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Red Blood Cell Transfusions: Does Storage Age Matter?

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Key Points

- Three multicenter, prospective randomized controlled trials performed to date do not demonstrate any benefit to transfusing "fresher" (versus "older") RBCs.
- Findings from three additional studies in this area will soon be published.
- While this debate still has not been settled fully, the current approach for selecting RBCs – which does not, in the great majority of cases, take product age into account – remains acceptable.

Liquid red blood cells (RBC) can be stored for up to 42 days depending on the anticoagulant-preservative storage solution(s) used. The standard of practice at most hospitals is a "first-in, first-out" policy where, for most situations, the oldest compatible units are issued first to minimize outdating.

The association of transfusions with "older" RBCs and poorer clinical outcomes has been a topic of debate for many years.[1] Many observational studies have reported that older units are associated with increased risks for infection, organ failure, prolonged hospital stays, and death. Limiting the generalizability of their findings is that they often were small, usually single institution, and non-randomized or controlled.[2] They also had varying primary endpoints, differed in their criteria used to define product "freshness," and may have suffered from unmeasured confounding variables. In short: they were useful for generating hypotheses but lacked the ability to establish a causal relationship between RBC age and clinical outcomes, which requires randomized controlled trials (RCTs).

Herein we summarize the most important findings and conclusions from the three RCTs published on this topic to date.

Age of Red Blood Cells in Premature Infants (ARIPI) Study[3]: Premature infants receiving small-volume RBC transfusions are often exposed to older blood due to "dedicated product" policies that reduce donor exposures and the associated risks. This study compared morbidity and mortality rates in very-low birth-weight infants being treated in the neonatal intensive care unit who were transfused with "very fresh" (<7 days old) vs. "standard issue" (dedicated units until depleted or expired) RBCs. The primary outcome was "a composite measure of major neonatal morbidities" (necrotizing enterocolitis, retinopathy of prematurity, intraventricular hemorrhage, bronchopulmonary dysplasia) and death. Secondary outcomes included the "individual complications comprising the composite outcome and rates of nosocomial infections. Of 377 randomized patients, 188 received RBC units having a mean age of 5.1 days (standard deviation [SD]: 2.0 days) and 189 were transfused with blood at a mean age of 14.6 days (SD: 8.3). No statistically significant differences were seen between patients receiving fresh vs. standard issue RBCs, for the primary outcome (52.7 vs. 52.9% respectively, relative risk [RR] = 1.00; 95%, confidence interval [CI]: 0.82 to 1.21) or for secondary outcomes (clinically suspected infections: 77.7 vs. 77.2%; RR = 1.01; 95% CI: 0.90 to 1.12; positive cultures: 67.5 vs. 64.0%; RR = 1.06; 95% CI: 0.91 to 1.22). The fresh RBC group had more donor exposures (3.7 vs. 2.1 donors/patient). While the safety of older units of blood in neonates has been demonstrated in smaller volume transfusions (10-20 ml/kg), there have been reports of an increased rate of hyperkalemia, including fatality, after large volume transfusion of older red cell units.[4]

Red-Cell Storage Duration Study (RECESS)[5]: This study evaluated patients ≥12 years of age undergoing complex cardiac surgery and likely to receive blood transfusion. The authors hypothesized that compromised cardiac output and the pro-inflammatory state after cardiopulmonary bypass might make such patients more susceptible to the effects of the RBC "storage lesion." Patients were randomized to ≤10-day-old leukoreduced

(LR) RBCs or ≥21-day-old LR RBCs. The primary outcome was the highest multiple organ dysfunction score (MODS) from the preoperative baseline to 7 days postoperatively or at death/discharge. Of 1,098 participants, 538 were transfused with younger units (mean age: 7.8 days; SD: 4.8) and 560 received older blood (mean: 28.3 days; SD: 6.7). No significant differences were found in the mean changes in MODS (increases of 8.5 vs. 8.7; p = 0.44), the 7-day mortality rate (2.8% vs. 2.0%; p = 0.43), or the 28-day mortality rate (4.4% vs. 5.3%; p = 0.57) with younger vs. older blood respectively.

Age of Blood Evaluation (ABLE) Trial[6]: In this study, critically ill adults expected to require mechanical ventilation were randomized to receive LR RBCs <8 days old vs. LR "standard-issue" RBCs (i.e., oldest compatible unit avalable). The primary outcome was 90-day, all-cause mortality. Pre-specified secondary outcomes included organ dysfunction, infections, length of stay in the ICU and the hospital, and the duration of respiratory, hemodynamic or renal support. Of the 2,430 participants, 1,211 received younger RBCs (mean age: 6.1 days; SD: 4.9) and 1,219 received standard-issue (mean: 22.0 days; SD: 8.4). No statistically significant difference was observed between the groups for the 90-day mortality rate (37.0% vs. 35.3% (absolute risk difference = 1.7 percentage points; 95% CI: –2.1 to 5.5), nor were significant differences in any of the secondary outcomes identified.

Published RCTs Examining the Impact of RBC Freshness (Note: additional findings available in main text)

	ARIPI Trial[3]	RECESS Trial[5]	ABLE Trial[6]
Study Population	377 very-low birth-weight infants	1,098 patients ≥12 years old having complex cardiac surgery	2,430 critically ill adults expected to require mechanical ventilation
RBC Storage Ages	<7days vs. "standard-issue"	≤10 days vs. ≥21 days	<8 days vs. "standard-issue"
Primary Outcome	Composite measure of neonatal morbidities coupled with death	Highest composite multiple organ dysfunction score up to 7 days postoperatively	90-day all-cause mortality
Results*	52.7% vs. 52.9% (RR = 1.00; 95% CI: 0.82 to 1.21)	Mean increases in MODS were 8.5 vs. 8.7 (p = 0.44)	37% vs. 35.3% (absolute risk difference = 1.7 percentage points; 95% CI: –2.1 to 5.5)

*Results compare attainment of primary endpoint to use of fresher vs. older RBCs, respectively

Conclusions: Despite observational studies suggesting that changes to RBCs and their storage media, over time, may be associated with poorer patient outcomes, three recently published RCTs have failed – as summarized in the table left – to identify any significant differences when using "fresher" vs. "standard-issue" RBC units.

Consistent with these RCTs, Swedish investigators, using the comprehensive SCANDAT2 and SWEDEHEART registries to link transfusion and clinical outcomes from 1997 to 2012, found no association between RBC storage age and risk of mortality (at 30 days, two years, and 10 years of follow up) among 47,071 cardiovascular surgical patients.[7] The findings from three additional studies are soon to be published,[8-10] and the debate is not yet entirely settled – particularly with respect to questions about the potential for detrimental effects following the transfusion of RBC units very near their outdates.[11] Nevertheless, a broad change in practice towards the use of fresher RBCs does not appear to be justified at this time.

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