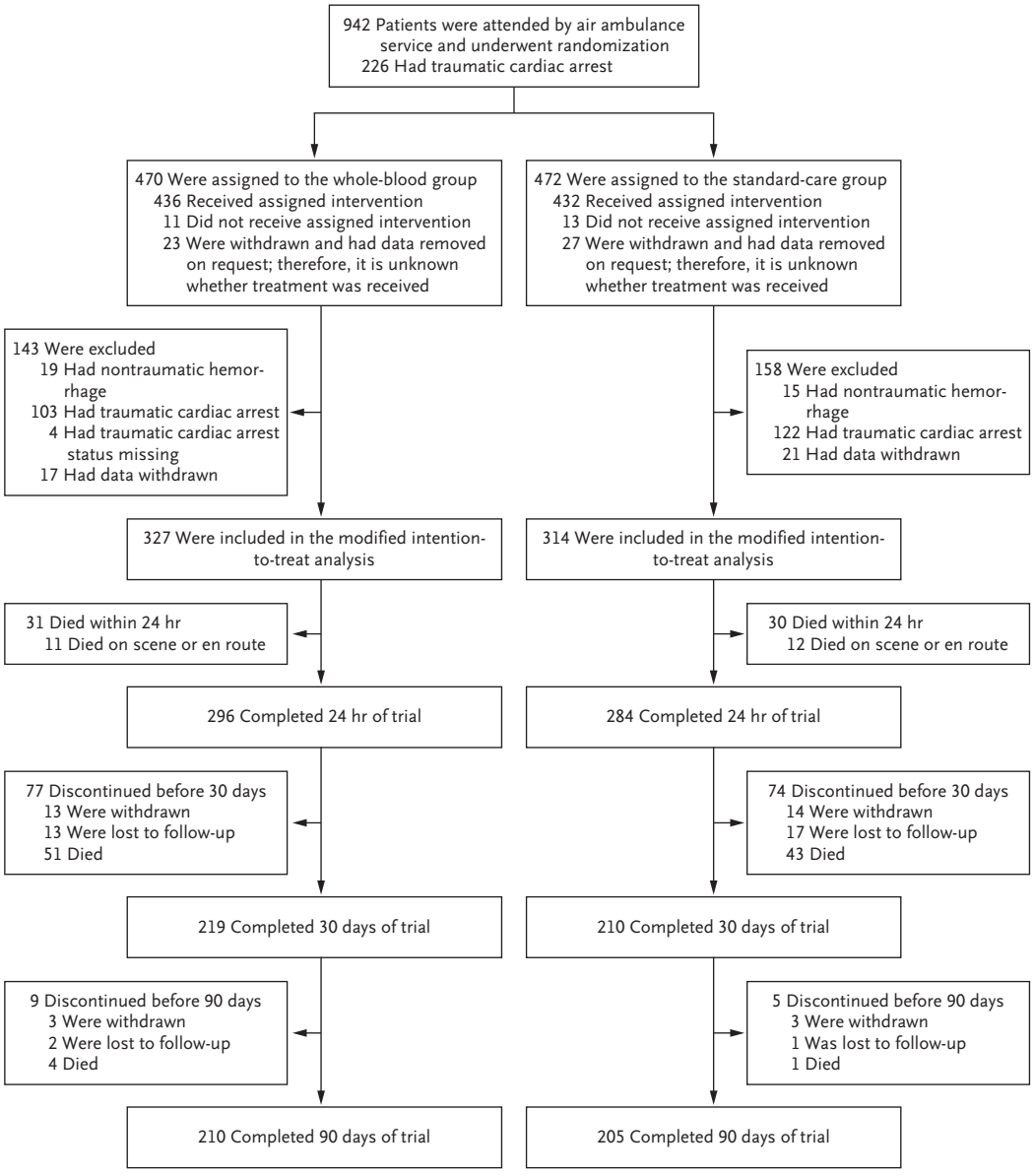

Figure 1. Screening, Randomization, and Follow-up.

