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A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

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ABSTRACT

Background To determine whether a restrictive strategy of red-cell transfusion and a liberal strategy produced equivalent results in critically ill patients, we compared the rates of death from all causes at 30 days and the severity of organ dysfunction.

Methods We enrolled 838 critically ill patients with euvolemia after initial treatment who had hemoglobin concentrations of less than 9.0 g per deciliter within 72 hours after admission to the intensive care unit and randomly assigned 418 patients to a restrictive strategy of transfusion, in which red cells were transfused if the hemoglobin concentration dropped below 7.0 g per deciliter and hemoglobin concentrations were maintained at 7.0 to 9.0 g per deciliter, and 420 patients to a liberal strategy, in which transfusions were given when the hemoglobin concentration fell below 10.0 g per deciliter and hemoglobin concentrations were maintained at 10.0 to 12.0 g per deciliter.

Results Overall, 30-day mortality was similar in the two groups (18.7 percent vs. 23.3 percent, P= 0.11). However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill — those with an Acute Physiology and Chronic Health Evaluation II score of ≤20 (8.7 percent in the restrictive-strategy group and 16.1 percent in the liberal-strategy group, P=0.03) — and among patients who were less than 55 years of age (5.7 percent and 13.0 percent, respectively; P=0.02), but not among patients with clinically significant cardiac disease (20.5 percent and 22.9 percent, respectively; P=0.69). The mortality rate during hospitalization was significantly lower in the restrictive-strategy group (22.2 percent vs. 28.1 percent, P=0.05).

Conclusions A restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina. (N Engl J Med 1999;340:409-17.)

RED-cell transfusions are a cornerstone of critical care practice,[1] but there are divergent views on the risks of anemia and the benefits of transfusion in this setting. One important concern is that anemia may not be well tolerated by critically ill patients.[2,3] Indeed, two recent studies suggested that anemia increases the risk of death after surgery in patients with cardiac disease[2] and in critically ill patients.[3] Red-cell transfusions are used to augment the delivery of oxygen in the hope of avoiding the deleterious effects of oxygen debt.[4] This view prompted the routine use of transfusion in patients with hemoglobin concentrations that were often more than 10.0 g per deciliter in studies evaluating resuscitation protocols.[5,6]

Critically ill patients may, however, be at increased risk for the immunosuppressive[7,8] and microcirculatory[9,10] complications of red-cell transfusions. In addition, concern about the supply and safety of blood has also encouraged a conservative approach to transfusions. For these reasons, the optimal transfusion practice for various types of critically ill patients with anemia has not been established.

To elucidate the potential risks of anemia and possible benefits of transfusions in critically ill patients, we conducted a randomized, controlled, clinical trial to determine whether a restrictive approach to red-cell transfusion that maintains hemoglobin concentrations between 7.0 and 9.0 g per deciliter is equiv-

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alent to a more liberal strategy of maintaining hemoglobin concentrations between 10.0 and 12.0 g per deciliter in critically ill patients with euvolemia after initial treatment.

METHODS

Study Population

We enrolled patients who were admitted to 1 of 22 tertiary-level and 3 community intensive care units in Canada (see the Appendix) between November 1994 and November 1997. We included patients who were expected to stay in the intensive care unit more than 24 hours, had a hemoglobin concentration of 9.0 g per deciliter or less within 72 hours after admission to the intensive care unit, and were considered to have euvolemia after initial treatment by attending physicians. Patients were excluded for any of the following reasons: an age of less than 16 years; inability to receive blood products; active blood loss at the time of enrollment, defined as evidence of ongoing blood loss accompanied by a decrease in the hemoglobin concentration of 3.0 g per deciliter in the preceding 12 hours or a requirement for at least 3 units of packed red cells during the same period; chronic anemia, defined as a hemoglobin concentration of less than 9.0 g per deciliter on at least one occasion more than one month before admission to the hospital; pregnancy; brain death or imminent death (within 24 hours); a question on the part of attending physicians whether to withhold or withdraw ongoing treatment; and admission after a routine cardiac surgical procedure. The study protocol was approved by the institutional review board of each participating institution, and informed consent was obtained from either the patient or the closest family member before enrollment in the study.

Study Design and Treatment Protocols

Consecutive critically ill patients with normovolemia were assigned to one of two treatment groups, stratified according to center and disease severity (an Acute Physiology and Chronic Health Evaluation [APACHE II] score of 15 or less or a score of more than 15, with higher scores indicating more severe disease),[11] and balanced with the use of permuted blocks of four or six.[12] Sealed, opaque envelopes arranged in a computer-generated random order were prepared by the data-coordinating center and distributed to each participating institution, where they were opened sequentially to determine the patients' treatment assignments. The envelopes were returned periodically to the coordinating center for auditing.

