CRITICAL CARE

COMMENTARY

Anemia, red blood cell transfusion, and outcomes after severe traumatic brain injury

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See related research by Sekhon *et al.*, http://ccforum.com/content/16/4/R128

Abstract

In the previous issue of *Critical Care*, Sekhon and colleagues report that mean 7-day hemoglobin concentration <90 g/l was associated with increased mortality among patients with severe traumatic brain injury (TBI). The adverse relationship between reduced hemoglobin concentrations and outcomes among those with TBI has been an inconsistent finding across available studies. However, as anemia is common among adults with severe TBI, and clinical equipoise may exist between specialists as to when to transfuse allogeneic red blood cells, randomized controlled trials of liberal versus restricted transfusion thresholds are indicated.

In the previous issue of *Critical Care*, Sekhon and colleagues conducted a single-center retrospective cohort study to determine whether hemoglobin concentration was associated with outcomes among 273 critically ill adults with severe traumatic brain injury (TBI) [1]. After adjusting for age, Glasgow Coma Scale scores, external ventricular drain insertion, and allogeneic red blood cell (RBC) transfusion, the authors report that the estimated odds of in-hospital mortality among patients with a mean 7-day hemoglobin concentration <90 g/l was 3.1 (95% confidence interval, 1.5 to 6.3) times the estimated odds of in-hospital mortality among those with a mean 7-day hemoglobin concentration ≥90 g/l.

Anemia is common among ICU patients [2]. The etiology of ICU anemia is multifactorial and includes the negative effects of the systemic inflammatory response on hematopoiesis, frequent phlebotomy, and hemodilution from intravenous fluid resuscitation [2]. Among ICU patients with TBI, the prevalence of reduced hemoglobin concentration ranges from 22 to 69%, depending on the presence or absence of extracranial hemorrhage and the timing of hemoglobin measurements [3].

Although a hemoglobin transfusion threshold >70 g/l was adopted for ICU patients following publication of the Transfusion Requirements in Critical Care trial [4], this target may be poorly tolerated by those with severe TBI [2]. Anemia-induced compensatory mechanisms result in cerebral arteriolar dilatation and increased brain blood flow [2], which could be detrimental for those with cerebral edema or intracranial hypertension. Moreover, as brain tissue oxygen tension is dependent on systemic hemoglobin, reduced hemoglobin concentrations among those with TBI could decrease cerebral oxygen delivery and contribute to brain hypoxia [2].

Although the findings of the study by Sekhon and colleagues provide support for the above physiologic concerns regarding reduced hemoglobin concentrations following brain injury [1], the adverse relationship between anemia and clinical outcomes is an inconsistent finding among available clinical studies [1,5-16]. Of the one randomized controlled trial [10] and the now 14 available cohort studies of which we are aware (two of which were based on *post-hoc* analyses of similar datasets derived from randomized controlled trials) [1,5-9,11-18], eight reported an association between anemia and an increased risk of poor neurological outcomes or mortality [1,5,9,11,13,14,17,18], while the remaining seven observed no such association. Moreover, in a recent systematic review of comparative studies, insufficient evidence was found to support a difference in outcomes between higher and lower hemoglobin levels among mostly TBI patients [19].

Possible explanations for the inconsistency in results across studies include differences in TBI severity among study patients and inadequate consideration of the effects of anemia during critical time periods [20]. Although a set hemoglobin threshold may exist under which harm may occur among those with TBI, adverse outcomes may be more likely to occur during times of low cerebral blood flow, brain hypoxia, and/or ineffective autoregulation

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[16,20]. Some support for this argument was afforded by the findings of a recent retrospective cohort study, which reported that although anemia alone did not appear to be detrimental among patients with severe TBI, the simultaneous combination of anemia and brain hypoxia was linked with an increased risk of unfavorable outcomes [16].

Another significant limitation of the existing literature on this topic has been the absence of a defined disease–exposure relationship among patients with TBI. Although it is plausible that development of reduced hemoglobin concentrations may be most important during the first 7 days following severe TBI [1], the use of the mean as a summary measure of exposure has the potential to result in exposure misclassification. Moreover, as the effects of anemia on outcomes following TBI are likely to be small, and a tremendous amount of brain hypoxia due to anemia would probably be needed to increase mortality, a sensitive measure of neurological performance or outcome is probably a more important outcome variable [20].

Possibly the most important limitation of the available literature relating anemia to outcomes among those with TBI, however, is the inadequate consideration of the effects of RBC transfusion [19]. Although RBC transfusion often results in a small incremental increase in brain tissue oxygen tension in this patient population, transfused blood has important differences from the patients' own blood and does not always improve cerebral metabolism [2]. Moreover, at least five retrospective cohort studies have reported that RBC transfusion increases the risk of death or worsened neurological outcome among those with TBI [9,13,14,21,22]. Admittedly, however, these observations could have been related to selection bias and an unbalanced distribution of outcome determinants between treatment groups [20]. Moreover, as anemia and RBC transfusion are probably highly correlated, those studies that used interaction terms for anemia and RBC transfusion in their regression models probably introduced multicollinearity, and therefore their estimated coefficients and odds ratios may be invalid [20].

In summary, although preclinical experiments suggest several potential adverse effects of anemia among patients with TBI, the results of the available clinical studies are conflicting, and it remains unclear whether RBC transfusion may further increase risk of adverse outcomes. However, because anemia is common among adults with severe TBI, and a recent survey reported that clinical equipoise may exist among specialists as to when to transfuse allogeneic RBCs [23], randomized controlled trials of liberal versus restricted transfusion thresholds are required among adults with severe TBI. These trials will probably require use of multimodal monitoring to understand whether improved outcomes are only witnessed among those with simultaneous signs of brain hypoxia or cerebral ischemia.

Abbreviations
RBC, red blood cell; TBI, traumatic brain injury.

Competing interests
The authors declare that they have no competing interests.

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