Red Blood Cell Transfusion Practices in the Neurointensive Care Unit: A Narrative Review

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Abstract

Anemia is common in neurointensive care unit (NICU) patients and is one of the common causes of systemic insults to the brain. Though the recent literature favors restrictive blood transfusion practices over liberal transfusion to correct anemia in the general ICU, whether a similar practice can be adopted in NICU patients is doubtful due to lack of strong evidence. Impairment of cerebral autoregulation and cardiac function following acute brain injury affects the body's compensatory mechanism to anemia and renders the brain susceptible to anemic hypoxia at different hemoglobin (Hb) thresholds. Hence, red blood cell transfusion (RBCT) practice based on a single Hb threshold value might be inappropriate. On the other hand, allogenic RBCT has its own risks, both in short and in long run, leading to adverse outcomes. Thus, instead of relying only on arbitrary Hb values, a better way to decide the need for RBCT in NICU patients is to target parameters based on systemic and regional cerebral oxygenation. This approach will help us to individualize RBCT practices. In this narrative review, based on the available literature, authors have discussed the impact of anemia and blood transfusion on the immediate and late neurological outcomes and the current role of regional brain monitoring in guiding blood transfusion practices. In the end, authors have tried to update on the current RBCT practices in neurosurgical and neuromedical patients admitted to the NICU.

Keywords
► red blood cell transfusion
► neurointensive care unit
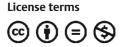► anemia
► acute brain injury

Introduction

Red blood cell transfusion (RBCT) practices in the intensive care unit (ICU) have undergone a paradigm shift from liberal (hemoglobin [Hb] threshold: 10–11 g/dL) to restrictive strategies (Hb threshold: 7–9 g/dL).[1–3] Systematic reviews have shown decreased or no change in adverse outcomes following a restrictive transfusion strategy.[4,5] However, most literature on RBCT has focused on stable patients in the general ICU. Hence, extrapolating these results to patients admitted to the neuro-ICU (NICU) should be done with caution. Recent literature, mainly observational, has shown adverse outcomes associated with both anemia and RBCT in the NICU patients.[6–14]

Concerns of Anemia in Patients in Neurointensive Care Unit

The World Health Organization (WHO) defines anemia as an Hb concentration < 11, 12, and 13 g/dL in children, women, and men, respectively.[15] Apart from preexisting anemia, patients during their NICU stay can develop anemia due to multiple factors, such as hemodilution following fluid resuscitation, blood loss (e.g., surgical drain, postoperative hematoma), repeated phlebotomies, associated multiple injuries, coagulopathies, impaired erythropoiesis, and reduced red blood cell (RBC) survival secondary to inflammation and nutritional deficiencies.[16,17] As the brain does not store its fuel, namely glucose and oxygen, it needs a constant supply of the same

through circulation of around 15% of cardiac output. Hence, it is vulnerable to hypoxia in anemic states. As a result of this, there is a general sense of hesitation among intensivists to follow restrictive RBCT in NICU patients. Acute brain injury (ABI) can impair cerebral autoregulation and cardiac function, thereby affecting the body's compensatory mechanism to anemia, which include systemic vasodilation, reduced viscosity, increased cardiac output, and increased oxygen extraction. These mechanisms, if present in ABI patients, can further compromise brain perfusion by increasing intracranial pressure (due to vasodilation and increased cerebral blood volume). This renders the brain susceptible to anemia at different Hb thresholds.[18–20] Hence, RBCT practice based on a single Hb value threshold might culminate into inappropriate RBCT, either inadequate or unwanted RBCT. Further, allogenic RBCT has its risks, both in short and in the long run, which in turn can lead to adverse outcomes.[21,22]

Concerns of Red Blood Cell Transfusion in Patients in Neurointensive Care Unit

The primary goal of RBCT in NICU patients is to improve the cerebral oxygen delivery (DO_2), which depends on cerebral blood flow (CBF) and arterial oxygen content (CaO_2), which include Hb and oxygen saturation (SaO_2). Improving DO_2 to the brain need not necessarily result in improved O_2 utilization (e.g., mitochondrial dysfunction).[23] Studies in varied neurosurgical population such as patients with traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) have documented adverse events such as delayed cerebral ischemia (DCI), infection, thrombotic events, allergic reactions, and transfusion-related lung injury. Further, whether improved oxygenation translates into improved outcomes largely remains unknown. Hence, the indication for RBCT in a given NICU patient cannot be decided solely by the Hb value.

