

ORIGINAL ARTICLE

Duration of Red-Cell Storage and Complications after Cardiac Surgery

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ABSTRACT

BACKGROUND

Stored red cells undergo progressive structural and functional changes over time. We tested the hypothesis that serious complications and mortality after cardiac surgery are increased when transfused red cells are stored for more than 2 weeks.

METHODS

We examined data from patients given red-cell transfusions during coronary-artery bypass grafting, heart-valve surgery, or both between June 30, 1998, and January 30, 2006. A total of 2872 patients received 8802 units of blood that had been stored for 14 days or less ("newer blood"), and 3130 patients received 10,782 units of blood that had been stored for more than 14 days ("older blood"). Multivariable logistic regression with propensity-score methods was used to examine the effect of the duration of storage on outcomes. Survival was estimated by the Kaplan–Meier method and Blackstone's decomposition method.

RESULTS

The median duration of storage was 11 days for newer blood and 20 days for older blood. Patients who were given older units had higher rates of in-hospital mortality (2.8% vs. 1.7%, $P=0.004$), intubation beyond 72 hours (9.7% vs. 5.6%, $P<0.001$), renal failure (2.7% vs. 1.6%, $P=0.003$), and sepsis or septicemia (4.0% vs. 2.8%, $P=0.01$). A composite of complications was more common in patients given older blood (25.9% vs. 22.4%, $P=0.001$). Similarly, older blood was associated with an increase in the risk-adjusted rate of the composite outcome ($P=0.03$). At 1 year, mortality was significantly less in patients given newer blood (7.4% vs. 11.0%, $P<0.001$).

CONCLUSIONS

In patients undergoing cardiac surgery, transfusion of red cells that had been stored for more than 2 weeks was associated with a significantly increased risk of postoperative complications as well as reduced short-term and long-term survival.

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MORE THAN 14 MILLION UNITS OF blood are transfused annually in the United States.¹ Considerable evidence suggests that transfusion increases the risk of serious complications and death in critically ill patients,²⁻⁴ especially in patients who are undergoing cardiac surgery.⁵⁻¹²

Some studies have suggested that the risk of complications after transfusion also increases when transfused blood has been stored for long periods.¹³⁻¹⁸ Blood collection and storage systems licensed by the Food and Drug Administration allow red cells to be stored for up to 42 days. (The median duration of storage of transfused red-cell units in the United States is 15 days.¹) During storage, preserved blood cells undergo progressive structural and functional changes that may reduce red-cell function and viability after transfusion.¹⁸⁻²²

The clinical importance of transfusing older red cells versus newer red cells remains unclear, with some studies identifying adverse consequences¹³⁻¹⁷ and others not.^{23,24} Previous investigations, however, have been limited by small sample sizes,^{15,25} heterogeneous patient populations,¹⁵ and inadequate control of confounding factors.²⁵ Furthermore, many reported end points, such as duration of hospitalization, lack sensitivity for specific organ function.²⁴ We tested the hypothesis that serious complications and mortality after cardiac surgery increase when red-cell units are transfused after they have been stored for more than 2 weeks.

METHODS

PATIENTS

The patient population consisted of adult patients (18 years of age or older) who were undergoing coronary-artery bypass grafting, cardiac-valve surgery, or a combination of the two procedures at the Cleveland Clinic from June 30, 1998 (when blood-bank data became available electronically), until January 30, 2006. We included data from patients who received exclusively red-cell units that had been stored for 14 days or less ("newer blood") or exclusively units that had been stored for more than 14 days ("older blood"). To reduce confounding factors, data from patients who received a mixture of newer and older blood were excluded from the study.

Standard cardiac surgical practice during the

period under study included the administration of aminocaproic acid (a plasmin inhibitor) to reduce intraoperative bleeding, as well as the use of cardiotomy suction to retrieve shed blood during the operation and return it to the patient's circulation through a cardiopulmonary-bypass pump. There was no uniform protocol for perioperative transfusion, although it has been our general practice to minimize the use of blood products. When blood was ordered for transfusion, the blood bank provided the oldest available matching unit for each request.

DATA SOURCES

We accessed Cleveland Clinic's cardiac anesthesia registry to retrieve baseline demographic and perioperative variables that had been prospectively collected by clinical coordinators concurrently with patient care and entered into the database by trained data-management personnel. The clinic's cardiovascular information registry was also accessed for additional variables. The clinic's blood-bank database was queried for the storage time of the red-cell units, their ABO blood type, and their leukocyte-reduced status. All three databases have been approved by the institutional review board of the Cleveland Clinic for use in research with patient consent waived.

