Commentary

Transfusion trigger in critically ill patients: has the puzzle been completed?

Eric Reiles and Philippe Van der Linden

Department of Anesthesiology Centre, Hospitalo-Unversitaire (CHU) Brugmann and Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), Place Van Gehuchten, B-1020, Brussels, Belgium

Corresponding author: Philippe Van der Linden, philippe.vanderlinden@chu-brugmann.be

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Abstract

In stable critically ill children, the adoption of a restrictive transfusion strategy based on a predefined hemoglobin threshold of 7 g/dl significantly decreased transfusion requirements without affecting outcome. These results strengthen previous observations made in volume resuscitated adults when a similar blood transfusion strategy was used. It also indirectly corroborates studies reporting the beneficial effects of leukoreduction of red blood cell (RBC) transfusion units on patient outcome. This study indicated that the maintenance of a higher hemoglobin concentration with RBC transfusion in an attempt to increase tissue oxygen delivery is not associated with a clinical benefit. This may be related to the storage process, which could affect the ability of RBCs to transport and deliver oxygen to the tissues. This point, however, remains controversial. It should also be remembered that increasing hemoglobin concentration will not always result in a greater oxygen delivery, as transfusion related increased blood viscosity could be associated with a reduction in blood flow. Further research should compare a symptomatic transfusion strategy to a hemoglobin-based strategy on the outcome of high risk patients.

The transfusion of red blood cell (RBC) concentrates in critically ill patients remains controversial and has generated much research and debate in the medical literature. A recent, large, noninferiority randomized clinical trial adds an important piece to this quite complicated 'puzzle' [1]. In stable critically ill anemic (hemoglobin <9.5 g/dl) children between 3 days and 14 years of age, this study demonstrated that a restrictive strategy, where the threshold hemoglobin concentration was 7 g/dl, significantly decreased transfusion requirements without increasing adverse outcome, defined as a composite of death and development of new or progressive organ failure, when compared to a liberal strategy with a threshold hemoglobin of 9.5 g/dl. Anemia is common in critically ill patients and results in a large number of RBC transfusions. Several studies reported that up to 50% of adult or children who were hospitalized in an intensive care unit received RBC transfusions [2-4]. Interestingly, all these observational studies reported that hemoglobin level, rather than clinical or physiological factors, drives transfusion decision. The adequacy of any hemoglobin concentration in a given clinical situation depends on whether a sufficient amount of oxygen is carried to the tissues to meet their metabolic requirements [5]. The optimal hemoglobin threshold for RBC transfusion in different populations, and especially in critically ill patients, remains unknown.

The study of Lacroix and colleagues [1] confirms the results reported by two other randomized trials that evaluated the impact of a restrictive strategy on the outcome of critically ill adults [6] and preterm infants [7]. Using 30-day mortality as the primary outcome in 838 euvolemic adult critically ill patients, Hébert and colleagues [6] demonstrated that a restrictive transfusion strategy was at least as effective as a liberal one. In addition, applying a liberal transfusion strategy resulted in a significantly higher multiple organ dysfunction score, a composite outcome taking into account 30-day mortality and the number of organ failures. This deleterious effect might be attributed to the fact that RBC units transfused in this study were not leukocyte-reduced, in contrast to the RBC units used in the study by Lacroix and colleagues. Two 'before and after' studies in adults and premature infants and one meta-analysis of randomized controlled trials have reported that leukoreduced RBC transfusion could significantly improve the outcome of high risk patients [8-10]. It has been decided, therefore, to repeat a prospective controlled randomized study to compare hemoglobin thresholds of 7 versus 9 g/dl [11]. Using a composite primary outcome including death before home discharge or survival with any of severe retinopathy, bronchopulmonary dysplasia or brain injury on cranial ultrasound in 451 infants with birth weight <1,000 g, Kirpalani and colleagues [7] demonstrated that maintaining a

RBC = red blood cell.

lower hemoglobin level did not increase neonatal morbidity. Interestingly, the thresholds developed in this study were based on whether or not the infant was receiving respiratory support. Although not specified, as the study was performed after 1999 and included Canadian centers, it may be reasonably assumed that the authors used leukoreduced RBC units. The results of this study are in contrast with those of Bell and colleagues [12], who reported in a smaller trial (N = 100) that infants in the restrictive-transfusion group were more likely to have intraparenchymental brain hemorrhage or periventricular leukomalacia. However, this combination was not a pre-specified outcome and the study was powered for the primary outcome of number of transfusions. In all these studies, the use of a restrictive approach was associated with a decreased number of transfusions and, in most of them, with a decrease in the number of patients exposed to RBC transfusion.

Using a more liberal approach to achieve a higher hemoglobin concentration in an attempt to increase oxygen delivery and thus tissue oxygenation in stable critically ill patients does not appear to be associated with a significant clinical benefit. Several authors have suggested that the RBC storage process could affect the ability of RBCs to transport and deliver oxygen, this phenomenon being responsible for the lack of apparent improvement in tissue oxygenation after transfusion. Human studies on the effects of stored RBCs are scarce and controversial. In nine healthy volunteers undergoing acute isovolemic hemodilution, there were no differences in the ability of transfused fresh (stored <5 hours) or stored (>3 weeks) RBCs to reverse the neurocognitive deficit observed during acute anemia [13]. In critically ill patients, the effect of RBC storage on gastric mucosal oxygenation remains controversial [14,15]. In a randomized multicenter pilot trial, Hébert and colleagues [16] did not observe differences in mortality rates or life-threatening complications in patients transfused with fresh (median age 4 days) versus old (median age 19 days) RBCs. In the study of Lacroix and colleagues [1], the average length of storage was about 16.0 ± 10 days in both strategy groups. The effect of RBC storage time on primary outcome was not evaluated.

For stable critically ill patients with a hemoglobin concentration ranging from 6 or 7 to 10 g/dl, there is increased evidence that a restrictive transfusion approach based on a predefined hemoglobin concentration does not influence outcome. The decision to transfuse such patients would, therefore, depend primarily on clinical judgment, taking into account the ability of the patient to increase cardiac output and oxygen extraction, and the level of tissue oxygen demand [5]. It remains to be demonstrated that, in high risk patients, a symptomatic transfusion strategy is as effective, or possibly superior, to a hemoglobin-based transfusion strategy. This is the aim of the ongoing 'FOCUS' study comparing these two strategies in patients 50 years of age or older who undergo surgical repair of a hip fracture and who have clinical evidence for cardiovascular disease or cardiovascular risk factors [17]. Although the study of Lacroix and colleagues adds an important piece to the 'puzzle', it still remains incomplete. Will it ever be completed?

Competing interests

The authors declare that they have no competing interests.

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