Transfusion guidelines for both study groups were developed from information obtained in a national survey of critical care practitioners in Canada[13] and a pilot study.[14] The hemoglobin concentrations of patients assigned to the restrictive strategy of transfusion were maintained in the range of 7.0 to 9.0 g per deciliter, with a transfusion given when the hemoglobin concentration fell below 7.0 g per deciliter. Among patients assigned to the liberal strategy of transfusion, the hemoglobin concentrations were maintained in the range of 10.0 to 12.0 g per deciliter, with a threshold for transfusion of 10.0 g per deciliter. It was not feasible to mask the assigned transfusion strategy from health care providers.

In Canada, red cells are separated from whole blood and stored in citrate–phosphate–dextrose–adenine anticoagulant solution without leukodepletion. The volume of a unit of red cells ranges from 240 to 340 ml, with a hematocrit of approximately 80 percent.[15]

The physicians caring for the patients were instructed to administer transfusions, one unit at a time, and to measure a patient's hemoglobin concentration after each unit was transfused. Although specific goals for oxygen delivery were not part of the protocol, we provided suggestions for the use of fluids and vasoactive drugs, when necessary, and advice when a transfusion was not indicated by the study protocol. All other management decisions were left to the discretion of the patients' physicians. Adherence to the transfusion protocols was required only during the patient's stay in the intensive care unit. When a patient was discharged from the intensive care unit, a copy of the American College of Physicians guidelines for transfusion[16] was placed in his or her medical record.

Compliance with the two transfusion protocols was monitored by daily measurements of hemoglobin concentrations in each patient. In addition, transfusion records were sent regularly to the study coordinating center, which monitored the ability of individual centers to maintain hemoglobin concentrations in the target range.

Base-Line Assessment and Data Collection

At the time of randomization, demographic, diagnostic, and therapeutic information as well as information necessary to determine the severity of illness — including APACHE II scores,[11] calculated from data gathered within 24 hours after admission to the intensive care unit, and the multiple-organ-dysfunction score[17] — was obtained for each patient. The worst laboratory values recorded during each patient's stay in the intensive care unit were noted for use in assessing organ dysfunction with use of the multiple-organ-dysfunction score[17] and the multiple-system organ-failure score.[18] Hemoglobin concentrations; the use of red-cell transfusions; medications given, including vasoactive drugs; and the need for mechanical ventilation, dialysis, and surgical intervention were recorded on a daily basis.

The principal reason for admission to the intensive care unit was recorded. We included as many as three secondary diagnoses and eight coexisting conditions. In postoperative patients, the underlying diagnosis and the surgical procedure were recorded. All data were abstracted from clinical records by trained study personnel and coded according to the *International Classification of Diseases, 9th Revision, Clinical Modification*. All diagnoses were reviewed by two of the four critical care physicians, and disagreements were resolved by consensus.

Outcome Measures

The primary outcome measure was death from all causes in the 30 days after randomization. Secondary outcomes included 60-day rates of death from all causes, mortality rates during the stay in the intensive care unit and during hospitalization, and survival times in the first 30 days. Measures of organ failure and dysfunction, including the number and rates of organ failure as defined previously[18] and the multiple-organ-dysfunction score,[17] were also assessed. To improve our ability to detect meaningful differences between groups, we used some composite outcomes that included death and organ dysfunction or failure as indicators of morbidity. Patients who died were assigned a multiple-system organ-failure score of 7 and a multiple-organ-dysfunction score of 24, the worst possible values for each scale, as a means of adjusting measures of organ dysfunction and failure for deaths. Lengths of stays in the intensive care unit and the hospital were also recorded.

Statistical Analysis

Since this was an equivalency trial, we used 95 percent confidence intervals to estimate the number of patients necessary for the study to have the power to rule out clinically meaningful differences in outcomes. We estimated that 2300 patients would be needed to rule out an absolute difference of 4 percent in 30-day mortality between the two groups, assuming a combined mortality rate of 18 percent (the rate for a group receiving standard care was estimated to be 20 percent[3]). An interim analysis conducted in a blinded fashion by the data-monitoring committee after 404 patients had been enrolled revealed that the combined 30-day mortality rate was actually 23 percent. This change increased the detectable difference to 4.5 percent for a sample of 2300 patients. Because of this increase in observed mortality, we decided to decrease the target sample to 1620 patients (primarily on the basis of the hypothesis-testing method, in which the mortality rate for the standard-care group was 26.6 percent, the type 1 and type 2 error rates were 5 percent, and there was no change in the relative

risk of 27.5 percent from the original estimate of sample size). The recalculated sample size allowed us to rule out an absolute difference in the 30-day mortality rate of 5.5 percent between groups.

The final analysis was conducted on an intention-to-treat basis. Comparisons of hemoglobin concentrations over time were made with use of analysis of variance with repeated measures, followed by Tukey's honestly-significant-difference test for pairwise comparisons.