COMPLICATIONS

We characterized individual in-hospital complications with the use of the definitions of the Society of Thoracic Surgeons (www.sts.org). Our primary end point, defined before analysis, was a composite of serious adverse events that included in-hospital death, myocardial infarction, asystole, ventricular tachycardia or fibrillation, tamponade, femoral or aortic dissection, renal failure, sepsis, respiratory insufficiency, pulmonary embolism, pneumonia, cerebral vascular accident, coma, deep or superficial sternal-wound infection, prolonged postoperative ventilation (>72 hours), multiorgan failure, and acute limb ischemia. This specific list of serious adverse events is based on the set of complications defined in the adult cardiac surgery database of the Society of Thoracic Surgeons. Each of these adverse events was also examined separately. Our secondary end point was long-term survival. Follow-up survival status of the patients was obtained from the Social Security Death Index.²⁶⁻²⁸ The closing date was September 20, 2006.

STATISTICAL ANALYSIS

Baseline characteristics, operative factors, and univariate outcomes were compared between patients receiving exclusively newer blood and those receiving exclusively older blood with two-sample tests. The Wilcoxon rank-sum test and the chi-square test were used for group comparisons among continuous and categorical variables, respectively.

In order to understand the dose–response relationship between the storage time of blood and the composite outcome, we defined a summary variable for the storage time for each patient as the longest storage time of all transfused units received by that patient when a patient received multiple units of blood with different storage times. We then performed a nonparametric logistic-regression analysis of the composite outcome and this summary variable.

To adjust for potential confounders, we used multivariable logistic-regression analysis of the composite outcome for all baseline variables and the groups receiving newer and older blood. A stepwise variable-selection procedure was applied to identify variables associated with the composite outcome. To control for confounding, a propensity score was calculated from a logistic regression as the probability of being in the group receiving newer blood, given all the baseline variables. This propensity score was then forced in the logistic model for the composite outcome to further adjust for confounding.

Kaplan–Meier analysis was used to examine differences in unadjusted survival, with the Wilcoxon and Tarone tests used for comparisons. The Wilcoxon and Tarone tests are generalizations of the log-rank tests with various weighting functions that have good power against early differences in survival curves. Risk-adjusted long-term survival was examined with the parametric hazard-decomposition method of Blackstone et al.²⁹

RESULTS

AGE OF RED CELLS

The maximum storage time of the transfused red cells was 42 days, and the median time was 15 days. Because newer and older blood units were delineated by the median storage time (i.e., 15 days), the number of patients receiving newer units and the number receiving older units were nearly equal. A total of 2872 patients received 8802 units of newer blood, and 3130 patients re-

ceived 10,782 units of older blood. The numbers of units transfused per patient were similar in the group receiving exclusively newer blood and in the group receiving exclusively older blood (Fig. 1A). Figure 1B depicts the mean duration of

