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Special Issue Articles

The Effects of red Blood Cell Transfusion on Tissue Oxygenation and the Microcirculation in the Intensive Care Unit: A Systematic Review

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ABSTRACT

The transfusion of red blood cells (RBCs) is a common intervention in intensive care unit (ICU) patients, yet the benefits are far from clear in patients with moderate anemia (eg, hemoglobin (Hb) levels of 7–10 g/dL). Determining which of these patients benefit, and how to even define benefit, from transfusion is challenging. As the intended physiological benefit underpinning RBC transfusion is to improve tissue oxygenation, several studies utilizing a wide range of assessment techniques have attempted to study the effects of transfusion on tissue oxygenation and microcirculatory function. The objective of this systematic review was to determine whether RBC transfusion improves tissue oxygenation/microcirculatory indices in the ICU population, and to provide an introduction to the techniques used in these studies. Eligible studies published between January 1996 and February 2017 were identified from searches of PubMed, Embase, Cinahl, ScienceDirect, Web of Science, and The Cochrane Library. Seventeen studies met inclusion criteria, though there was significant heterogeneity in study design, patient population, assessment techniques and outcomes reported. Overall, the majority of studies (11 of 17) concluded that transfusion did not generally improve tissue oxygenation or microcirculation. Inter-individual effects were highly variable, however, and closer review of sub-groups available in 9 studies revealed that patients with abnormal tissue oxygenation or microcirculatory indices prior to transfusion had improvement in these indices with transfusion, irrespective of assessment method. This finding suggests a new strategy for future trials in the ICU: utilizing tissue oxygenation/microcirculatory parameters to determine the need for transfusion rather than largely arbitrary hemoglobin concentrations.

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Anemia is an extremely common phenomenon in critically ill patients, ranging from mild, asymptomatic forms to the severe and life threatening. Although red blood cell (RBC) transfusion is demonstrably a life-saving intervention for severe anemia or hemorrhagic shock, the benefits of transfusion are far less clear in patients with moderate anemia (e.g.: hemoglobin (Hb) levels of 7–10 g/dL), even in the setting of critical illness. Clinical trials over the past decade have uniformly failed to prove the superiority of more liberal transfusion strategies over conservative ones [1-6] in terms of mortality and major morbidity. In fact, several reviews have concluded that for patients in the intensive care unit (ICU), RBC transfusion carries more risk than benefit [7-9]. That said, the idea that RBC transfusion is beneficial in *some* critically ill patients remains compelling—the challenge that practitioners in this arena face, then, is properly discriminating the patient who stands to benefit from RBC transfusion from those who will be hurt by it.

Ascertaining when a critically ill patient benefits from a RBC transfusion is difficult. Not only are these patients physiologically complex, they often undergo multiple interventions in a short period of time, of which transfusion is only one among many. "Hard" clinical endpoints such as mortality, organ failure, or morbidity index scores [10-12] are muddied by these multi-modal interventions, and the studies [2,4] of RBC transfusion in the ICU have failed to identify any distinct patient population that consistently benefits. Over the past 2 decades, researchers have increasingly used physiologic parameters rather than clinical endpoints to assess the benefit (or harm) of RBC transfusion.

The most meaningful assessments of whether or not RBC transfusion is fulfilling its intended goal are assessments of tissue oxygenation. Numerous techniques have been developed to study different aspects of tissue oxygenation in the critically ill, including techniques to study microcirculatory function. While there is a robust collection of studies linking tissue oxygenation and microcirculatory abnormalities to poor clinical outcomes [13-16], literature on the tissue oxygenation/microcirculatory effects of RBC transfusion is far less cohesive and much more limited in scope. In order to determine what, if any, conclusions can be drawn from the disparate, wildly heterogeneous writings on this subject, the authors of this review set out to systematically gather and assess the research performed to date, along with providing a general introduction to the technologies and techniques employed in the various studies.

Methods

Eligibility

To be eligible for inclusion in this review, studies had to meet the following criteria:

[1] The study must investigate the use of RBC transfusion in critically ill patients, where the location of the transfusion and relevant physiological monitoring exclusively took place in an intensive care unit;
[2] Irrespective of primary end-point(s), the study must have reported data on the effect of RBC transfusion upon tissue oxygenation and/or microcirculatory indices.

Studies were excluded from this review if they:

(1) Enrolled neonatal patients or infants;
(2) Enrolled patients with traumatic brain injury or sub-arachnoid hemorrhage;
(3) Enrolled actively hemorrhaging patients or studied the effects of intra-operative transfusion;
(4) Utilized non-standard or autologous RBC units.

Studies in the first two categories were excluded as the effects of RBC transfusions on these patients populations have been comprehensively reviewed elsewhere [17-22], studies in the third category were excluded due to technical limitations as well as frequent overlaps in the location of transfusion between the ICU and the operating room (OR), and studies in the final category excluded due to lack of clinical generalizability.

There were no restrictions on the specific intensive care setting (Surgical/Trauma versus Medical ICU), patient characteristics (including adult versus pediatric) or study type, as long as the inclusion and exclusion criteria were fulfilled.

All records identified by the search were screened for eligibility using titles and abstracts by two authors (NDN, CW). Any disagreements on study eligibility were resolved by discussion between these two authors, with final adjudication by the lead author (N.D.N.).

Search Strategy

PubMed, Embase (Ovid, 1974–2017), Cinahl (EBSCOHost, 1937–2017), ScienceDirect, Web of Science, and The Cochrane Library were searched from January 1996 through February 2017. The search was not limited by language or publication type. See Fig 1 for a schematic of the selection process, and Appendix A for full details of the search strategy.

Study Analysis

The heterogeneity of study design, patient populations, methodologies and outcomes reporting led the authors to conclude that any attempt at a meta-analysis would be inappropriate. Therefore, the review is descriptive and any statistical analyses reported are from the original studies themselves.