ORIGINAL ARTICLE

Effect of Short-Term vs. Long-Term Blood Storage on Mortality after Transfusion

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ABSTRACT

BACKGROUND

Randomized, controlled trials have suggested that the transfusion of blood after prolonged storage does not increase the risk of adverse outcomes among patients, although most of these trials were restricted to high-risk populations and were not powered to detect small but clinically important differences in mortality. We sought to find out whether the duration of blood storage would have an effect on mortality after transfusion in a general population of hospitalized patients.

METHODS

In this pragmatic, randomized, controlled trial conducted at six hospitals in four countries, we randomly assigned patients who required a red-cell transfusion to receive blood that had been stored for the shortest duration (short-term storage group) or the longest duration (long-term storage group) in a 1:2 ratio. Only patients with type A or O blood were included in the primary analysis, since pilot data suggested that our goal of achieving a difference in the mean duration of blood storage of at least 10 days would not be possible with other blood types. Written informed consent was waived because all the patients received treatment consistent with the current standard of care. The primary outcome was in-hospital mortality, which was estimated by means of a logistic-regression model after adjustment for study center and patient blood type.

RESULTS

From April 2012 through October 2015, a total of 31,497 patients underwent randomization. Of these patients, 6761 who did not meet all the enrollment criteria were excluded after randomization. The primary analysis included 20,858 patients with type A or O blood. Of these patients, 6936 were assigned to the short-term storage group and 13,922 to the long-term storage group. The mean storage duration was 13.0 days in the short-term storage group and 23.6 days in the long-term storage group. There were 634 deaths (9.1%) in the short-term storage group and 1213 (8.7%) in the long-term storage group (odds ratio, 1.05; 95% confidence interval [CI], 0.95 to 1.16; P=0.34). When the analysis was expanded to include the 24,736 patients with any blood type, the results were similar, with rates of death of 9.1% and 8.8%, respectively (odds ratio, 1.04; 95% CI, 0.95 to 1.14; P=0.38). Additional results were consistent in three prespecified high-risk subgroups (patients undergoing cardiovascular surgery, those admitted to intensive care, and those with cancer).

CONCLUSIONS

Among patients in a general hospital population, there was no significant difference in the rate of death among those who underwent transfusion with the freshest available blood and those who underwent transfusion according to the standard practice of transfusing the oldest available blood. (Funded by the Canadian Institutes of Health Research and others; INFORM Current Controlled Trials number, ISRCTN08118744.)

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Red-cell transfusion is one of the most common medical interventions.[1] Blood is stored for up to 42 days before transfusion. Biochemical, structural, and functional changes during storage may reduce oxygen delivery to tissues, and the release of extracellular vesicles and cell-free DNA during storage may cause a hypercoagulable state.[2] Observational studies have suggested that prolonged blood storage is associated with an increased risk of cardiovascular events.[3] Randomized, controlled trials have not shown harm in transfusing red-cell units with a longer duration versus a shorter duration of storage. However, most of these trials have been restricted to high-risk populations and have not been powered to detect small but clinically important differences in mortality.[4-7]

We report the results of a large, multicenter, pragmatic, randomized trial involving hospitalized patients requiring a red-cell transfusion. Our goal was to determine whether the in-hospital rate of death among patients requiring transfusion was lower among those who received blood after short-term storage than among those who received blood after long-term storage.

Methods

Study Design

In the Informing Fresh versus Old Red Cell Management (INFORM) trial, we assigned hospitalized patients to receive transfusions of the freshest red cells in the inventory (short-term storage group) or the oldest available red cells (long-term storage group).[8] The steering committee designed the trial protocol, which is available with the full text of this article at NEJM.org. The McMaster Centre for Transfusion Research was the sponsor and coordinating center for the study and was responsible for the randomization design, coordination of data collection and data management, data validation, analyses, and trial-center coordination. The steering committee vouches for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

The trial was funded by the Canadian Institutes of Health Research, Canadian Blood Services, and Health Canada. None of the funding sources had a role in the design or conduct of the trial, data collection, analyses, or manuscript preparation. The ethics review committee at each study center approved the study and waived the need for individual patient consent because all the patients received treatment that was consistent with the current standard of care, including a maximum blood-storage duration of 35 or 42 days, depending on the study center.

