Equipoise and the Continued Transfusion of “Old” Blood

With >400,000 transfusion episodes and 100,000 deaths, the database of Edgren et al excluded patients who had received units with mixed storage times. Because fresh RBC units are usually issued for special indications, patients who had exclusively received RBCs stored for 10 to 19 days were considered to represent the appropriate “reference” group in the study of Edgren et al; patients who had exclusively received RBCs stored for 30 to 42 days were designated as recipients of “old” RBCs. However, all patient

Figure 7-7. Odds ratios (ORs) and their 95% confidence intervals (CIs) for the effect of Red Blood Cell (RBC) storage on short-term (7-day) and long-term (2-year) mortality of all transfusion recipients, recipients stratified by number of transfused RBC units, and recipients of white blood cell (WBC)-reduced units. The figure is based on the analysis of all patients receiving RBC transfusions in Denmark and Sweden between 1995 and 2002, as reported by Edgren et al.
groups (ie, recipients of RBCs <9, 20-29, and 30-42 days old, as well as the recipients of mixed-age units) were compared with the “reference” group of patients. In no case did an association between an RBC storage category and short-term mortality attain significance.

Finally, one ICU study reported that the effect of a composite variable defined as the mean storage of all transfused RBCs multiplied by the number of transfused units was not significant. Two medically heterogeneous studies (one in cardiac surgery and one in the pediatric ICU) reported the unadjusted mean ± SD duration of storage of all RBCs transfused to survivors or nonsurvivors, and it observed no difference between the groups. One study enrolling 31 ICU patients reported that the median storage of RBCs transfused to nonsurvivors was significantly (p<0.05) longer than that of RBCs administered to survivors, but a multivariate analysis was not included in the report.

Organ Failure

Seven studies presented adjusted or unadjusted results for the effect of RBC storage on single- or multi-organ failure or a similar outcome. Gajic et al observed no association between storage and acute lung injury (ALI) in a matched and a univariate analysis; the latter study was not followed by a multivariate analysis because no univariate association was recorded. In the matched analysis, the median duration of storage of transfused RBCs was 22.9 (17-31) days in subjects with ALI and 22.9 (15-30) days in controls (n = 35 matched pairs of ICU patients). In addition, among 181 ICU patients, those who developed ALI had received RBCs stored for a mean (range) of 17.7 (13-22) days, as compared with 18.5 (15-23) days for subjects who did not develop ALI. In that study, there also was no association between transfusion of RBCs stored for >20 days and ALI (OR = 0.83; 95% CI = 0.42-1.66). A multivariate analysis of trauma patients also failed to detect an association between transfusion of RBCs stored for >14 days and acute respiratory distress syndrome (ARDS) (OR = 1.03; 95% CI = 0.89-1.19).

Two cardiac surgery studies reported adjusted associations between RBC storage and renal failure. The studies were homogeneous in the duration of storage of the oldest transfused RBC unit (p>0.05 for the Q test statistic), and—across the two studies—the age of the oldest unit was not associated with renal failure (summary OR = 0.993; 95% CI = 0.963-1.024). The two studies were extremely heterogeneous in the mean storage of all transfused RBCs (p<0.00001 for the Q test statistic), as the 95% CIs for the ORs calculated from within each study did not even overlap. For this reason, these two studies could not be combined in the analysis of mean storage. A relationship between transfusion of RBCs stored for >14 days and renal failure was reported in trauma patients from a multivariate analysis that did not adjust for the number of transfused RBC units.

Two studies reported adjusted associations between a composite outcome or multiple-organ failure (MOF) and RBC storage. In cardiac surgery, the odds of occurrence of the composite outcome were greater (p = 0.03) in recipients of RBCs stored for >14 days than in recipients of RBCs stored for <14 days, but this analysis did not adjust for the effect of the number of transfused RBC units or of multiple comparisons. In trauma, 23 subjects who developed MOF received older RBCs than did 40 controls who did not develop MOF (mean ± SD RBC age: 30.5 ± 7.68 and 24.0 ± 3.16 days, respectively).