Role of Physiological Triggers in Guiding Red Blood Cell Transfusion

A better approach to decide the need for RBCT would be to look at the physiological parameters, which provide information on the oxygen delivery and consumption balance. These parameters, called *physiological triggers*, can be global such as central venous oxygen saturation ($ScvO_2$), jugular venous oximetry ($SjvO_2$), or regional like near-infrared spectroscopic-based cerebral oximetry (rSO_2), brain tissue oxygen tension ($PbtO_2$), and cerebral microdialysis (CMD). In recent years, there is a great interest in utilizing these cerebral oxygenation monitoring modalities to decide the need for RBCT. Studies have shown improvement in cerebral oxygenation and metabolic parameters following RBCT, though not the neurologic outcome.[24–27]

Recent Guidelines on Red Blood Cell Transfusion

Due to the lack of high-quality evidence, transfusion triggers in NICU patients remains controversial. Thus, in the panorama of the RBCT practices in NICU patients, there is an urgent need to identify threshold cutoffs for Hb (which is routinely monitored) and other physiological parameters to guide the RBCT practices. Recent guidelines published by various scientific societies recommend the use of restrictive RBCT strategy with Hb trigger < 7g/dL, mostly in hemodynamically stable general ICU patients of all ages.[4,5,28–32] However, just a few societies have attempted to address the transfusion trigger in the NICU patients and are summarized in ►Table 1.[28,30,32] Some of these guidelines also recommend considering the clinical status of patients before deciding on RBCT.[5,29]

Intercontinental Disparity in Red Blood Cell Transfusion Practices

In spite of the existence of published guidelines for determining the need for RBCT, it is not uniformly practiced. There is a considerable variation in transfusion practices between individuals, institutions, and countries. Recently published two international surveys showed wide inter-ICU variation and lack of consensus in RBCT practices. In a survey conducted across the European and Israel ICUs, in TBI patients (CENTER-TBI), only 52% of the ICUs had a

Table 1 Recommendations on RBC transfusion in patients admitted to NICU

Neurologic condition/disease	Currently available recommendation
TBI	– No benefit of a "liberal" transfusion strategy. Transfusion (when Hb < 10 g/dL) in patients with moderate to severe TBI[28#] – In TBI patients, the target Hb should be 7–9 g/dL[30*] – In TBI patients with the evidence of cerebral ischemia, the target Hb should be > 9 g/dL[30*]
aSAH	– In SAH patients, the target Hb should be 8–10 g/dL[30]
Acute ischemic stroke	– In patients with acute ischemic stroke, the Hb should be maintained above 9 g/dL[30*]
Pediatric ABI (e.g., severe TBI or cerebrovascular stroke)	RBC transfusion could be considered if the Hb falls between 7 and 10 g/dL (expert-based recommendation).[32$]

Abbreviations: ABI, acute brain injury; aSAH, aneurysmal subarachnoid hemorrhage; Hb, hemoglobin; NICU, neurointensive care unit; RBC, red blood cell; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.
Adapted from refs.[28,30,32] Readers are referred to references 28,30 and 32 for detailed descriptions of the recommendations.
#Society of Critical Care Medicine Recommendations (2009)[28]
*British Committee for Standards in Haematology Guidelines (2012)[30]
$Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) (2018)[32]

defined Hb-target for initiating RBCT, of which 41% transfused at Hb threshold of 7 to 9 g/dL and the remaining 59% transfused at Hb threshold of 10 g/dL.[33] Another international survey was done in ABI patients (both neurotrauma and nontraumatic neurological conditions), Hb trigger of 7–8 g/dL was used to initiate RBCT by 54% of the ICU clinicians. However, in certain neurological conditions such as TBI, SAH, and ischemic stroke, 57% of physicians chose a higher Hb-trigger of around 9 g/dL.[34]

In this narrative review, authors have discussed the effect of anemia and RBCT in specific neurological/neurosurgical disorders and their effects on the neurologic outcome. The authors have tried to update on the current trends and practices of RBCT, current role of regional brain monitoring in guiding the RCBT, and probable transfusion trigger based on the available published literature and guidelines in these disorders. MeSH keywords used to search the databases (Google Scholar, EMBASE, PubMed) include "red blood cell transfusion," "anemia," "neurointensive care unit," and "acute brain injury," "aneurysmal subarachnoid hemorrhage," "stroke," "acute ischemic stroke," "intracerebral hemorrhage," "central venous thrombosis," "elective neurosurgery," "spine surgery," "spine trauma," "pediatric neurosurgery," "myasthenia gravis," "Guillain-Barre syndrome," "neuro-infections," and "neurologic outcome."