Mortality rates, the number of organs that failed per patient, and the rates of multiorgan failure were compared with use of Fisher's exact test. A forward, stepwise logistic-regression procedure was then performed to adjust raw mortality data with use of covariates that were found to be significant predictors of outcomes. Covariates were entered into the logistic model at a P value of ≤ 0.10. A second logistic regression was performed in which potential confounders, including age, APACHE II score, coexisting illnesses, diagnostic category, and study center, were forced into the model. Kaplan–Meier survival curves for each group were compared with use of a log-rank test statistic. Multiple-organ-dysfunction scores were analyzed with use of an independent t-test. To account for the influence of death on the assessment of organ failure and organ dysfunction, we conducted an additional analysis in which all patients who died were assigned the maximal scores. The complication rates were compared with use of a chi-square test. Lengths of stay in the intensive care unit and the hospital were analyzed with use of the Wilcoxon rank-sum test for independent samples.

A priori subgroup analyses of patients at potential risk for the adverse effects of anemia included patients who were 55 years of age or older, patients with cardiac disease, and patients with APACHE II scores indicating more severe illness. In the final analysis, we increased the threshold value for APACHE II scores from 15 to 20 because less than 20 percent of all patients had an APACHE II score below 15 and because a score of 20 was considered to be a better indicator of severe illness. We also examined patients with systemic infections. Differences in primary outcomes were considered statistically significant when the overall two-sided alpha level was 0.05 or less. No adjustments were made for multiple comparisons. Where appropriate, absolute P values are reported with 95 percent confidence intervals for differences between the groups.

RESULTS

Study Population

A total of 6451 patients were assessed for eligibility (Fig. 1). After exclusions for a variety of medical and administrative reasons, 838 patients were en-

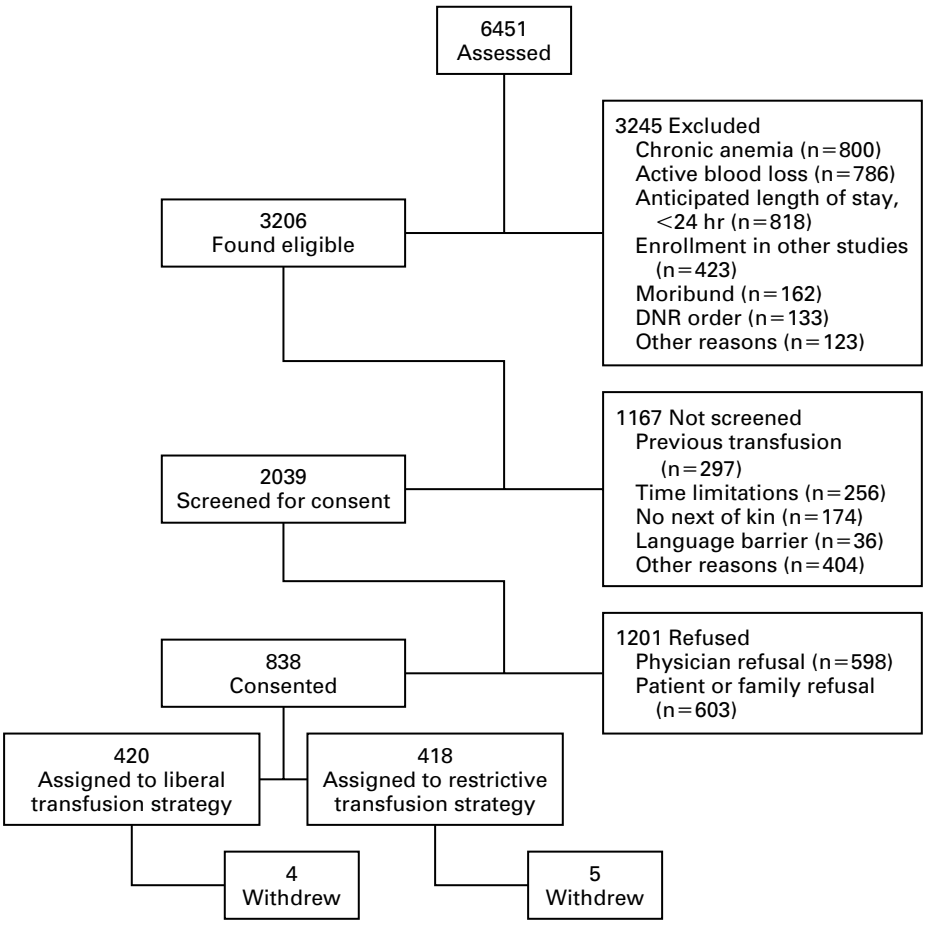

Figure 1. Numbers of Patients Assessed and Enrolled in the Trial.

DNR denotes do not resuscitate. Previous transfusion indicates receipt of transfusion that increased the hemoglobin concentration to more than 9.0 g per deciliter.

rolled in the study: 418 patients were assigned to a restrictive strategy of transfusion and 420 were assigned to a liberal strategy of transfusion. The consent rate was 41 percent (838 of 2039 patients). As compared with the patients who were enrolled in the study, those who were not enrolled were slightly older (mean [±SD] age, 57.6±18.2 vs. 59.4±18.8 years; P=0.04), but they had similar APACHE II scores (P=0.36) and diagnoses (P=0.26) with the exception of cardiac disease. Twenty-six percent of enrolled patients had cardiac disease, as compared with 20 percent of those who were not enrolled (P<0.01). Nine patients (1 percent) did not complete the trial; four were in the liberal-strategy group and five were in the restrictive-strategy group. Three additional patients were lost to follow-up at 60 days. The executive committee, without foreknowledge of treatment-specific outcomes, decided to terminate the study prematurely because of a decrease in enrollment to below 20 percent of predicted levels over a period of several months.

