

Anemia and Blood Transfusion in Subarachnoid Hemorrhage

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Anemia in Subarachnoid Hemorrhage

Anemia is a common problem among critically ill patients. Nearly two thirds of patients are anemic on admission to the intensive care unit (ICU)¹ and between 70-95% of patients develop anemia by day 3.^{2,3} Lower hemoglobin levels decrease the oxygen carrying capacity of blood and may reduce tissue oxygenation. This is particularly detrimental for patients with subarachnoid hemorrhage (SAH) as they are subject to increased metabolic demand for oxygen from cerebral ischemia.

The optimal hemoglobin concentration in patients with subarachnoid hemorrhage (SAH) is unknown. Thirty per cent of SAH patients have a hemoglobin <10 g/dl during hospitalization.⁴ Many patients are routinely hemodiluted as a part of hypertensive, hypervolemic, hemodilution (triple H) therapy. Hemodilution may improve blood rheology, but it has also been shown to impair brain tissue oxygenation and increase secondary brain injury.⁵

Patients with SAH are at risk for vasospasm and delayed ischemic deficits. Compromised oxygen carrying capacity could further predispose to ischemia. Anemia has been associated with increased ischemic deficits, but has not consistently been associated with development of vasospasm.⁶⁻⁹ One study demonstrated fewer ischemic events in subarachnoid hemorrhage patients with higher hemoglobin concentrations.⁷ Another study found that although transfusion significantly increased global cerebral oxygen delivery, it also resulted in reduced cerebral blood flow in areas affected by vasospasm.¹⁰ The decreased perfusion was thought to be mediated by increased viscosity.

In the uninjured brain, vasodilation of the cerebral arteries can compensate for decreased oxygen carrying capacity. Brain hypoxia is usually only manifest at hemoglobin concentrations less than 6g/dl¹¹. When cerebral autoregulation is impaired, tissue hypoxia may occur at higher hemoglobin concentrations. However, the hemoglobin threshold below which cerebral metabolic dysfunction occurs remains unknown. One study sought to define this threshold in patients with high grade SAH (Hunt Hess grade IV or V) by measuring cerebral metabolism through the use of brain tissue oxygen tension monitoring (PbtO₂) and lactate to pyruvate (LPR) measurements via cerebral microdialysis.⁹ Reduced PbtO₂ levels and increased extracellular LPR are markers of cerebral metabolic dysregulation. They found that the incidence of brain hypoxia and cell energy dysfunction increased when hemoglobin levels were less than 9 g/dl independent of other factors such as cerebral perfusion pressure and vasospasm. The authors concluded that maintenance of hemoglobin levels greater than 9g/dl may prevent secondary brain injury in poor-grade patients with SAH.

Anemia is not only associated with increased ICU length of stay and increased risk of death in critically ill patients, but it also has been shown to be a predictor of poor outcome in SAH patients.^{1,8,12,13} Anemia is common in SAH, occurring in 36-39% of patients.^{8,13} One study of 580 SAH patients found that anemia was an independent predictor of death or severe disability at 90 days.¹³ Another study demonstrated that aneurysmal SAH patients with poor outcomes had lower daily hemoglobin levels.¹²

It is clear that anemia worsens outcome in subarachnoid hemorrhage, but it remains unclear whether blood transfusion to correct acute anemia is warranted. A meta-analysis of 4 concluded that in adult critically ill, trauma, and surgical patients, blood transfusion therapy was associated with increased morbidity and mortality.¹⁴

The treatment of anemia in the neurological ICU remains unclear in part because transfusion strategy trials have not included a significant number of neurologically critically ill patients. Some studies including patients with active cardiac ischemia have suggested benefit from a liberal transfusion approach^{1,15}; however, this has not been shown consistently. It is unclear whether results from these

trials can be extrapolated to patients with cerebral ischemia. Neurological patients often require augmentation of cerebral blood flow to maintain perfusion and avoid ischemia.

Packed red blood cell (PRBC) transfusion has also been associated with increased cerebral vasospasm. In a retrospective study of 441 SAH patients, post-operative PRBC transfusion was associated with an increased risk of both angiographic and symptomatic vasospasm.¹⁶ One of the postulated mechanisms suggested that transfused RBCs may be depleted of nitric oxide and therefore result in a blunted vasodilatory response to vasospasm.

