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Is old blood bad blood?

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Approximately 13.8 million units of allogeneic RBCs are administered in the US annually, with over 2 million units alone going to patients undergoing cardiovascular surgery. Allogeneic RBCs that are stored in modern preservative solutions are approved for use within 42 days after collection. This 42 day shelf life is based largely on the ability of these cells to persist in the circulation for > 24 hours. As previously summarized⁽¹⁾, it is well known that RBCs undergo significant biochemical and structural changes during the 42 day period of storage (e.g. decreased RBC deformability, decreased ATP and 2,3-DPG, and a significant increase in abnormally shaped RBCs).

For example we recently published the most comprehensive assessment of stored red blood cells⁽²⁾. We analyzed changes occurring during RBC storage focusing on RBC deformability, RBC-dependent vasoregulatory function, and S-nitrosohemoglobin (SNO-Hb). Five hundred ml of blood from each of 15 healthy volunteers was processed into leuko-filtered, additive solution 3-exposed RBCs and stored at 1-6 °C according to AABB standards. Blood was subjected to 26 assays at 0, 3, 8, 24 and 96 h, and at 1, 2, 3, 4, and 6 weeks. Numerous changes occurred including previously described deterioration in levels of 2,3-DPG and potassium. RBC deformability assayed at a physiological shear stress decreased gradually over the 42-day period. In addition, SNO levels, and their physiological correlate, RBC-dependent vasodilation, become depressed soon after collection, suggesting that even «fresh» blood may have developed adverse biological characteristics. Time courses vary for several storage-induced

defects that might account for recent observations linking blood transfusion with adverse outcomes.

There is evidence from «association studies» that the administration of allogeneic RBCs of longer storage duration may be independent predictor of mortality in surgical, trauma, and other critically ill patients. For example, an observational study of 6,002 cardiac surgical patients by Koch et al. published in the *New England Journal of Medicine* showed that increased storage duration was an independent predictor of mortality and other adverse outcomes⁽³⁾.

No large randomized trial has examined the impact of duration of stored RBCs on organ dysfunction and mortality in high risk patients. In humans there is no Level I evidence to guide clinicians, and most of the existing data come from non-randomized cohort studies (Level 3). Therefore, high risk hospitalized patients routinely receive allogeneic RBCs that have been stored for a prolonged period of time, largely because there is no definitive proof that the duration of storage of RBCs is of clinical relevance.

In humans, several randomized trials involving storage duration are underway (e.g. RECESS, ABLE, Cleveland), however, for largely pragmatic reasons, these trials are testing whether clinical outcome is influenced by «younger» (7-10 days) vs. largely «middle-aged» (> 21 days) RBCs. In these trials, it is likely that patients will have limited exposure to the «oldest» RBCs (42 days). In addition, since patients can receive a mixture of ages within their study arm, eg, 1 unit 22 days, 1 unit 31 days, 1 unit 41 days, it will be challenging in these studies to tease out the effects of different durations of storage. Therefore, while the ongoing trials may have important results, it is possible that they will not address the fundamental question of whether «older» units deliver oxygen as effectively as «younger» units.

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