There were no significant differences in any baseline characteristics between the two groups (Table 1). The two most common reasons for admission to the intensive care unit were respiratory and cardiac diseases. The average APACHE II score was 21, and more than 80 percent of the patients were receiving mechanical ventilation. A total of 222 patients (26.5 percent) had an infection as either a primary or a secondary diagnosis.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.*

CHARACTERISTIC	RESTRICTIVE-TRANSFUSION STRATEGY (N=418)	LIBERAL-TRANSFUSION STRATEGY (N=420)
Male sex — no. (%)	269 (64)	255 (61)
Age — yr	57.1±18.1	58.1±18.3
APACHE II score†	20.9±7.3	21.3±8.1
Multiple-organ-dysfunction score‡	7.4±3.5	7.6±3.6
No. of organs failing — no. (%)		
0	108 (26)	95 (23)
1	175 (42)	203 (48)
2	100 (24)	83 (20)
3	30 (7)	29 (7)
>3	5 (1)	10 (2)
Primary diagnosis — no. (%)		
Respiratory disease	118 (28)	124 (30)
Cardiovascular disease	76 (18)	94 (22)
Trauma	85 (20)	80 (19)
Gastrointestinal disease	58 (14)	64 (15)
Sepsis	23 (6)	18 (4)
Neurologic abnormality	26 (6)	13 (3)
Other	32 (8)	27 (6)
Serious coexisting illness — no. (%)	126 (30)	149 (35)
Infection — no. (%)	114 (27)	108 (26)
Location before admission to ICU — no. (%)		
Operating room or recovery room	164 (39)	141 (34)
Emergency department	67 (16)	82 (20)
Another ward	112 (27)	113 (27)
Another hospital	58 (14)	64 (15)
Other	17 (4)	20 (5)
Interventions in ICU — no. (%)		
Mechanical ventilation	340 (81)	346 (82)
Pulmonary-artery catheter	141 (34)	150 (36)
Dialysis	21 (5)	18 (4)
Oxygen-delivery variables		
Hemoglobin — g/dl§	8.2±0.7	8.2±0.7
Red-cell transfusion — units¶	2.5±6.5	2.3±4.6
Total fluid intake — ml‖	3947±2209	3986±1707
Vasoactive drugs — no. (%)**	153 (37)	154 (37)
Lactate — mmol/liter††	1.8±1.8	1.8±2.1

*Plus–minus values are means ±SD. There were no significant differences between the two groups. Because of rounding, percentages may not total 100. ICU denotes intensive care unit.

†APACHE II denotes the Acute Physiology and Chronic Health Evaluation. The patients were assessed on the day of admission to the ICU. The range of scores for this test is 0 to 71, with higher scores indicating more severe illness.

‡The patients were assessed on the day of admission to the ICU. The range of scores for this test is 0 to 24, with higher scores indicating more severe organ dysfunction.

§Values are the lowest values recorded within 24 hours after randomization.

¶Values are the number of units transfused from the time of admission to the hospital to the time of admission to the ICU.

‖Values reflect the total fluid balance in the 24 hours before randomization.

**The values are the numbers of patients who required more than 5 μg of dopamine per kilogram of body weight per minute or any dose of another vasoactive drug.

††Values are the highest values recorded in the 24 hours before randomization.

Success of Treatment

The average daily hemoglobin concentrations were 8.5±0.7 g per deciliter in the restrictive-strategy group and 10.7±0.7 g per deciliter in the liberal-strategy group (P<0.01). The average hemoglobin concentrations also differed significantly between the groups during each day of the 30-day study (P<0.01). An average of 2.6±4.1 red-cell units per patient was administered in the restrictive-strategy group, as compared with an average of 5.6±5.3 units per patient in the liberal-strategy group (P<0.01). This equals a relative decrease of 54 percent in the number of transfusions when the lower threshold was used. In addition, 33 percent of the patients in the restrictive-strategy group did not receive any red cells after randomization, as compared with 0 percent of the patients in the liberal-strategy group (P<0.01).