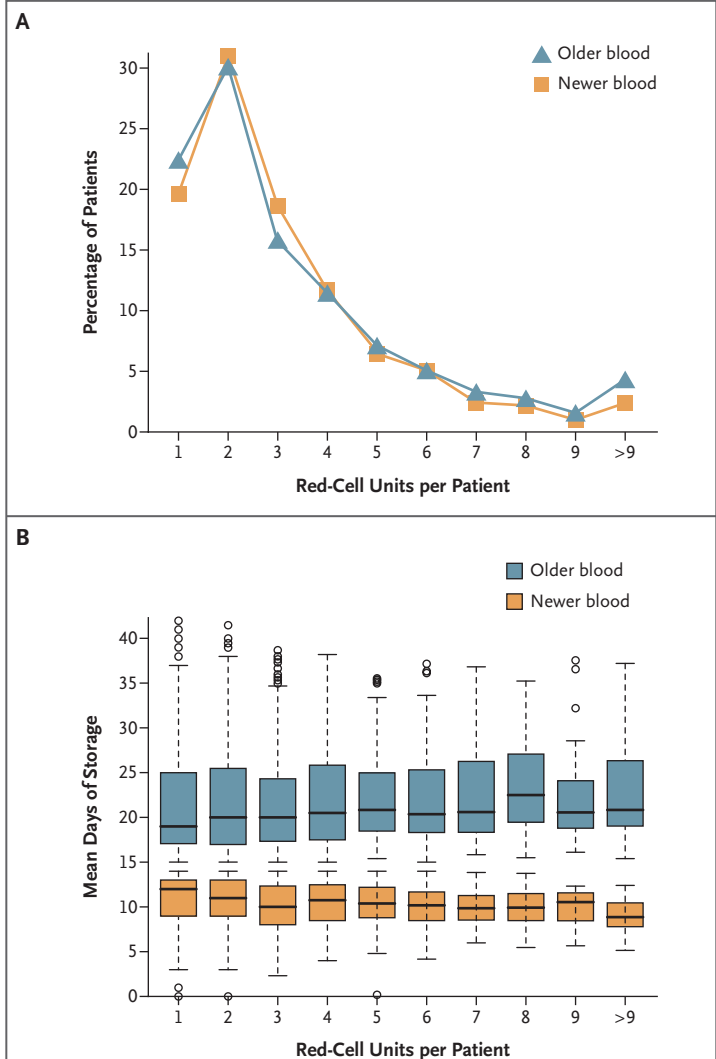


Figure 1. Number of Red-Cell Units Transfused in Relation to the Percentage of Patients Receiving Transfusion and Box Plots of the Duration of Storage of Blood.

Panel A shows the distribution of the number of red-cell units transfused in 2872 patients who were given exclusively newer blood (stored for 14 days or less) and in 3130 patients given exclusively older blood (stored for more than 14 days). The distributions are similar in the two groups ($P=0.99$ by the Wilcoxon rank-sum test). Panel B shows the number of red-cell units transfused per patient in relation to the duration of storage of newer blood and older blood. The lower and upper bounds of the boxes represent the 25th and 75th percentiles, and the heavy horizontal lines represent means. The I bars represent the maximum and minimum values for each group, excluding the possible outliers, which are represented by open circles.

storage per number of red-cell units transfused for both patient groups. There were also 2364 patients in our study sample who received a mixture of units of newer and older blood and were

not included in the analysis. These patients received considerably more units than those in either study group.

Table 1 displays baseline and operative vari-

Table 1. Characteristics of Transfused Blood and Demographic and Clinical Features of the Patients.*

| Variable | Patients Receiving Newer Blood (N=2872) [†] | Patients Receiving Older Blood (N=3130) [‡] | P Value |
|---|--|--|---------|
| Transfused blood | | | |
| Duration of storage — days | | | |
| Median | 11 | 20 | |
| Interquartile range | 9–3 | 17–25 | |
| No. of red-cell units per patient | | | 0.99 |
| Median | 2 | 2 | |
| Interquartile range | 2–4 | 2–4 | |
| Blood group — no. of units/total no. of units (%) | | | <0.001 |
| A | 3340/8802 (37.9) | 6116/10,782 (56.7) | |
| B | 778/8802 (8.8) | 1291/10,782 (12.0) | |
| O | 4674/8802 (53.1) | 3349/10,782 (31.1) | |
| AB | 10/8802 (0.1) | 26/10,782 (0.2) | |
| Leukocyte reduction — no. of patients (%) | | | <0.001 |
| Yes | 1037 (36.1) | 1723 (55.0) | |
| No | 1724 (60.0) | 1050 (33.5) | |
| Mixed | 111 (3.9) | 357 (11.4) | |
| Fresh frozen plasma — no. of patients (%) | 301 (10.5) | 335 (10.7) | 0.78 |
| Platelets — no. of patients (%) | 454 (15.8) | 509 (16.3) | 0.63 |
| Demographic features | | | |
| Race — no. of patients (%)§ | | | 0.09 |
| White | 2421 (84.3) | 2700 (86.3) | |
| Black | 189 (6.6) | 188 (6.0) | |
| Other | 262 (9.1) | 242 (7.7) | |
| Age — yr | | | 0.05 |
| Median | 69 | 70 | |
| Interquartile range | 60–76 | 61–77 | |
| Female sex — no. of patients (%) | 1208 (42.1) | 1311 (41.9) | 0.89 |
| Body-surface area — m ² | | | 0.03 |
| Median | 1.93 | 1.94 | |
| Interquartile range | 1.75–2.09 | 1.77–2.10 | |
| Blood group — no. of patients/total no. of patients (%) | | | <0.001 |
| A | 992/2860 (34.7) | 1542/3120 (49.4) | |
| B | 303/2860 (10.6) | 449/3120 (14.4) | |
| O | 1456/2860 (50.9) | 949/3120 (30.4) | |
| AB | 109/2860 (3.8) | 180/3120 (5.8) | |
| Clinical features | | | |
| Preoperative laboratory values | | | |
| Hematocrit — % | | | 0.41 |
| Median | 38.2 | 38.0 | |
| Interquartile range | 34.4–41.1 | 34.3–41.0 | |
| Creatinine — mg/dl | | | 0.12 |
| Median | 1.0 | 1.0 | |
| Interquartile range | 0.8–1.3 | 0.8–1.3 | |