Traumatic Brain Injury

The acute phase of TBI is associated with reduced CBF, in addition to hypotension and/or anemia. All these worsen cerebral oxygen supply thereby compromising neuronal survival has got prognostic implications.[9,35–38] Anemia-induced compensatory vasodilation can increase intracranial pressure and further worsen cerebral ischemia. Anemia has been shown to have an inverse linear relation with poor outcome (i.e., low values associated with poor outcomes).[38] Baseline Hb of < 9 g/dL predicted worse outcome and increased mortality in TBI patients, but when Hb was > 10 g/dL, outcomes were found to be better.[9,10,39]

TBI patients are prone to receive RBCT in the NICU due to blood loss in the surgical drain, blood loss from associated extracranial injuries, and blood loss from acute trauma-induced coagulopathy. However, administration of RBCT is not always associated with better outcomes, especially if it is done for the sole purpose of increasing Hb values (e.g., to target > 10 g/dL).[40–44] Moreover, RBCT is associated with increased complications, and risk factors identified for increased complications following RBCT in TBI patients included nonanemic/nonbleeding patients during RBCT, younger patients (< 55 years), absence of associated comorbidities, and volume of RBCT.[14,40,43,45,46] Literature on long-term functional outcomes with RBCT in TBI patients is limited and fails to show any improvement following RBCT.[45–47]

Both Hb and cerebral oxygenation-based targets have been used and studied to decide RBCT in these patients. In studies targeting physiologic parameters, RBCT has shown differential improvement in TBI patients. In a recently published prospective study, the authors proposed $ScvO_2$ as a physiologic trigger to decide RBCT requirement and identified

$ScvO_2$ < 70% as the cutoff for deciding RBCT in stable adult patients admitted to NICU.[25] In another study, RBCT led to a significant improvement in the near-infrared–based regional cerebral oxygenation (rSO_2) and reductions in the cerebral fractional oxygen extraction (CFOE) in TBI patients, especially when their baseline rSO_2 was ≤ 60%.[26] However, in both these studies, neurologic outcomes were not studied. McCredie et al did not observe improvement in the rSO_2 following RBCT in their cohort of severe TBI patients, which could be due to high baseline rSO_2 (69%) in their patients.[48] In a randomized controlled trial conducted on NICU patients, RBCT requirements reduced when RBCT was guided by rSO_2 (< 60%) as against Hb-guided, though the overall outcomes remained the same.[27] Changes in brain tissue oxygenation ($PbtO_2$) were studied following RBCT in TBI patients.[23,24] It was shown that Hb levels < 9 g/dL were associated with $PbtO_2$ < 20 mm Hg and an unfavorable outcome.[49] Baseline $PbtO_2$ < 15 mm Hg predicted maximum increase in brain oxygenation following RBCT.[24] In a randomized clinical trial comparing two different Hb thresholds (< 7 vs. 10 g/dL) for RBCT, hypoxic episodes ($PbtO_2$ < 15 mm Hg) were observed more frequently in patients with low transfusion trigger ($p = 0.04$).[50] Administering RBCT based on Hb values, in spite of a normal $PbtO_2$, results in impaired cerebral autoregulation.[51] Although CMD seems to be useful for neuroprognostication, there is no literature describing the role of CMD in deciding RBCT in TBI patients. Thus, the clinical utility of CMD-guided RBCT is still unexplored.[52,53]

The existing literature and guidelines suggest that RBCT at Hb > 10 g/dL is not warranted in TBI patients. Acceptable Hb trigger for RBCT should be between 7 and 9 g/dL, with due consideration given to the underlying clinical condition, ongoing blood loss, hemodynamic status, associated extracranial injuries, and cerebral oxygenation-based information.[28,30]