Noncompliance of physicians with the study regimen, as indicated by a finding of hemoglobin concentrations outside the prespecified ranges for at least 48 hours, occurred in 4.3 percent of patients in the liberal-strategy group (18 of 420) and 1.4 percent of patients in the restrictive-strategy group (6 of 418) (P=0.02). A subgroup of these patients were inadvertently crossed over from one group to the other when physicians either administered or withheld red-cell transfusions. The overall rate of cross-

TABLE 2. OUTCOMES.*

OUTCOME MEASURE	RESTRICTIVE-TRANSFUSION STRATEGY (N=418)	LIBERAL-TRANSFUSION STRATEGY (N=420)	ABSOLUTE DIFFERENCE BETWEEN GROUPS	95% CONFIDENCE INTERVAL	P VALUE
			percent		
Death — no. (%)					
30-day	78 (18.7)	98 (23.3)	4.7	−0.84 to 10.2	0.11
60-day†	95 (22.7)	111 (26.5)	3.7	−2.1 to 9.5	0.23
ICU	56 (13.4)	68 (16.2)	2.3	−2.0 to 7.6	0.29
Hospital	93 (22.2)	118 (28.1)	5.8	−0.3 to 11.7	0.05
Multiple-organ-dysfunction score					
Unadjusted score	8.3±4.6	8.8±4.4	0.5	−0.1 to 1.1	0.10
Adjusted score‡	10.7±7.5	11.8±7.7	1.1	0.8 to 2.2	0.03
Change from base-line score§	3.2±7.0	4.2±7.4	1.0	0.1 to 2.0	0.04
No. of organs failing — no. (%)					
0	100 (23.9)	82 (19.5)			
1	136 (32.5)	149 (35.5)			
2	109 (26.1)	108 (26.0)			
3	51 (12.2)	63 (15.0)			
>3	22 (5.3)	18 (4.3)	1.8¶	−3.4 to 7.1¶	0.53¶
Length of stay — days					
ICU	11.0±10.7	11.5±11.3	0.5	−1.0 to 2.1	0.53
Hospital	34.8±19.5	35.5±19.4	0.7	−1.9 to 3.4	0.58

*Plus–minus values are means ±SD. ICU denotes intensive care unit. Because of rounding, percentages may not total 100.

†Three patients were lost to follow-up at 60 days: two in the restrictive-strategy group and one in the liberal-strategy group.

‡All patients who died were given a score of 24 (the highest score).

§Adjusted scores were used.

¶The comparison is between three or more organ failures and fewer than three organ failures.

over was 1.8 percent (15 of 838): 2.6 percent (11) in the liberal-strategy group and 1 percent (4) in the restrictive-strategy group (P=0.12).

Given that the investigators were aware of the patients' treatment assignments, other interventions may have influenced outcomes. The use of medications, including vasoactive drugs; the administration of fluids and daily fluid balance; and the use of pulmonary-artery catheters were similar in both groups throughout the stay in the intensive care unit (P=0.15). The use of other interventions such as dialysis, mechanical ventilation, and surgical procedures was also similar (P=0.58).

Outcome Measures

The primary outcome — the rate of death from all causes in the 30 days after admission to the intensive care unit — was 18.7 percent in the restrictive-strategy group and 23.3 percent in the liberal-strategy group (95 percent confidence interval for the difference between the groups, −0.84 percent to 10.2 percent; P=0.11) (Table 2). The mortality rates during hospitalization were lower in the restrictive-strategy group (22.2 percent vs. 28.1 percent, P=0.05). Other mortality rates including the mortality rate during the entire stay in the intensive care unit (13.9 percent vs. 16.2 percent, P=0.29) and the 60-day mortality rate (22.7 percent vs. 26.5 percent, P=0.23) were also lower in the restrictive-strategy group but not significantly so.

Kaplan–Meier survival curves were similar for the patient group as a whole, but they were significantly different in the subgroup of patients with an APACHE II score of 20 or less (P=0.02) and in the subgroup of patients who were younger than 55 years (P=0.02) (Fig. 2). The unadjusted odds ratio for death within 30 days in the restrictive-strategy group as compared with the liberal-strategy group was 0.75 (P=0.09). Adjustment for the influence of age, APACHE II score, diagnosis, and coexisting illnesses with use of logistic-regression analysis did not change the odds ratio significantly (odds ratio, 0.72; 95 percent confidence interval, 0.50 to 1.07; P=0.07).

The number of patients with multiorgan failure (more than three organs), which was analyzed as a dichotomous variable (present or absent) for each of seven organ systems,[18] was not significantly different between the restrictive-strategy and liberal-strategy groups (5.3 percent vs. 4.3 percent, P=0.36). The mean multiple-organ-dysfunction score was marginally lower in the restrictive-strategy group than in the liberal-strategy group (8.3±4.6 vs. 8.8±4.4, P=0.10).