Table 1. (Continued.)

| Variable | Patients Receiving Newer Blood (N=2872) [†] | Patients Receiving Older Blood (N=3130) [‡] | P Value |
|--|--|--|---------|
| Bilirubin — mg/dl | | | 0.81 |
| Median | 0.5 | 0.6 | |
| Interquartile range | 0.4–0.8 | 0.4–0.8 | |
| Cardiac features | | | |
| Abnormal left ventricular function — no. of patients (%) | 1662 (57.9) | 1975 (63.1) | <0.001 |
| Heart failure — no. of patients (%) | 1294 (45.1) | 1469 (46.9) | 0.15 |
| NYHA class — no. of patients (%) | | | <0.001 |
| I | 316 (11.0) | 370 (11.8) | |
| II | 1474 (51.3) | 1622 (51.8) | |
| III | 700 (24.4) | 827 (26.4) | |
| IV | 382 (13.3) | 311 (9.9) | |
| Prior myocardial infarction — no. of patients (%) | 1502 (52.3) | 1564 (50.0) | 0.07 |
| Aortic regurgitation — no. of patients (%) | 1102 (38.4) | 1157 (37.0) | 0.26 |
| Mitral regurgitation — no. of patients (%) | 1842 (64.1) | 2105 (67.3) | 0.01 |
| >70% Stenosis of left main trunk — no. of patients (%)¶ | 353 (12.7) | 367 (12.2) | 0.55 |
| Clinical presentation — no. of patients (%) | | | |
| Preoperative IABP | 63 (2.2) | 68 (2.2) | 0.96 |
| Emergency surgery | 37 (1.3) | 48 (1.5) | 0.42 |
| Coexisting conditions | | | |
| Hypertension — no. of patients (%) | 2135 (75.3) | 2402 (77.1) | 0.11 |
| COPD — no. of patients (%) | 345 (12.0) | 391 (12.5) | 0.57 |
| Smoking — no. of patients (%) | 1649 (57.4) | 1751 (55.9) | 0.25 |
| Diabetes — no. of patients (%)** | 843 (29.5) | 968 (31.1) | 0.19 |
| Stroke — no. of patients (%) | 307 (10.7) | 376 (12.0) | 0.11 |
| Peripheral vascular disease — no. of patients (%) | 1563 (54.4) | 1830 (58.5) | 0.002 |
| Perioperative factors | | | |
| Cardiopulmonary-bypass time — min | | | 0.55 |
| Median | 101 | 100 | |
| Interquartile range | 80–126 | 78–127 | |
| Aortic-clamp time — min | | | 0.98 |
| Median | 78 | 78 | |
| Interquartile range | 62–97 | 60–98 | |
| Reoperation — no. of patients (%) | 916 (31.9) | 1040 (33.2) | 0.27 |
| Operative procedure — no. of patients (%) | | | |
| Isolated CABG | 1251 (43.6) | 1336 (42.7) | 0.49 |
| Isolated valve replacement | 754 (26.3) | 844 (27.0) | 0.53 |
| Use of internal thoracic artery as bypass conduit | 1407 (49.0) | 1552 (49.6) | 0.65 |

* Continuous variables are summarized by medians and interquartile ranges, and P values were calculated by the Wilcoxon rank-sum test; categorical variables are summarized by numbers and percentages, and P values were calculated by the chi-square test. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, IABP intraaortic balloon pump, and NYHA New York Heart Association. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

[†] Newer blood was stored for 14 days or less.

[‡] Older blood was stored for more than 14 days.

§ Race was self-reported.

¶ A total of 2770 patients receiving newer blood and 3003 receiving older blood were tested for this variable.

|| A total of 2834 patients receiving newer blood and 3115 receiving older blood were tested for this variable.