Aneurysmal Subarachnoid Hemorrhage

The principal cause of secondary brain injury following aneurysmal subarachnoid hemorrhage (aSAH) is DCI that is commonly caused by cerebral vasospasm (CVS). In the setting of cerebral ischemia, as the flow cannot be increased through narrow spastic vessels, it seems logical to keep the Hb levels high to increase oxygen delivery and minimize ischemia. Clinical studies have also shown an increased incidence of DCI, cerebral infarction, and poor outcome in anemic SAH patients.[8,12,54–56] However, in a multicenter cohort study on SAH patients, RBCs were transfused only when the Hb fell below 8 g/dL (66.3% of cohorts), and this practice was not associated with poor outcome.[13] In fact, researchers have shown that administering blood despite Hb > 10 g/dL has led to improved outcomes.[55] In a multicenter cohort study, most patients received RBCT when Hb was < 8 g/dL (66.3%), which was not associated with poor outcome.[13] The same group is currently doing a multicenter randomized pilot trial comparing two transfusion thresholds for Hb 8 versus 10 g/dL in SAH patients (SAHaRA [Aneurysmal SubArachnoid Hemorrhage–Red Blood Cell Transfusion And Outcome] trial) (NCT03309579). On the contrary, there are studies on SAH patients, which have shown poor outcomes and increased thrombotic and infectious complications with RBCT.[12,57–60]

Recently, scientists have focused on brain oxygenation and metabolism monitoring to titrate RBCT in SAH patients. They observed brain tissue hypoxia ($PbtO_2$ < 15 mm Hg) when Hb fell below 9 g/dL.[61–63] Diringer group showed improved DO_2 following RBCT in SAH patients using positron emission tomography (PET).[64] They could reproduce their results for a wider range of Hb (7–13 g/dL) in patients at risk for DCI.[65] Other brain-specific monitoring such as cerebral oximetry and cerebral microdialysis has been used to study changes during RBCT in SAH patients.[53,66]

In aSAH patients, the British Committee for Standards in Haematology (BCSH) and Neurocritical Care Society recommend RBCT to target Hb > 8–10 g/dL.[30,67] Existing literature suggests keeping the Hb concentration > 9 g/dL to improve patients' outcome. Until further evidence is generated, restrictive transfusion practices do not seem to be suitable in SAH patients who show evidence of cerebral ischemia.

Stroke
Ischemic Stroke
Most of the existing work suggests that both extremes of Hb concentrations are associated with increased risk of death and disability at short- and long-term follow-up (nonlinear or U-shaped relationship).[6,68–70] In a recent systematic review and meta-analysis, anemia was found to be associated with an increased risk of mortality in ischemic stroke as well as in patients with hemorrhagic stroke, albeit at a lower magnitude of association (odds ratio [OR]: 1.46, confidence interval [CI]: 95% 1.23–1.74).[70] However, the literature also exists refuting anemia as a predictor of poor outcome after stroke.[71] Recently published two studies did not find an association between both anemia and RBCT with the mortality and 3 months functional outcome, though anemia increased the length of ICU stay and increased the duration of mechanical ventilation.[71–74] Using a mathematical modeling study, progressive reduction in the oxygen uptake was noted in the ischemic penumbra at Hb of < 10 g/dL.[75]

Intracranial Hemorrhage
Stroke due to intracranial hemorrhage (ICH) is associated with very high mortality, and the most important factor determining the prognosis is the volume of ICH. Anemia has been found to be an independent predictor of hematoma volume and 30-day mortality.[76] RBCT seems to improve 30-day survival rate in elderly patients.[77] However, in patients with Glasgow coma scale (GCS) of 4–8, RBCT failed to improve $PbtO_2$ or reduce lactate-pyruvate ratio. Only when the Hb was < 7 g/dL, RBCT increased cerebral perfusion pressure consequent to an increase in mean blood pressure.[78]

Cerebral Venous Thrombosis
Cerebral venous thrombosis (CVT) manifests commonly as hemorrhagic infarction. It is an uncommon cause of stroke as compared with arterial stroke and occurs in both children and in adults. Common causes include steroid therapy, pregnancy, oral contraceptive use, alcohol consumption, blood dyscrasia, infection, anemia, and dehydration. Anemia is found to be an independent predictor of poor functional outcome in patients with CVT.[79,80] Currently there are no data published on transfusion practices in CVT patients.

The optimal Hb for the management of stroke remains unclear. Guidelines recommend maintaining an Hb concentration > 9 g/dL in patients with an acute ischemic stroke. Literature is sparse on ICH and none in CVT to guide RBCT, and hence the above-mentioned threshold can be followed until further evidence is available.