We also examined composite outcomes. When or-

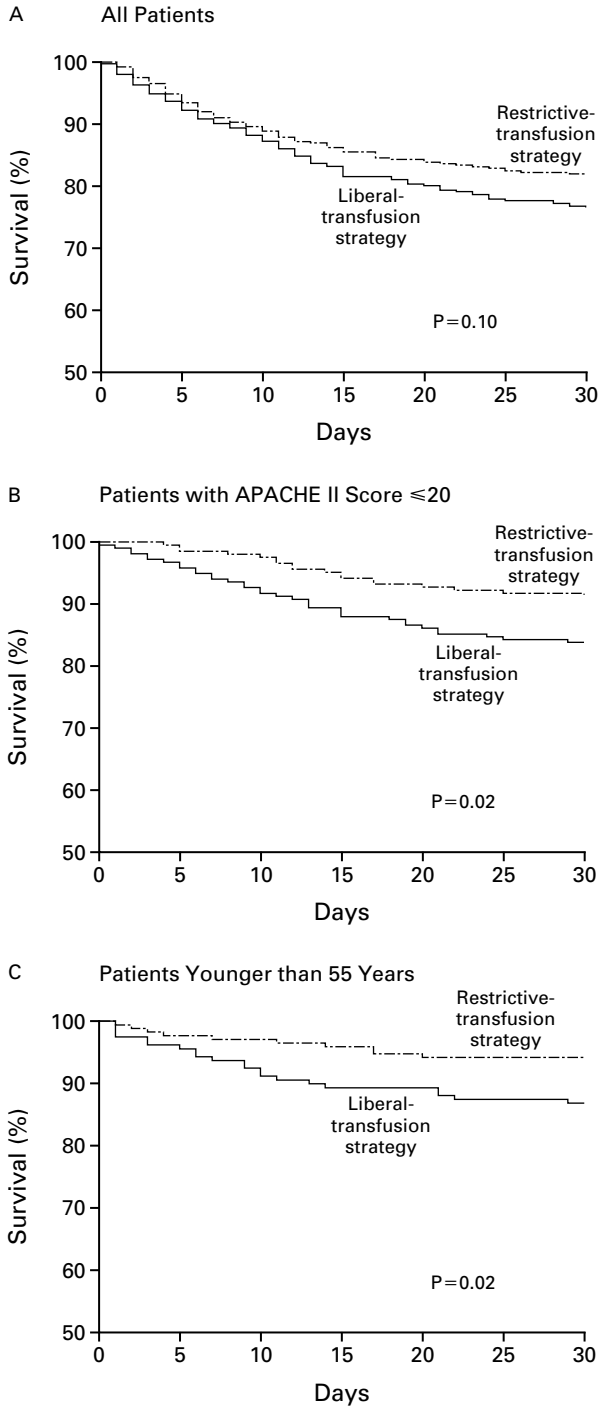

Figure 2. Kaplan–Meier Estimates of Survival in the 30 Days after Admission to the Intensive Care Unit in the Restrictive-Strategy and Liberal-Strategy Groups.

Panel A shows the survival curves for all patients in the study groups. Panel B shows the survival curves in the subgroup of patients with an APACHE II score of 20 or less. Panel C shows the survival curves in the subgroup of patients who were younger than 55 years.

gan-failure scores of 7 were assigned to all patients who died within 30 days after admission to the intensive care unit, the number of patients with multiorgan failure was substantially increased in both groups, and the results were marginally better in the restrictive-strategy group (20.6 percent vs. 26.0 percent, P=0.07). Similarly, when all patients who died were given a multiple-organ-dysfunction score of 24, the total scores (P=0.03) and the changes in the scores from base line (P=0.04) were significantly lower in the restrictive-strategy group (Table 2).

Cardiac events, primarily pulmonary edema and myocardial infarction, were more frequent in the liberal-strategy group than in the restrictive-strategy group during the stay in the intensive care unit (P<0.01) (Table 3). However, there were no significant differences in the rates of cardiac events (41 percent in the restrictive-strategy group and 44 percent in the liberal-strategy group, P=0.86), infectious complications (3 percent and 4 percent, respectively; P=1.00), or multiorgan failure (37 percent and 32 percent, respectively; P=0.59) in the 48 hours preceding death among the patients who died (Table 4).

Subgroup Analyses

When the patients were analyzed according to age (<55 years vs. ≥55 years) and APACHE II score (≤20 vs. >20), there were no significant differences in base-line characteristics. In the restrictive-strategy group, 173 patients were younger than 55 years, 207 patients had an APACHE II score of 20 or less, 151 patients had cardiac disease, 100 had a traumatic injury, and 114 had a severe infection or septic shock. In the liberal-strategy group, 161 patients were younger than 55 years, 217 had an APACHE II score of 20 or less, 175 had cardiac disease, 100 had a traumatic injury, and 104 had a severe infection or septic shock. All outcomes in the two transfusion-strategy groups were similar for the patients who were older than 55 years and for those with an APACHE II score of more than 20 (P>0.36). However, 30-day mortality was significantly lower in the restrictive-strategy group than in the liberal-strategy group among the patients with an APACHE II score of 20 or less (8.7 percent vs. 16.1 percent; 95 percent confidence interval for the absolute difference, 1.0 to 13.6 percent; P=0.03) and among the patients who were less than 55 years of age (5.7 percent vs. 13.0 percent; 95 percent confidence interval, 1.1 to 13.5 percent; P=0.02). There were no significant differences in 30-day mortality between treatment groups in the subgroup of patients with a primary or secondary diagnosis of cardiac disease (20.5 percent in the restrictive-strategy group and 22.9 percent in the liberal-strategy group; 95 percent confidence interval for the difference, −6.7 to 11.3 percent; P=0.69), in the subgroup of patients with severe infections and septic shock (22.8 percent and

TABLE 3. COMPLICATIONS THAT OCCURRED DURING THE PATIENTS' STAYS IN THE INTENSIVE CARE UNIT.