** A total of 2856 patients receiving newer blood and 3116 receiving older blood were tested for this variable.

ables for patients receiving newer and older blood. Many of the baseline and operative variables were similar between the groups. However, the distribution of ABO blood types, both for the recipients and for the units transfused, differed between the two groups ($P<0.001$ for both comparisons). In addition, patients given newer blood were less likely to receive leukocyte-reduced red-cell units (36.1% vs. 55.0%, $P<0.001$), were more often classified as New York Heart Association class IV (13.3% vs. 9.9%, $P<0.001$), and had a smaller body-surface area (1.93 vs. 1.94 m², $P=0.03$). In contrast, slightly more patients in the group receiving older blood had preoperative mitral regurgitation (67.3% vs. 64.1%, $P=0.01$), abnormal left ventricular function (63.1% vs. 57.9%, $P<0.001$), and peripheral vascular disease (58.5% vs. 54.4%, $P=0.002$).

COMPLICATIONS

Patients who were given older blood had greater in-hospital mortality (2.8% vs. 1.7%, $P=0.004$), were more likely to need prolonged ventilatory support (9.7% vs. 5.6%, $P<0.001$), and were more likely to have renal failure (2.7% vs. 1.6%, $P=0.003$), septicemia or sepsis (4.0% vs. 2.8%, $P=0.01$), or multisystem organ failure (0.7% vs. 0.2%, $P=0.007$) than patients who were given newer blood (Table 2). Patients who were given older blood were also more likely to have the composite outcome of multiple serious adverse events (25.9% vs. 22.4%, $P=0.001$). The dose-response relationship between the composite outcome and the maximum age of blood for each patient is presented in Figure 2. This unadjusted relationship indicates a trend, especially for the group receiving older blood, toward an association between blood-storage time and the composite outcome. This association remained significant after adjustment for the baseline risk factors listed in Table 1 (adjusted odds ratio for patients receiving older blood as compared with those receiving newer blood, 1.16; 95% confidence interval, 1.01 to 1.33; $P=0.03$).

Survival was lower and the risk of death was higher for patients who received older blood ($P=0.001$ by the Wilcoxon test, $P=0.004$ by the Tarone test). The 1-year survival rate was 92.6% for the group receiving newer blood and 89.0% for the group receiving older blood ($P<0.001$) (Fig. 3); the corresponding 1-year rates of death from all causes were 7.4% and 11.0%, respective-

ly. On the basis of these results, it would be necessary to restrict blood-storage time to 2 weeks or less for 28 patients undergoing cardiac surgery to prevent one death during the first year after the operation. Hazard-rate analysis indicates that most deaths associated with the transfusion of older blood occurred within the first 6 postoperative months (Fig. 3, inset). The multivariate model that we developed can be used to estimate the predicted survival of a patient undergoing heart surgery, given the relevant clinical characteristics and the age and number of units of transfused blood (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

DISCUSSION

Transfusion of red cells that had been stored for more than 14 days was associated with a significantly increased risk of postoperative complications and reduced survival after cardiac surgery. In-hospital death, prolonged intubation, renal failure, septicemia or sepsis, multiorgan failure, and a composite of serious complications were all more frequent in patients given blood stored for more than 14 days. Furthermore, survival — particularly in the first 6 months after surgery — was significantly reduced. The adverse effects of transfusing older blood persisted even after adjustment for perioperative factors known to be associated with an adverse outcome in this population, including the number and ABO blood group of the transfused red-cell units, the blood group of the patient, the demographic characteristics of the patient, laboratory values, coexisting conditions, and the type of operative procedure.

Although the mechanism linking adverse outcomes with increased duration of red-cell storage remains unclear, several factors may contribute. Preserved blood cells undergo progressive functional and structural changes.^{19-21,30} This “storage lesion” is an amalgamation of reversible and irreversible changes that begin after 2 to 3 weeks of storage, progress with duration of storage,²⁰ and reduce red-cell function and viability after transfusion.²¹ The effects of prolonged storage on red cells include decreased deformability, which can impede microvascular flow^{19,20,31}; depletion of 2,3-diphosphoglycerate (2,3-DPG), which shifts the oxyhemoglobin dissociation curve to the left and reduces oxygen delivery³²;

Table 2. Postoperative Complications, According to the Duration of Blood Storage.