Of the 50 participants who were withdrawn from the trial and requested data removal, 21 were involved in a serious breach of protocol and their "treatment received" data were removed (11 participants in the whole-blood group and 10 participants in the standard-care group). Of the 34 participants who were excluded because of nontraumatic hemorrhage, 2 were involved in a serious protocol breach. Of the 38 participants who were excluded because they had data withdrawn, 17 were involved in a serious protocol breach and their data regarding traumatic cardiac arrest status were removed (9 participants in the whole-blood group and 8 participants in the standard-care group); therefore, we could not assess these exclusions. There were 2 participants involved in a serious protocol breach who were withdrawn more than 90 days after randomization. All other withdrawals were related to patient or consultee withdrawal. One patient who was withdrawn from the trial had nontraumatic hemorrhage and traumatic cardiac arrest; this patient was included in the group of 226 participants who were in traumatic cardiac arrest when the air ambulance service arrived but not in the group of 225 participants with traumatic cardiac arrest.

whole-blood group and 472 in the standard-care group). After the exclusion of participants with nontraumatic hemorrhage, 908 participants remained (Fig. 1). The follow-up period was 90 days, and the last enrolled participant completed follow-up in December 2024. Owing to the pragmatic design of the trial, 301 participants (143 in the whole-blood group and 158 in the standard-care group) were excluded from the modified intention-to-treat population because they were in traumatic cardiac arrest when the air ambulance service arrived (225 participants) or because they received transfusion for nontraumatic hemorrhage (33 participants). In addition, 1 participant had cardiac arrest and nontraumatic hemorrhage. Exclusions also included 4 participants who had missing traumatic cardiac arrest status and 38 participants whose data were withdrawn from the trial. In April 2024, a serious breach of protocol affected 21 participants who had been enrolled under an emergency waiver of consent but were not subsequently approached for informed consent, data collection, or safety monitoring. After consultation with the research ethics committee, their data were deleted and excluded from the analysis.

A total of 641 participants (327 in the whole-blood group and 314 in the standard-care group) comprised the modified intention-to-treat population. The characteristics of the participants at baseline appeared to be well balanced in the two trial groups (Table 1); most participants were male (75.5%), and the majority had sustained blunt trauma (71.3%), features that are generally representative of the population of patients with major trauma in the United Kingdom (Table S37).

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline and Treatment Characteristics.*

Characteristic	Whole-Blood Group (N=327)	Standard-Care Group (N=314)
Patient characteristics		
Median age (IQR) — yr†	38 (25–58)	35 (24–57)
Age <16 yr — no./total no. (%)	12/325 (3.7)	9/314 (2.9)
Male sex — no./total no. (%)‡	228/306 (74.5)	221/289 (76.5)
Median estimated weight on arrival of air ambulance service (IQR) — kg§	80 (70–90)	80 (70–90)
Injury characteristics		
Injury type — no./total no. (%)		
Blunt	238/325 (73.2)	214/309 (69.3)
Penetrating	87/325 (26.8)	95/309 (30.7)
Abbreviated Injury Scale score for the head — no./total no. (%)¶		
<3	127/219 (58.0)	104/196 (53.1)
≥3	92/219 (42.0)	92/196 (46.9)
Median Injury Severity Score (IQR)‖	33 (18–48)	34 (18–45)
Prehospital measurements**		
Median systolic blood pressure (IQR) — mm Hg	95 (75–121)	96 (79–120)
Median heart rate (IQR) — beats/min	110 (85–129)	110 (83–130)
Median respiratory rate (IQR) — breaths/min	22 (16–29)	23 (17–30)
Median oxygen saturation (IQR) — %††	95 (85–99)	94 (85–99)
Glasgow Coma Scale score — no./total no. (%)‡‡		
≤8	126/317 (39.7)	116/310 (37.4)
9–12	38/317 (12.0)	40/310 (12.9)
≥13	153/317 (48.3)	154/310 (49.7)
Median Glasgow Coma Scale score (IQR)	12 (5–15)	12 (6–15)

Table 1. (Continued.)