Patient Population

Hospitalized patients who were 18 years of age or older and who required a red-cell transfusion were eligible. Patients were excluded if they were expected to receive a massive transfusion (a request for 10 or more red-cell units at a time), required blood that had not been cross-matched, required autologous or directed transfusion, or had an indication for fresh-only red-cell transfusion. Some patients with alloimmunity to red-cell antigens were excluded if it would be difficult to find compatible blood. Patients were recruited from six hospitals in four countries (Australia, Canada, Israel, and the United States). At the U.S. study center, patients who were undergoing cardiac surgery were excluded because of a competing study,[9] and at one Canadian study center, patients in the intensive care unit (ICU) were excluded until a competing study was completed in August 2014.[5]

Randomization and Intervention

Randomization was performed by the staff of the hospital blood bank after receipt of a transfusion request. Patients were assigned in a 1:2 ratio to receive blood that had been stored for the shortest period of time (short-term storage group) or for the longest period of time (long-term storage group). Study-group assignments were performed with the use of a computer-generated randomization schedule stratified according to study center and patient blood type (A, B, AB, or O). The 1:2 ratio was used to avoid excessive outdating of red cells. Within each stratum, treatment assignments were made with the use of random block sizes (3 and 6). The trial was not blinded, since regulatory agencies require blood suppliers to label all red-cell products with the date of blood collection or expiration.

Patients received either the freshest red cells in the blood bank's inventory or the oldest red cells available, according to their study-group assignment. Local policies regarding the duration of red-cell storage and transfusion thresholds

were observed (see Table S1 in the Supplementary Appendix, available at NEJM.org). The study protocol prespecified the goal of a minimum difference of 10 days in the mean duration of red-cell storage between the two study groups. Patients received red cells according to their assigned study group throughout the initial admission and any subsequent admissions during the study period. The conduct of the trial did not affect blood inventory policies, the decision to transfuse, the number of red-cell units transfused, or the administration of any other therapies or procedures.

OUTCOMES

The primary outcome was in-hospital mortality. The secondary outcome was the interval from hospital admission to in-hospital death. The primary analyses were restricted to patients with type A or O blood, since pilot studies had showed that a difference in the average storage duration of at least 10 days would not be achievable in patients with the less common B and AB blood types.[10] Secondary analyses included patients with any blood type.

DATA COLLECTION

We collected all trial data from hospital electronic medical records. Such data included demographic information, diagnoses, duration of hospital stay, and vital status at discharge. We obtained information on all transfused red cells (blood type and storage duration) electronically from hospitals' laboratory information systems, which have been validated for accuracy and approved by regulatory bodies. We also monitored the number of red-cell units that were outdated.

STATISTICAL ANALYSIS

We determined that a sample size of 24,400 patients with any blood type would provide a power of 90% to detect a 15% lower relative risk of in-hospital death in the short-term storage group than in the long-term storage group among patients with type A or O blood, assuming a 1:2 ratio for randomization and a 10% rate of in-hospital death in the long-term storage group. This calculation also assumed that 20% of all the patients who underwent randomization would not receive a transfusion (to account for blood stored in a remote refrigerator or sent to the operating suite in a cooler but not used) and that these patients would not be included in the analyses. We increased the sample size to 31,497 patients with any blood type after 12,555 patients had undergone randomization because the overall observed frequency of in-hospital death (approximately 8.2%) was lower than expected. The new sample-size calculation (performed in September 2014) was based on 8% mortality in the long-term storage group and a 15% relative risk reduction in mortality in the short-term storage group (absolute risk reduction, 1.2 percentage points).

We performed two prespecified interim analyses when approximately 50% and 75% of the events had occurred. The modified Haybittle–Peto stopping boundary (i.e., 4 and 3 SD when 50% and 75% of events were accrued, respectively) was prespecified. If the threshold was crossed, confirmatory testing would be repeated 3 months later. No adjustment of the final significance level was made owing to the highly conservative stopping rule.

The primary analysis was based on a modified intention-to-treat principle that included patients with type A or O blood and excluded patients who were not hospitalized or did not receive a blood transfusion. Only data from a patient's first admission were included in the analysis. Patients were followed until in-hospital death or discharge. Data for patients who underwent randomization near the end of the accrual period were censored after 30 days of follow-up if they were still hospitalized; such patients were listed in the binary analyses as being alive. We repeated all analyses that included patients with type A or O blood as secondary analyses for patients with any blood type.