| Complication | Patients Receiving Newer Blood (N=2872)* | Patients Receiving Older Blood (N=3130)† | P Value‡ |
|-----------------------------|--|--|----------|
| | no. (%) | | |
| In-hospital death | 49 (1.7) | 88 (2.8) | 0.004 |
| Cardiac | | | |
| Myocardial infarction | 15 (0.5) | 16 (0.5) | 0.95 |
| Ventricular tachycardia | 155 (5.4) | 175 (5.6) | 0.74 |
| Ventricular fibrillation | 35 (1.2) | 31 (1.0) | 0.40 |
| Cardiac arrest or asystole | 47 (1.6) | 54 (1.7) | 0.79 |
| Cardiac tamponade | 48 (1.7) | 67 (2.1) | 0.19 |
| Aortic dissection | 1 (<1) | 2 (0.1) | 0.99 |
| Neurologic | | | |
| Stroke | 49 (1.7) | 61 (1.9) | 0.48 |
| Coma >24 hr | 9 (0.3) | 12 (0.4) | 0.65 |
| Pulmonary | | | |
| Ventilation >72 hr | 160 (5.6) | 304 (9.7) | <0.001 |
| Pneumonia | 81 (2.8) | 111 (3.5) | 0.11 |
| Pulmonary embolism | 5 (0.2) | 7 (0.2) | 0.67 |
| Respiratory insufficiency | 177 (6.2) | 278 (8.9) | <0.001 |
| Renal | | | |
| Renal failure | 45 (1.6) | 84 (2.7) | 0.003 |
| Infectious | | | |
| Septicemia or sepsis | 80 (2.8) | 125 (4.0) | 0.01 |
| Deep sternal wound | 25 (0.9) | 25 (0.8) | 0.76 |
| Superficial sternal wound | 44 (1.5) | 62 (2.0) | 0.19 |
| Multiorgan failure | 7 (0.2) | 23 (0.7) | 0.007 |
| Peripheral vascular | | | |
| Iliac or femoral dissection | 0 | 0 | |
| Acute limb ischemia | 7 (0.2) | 18 (0.6) | 0.05 |
| Composite outcome§ | 642 (22.4) | 810 (25.9) | 0.001 |

* Newer blood was stored for 14 days or less.

† Older blood was stored for more than 14 days.

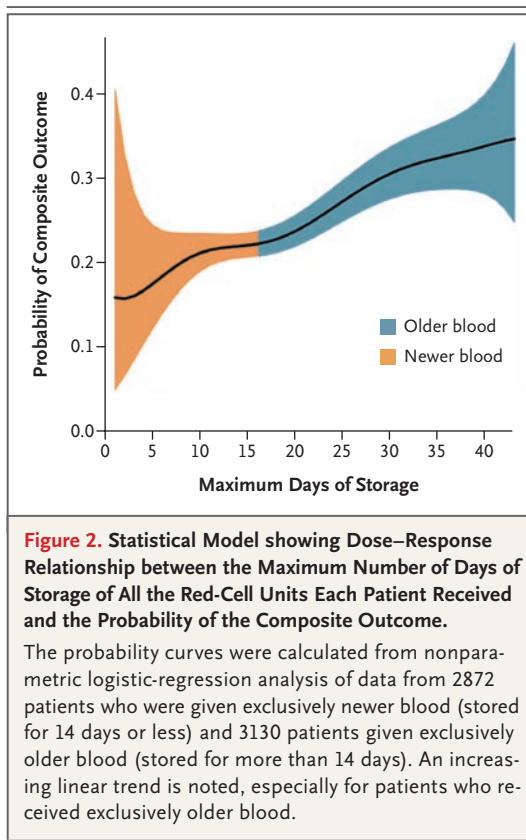
‡ All P values are for unadjusted comparisons between the two groups. The chi-square test or Fisher's exact test was used for comparisons of categorical variables.

§ The composite outcome incorporates all the complications listed in the table.

increased adhesiveness and aggregability³¹; reduction in the concentrations of nitric oxide and adenosine triphosphate³³; and accumulation of proinflammatory bioactive substances.³¹ Impairment results in part from priming of the nicotinamide adenine dinucleotide phosphate oxidase system, which is thought to result from accumulation of proinflammatory lipids.³⁴⁻³⁶ Abnormal flow and abnormal biochemical properties of

blood cells in stored blood are partially reversible by restoration of intracellular 2,3-DPG. However, recovery of 2,3-DPG is a slow process, and 2,3-DPG levels remain at only 50 to 70% of the normal range 24 hours after red-cell transfusion.^{37,38}

Because the storage lesion becomes apparent after about 2 weeks, we dichotomized our population into a group that was given only blood



stored for 14 days or less and a group given blood that was stored for more than 14 days. It happened that the median red-cell storage time was 15 days, so that a 2-week cutoff resulted in two groups of nearly equal size.