COMPLICATION*	RESTRICTIVE-TRANSFUSION STRATEGY (N=418)	LIBERAL-TRANSFUSION STRATEGY (N=420)	ABSOLUTE DIFFERENCE BETWEEN GROUPS	95% CONFIDENCE INTERVAL†	P VALUE
	no. (%)		percent		
Cardiac	55 (13.2)	88 (21.0)	7.8	2.7 to 12.9	<0.01
Myocardial infarction	3 (0.7)	12 (2.9)	2.1	—	0.02
Pulmonary edema	22 (5.3)	45 (10.7)	5.5	1.8 to 9.1	<0.01
Angina	5 (1.2)	9 (2.1)	0.9	—	0.28
Cardiac arrest	29 (6.9)	33 (7.9)	0.9	−2.6 to 4.5	0.60
Pulmonary	106 (25.4)	122 (29.0)	3.7	−2.3 to 9.7	0.22
ARDS	32 (7.7)	48 (11.4)	3.8	−0.2 to 7.8	0.06
Pneumonia	87 (20.8)	86 (20.5)	−0.3	−5.8 to 5.1	0.92
Infectious	42 (10.0)	50 (11.9)	1.9	−2.4 to 6.1	0.38
Bacteremia	30 (7.2)	40 (9.5)	2.3	−1.4 to 6.1	0.22
Catheter-related sepsis	21 (5.0)	17 (4.0)	−1.0	−3.8 to 1.8	0.50
Septic shock	41 (9.8)	29 (6.9)	−2.9	−6.7 to 0.8	0.13
Hematologic‡	10 (2.4)	10 (2.4)	0	−2.1 to 2.1	1.00
Gastrointestinal§	13 (3.1)	19 (4.5)	1.4	−1.2 to 4.0	0.28
Neurologic¶	25 (6.0)	33 (7.9)	1.9	−1.6 to 5.3	0.28
Shock‖	67 (16.0)	55 (13.1)	−2.9	−7.7 to 1.8	0.23
Any complication	205 (49.0)	228 (54.3)	5.2	−1.5 to 12.0	0.12

*Patients may have had more than one type of complication. ARDS denotes acute respiratory distress syndrome.

†In some cases, the number of patients in a group was too small to allow calculation of the 95 percent confidence interval.

‡This category includes transfusion reactions, hemolytic anemia, disseminated intravascular coagulation, and other blood dyscrasias.

§This category includes gastrointestinal bleeding, bowel perforation, and ischemic bowel syndrome.

¶This category includes cerebrovascular accidents and encephalopathies.

‖This category includes hypovolemic shock, cardiogenic shock, and all other types of shock except septic shock.

29.7 percent, respectively; P=0.36), or in the subgroup of patients with trauma (10.0 percent and 8.8 percent, respectively; P=0.81).

The results for the rates of organ dysfunction in the subgroups were similar to those for other subgroup analyses. The multiple-organ-dysfunction scores adjusted for patients who died did not differ significantly in the subgroup of patients with an APACHE II score of more than 20, the subgroup more than 55 years of age, and the subgroup with specific diagnoses, including cardiac disease, trauma, and severe infections and septic shock (all P>0.30). However, adjusted multiple-organ-dysfunction scores were significantly lower in the subgroup of patients with an APACHE II score of 20 or less (8.3±6.2 in the restrictive-strategy group and 10.0±7.2 in the liberal-strategy group, P=0.01) and in the subgroup of patients who were younger than 55 years of age (8.8±5.7 and 10.3±6.6, respectively; P=0.03).

DISCUSSION

Our findings indicate that the use of a threshold for red-cell transfusion as low as 7.0 g of hemoglobin per deciliter, combined with maintenance of hemoglobin concentrations in the range of 7.0 to 9.0 g per deciliter, was at least as effective as and possibly superior to a liberal transfusion strategy (threshold, 10.0 g per deciliter; maintenance range, 10.0 to 12.0) in critically ill patients with normovolemia. There was a trend toward decreased 30-day mortality among patients who were treated according to the restrictive transfusion strategy. The significant differences in mortality rates during hospitalization, rates of cardiac complications, and rates of organ dysfunction all favored the restrictive strategy.

We also found that maintaining hemoglobin concentrations in the range of 7.0 to 9.0 g per deciliter decreased the average number of red-cell units transfused by 54 percent and decreased exposure to any red cells after randomization by 33 percent. Concern about exposure to blood products has increased the use of expensive drugs such as epoetin alfa and aprotinin, which reduce perioperative exposure by an average of one to two red-cell units, with little evidence of overall effectiveness. In contrast, a simple and inexpensive intervention that lowers the transfusion threshold improved clinical outcomes and reduced exposure to red cells.