Packed red blood cell transfusion increases blood viscosity. Increased blood viscosity coupled with increased oxygen carrying capacity may induce autoregulatory vasoconstriction, which would reduce, not augment, cerebral blood flow. A study of 8 anemic aneurysmal SAH patients who underwent pre- and post-transfusion PET scan evaluation, demonstrated a significant increase in oxygen delivery without compromising global cerebral blood flow. The rise in oxygen delivery was greater in regions of baseline oligemia, defined as areas of low oxygen delivery and a high oxygen extraction fraction. However, in territories of angiographic vasospasm, cerebral blood flow fell by 7 per cent. This was thought due to impaired autoregulation compounded by increase blood viscosity in blood vessels affected by vasospasm.

Concern about the safety of packed red blood cell transfusion, including immunosuppressive and microcirculatory complications, has led to a reappraisal of transfusion practices. The Transfusion Requirements in Critical Care (TRICC) trial was designed to determine whether a restrictive versus liberal transfusion strategy in the intensive care unit produced equivalent all cause mortality at 30 days and equivalent organ dysfunction.¹ In this randomized controlled study, either a hemoglobin concentration of 7-9 g/dl or 10-12 g/dl was targeted as a trigger for transfusion. The in-hospital mortality rate was lower in the restrictive transfusion group, although the primary endpoint of 30-day mortality was not significantly different between the two groups. The authors recom-

mended that critically ill patients receive PRBC transfusion when the hemoglobin concentration falls below 7 g/dl and that hemoglobin levels be maintained between 7 - 9 g/dl.

Infectious complications of blood transfusion also limit its utility. A meta-analysis of 9 observational studies concluded that among transfused adult critically ill, trauma, and surgical patients, the pooled odds ratio for infection was 1.88 (CI 1.52 - 2.24).¹⁴ Seventeen of eighteen studies included in that meta-analysis demonstrated that RBC transfusion was an independent predictor of death. In a study of trauma patients, transfusion of more than four units of blood increased the risk of peri-operative infection by a factor of 9.28.¹⁷ Ninety-two per cent of infections occurred in anemic patients and the rate of post-operative infections correlated with decreasing hemoglobin levels. Other studies of trauma patients have determined that blood transfusion therapy is an independent predictor of the systemic inflammatory response syndrome¹⁸, multi-organ dysfunction¹⁹, increased nosocomial infections²⁰ and mortality.²¹

The infectious complications of transfusion are thought to occur in large part from white blood cells and inflammatory cytokines that are present in stored red blood cells preparations. Transfusion of RBCs has been shown to trigger neutrophil activation and the release of proinflammatory cytokines.²² These factors may exacerbate the inflammatory changes known to be associated with vasospasm from aneurysmal SAH. Subarachnoid blood stimulates expression of cell adhesion molecules (CAMs) on the luminal surface of endothelial cells.²³ Macrophages and neutrophils bind to the endothelial cells via these CAMs, and enter the subarachnoid space, where they phagocytose red blood cells. The macrophages and neutrophils die and degranulate two to four days after entering the subarachnoid space, releasing endothelins and oxygen free radicals which result in vasoconstriction.

Transfusion related acute lung injury (TRALI) is another significant complication of transfusion therapy that carries a mortality of 5 -10%.²⁴⁻³⁰ It is the third most common cause of fatal transfusion reactions next to blood type incompatibility and hepatitis.³¹ TRALI is characterized by noncardiogenic pulmonary edema that develops during or soon after blood product transfusion. The signs and symptoms of TRALI are often mistaken for volume overload or pneumonia.

Conclusion

Anemia is common in subarachnoid hemorrhage and the optimal target hemoglobin in this disease remains unknown. Red blood cell transfusions in the intensive care unit are intended to augment oxygen delivery to tissues to improve tissue oxygenation. It is presumed that increased hemoglobin concentration increases oxygen carrying capacity and provides more oxygen to delivery-dependent tissue. However, whether blood transfusion successfully achieves improved tissue oxygenation remains unclear.

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