In a study in a pediatric ICU, Gauvin et al recently reported an association between duration of storage of the oldest (WBC-reduced) RBC unit and development of new or progressive multiple-organ dysfunction score (MODS). These authors reported multiple analyses, defining transfusion of old RBCs as receipt of ≥1 unit stored for ≥7 days, ≥1 unit stored for ≥14 days, or ≥1 unit stored for ≥21 days. They also reported on a subgroup analysis of critically ill children transfused with 1 RBC unit. In that patient subgroup, the effect of the duration of storage of the single transfused RBC unit was
not confounded by the number of transfused RBC units. There was no difference in new or progressive MODS when ≥7- or ≥14-day-old RBCs were compared with fresher (<7 or <14-day-old, respectively) RBCs. However, when old RBCs included only ≥21-day-old RBCs and were compared to units stored for <21 days, the OR of developing new or progressive MODS was significantly increased (OR = 3.27; 95% CI = 1.38-7.74; p<0.05). There was also a significant association between transfusion of RBCs >14 days old and FFP transfusion—probably reflecting the fact that sicker children (who were at greater risk of needing FFP transfusion) were also more likely to receive an older RBC unit.36 This finding led the authors to conclude that—without conducting an RCT—“[i]t is not possible to discern the impact of older blood from the possible impact of FFP transfusion on outcome.”36 ABO blood group [owing to the higher Factor VIII levels in non-group O (compared with group O) individuals—an attribute that may predispose to thrombosis] is another possible confounder not controlled but commented upon in the discussion by Gauvin et al.36

Concerning the question of multiple comparisons in the analysis of Koch et al,33 it is noted that most published observational studies had considered several adverse outcomes and had presented adjusted results for only some of them. Thus, Koch et al33 reported on six outcomes in their abstract (ie, in-hospital mortality, 1-year mortality, intubation for >72 hours, renal failure, sepsis, and a composite of complications), only one of which (a composite of complications) had been adjusted for the effects of confounding factors94 (albeit not for the number of transfused RBCs20,22,35,89). Even if the lack of adjustment for this latter (and most important) confounder were to be ignored, the reported adjusted finding (p = 0.03) would no longer be significant if it were adjusted further for the effect of multiple comparisons.94,95 The same concern about multiple comparisons95 would apply to the results of the meta-analysis.33 had the findings of the overview been positive. When synthesis of results from multivariate analyses was feasible, however, the results of the meta-analysis55 were either negative or impossible to evaluate because of the effects of uncontrolled confounders.

**Nosocomial Infection**

Figure 7-8 shows the unadjusted results of observational studies reporting on the association between RBC storage and postoperative pneumonia in cardiac surgery.84-86 Although there was an association between the oldest85,86 (or oldest and second-oldest84) transfused RBC unit and postoperative pneumonia before adjustment for the effects of confounding factors, no association was detected when the adjusted results from the same observational studies84-86 were integrated (Fig 7-9). Four studies83,86 have presented adjusted results on the effect of RBC storage on pneumonia, but one of them, a trauma study,83 did not adjust for the number of transfused RBCs. Weinberg et al83 reported an association between transfusion of RBCs stored for >14 days and pneumonia (OR = 1.10; 95% CI = 1.04-1.17; p<0.05).

A study of 61 trauma patients71 found an association (p<0.05) between the transfusion of RBCs older than 14 or 21 days and major infection, after adjustment for patient age and Injury Severity Score, but not for the number of transfused RBCs. In contrast, a study of 448 ICU patients that evaluated the effect of both the length of storage and the number of transfused RBCs concluded that only the number of transfusions was associated with major infection.74 One87 of two 87,88 colorectal surgery studies reported an association between transfusion of RBCs stored for >21 days and postoperative infection (excluding urinary tract infection), on the basis of a multivariate analysis that did not adjust for the number of transfused RBCs.

**RCTs Currently Under Way in the United States and Canada**

Several RCTs comparing recipients of fresh RBCs with recipients of standard or old RBCs are currently ongoing (see http://www.clinicaltrials.gov and http://www.controlled-trial.com).96