A logistic-regression model was fitted with in-hospital death as the outcome, and stratified according to study center and patient blood type.[11] We obtained odds ratios and 95% confidence intervals from this model. We used a Wald test to assess the null hypothesis of no between-group difference in the rates of in-hospital death. A secondary analysis was based on a Cox regression model of the interval between admission and in-hospital death that was fitted for all patients with type A or O blood and stratified according to study center and patient blood type. Model diagnostics for the proportional-hazards assumption were based on Schoenfeld residuals and associated tests.[12,13] The cumulative probabil-

ity of in-hospital death was estimated nonparametrically, with hospital discharge treated as a competing risk.[14]

Subgroup analyses were performed to assess the homogeneity of the treatment effect among study centers, countries, blood types, and main diagnosis categories (cardiovascular disease, cancer, trauma, digestive diseases, and "other"). Four logistic-regression models were fitted for patients with type A or O blood, including main effects for each group variable and the interaction term between the treatment indicator and the group variable. Primary and secondary analyses were also carried out for three prespecified high-risk subgroups of the trial cohort: patients undergoing cardiovascular surgery, those admitted to the ICU, and those with cancer.

Additional exploratory analyses were conducted to further assess the effect of storage duration on in-hospital mortality. Cox regression models were fitted to include a time-dependent covariate representing the maximum storage duration of red-cell units received and stratified according to study center, blood type, and the cumulative number of units of blood received; the latter stratification variable is a potential confounder, since patients requiring more units are at increased risk for both exposure to older blood and death. An additional analysis used the cumulative mean storage duration of units received.

All the analyses were performed with the use of SAS software, version 9.4 (SAS Institute). A P value of less than 0.05 was considered to indicate statistical significance, with no adjustments for multiple testing.