Characteristic	Whole-Blood Group (N = 327)	Standard-Care Group (N = 314)
Prehospital treatment characteristics		
Intervention — no./total no. (%)§§		
Airway support	142/289 (49.1)	133/266 (50.0)
Breathing support	139/289 (48.1)	141/266 (53.0)
Thoracostomy	80/289 (27.7)	68/266 (25.6)
Spinal immobilization	118/289 (40.8)	116/266 (43.6)
Chest drain	8/289 (2.8)	10/266 (3.8)
Other	132/289 (45.7)	120/266 (45.1)
Median age of blood transfused (IQR) — days¶¶	13.5 (10–17)	18 (13–22.3)

* Some of the prehospital interventions may have occurred after administration of the intervention and therefore are not strictly baseline characteristics. The baseline data do not include data for participants with traumatic cardiac arrest. Data on the Abbreviated Injury Scale score, the Injury Severity Score, and prehospital interventions were obtained from the National Major Trauma Registry form. IQR denotes interquartile range.
† The median age was estimated for participants who died before arrival at the hospital. Data were missing for 2 participants.
‡ The sex of the participants was not known for those who died before arrival at the hospital.
§ Data were missing for 21 participants.
¶ The Abbreviated Injury Scale scores range from 0 to 6, with higher scores indicating more severe injury; a score of ≥3 indicates a severe traumatic brain injury.
‖ The Injury Severity Score was defined as the sum of the squares of the highest Abbreviated Injury Scale grade in each of the three most severely injured areas. Scores range from 0 to 75, with higher scores indicating more severe injury; a score higher than 15 indicates major trauma. If the patient was dead on arrival at the hospital, then the Injury Severity Score was not calculated and hence was assumed to be 75 (maximum score). Data were missing for 201 participants.
** Measurements of systolic blood pressure were missing for 15 participants, heart rate for 9 participants, respiratory rate for 27 participants, and oxygen saturation for 111 participants.
†† Oxygen saturation was measured by pulse oximetry.
‡‡ Scores on the Glasgow Coma Scale range from 3 to 15, with higher scores indicating a greater level of consciousness.
§§ Multiple interventions could have been selected for each patient. If no interventions were selected but other data from the surrounding questions on the same form were complete, it was assumed that no intervention was delivered. If data from surrounding questions were missing and no interventions were reported, these data were considered by the investigator to be missing.
¶¶ The age of blood transfused was calculated only when the correctly assigned product or component was administered. The age of blood was calculated as the number of days elapsed between the date the donor blood was collected (bled) and the date of transfusion to the recipient. For the standard-care group, only the age of the red cells was used in this calculation. If 2 units of blood were used, the average of the 2 units was taken. Data were missing for 51 participants.

The median Injury Severity Score was 33 (interquartile range, 18 to 48). The percentage of participants with a score of 3 or greater on the Abbreviated Injury Scale for the head and all other prehospital measurements appeared to be similar in the two groups (Table 1).

PROTOCOL ADHERENCE

A protocol deviation occurred in a similar percentage of participants in the whole-blood group and the standard-care group (6.9% and 6.8%, respectively). The incidence of randomization errors was also similar in the two groups (5.1% in the whole-blood group and 5.7% in the standard-care group), which included participants with nontraumatic hemorrhage (4.0% and 3.2%, respectively). The randomization of participants with nontraumatic hemorrhage was anticipated, given the trial setting.

The percentage of participants who withdrew from the trial was 8% in the whole-blood group and 9% in the standard-care group. Six participants (2 in the whole-blood group and 4 in the standard-care group) who were coenrolled in other nonpermissible studies were included in the modified intention-to-treat population but excluded from the per-protocol population. Before hospitalization, 7 participants in the standard-care group received whole blood because of mispacked trial boxes (4 participants) or because only whole-blood trial boxes were available (3 participants). Participants in the whole-blood group who re-

Table 2. Primary Outcome.

Outcome	Whole-Blood Group (N=327)	Standard-Care Group (N=314)	Relative Risk (95% CI)*	P Value†
Death or massive transfusion within 24 hours after randomization — no./total no. (%)				
Modified intention-to-treat population	153/314 (48.7)	144/302 (47.7)	1.02 (0.80–1.31)	0.84
Per-protocol population	145/291 (49.8)	130/273 (47.6)	1.05 (0.83–1.32)	

* The relative risks with 95% confidence intervals were calculated with the use of a mixed logistic-regression model, with air ambulance services fitted as a random effect and treatment group fitted as a fixed effect.
† The P value for the between-group comparison was obtained from a marginal mixed model.

quired further component therapy within 24 hours received additional red cells (220 participants) and plasma (191 participants), in accordance with routine care.