The results of previous studies evaluating the effect of red-cell age on outcomes are contradictory, perhaps because most studies were small and had substantial methodologic limitations. For example, Marik and Sibbald³⁹ noted an inverse association between changes in gastric intramucosal pH and the age of transfused blood for patients who received red cells stored for more than 15 days. In addition, evidence of splanchnic ischemia developed in patients given older blood.³⁹ Other studies demonstrated an association between an increased duration of storage and multiorgan failure,¹³ infectious complications,¹⁴⁻¹⁶ and death.¹⁷

Other investigations, however, showed no relationship between the duration of red-cell storage and adverse outcomes.^{23,24,40-42} Van de Watering and colleagues²⁴ examined broad outcome measures, such as length of stay and 30-day mortal-

ity, in 945 patients receiving exclusively red cells stored for less than 18 days and in 950 patients receiving exclusively red cells stored for more than 18 days. The authors reported similar outcomes in both groups; however, there were only a small number of outcome events.

Our study, which is based on data from patients receiving more than 19,000 units of transfused red cells in cardiac surgery, is a very large investigation of the effect of the duration of red-cell storage. Furthermore, the homogeneous patient population in our study did not include patients with trauma or patients with heterogeneous chronic diseases.

One limitation of transfusion studies is that "duration of storage" becomes difficult to define meaningfully if more than 1 unit is used. Previous investigators have used average, median, or maximum duration of storage.^{23,24} We instead restricted our analysis to patients given only newer blood or only older blood to better characterize the effect of duration of storage on major illnesses and death.

Observational cohort investigations may result in an imbalance in confounding variables among groups under comparison when group assignment is not at random. The provision of units of blood by a blood bank is not a random process, since it is constrained by blood-type compatibility. In addition, the blood bank is not blinded to the identity of transfusion recipients, and staff may become aware of the specific blood requirements of a rapidly bleeding patient. Such knowledge could influence decisions about the units of blood provided for transfusion. This effect was probably minimized by the fact that, during the period of the study, the blood bank routinely prepared 2 to 4 units of red cells the evening before planned surgical procedures and delivered them to the operating rooms the morning of surgery. Actual use of these units did not necessitate a call to the blood bank. As shown in Figure 1, a majority of patients received 1 or 2 units of blood, amounts not associated with active bleeding.

Nonetheless, given the fact that the distribution of blood units was not truly random, we investigated potential differences between the two study groups that might confound the comparison of interest. Although most baseline variables were similarly distributed between patients given older blood and those given newer blood, some