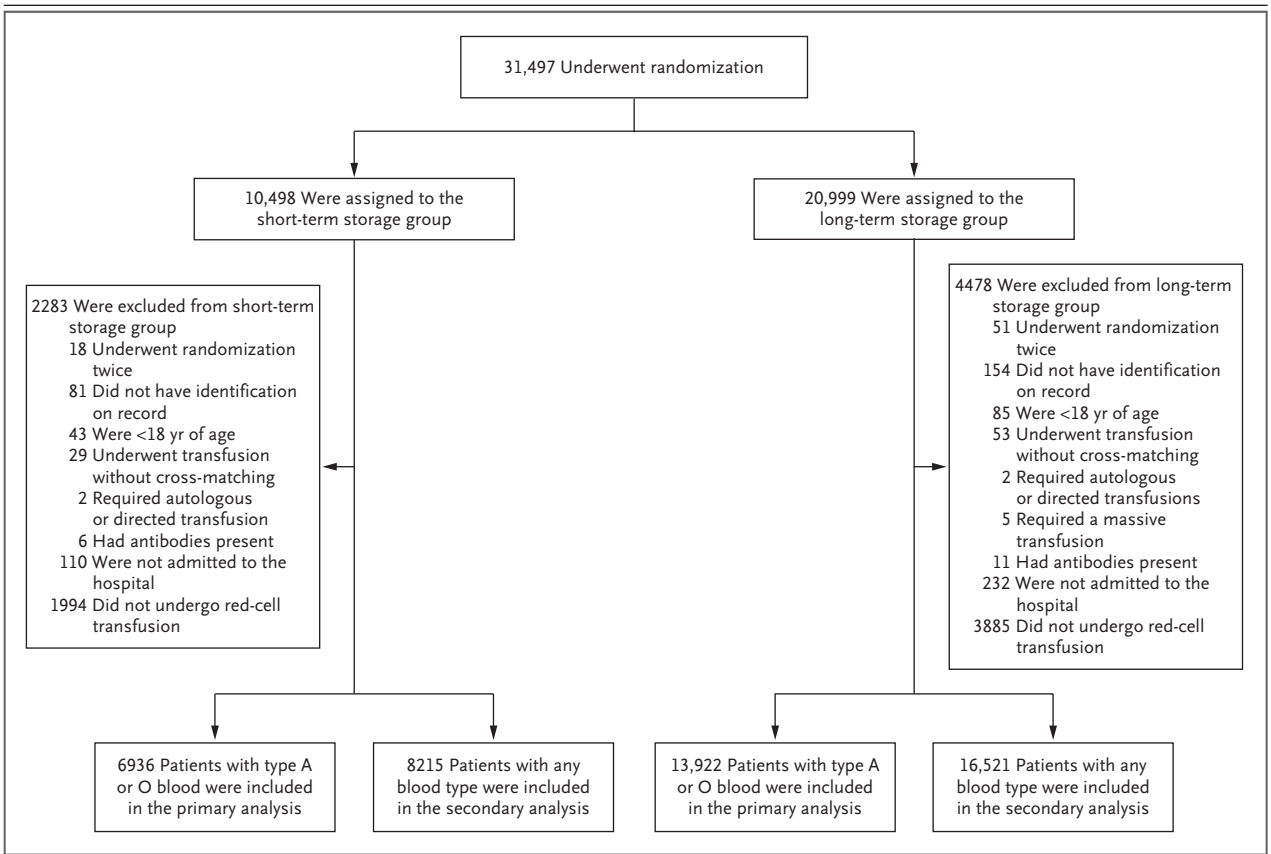

Figure 1. Enrollment and Outcomes.

Hospitalized patients who required a red-cell transfusion were assigned to receive blood that had been stored for the shortest time (short-term storage group) or for the longest time (long-term storage group). The criteria for the exclusion of patients from the primary and secondary analyses were not mutually exclusive and were applied in a hierarchical order, as listed here.

RESULTS

PATIENTS

From April 2012 through October 2015, a total of 31,497 patients underwent randomization (Fig. 1). Of these patients, 6761 were excluded after randomization, which left 24,736 who met all the enrollment criteria. A total of 3878 patients had type B or AB blood, which left 20,858 patients for inclusion in the primary analysis (6936 in the short-term storage group and 13,922 in the long-term storage group). The characteristics of the patients with type A or O blood in the two study groups were well balanced at baseline (Table 1,

Table 1. Demographic and Clinical Characteristics of the Patients (Primary Analysis).*

Characteristic	Short-Term Storage Group (N = 6936)	Long-Term Storage Group (N = 13,922)
Female sex — no. (%)†	3442 (49.6)	6913 (49.7)
Median age (IQR) — yr	69 (57–79)	69 (57–79)
Blood type — no. (%)		
A	3307 (47.7)	6613 (47.5)
O	3629 (52.3)	7309 (52.5)
No. of days from admission to first transfusion		
Median (IQR)	2 (0–5)	2 (0–5)
5th to 95th percentile	0–17	0–17
Category of disease diagnosis — no. (%)‡		
Infectious or parasitic	207 (3.0)	370 (2.7)
Neoplasms	891 (12.8)	1931 (13.9)
Blood or blood-forming organs and immune-system disorders	439 (6.3)	840 (6.0)
Endocrine, nutritional, or metabolic	165 (2.4)	327 (2.3)
Circulatory system	1947 (28.1)	3818 (27.4)
Respiratory system	303 (4.4)	576 (4.1)
Digestive system	847 (12.2)	1676 (12.0)
Musculoskeletal system and connective tissue	342 (4.9)	661 (4.7)
Genitourinary system	236 (3.4)	517 (3.7)
Pregnancy, childbirth, and puerperium	132 (1.9)	295 (2.1)
Injury, poisoning, or external causes, including trauma	965 (13.9)	1916 (13.8)
Factors influencing health status and contact with health services§	113 (1.6)	229 (1.6)
Symptoms, signs, and abnormal clinical and laboratory findings¶	202 (2.9)	387 (2.8)
Other diagnosis‖	147 (2.1)	379 (2.7)

* All the patients who were included in the primary analysis had type A or O blood. Hospitalized patients who required a red-cell transfusion were assigned to receive blood that had been stored for the shortest duration (short-term storage group) or the longest duration (long-term storage group). There were no significant differences between the two groups. IQR denotes interquartile range.

† Data regarding sex were missing for 1 patient in the long-term storage group.

‡ Diagnosis categories are based on version 10 of the *International Classification of Diseases* (ICD) for study centers in Australia and Canada and version 9 for those in the United States and Israel. Data were missing for 16 patients in the short-term storage group and 40 in the long-term storage group.

§ This category includes factors influencing individual health status (e.g., potential health hazards related to communicable disease) and reasons for contact with health services (e.g., specific procedures, examinations, and investigations).

¶ This category includes symptoms and signs of the various body systems (e.g., nervous and respiratory) that are not classified elsewhere and abnormal findings with respect to body fluids (e.g., blood and urine), substances and tissues without diagnosis, and poorly defined or unknown causes of death.