PRIMARY OUTCOME

Among the 641 participants in the modified intention-to-treat population, data on participant status at 24 hours were available for 618 (96.4%), and data on blood components or products were available for 593 (92.5%). Overall, data on the primary outcome were available for 616 of the participants (96.1%; 314 in the whole-blood group and 302 in the standard-care group). In the adjusted modified intention-to-treat analysis (Table 2), 48.7% of the participants in the whole-blood group and 47.7% of those in the standard-care group died or received a massive transfusion within 24 hours after randomization (adjusted relative risk, 1.02; 95% confidence interval [CI] 0.80 to 1.31; P=0.84). Missing data for the primary outcome were assumed to be missing completely at random. Assumptions regarding the missingness mechanism were tested and did not fail. Therefore, a complete case analysis was deemed to be acceptable for the primary analysis. There were no clear patterns of missingness across relevant baseline characteristics. Primary-outcome data were available for 564 of the 583 participants in the adjusted per-protocol analysis (291 in the whole-blood group and 273 in the standard-care group). Results of this adjusted per-protocol analysis suggested no difference between the treatments with regard to the primary outcome, which was in line with the primary analysis; 49.8% of the participants in the whole-blood group and 47.6% of those in the standard-care group died or received a massive transfusion within 24 hours after randomization (relative risk, 1.05; 95% CI, 0.83 to 1.32). Results appeared to be similar in the sensitivity analyses that accounted for missing data (Table S25), in the conditional model, in the subgroup analyses (Tables S21 through S24), and in trial subpopulations (Tables S12 through S16), including the traumatic cardiac arrest population.

SECONDARY OUTCOMES

The percentages of participants who had died from any cause at 6 hours, 24 hours, 30 days, and 90 days after randomization, as well as the percentage of participants who received massive transfusion within 24 hours, appeared to be similar in the two groups. The prothrombin time was reported for 464 of 618 participants (75.1%). A prothrombin time that exceeded the normal range occurred in 40.7% of the participants in the whole-blood group and in 30.5% of those in the standard-care group (relative risk, 1.31; 95% CI, 1.10 to 1.56). Findings for all other secondary outcomes appeared to be similar in the two groups (Table 3).

SAFETY

Slightly more serious adverse events occurred in the standard-care group (37 events) than in the whole-blood group (31 events). At 14 days after randomization, two transfusion-related events in the standard-care group and none in the whole-blood group had occurred (Table 4). The incidence of thrombotic events appeared to be similar in the two groups. Additional safety data are provided in the Supplementary Appendix.

DISCUSSION

In this pragmatic, multicenter, randomized, controlled trial involving participants with major