TABLE 4. CHARACTERISTICS OF THE 176 PATIENTS WHO DIED.*

CHARACTERISTIC	RESTRICTED-TRANSFUSION STRATEGY (N=78)	LIBERAL-TRANSFUSION STRATEGY (N=98)	P VALUE
Demographic and diagnostic variables			
Age — yr	68.7±12.0	65.9±15.2	0.16
Male sex — no. (%)	48 (62)	58 (59)	0.76
APACHE II score	25.3±7.0	24.6±8.5	0.53
Primary diagnosis at death — no. (%)			0.27
Cardiovascular disease	15 (19)	15 (15)	
Respiratory disease	28 (36)	44 (45)	
Gastrointestinal disease	11 (14)	9 (9)	
Neurologic abnormality	9 (12)	6 (6)	
Other	15 (19)	25 (26)	
Events occurring 48 hr before death — no. (%)			
No. of organs failing			0.54
0	13 (17)	13 (13)	
1	23 (29)	31 (32)	
2	21 (27)	30 (31)	
3	19 (24)	24 (24)	
>3	2 (3)	0	
Complications†			
Cardiac events	25 (41)	32 (44)	0.86
Infection	2 (3)	3 (4)	1.00
Pulmonary events	6 (10)	9 (12)	0.79
Shock	8 (15)	12 (18)	0.81
Failure of ≥3 organs	23 (37)	24 (32)	0.59
Any type	40 (66)	44 (60)	0.59
Interventions†			
Antibiotics	52 (83)	64 (85)	0.87
Vasoactive drugs	38 (62)	46 (63)	0.88
Mechanical ventilation	55 (90)	67 (92)	0.77
Dialysis	6 (10)	10 (14)	0.60

*Plus–minus values are means ±SD. APACHE II denotes the Acute Physiology and Chronic Health Evaluation.

†No data on complications or interventions were available for the 42 patients who died outside the intensive care unit. Complications or interventions were recorded for 134 patients who died in the intensive care unit: 61 in the restrictive-strategy group and 73 in the liberal-strategy group.

A recent systematic review of transfusion practice[19] identified five randomized, controlled clinical trials that compared clinical outcomes after the implementation of two transfusion strategies. The only large trial, in patients with chronic anemia due to sickle cell disease, did not demonstrate decreases in the incidence of sickle cell crises among patients assigned to a liberal transfusion strategy.[20] The four other trials were quite small. Two studies in patients undergoing bypass surgery[21,22] and our pilot study[14] did not find differences between the transfusion strategies but were too small to yield clinically useful inferences. The fifth trial, in patients with nonvariceal gastrointestinal hemorrhage, found that administering transfusions liberally or expectantly resulted not only in increased overall use of transfusions but also in a higher frequency of coagulation abnormalities.[23]

A number of randomized, controlled clinical trials have addressed the hypothesis that oxygen delivery should be increased or maintained at high levels to minimize the effects of tissue hypoxia caused by disease processes that interfere with oxygen delivery or the body's ability to extract oxygen. One meta-analysis[24] found that oxygen delivery was increased when oxygen therapy was initiated preoperatively, but this benefit was not observed in studies that evaluated patients admitted to the intensive care unit. In all the previous studies, the transfusion thresholds exceeded 10.0 g per deciliter; therefore, it was not possible to make inferences about optimal strategies for red-cell transfusion. In our study, red-cell transfusions, used as a means of augmenting oxygen delivery, did not offer any survival advantage in patients with normovolemia when hemoglobin concentrations exceeded 7.0 g per deciliter.

There is also concern about the adverse effects of anemia in patients with ischemic heart disease. Two large cohort studies found that an increasing severity of anemia was associated with a disproportionate increase in mortality rates among patients with ischemic heart disease.[2,3] In our study, however, patients with diagnoses of cardiac disease did not have more adverse outcomes when a transfusion threshold of 7.0 g per deciliter was used. The apparent discrepancy between our results and those of previous studies may be the result of confounding[3] or an inability to document the negative effects of transfusion[2] in the observational studies.

In most clinical trials, there are more patients who are asked to participate than actually agree to participate. There is therefore a possibility that refusals on the part of patients, their surrogates, or their physicians affect the generalizability of the results. A greater proportion of patients with severe cardiac disease than with other types of disease had attending physicians who declined to enroll them in our study. Nevertheless, we believe that a restrictive strategy can be implemented in patients with coronary artery disease but should be considered with caution in patients with acute myocardial infarction and unstable angina.

On the basis of our results, we recommend that critically ill patients receive red-cell transfusions when their hemoglobin concentrations fall below 7.0 g per deciliter and that hemoglobin concentrations should be maintained between 7.0 and 9.0 g per deciliter. The diversity of the patients enrolled in this trial and the consistency of the results suggest that our conclusions may be generalized to most critically ill patients, with the possible exception of patients with active coronary ischemic syndromes.

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APPENDIX

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