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Review Article

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Optimizing RBC Transfusion Strategies in Traumatic Brain Injury: Insights on Early Resuscitation and Cerebral Oxygenation

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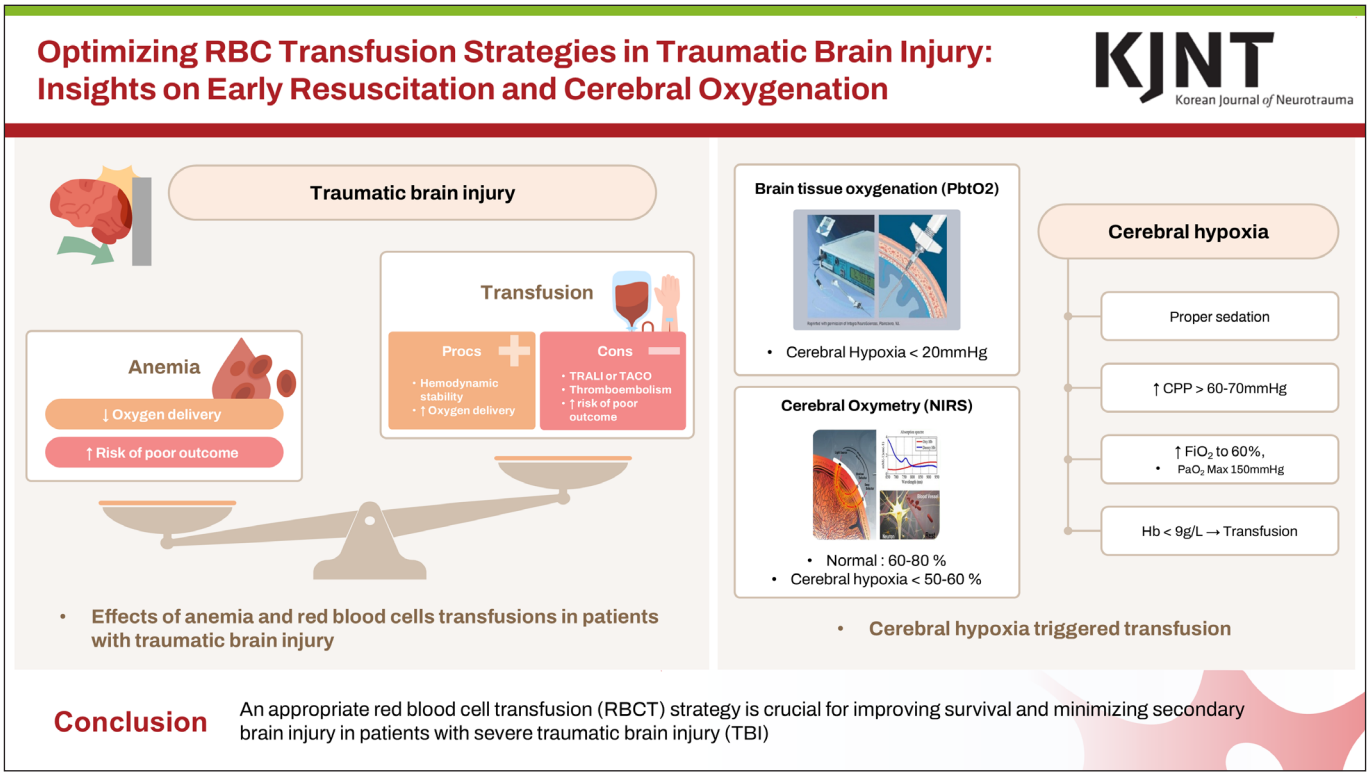
ABSTRACT

Effective early resuscitation and maintenance of brain oxygenation are critical for improving the outcomes of patients with severe traumatic brain injury (TBI). Red blood cell (RBC) transfusion plays a vital role in this process. Although RBC transfusion can enhance cerebral oxygenation and stabilize hemodynamics, it also poses significant risks including transfusion-related lung injury and transfusion-associated circulatory overload, highlighting the importance of meticulous transfusion management. This review explores transfusion strategies during the early resuscitation phase and the management of anemia in patients with severe TBI, focusing on appropriate treatment targets, utilizing monitoring-based personalized approaches, and summarizing recent research and current insights.

Keywords: Blood transfusion; Traumatic brain injury; Anemia; Oxygen saturation

Graphical Abstract



Ethics Approval

This research did not require ethical approval as it does not involve human subjects, their data, or biological samples.