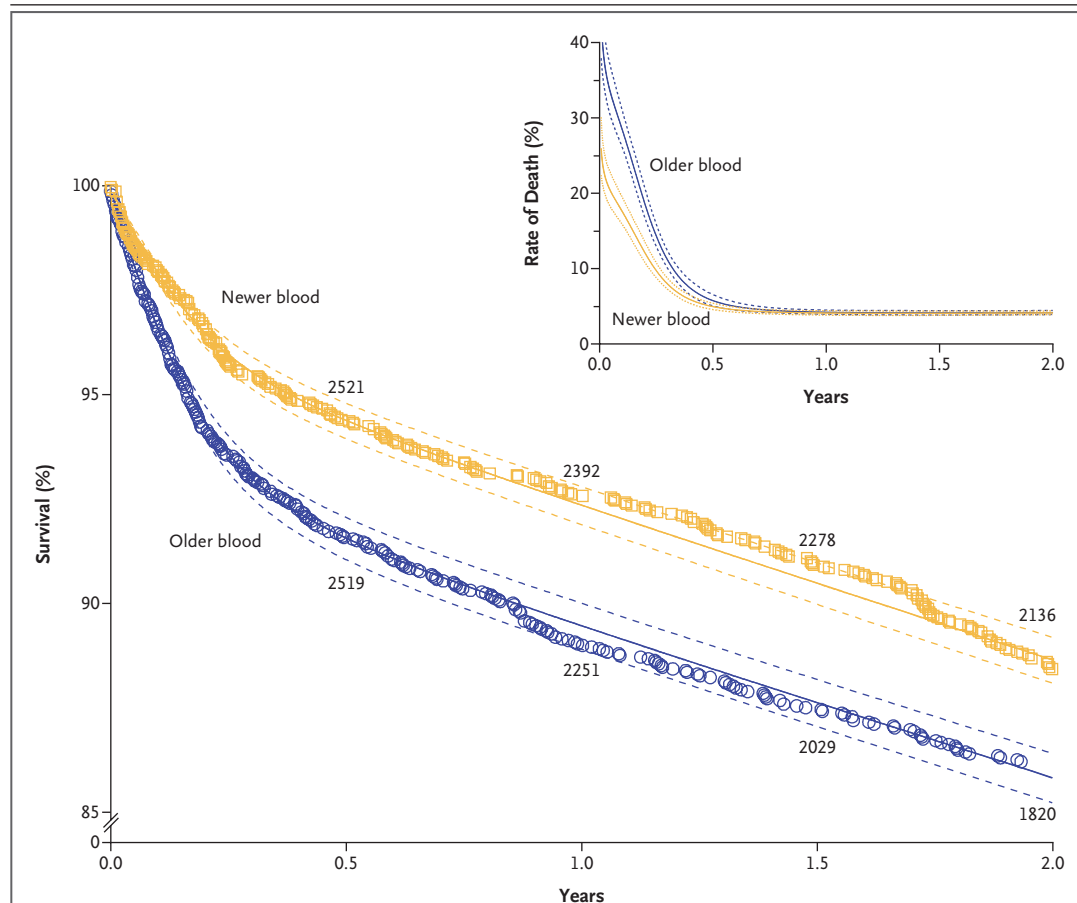


Figure 3. Kaplan–Meier Estimates of Survival and Death.

The curves show data from 2872 patients who were given exclusively newer blood (stored for 14 days or less) and 3130 patients given exclusively older blood (stored for more than 14 days). The numbers above and below the curves represent the numbers of patients who were alive and under follow-up observation in each group at that time. The solid lines of the same color represent estimated survival or the rate of death, and the dotted lines represent pointwise 95% confidence intervals. The nonparametric survival estimator (orange squares or blue circles), as determined by the Kaplan–Meier method, is superimposed on the parametric survival function estimator. In this unadjusted comparison, the percentage of patients receiving older blood who survived was lower than the percentage of those receiving newer blood who survived, especially during the initial follow-up period.

were not (Table 1). We therefore used multivariable regression as well as propensity-score methods to adjust for the imbalance in potentially confounding variables. The homogeneity of the patient population and the incorporation of a propensity score in the multivariable analyses strengthened the finding of an association between increased duration of storage and adverse outcomes.

There is increasing observational evidence that the risk of adverse outcomes increases incrementally with each unit of red cells that is transfused.^{5–7} However, the number and distribution

of units transfused in the two groups were fully balanced, and the number of units was included as a variable in the multivariable modeling; therefore, the adverse effects of transfusion per se do not confound our conclusion that outcomes are worse with older blood. In contrast, since patients given a mixture of older and newer blood received substantially more blood than either study group, we did not include them in our analysis.

The clinical implications of our findings require some consideration. About half of all patients undergoing cardiac surgery are given blood,

typically 1 or 2 units. We report that the relative risk of postoperative death is increased by 30% in patients given blood that has been stored for more than 2 weeks. These results may appear to suggest that blood should be classified as outdated earlier than current recommendations. However, maintaining an adequate blood supply depends on the balance between blood donation and use. Improving donation is challenging, and obtaining and processing blood is expensive. It seems unlikely that donation can be substantially increased on an ongoing basis, although the public response to disasters and emergencies suggests the potential to increase donation episodically.⁴³

Other possible approaches to reduce the mean storage time of transfused blood include a reduction in the amount of blood transfused (a course that has been facilitated in part by methods to retrieve and reuse shed blood during surgery⁴⁴ and that is receiving further impetus from studies suggesting that it is desirable to limit transfusion),⁵⁻⁷ the development of newer methods of

blood storage to retard the progression of storage-related changes,⁴⁵ the use of blood substitutes,⁴⁶ and the use of mathematical methods of inventory optimization to increase the preferential use of newer blood units without increasing waste.^{47,48} Further investigation will be necessary, however, before any substantial changes in blood-banking practices can be considered for broad implementation on the basis of our data.

In conclusion, we compared the outcomes among patients undergoing cardiac surgery who received transfusions of blood stored for more than 2 weeks with the outcomes among patients receiving blood stored for 2 weeks or less. Transfusion of red cells stored for more than 2 weeks was associated with a significantly increased risk of postoperative complications and a reduction in both short-term and long-term survival after cardiac surgery.

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No potential conflict of interest relevant to this article was reported.

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