Neurosurgery
Perioperative anemia in neurosurgical patients, irrespective of its severity, has been found to be associated with increased hospital stay though not mortality and morbidity.[81] Intraoperative blood loss and volume deficits remain the most common indication necessitating intra- and postoperative RBCT. Infants and pediatric patients require more RBCT when compared with adults, especially in procedures such as craniosynostosis.[82–85] Among the elective neurosurgical procedures, significant blood loss is seen in meningiomas, cerebellopontine tumors, hemangioblastomas, metastatic tumors, vascular lesions, and spine surgeries.[85–87] A certain class of intracranial tumors such as metastatic lesions are more prone to induce disseminated intravascular coagulation that in turn increases RBCT requirements.[88,89]

Apart from the conventional complications associated with RBCT, there is a concern regarding transfusion-related immunomodulatory effects in neuro-oncology patients. It is speculated that RBCT may promote tumor growth by impairing the body's innate ability to suppress tumor growth and spread.[90] Allogenic leucocytes and stored RBCs are probably responsible for this immunomodulatory effect. Also, perioperative leukodepleted RBCT is associated with increased recurrence of tumor and decreased survival.[22,91] For fear of these side effects, many clinicians adopt various strategies to reduce allogenic RBCT in neuro-oncology patients. These include preoperative autologous blood donation (PAD), intraoperative autologous blood transfusion (ABT), preoperative administration of erythropoiesis-stimulating agents (EPO), and use of hemostatic agents such as tranexamic acid.[84,92–96]

Spine Injury and Spine Surgeries
Patients with traumatic spinal cord injury (SCI) and following complicated spine surgeries frequently require prolonged NICU care and are prone to acute (due to the intraoperative blood loss) as well as chronic anemia, which in turn can affect the outcome.[97,98] The optimum Hb trigger in the ICU management of traumatic SCI or other spine surgeries is not known. In a retrospective study, it was noted that spine surgery patients who received RBCT and whose nadir Hb values were between 8 and 10 g/dL had prolonged hospital stay, more surgical site infections, and mortality.[99] This questions the practice of liberal transfusion strategy extrapolated from brain injury patients, in this subset of patients. On the other hand, one must keep in mind that anemia is an important risk factor for ischemic optic neuropathy, which is one of the common causes of postoperative visual loss in prone spine surgeries.[100]

Pediatric Neurocritically Ill Patients

There is no direct evidence to guide the transfusion practice in the pediatric NICU patients. Very recently, based on the existing limited literature, the Pediatric Critical Care Transfusion and Anemia Expertise Initiative Consensus Conference recommended consideration of RBCT for Hb concentration between 7 and 10 g/dL in a critically ill child with ABI and did not support the use of $PbtO_2$ monitoring to guide RBCT decisions.[32] Cerebral oximetry is extensively studied in the non-neurocritically ill pediatric patients, and with regard to RBCT, it seems promising.[101]

Miscellaneous Neurologic Conditions

NICU also caters to patients with myasthenia gravis (MG), Guillain-Barre syndrome (GBS), status epilepticus (SE)/refractory SE, and neuroinfections. Normally these patients have a prolonged ICU course with frequent laboratory testing, thereby resulting in iatrogenic anemia. Iron deficiency anemia and low body iron status are associated with febrile seizures.[102,103] In a recent survey, most respondent physicians did not feel the need for separate transfusion strategies in these patient populations as compared to general critically ill patients.[35]

Standard Practice Points Based on Available Evidence and Guidelines

- Minimize phlebotomies for diagnostic laboratory testing.
- In general, restrictive transfusion practices can be recommended, except in SAH and stroke patients with high chances of cerebral ischemia. However, due consideration should be given to the clinical status, associated comorbidities, and physiologic triggers.
- In hemodynamically stable patients, administer a single unit at a time and reassess the need before ordering the second unit.
- In pediatric patients, weight-based volumes should be infused (10–15 mL/kg).
- Use leukoreduced RBC or leuco-filters for RBCT.

Conclusion

Though RBCT is extremely common in the NICU, the available evidence is poor and insufficient to guide RBCT practices. Stringent restrictive strategies may not be suitable in this population, especially in aSAH and stroke patients in whom higher Hb concentration (> 9 g/dL) seems to be associated with favorable outcome. However, in patients with other causes of ABI, blood transfusion may be considered between Hb concentration of 7 to 10 g/dL giving due consideration to the underlying clinical condition. Also, transfusion practices based on cerebral oxygenation parameters seem to have a potential to individualize the transfusion therapy and remain an important avenue of future research. Thus, further randomized studies comparing the different nadir Hb concentrations together with the systemic and cerebral physiological triggers will immensely help in understanding and optimizing the transfusion practices in the NICU.

Conflict of Interest

None declared.

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