‖ This category includes ICD-10 categories in which the frequency within each group was 1% or less or the diagnosis was missing. (See Table S2 in the Supplementary Appendix for a more detailed description of all 21 main diagnosis categories.)

Table 2. Transfusion Data (Primary Analysis).

Variable	Short-Term Storage Group (N=6936)	Long-Term Storage Group (N=13,922)	P Value
Median interval from randomization to issue of first red-cell unit for transfusion (IQR) — hr	0.1 (0.0–0.5)	0.1 (0.0–0.6)	0.08
No. of red-cell units transfused	25,466	50,890	
No. of red-cell units transfused per patient*			0.57
Median (IQR)	2 (2–4)	2 (2–4)	
Range	1–227	1–92	
No. of red-cell transfusion episodes per patient†			0.78
Median (IQR)	1 (1–2)	1 (1–2)	
Range	1–87	1–58	
Duration of storage of transfused red cells — days‡			<0.001
Mean ±SD	13.0±7.6	23.6±8.9	
Median (IQR)	11 (8–16)	23 (16–31)	
Duration of storage of transfused red cells per patient — days			<0.001
Median of the mean age of red cells transfused per patient (IQR)	11 (8–15)	24 (18–30)	
Median of the oldest red cells transfused per patient (IQR)	12 (8–18)	27 (19–36)	
Other transfusions — no. (%)			
Platelets	1289 (18.6)	2579 (18.5)	0.91
Plasma	1155 (16.7)	2270 (16.3)	0.49
Cryoprecipitate	403 (5.8)	755 (5.4)	0.23

* A small number of patients had a large maximum number of red-cell transfusions.
† A transfusion episode is defined as all transfusions given on a single day.
‡ The protocol specified a minimum difference of 10 days in the mean duration of red-cell storage between the two treatment groups.

and Table S2 in the Supplementary Appendix). Circulatory disorders, trauma, neoplasms, and digestive diseases were the most common diagnoses and accounted for approximately 67% of the study patients.

TRANSFUSION DATA

Patients with type A or O blood received 76,356 units of red cells (25,466 in the short-term storage group and 50,890 in the long-term storage group) (Table 2, and Table S3 in the Supplementary Appendix). Patients in each group received a median number of 2 red-cell units (interquartile range, 2 to 4). The mean (±SD) storage duration of the transfused blood was 13.0±7.6 days in the short-term storage group and 23.6±8.9 days in the long-term storage group (P<0.001) (Table 2 and Fig. 2). The proportions of patients in each study group who also received platelets, plasma, or cryoprecipitate were similar. The frequency of discarded red cells that were outdated was low (0.5%) and did not increase during the study. No crossovers occurred during the study.

OUTCOMES

Among the patients with type A or O blood, death was reported in 634 of 6936 (9.1%) in the short-term storage group and in 1213 of 13,922 (8.7%) in the long-term storage group (odds ratio, 1.05; 95% confidence interval [CI], 0.95 to 1.16; P=0.34). Similar findings were obtained when the study center was treated as a random effect. No significant interactions according to subgroup were found for the study center, country, blood type, or diagnosis (Fig. 3). The median duration of hospitalization was 10 days (interquartile range, 5 to 19) for patients in the short-term storage group and 10 days (interquartile range, 5 to 20) in the long-term storage group.

The hazard ratio for in-hospital death in the stratified Cox regression model was 1.08 (95% CI, 0.98 to 1.19; P=0.13). A plot of the cumulative probability of in-hospital death according to study

group for patients with type A or O blood shows the absolute effect on in-hospital mortality. For example, at 30 days, the cumulative probability of death was 6.9% in the short-term storage group and 6.5% in the long-term storage group (Fig. S1 in the Supplementary Appendix).

The analyses of high-risk subgroups did not show significant differences in mortality in the short-term storage group and the long-term storage group among those undergoing cardiovascular surgery (12.3% and 11.2%, respectively; P=0.08), those in the ICU (13.3% and 12.8%, P=0.52), and those with cancer (8.4% and 8.8%, P=0.82) (Fig. 3). Similar conclusions were obtained from the Cox regression models (Fig. S2 in the Supplementary Appendix). Data regarding transfusion exposure among the high-risk subgroups are provided in Table S4 in the Supplementary Appendix.