INTRODUCTION

Traumatic brain injury (TBI) is a critical global health challenge that contributes to significant disability and mortality.[4] Early resuscitation from hemorrhagic shock and maintenance of adequate brain oxygenation are crucial for improving survival and neurological outcomes in patients with moderate to severe TBI. Red blood cell transfusion (RBCT) is an important therapeutic strategy in this context.

Historically, a liberal transfusion approach targeting higher hemoglobin levels (>9–10 g/dL) has been preferred for TBI management. However, recent evidence highlighting the benefits of a restrictive transfusion strategy (hemoglobin >7–8 g/dL) in critically ill patients has prompted studies to explore its application in TBI.[24,32] Despite ongoing debates, establishing an appropriate transfusion strategy is crucial, considering both the benefits and potential risks of RBCT.

This review evaluates the role and effectiveness of RBCT in TBI, assessing the current evidence and limitations in determining optimal transfusion strategies and hemoglobin targets. It also explores the potential for individualized transfusion approaches using brain monitoring technologies in neurocritical care and suggests directions for future research.

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ANEMIA IN PATIENTS WITH TBI

Anemia frequently arises as a complication in patients with TBI and has significant implications for cerebral oxygenation and overall prognosis. Multiple studies have documented an increasing prevalence of anemia during hospitalization driven by factors such as ongoing blood loss, inflammatory responses, and dilutional effects associated with large-volume transfusions. Patients with TBI who initially present with normal hemoglobin levels often develop anemia as their hospital stay progresses. Vanhala et al.[33] found that approximately 45.8% of patients with moderate to severe TBI developed anemia within the first 48 hours of hospitalization. Similarly, Salim et al.[28] highlighted the high incidence of anemia in severe TBI cases, emphasizing its detrimental impact on patient recovery. The severity of anemia is directly correlated with the risk of secondary brain injury, as insufficient oxygen supply to brain tissues can exacerbate neurological damage.[28] Litofsky et al.[21] found that anemia negatively impacts neurological recovery in patients with TBI and can significantly increase mortality in severe cases. The detrimental effects of anemia extend beyond reduced oxygen delivery. Anemia can induce systemic hypoxia, compromising the function of vital organs such as the heart and kidneys, and further delay patient recovery. Carlson et al.[5] associated anemia in patients with TBI with longer hospital stays, higher medical costs, and worse neurological outcomes (**FIGURE 1**).

CEREBRAL AND SYSTEMIC EFFECTS OF RBC TRANSFUSION IN TBI

RBCT has significant implications on cerebral metabolism, particularly in patients with TBI. One of the primary benefits of RBCT is improved oxygen delivery to the brain. In patients with TBI, where the risk of secondary brain injury due to hypoxia is high, increasing hemoglobin

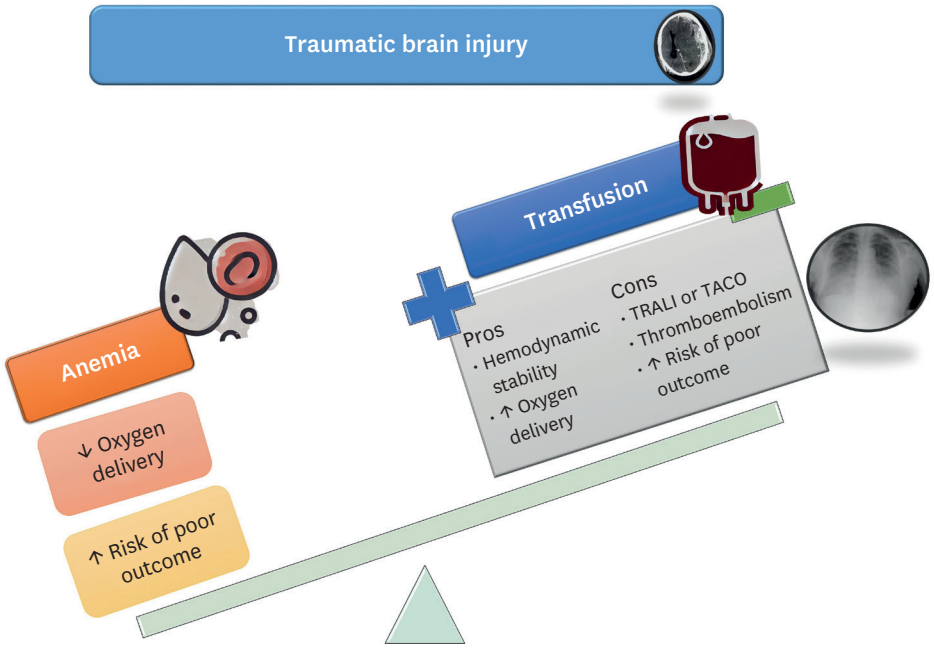

FIGURE 1. Effects of anemia and red blood cells transfusions in patients with traumatic brain injury.
TRALI: transfusion-associated acute lung injury, TACO: transfusion-associated circulatory overload.