Table 3. Secondary Outcomes in the Modified Intention-to-Treat Population.*

Population and Outcome	Whole-Blood Group (N=327)	Standard-Care Group (N=314)	Treatment Difference (95% CI)†
mITT			
Death from any cause — no./total no. (%)‡			
6 hr after randomization	27/318 (8.5)	22/301 (7.3)	RR, 1.16 (0.38–3.55)
24 hr after randomization	32/317 (10.1)	30/301 (10.0)	RR, 1.02 (0.39–2.66)
30 days after randomization	82/298 (27.5)	73/281 (26.0)	RR, 1.06 (0.70–1.61); HR, 1.08 (0.79–1.48)
90 days after randomization	87/286 (30.4)	74/272 (27.2)	RR, 1.12 (0.74–1.70); HR, 1.13 (0.83–1.55)
Massive transfusion — no./total no. (%)‡	136/303 (44.9)	123/290 (42.4)	RR, 1.07 (0.80–1.41)
Units of blood component received in the 24 hr after randomization, including prehospital transfusions — median (IQR); no. of participants with data§¶			
Whole blood	4 (2–4); 314	4 (2–4); 7	RRa, NA
Red cells	4 (2–7); 220	4 (2–7); 294	RRa, 1.02 (0.85–1.22)
Fresh-frozen plasma	4 (2–7); 191	3 (2–6); 289	RRa, 1.14 (0.94–1.38)
Lyophilized plasma	2 (1–4); 11	2 (2–4); 18	RRa, NA
Platelets	1 (1–2); 94	1 (1–2); 89	RRa, 0.95 (0.58–1.54)
Cryoprecipitate	2 (2–3); 85	2 (2–4); 82	RRa, 0.91 (0.67–1.22)
Octaplas	4 (2–4); 4	4 (3–6); 3	RRa, NA
mITT minus those who died before arrival at acute care hospital‖			
Prothrombin time above normal range on hospital arrival — no./total no. (%)	94/231 (40.7)	71/233 (30.5)	RR, 1.31 (1.10–1.56)
mITT minus those who died before arrival at acute care hospital or withdrew within 30 days after randomization††**			
Overall days free from organ failure within 30 days after randomization — median (IQR); no. of participants with data	22 (0–29); 285	21 (0–29); 266	
Days free from advanced cardiovascular support — median (IQR); no. of participants with data	27 (12–30); 285	27 (10–30); 266	
Days free from advanced respiratory support — median (IQR); no. of participants with data	23 (1–29); 285	22 (0–29); 266	
Days free from advanced renal support — median (IQR); no. of participants with data	30 (18–30); 285	30 (24–30); 266	
mITT minus those who died before arrival at acute care hospital or withdrew within 90 days after randomization††‡‡			
Time in critical care up to 90 days — median (IQR); no. of participants with data	8 (4–19.5); 184	8 (3–19); 180	
Time in acute care hospital up to 90 days — median (IQR); no. of participants with data	17.5 (6–41); 300	20 (6–48); 284	

* HR denotes hazard ratio, mITT modified intention-to-treat, NA not applicable, RR relative risk, and RRa rate ratio.

† The estimated between-group differences are reported as relative risks, hazard ratios, or rate ratios. Relative risks were calculated with the use of a marginal logistic-regression model, with adjustment for air ambulance service as a random effect. Rate ratios were calculated with the use of an unadjusted zero inflated negative binomial model. Hazard ratios were calculated with the use of a marginal Cox regression model, with adjustment for air ambulance service. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

‡ Death from any cause and massive transfusion were evaluated in the modified intention-to-treat population (327 participants in the whole-blood group and 314 in the standard-care group), which excluded participants with nontraumatic hemorrhage and those who were in traumatic cardiac arrest on arrival of the air ambulance service.

§ Data are for adults only (633 participants) (see the Supplementary Appendix for summaries of components or products received in pediatric participants <16 years of age [8 participants]).

¶ The participants with data include those who reported receiving any of the product in the first 24 hours after randomization. The number of participants included in the zero-inflated negative binomial model differ from these values and are provided in Table S9 in the Supplementary Appendix.

‖ A total of 316 participants in the whole-blood group and 302 participants in the standard-care group were evaluated in this analysis, which excluded participants who died before arrival at an acute care hospital (11 participants in the whole-blood group and 12 participants in the standard-care group).

** A total of 303 participants in the whole-blood group and 287 participants in the standard-care group were evaluated in this analysis, which excluded participants who died before arrival at an acute care hospital (11 participants in the whole-blood group and 12 participants in the standard-care group) and any patient who withdrew before 30 days (13 participants and 15 participants, respectively).

†† Shown are the unadjusted median and IQR, which make no allowance for differential follow-up due to death.

‡‡ A total of 300 participants in the whole-blood group and 284 participants in the standard-care group were evaluated in this analysis, which excluded participants who died before arrival at an acute care hospital (11 participants in the whole-blood group and 12 participants in the standard-care group) and any patient who withdrew before 90 days (16 participants and 18 participants, respectively).

Table 4. Safety Outcomes.