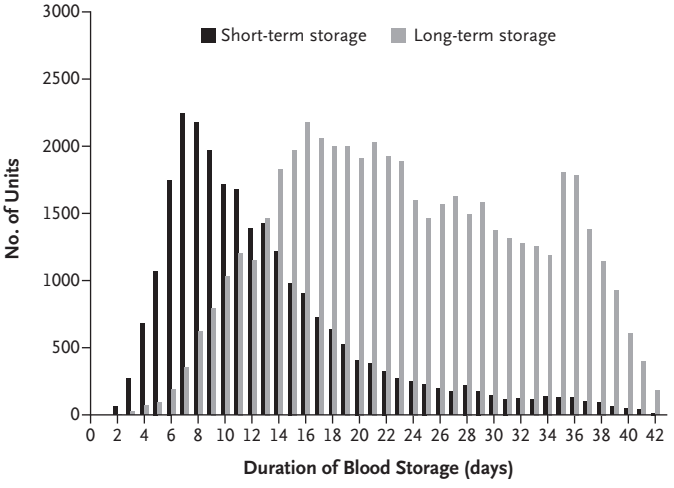

Figure 2. Duration of Blood Storage before Transfusion (Primary Analysis).
All the patients who were included in the primary analysis had type A or O blood.

ANALYSES IN PATIENTS WITH ANY BLOOD TYPE

When the 24,736 patients with any blood type were considered, the demographic characteristics were similar in the two study groups (Table S5 in the Supplementary Appendix). The median storage duration of the transfused blood was 11 days (interquartile range, 8 to 17) in the short-term storage group and 23 days (interquartile range, 16 to 31) in the long-term storage group (P<0.001) (Table S6 and Fig. S3 in the Supplementary Appendix). A total of 30,185 red-cell units were transfused in the short-term storage group and 60,424 in the long-term storage group (Tables S6 and S7 in the Supplementary Appendix). In-hospital death was reported in 750 of 8215 patients (9.1%) in the short-term storage group and in 1446 of 16,521 (8.8%) in the long-term storage group (odds ratio, 1.04; 95% CI, 0.95 to 1.14; P=0.38). No significant interactions according to subgroup were found for the study center, country, blood type, or diagnosis (Fig. S4 in the Supplementary Appendix). The hazard ratio for the Cox regression model was 1.06 (95% CI, 0.97 to 1.16; P=0.18) (Figs. S5 and S6 in the Supplementary Appendix). No significant between-group differences in mortality were found in any of the high-risk subgroups.

EXPLORATORY ANALYSES

In the exploratory analysis in patients with type A or O blood, when the maximum storage duration (in days) of transfused red cells was used as a time-dependent covariate in the Cox model stratified according to study center, blood type, and the cumulative number of units received, there was no evidence of an association between the age of the blood and in-hospital mortality (hazard ratio, 1.00; 95% CI, 0.99 to 1.00; P=0.54). A similar result was observed when the cumulative mean storage duration was used (hazard ratio, 1.00; 95% CI, 0.99 to 1.00; P=0.61).

DISCUSSION

In our study, we did not find a significant difference in the rate of death according to the duration of blood storage among patients in a general hospital population who underwent transfusion. No benefit of fresher blood was seen in the primary and secondary analyses, a finding that was consistent in the prespecified subgroups and high-risk subgroups. The lower boundary of the 95% confidence interval for the odds ratio for in-hospital mortality (i.e., 0.95) provided reassurance that the transfusion of older red cells was unlikely to result in an increased risk of death. In a separate exploratory analysis, we also found no association between the age of blood analyzed as a continuous variable and in-hospital mortality.

Investigators have explored the potential benefit of transfusing fresher blood in at least 13 randomized trials, including those involving neonates, children, patients in the ICU, and those

Subgroup	Short-Term Storage Group	Long-Term Storage Group	Odds Ratio (95% CI)	P Value	P Value for Homogeneity
	no./total no. (%)				
All patients	634/6936 (9.1)	1213/13,922 (8.7)	1.05 (0.95–1.16)	0.34	
Hospital site					0.88
Australia site	101/1639 (6.2)	204/3350 (6.1)	1.01 (0.79–1.30)	0.92	
Canada site 1	164/1500 (10.9)	305/3002 (10.2)	1.09 (0.89–1.33)	0.42	
Canada site 2	111/967 (11.5)	232/1893 (12.3)	0.93 (0.73–1.18)	0.55	
Canada site 3	71/539 (13.2)	123/1073 (11.5)	1.17 (0.86–1.60)	0.32	
Israel site	43/383 (11.2)	79/761 (10.4)	1.09 (0.74–1.62)	0.67	
U.S. site	144/1908 (7.5)	270/3843 (7.0)	1.08 (0.88–1.33)	0.47	
Country					0.98
Australia	101/1639 (6.2)	204/3350 (6.1)	1.01 (0.79–1.30)	0.92	
Canada	346/3006 (11.5)	660/5968 (11.1)	1.05 (0.91–1.20)	0.52	
Israel	43/383 (11.2)	79/761 (10.4)	1.09 (0.74–1.62)	0.67	
United States	144/1908 (7.5)	270/3843 (7.0)	1.08 (0.88–1.33)	0.47	
Patient blood type					0.71
A	320/3307 (9.7)	600/6613 (9.1)	1.07 (0.93–1.24)	0.35	
O	314/3629 (8.7)	613/7309 (8.4)	1.03 (0.89–1.19)	0.68	
Diagnosis					0.51
Cancer	75/891 (8.4)	169/1931 (8.8)	0.95 (0.71–1.26)	0.73	
Cardiovascular	147/1947 (7.6)	311/3818 (8.1)	0.92 (0.75–1.14)	0.45	
Digestive	84/847 (9.9)	155/1676 (9.2)	1.08 (0.82–1.43)	0.59	
Trauma	75/965 (7.8)	132/1916 (6.9)	1.13 (0.84–1.52)	0.41	
Other	253/2286 (11.1)	446/4581 (9.7)	1.14 (0.97–1.35)	0.11	
High-risk subgroup					—
Cardiovascular surgery	376/3051 (12.3)	697/6234 (11.2)	1.13 (0.99–1.29)	0.08	
Patients in the ICU	472/3553 (13.3)	901/7025 (12.8)	1.04 (0.92–1.17)	0.52	
Patients with cancer	75/891 (8.4)	169/1931 (8.8)	0.97 (0.73–1.29)	0.82	

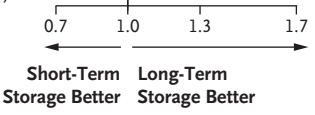

Figure 3. Subgroup Analysis of In-Hospital Mortality after Transfusion.

Odds ratios for in-hospital death among patients with type A or O blood were calculated with the use of a logistic-regression model that was stratified according to study center and blood type. Homogeneity testing was not performed for the prespecified high-risk subgroups. CI denotes confidence interval.

undergoing cardiac surgery.[4-7,10,15-22] None of these trials has shown a benefit of transfusing fresher blood. A meta-analysis that included 12 trials and a total of 5229 patients showed a risk ratio for death (freshest vs. oldest blood) of 1.04 (95% CI, 0.94 to 1.14).[23] The largest trial in this meta-analysis enrolled 2412 patients.[5] The results of our study, which included a much broader population, are consistent with these findings. None of the studies involving humans have been designed to determine whether the transfusion of the very oldest red cells (i.e., those stored for 35 to 42 days) affect patient outcomes, a question that remains unresolved.[24]

Our trial had a pragmatic design, which allowed for broad patient enrollment, efficient capture of electronic data, waived consent, and an objective outcome (i.e., mortality).[25] The combination of electronic-data capture and waived consent allowed us to randomly assign more than 31,000 patients over a period of approximately 3 years at a cost of about $40 (in U.S. dollars) per patient. The enrollment of a broad patient population enhances the generalizability of the findings. By using an unbalanced ratio of 1:2 to assign patients to the short-term storage group versus the long-term storage group, we were able to maintain a minimum difference of 10 days in the mean duration of red-cell storage between the two groups without increasing the rate of blood outdating.

However, the pragmatic design of our study also has limitations. First, electronic databases do not systematically record detailed information on coexisting illnesses, reasons for transfusion, cointerventions, nonfatal cardiovascular

outcomes, and causes of death. Second, our results may not be directly applicable to patients with blood type B or AB. However, we are unaware of any reason why our results would differ according to blood type.

In conclusion, there was no significant difference in the rate of death among patients in a general hospital population who underwent transfusion with the freshest available blood and those who underwent transfusion according to the standard practice of transfusing the oldest available blood.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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