Outcome	Whole-Blood Group (N=327)	Standard-Care Group (N=314)	Total (N=641)
Serious adverse events*			
Total no. of events	31	37	68
Participants with ≥1 serious adverse event — no. (%)	24 (7.3)	31 (9.9)	55 (8.6)
Transfusion-associated adverse events reported to National Hemovigilance scheme up to 14 days after randomization			
Participants with ≥1 event — no. (%)	0	2 (0.6)	2 (0.3)
Thrombotic events within 30 days after randomization			
Pulmonary embolus — no./total no. (%)	17/268 (6.3)	17/252 (6.7)	34/520 (6.5)
Deep venous thrombosis — no./total no. (%)	13/268 (4.9)	11/252 (4.4)	24/520 (4.6)
Myocardial infarction — no./total no. (%)	0/268 (0.0)	1/252 (0.4)	1/520 (0.2)
Stroke — no./total no. (%)	6/268 (2.2)	7/252 (2.8)	13/520 (2.5)
Peripheral ischemia causing tissue loss — no./total no. (%)	1/268 (0.4)	2/252 (0.8)	3/520 (0.6)
Other — no./total no. (%)	11/268 (4.1)	9/252 (3.6)	20/520 (3.8)
Participants with ≥1 event — no./total no. (%)†	38/268 (14.2)	40/252 (15.9)	78/520 (15.0)

* Serious adverse events that occurred up to 14 days after treatment or until discharge from acute care (whichever occurs first). Serious adverse events are reported only for those that occurred during the primary hospital admission.

† The relative risk of a patient having at least one thrombotic event within 30 days after randomization in the whole-blood group, as compared with the standard-care group, was 0.89 (95% CI, 0.61 to 1.28), as calculated with the use of a marginal mixed logistic-regression model, with adjustment for air ambulance service as a random effect.

traumatic hemorrhage, prehospital transfusion of up to 2 units of whole blood was not superior to standard care (transfusion of red cells and plasma) in reducing the risk of death or massive transfusion at 24 hours. The number of participants who died (at all prespecified time points), the incidence of massive transfusion (at 24 hours), and other secondary clinical outcomes (apart from the prothrombin time, measured on hospital arrival) appeared to be similar in the two groups. No safety concerns were identified with whole-blood transfusion.

Trauma resuscitation has shifted from a crystalloid-based approach toward earlier, balanced transfusion strategies. However, platelet transfusion remains impractical owing to storage requirements (i.e., continuous agitation of platelets). In addition, carrying multiple components increases weight, storage needs, and administration challenges, particularly in patients with limited intravenous access. These constraints, along with the desire for a simplified approach to balanced resuscitation,[18-20] have driven the interest in whole blood, which delivers all three components in a single unit.[11]

Data from observational studies have suggested possible benefits of whole blood, which include a reduction in the overall use of blood products.[21] Previous systematic reviews[6-8] have identified one small, single-center pilot trial that was not powered to assess survival and, more importantly, used whole blood that lacked platelets owing to processing with leukodepletion.[22]

A prothrombin time that exceeded the normal range appeared to occur more often in the whole-blood group than in the standard-care group; however, this finding did not translate into any difference in clinical outcomes, an indication of limited clinical relevance. A plausible explanation for this finding could be the age of the plasma in the two groups — plasma within the whole-blood units was up to 21 days old, as compared with plasma that was typically less than 5 days old in the standard-care group. In vitro studies have shown that coagulation factors decline with storage, which suggests that older

plasma exhibits reduced clotting factor levels as compared with fresher plasma.[13,23,24]

When subgroup analyses were possible, the results appeared to be consistent with those of the primary analysis, which reinforces the conclusion that no substantial differences were observed between the whole-blood group and the standard-care group. In addition, the dose of whole blood (up to 2 units) may have been insufficient to show an effect. Future research may clarify whether specific populations might benefit from the use of whole blood.

This trial has several limitations. First, the variability inherent to the prehospital environment and time-critical decision making may have influenced treatment delivery and adherence to the protocol. Second, the pragmatic design, which relied on clinical judgment to initiate transfusion, may have introduced population heterogeneity and led to the inclusion of some patients without life-threatening hemorrhage. In addition, the pragmatic trial design was dependent on the routine use of the Trauma Audit and Research Network database for injury characteristics; a cyberattack on this database in 2023 resulted in some missing data.

This trial provides key evidence to inform the use of whole blood within civilian prehospital trauma systems. Decisions about adopting the use of whole blood must balance logistic advantages against supply constraints, cost, and the overall availability of blood.

Among participants with life-threatening hemorrhage, prehospital transfusion of up to 2 units of whole blood was not superior to standard transfusion with component therapy in reducing the risk of death or massive transfusion at 24 hours after randomization. The safety profile also appeared to be similar with whole blood and standard care.

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