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levels enhance the oxygen-carrying capacity of the blood, helping to maintain adequate brain oxygenation. However, increased oxygen content may lead to a reduction in cerebral blood flow due to autoregulatory mechanisms in the brain. This reduction can result in insufficient perfusion of certain brain regions, particularly if autoregulation is impaired.[5]

The systemic effects of RBCT are also critical as they can influence the overall outcome in patients with TBI. One of the most important systemic benefits is the restoration of hemodynamic stability in patients experiencing hemorrhagic shock. By increasing blood volume and oxygen-carrying capacity, RBCT helps maintain blood pressure and improves perfusion to vital organs.[11]

However, transfusions can trigger inflammatory responses. Leukocytes and other components in stored blood can activate the immune system, leading to the release of pro-inflammatory cytokines and potentially resulting in conditions such as transfusion-related acute lung injury (TRALI).[1] Another serious complication is transfusion-associated circulatory overload, which can lead to pulmonary edema and increased cardiac strain, particularly in patients with pre-existing heart conditions.[20] Additionally, the metabolic effects of transfused blood can have significant consequences. Stored red blood cells (RBCs) undergo changes during storage, including a decrease in 2,3-diphosphoglycerate levels, which impairs the oxygen-release capacity of hemoglobin. Moreover, elevated levels of potassium and other metabolic byproducts in stored blood can disrupt the electrolyte balance and acid-base status, leading to further complications (**FIGURE 1**).

Although RBCT provides critical support in terms of oxygen delivery and hemodynamic stability in patients with TBI, it carries several risks. These factors necessitate careful planning and individualized transfusion strategies to maximize the benefits while minimizing the potential harm.

RBCT FOR RESUSCITATION IN TBI WITH HEMORRHAGIC SHOCK

Hemorrhagic shock results from significant blood loss, which leads to decreased circulating blood volume, reduced oxygen-carrying capacity, and impaired tissue perfusion. In this context, the primary goal of RBCT is to restore sufficient oxygen delivery to the tissues and maintain the function of vital organs, including the brain and heart.

Hemoglobin targets in hemorrhagic shock

In contrast to stable patients, patients in hemorrhagic shock require more aggressive transfusion strategies. The rapid restoration of blood volume is crucial for preventing cardiovascular collapse and organ failure. Additionally, preferential whole blood transfusion during early resuscitation is preferred because it includes all blood components (RBCs, plasma, and platelets), thereby rapidly restoring blood volume and simultaneously addressing coagulopathy.[3,17] Gabrielle et al.[10] indicated that whole blood transfusion in patients with TBI with hemorrhagic shock is associated with decreased overall and TBI-related mortality compared to component therapy.

In the acute phase of hemorrhagic shock, it is generally recommended to set a higher hemoglobin target than in non-bleeding patients, typically around 9–10 g/dL.[13] This target may vary

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depending on the patient's condition and the severity of the shock. Continuous monitoring of hemoglobin levels, lactate levels, base deficits, and signs of organ perfusion (e.g., urine output and mental status) is essential during resuscitation to guide transfusion decisions.

Managing coagulopathy and massive transfusion

Increase in RBCT volumes, specifically in cases of massive transfusion (defined as transfusion of > 10 units of packed RBCs), results in a risk of dilutional coagulopathy, where the dilution of clotting factors exacerbates bleeding.[15] This risk underscores the importance of massive transfusion protocol, which involves transfusing RBCs, plasma, and platelets in a 1:1:1 ratio.[12] Research indicates that a balanced ratio of fresh frozen plasma to RBCTs provides a survival benefit in patients with acute traumatic coagulopathy, although the specific benefits in patients with TBI require further investigation.[16,27]

Recent studies have suggested that thromboelastography-guided resuscitation may offer additional benefits by providing real-time assessment of the patient's coagulation status, allowing for more targeted and effective transfusion strategies.[2,8,23]

Once hemodynamic stability is achieved, overtransfusion must be avoided. Excessive transfusion can lead to unnecessary complications; therefore, careful monitoring and judicious use of blood products are essential for optimizing patient outcomes while minimizing risks.

RBCT STRATEGIES IN INTENSIVE CARE UNIT: RESTRICTIVE VS. LIBERAL

Generally, in critical care, the emergence of a restrictive transfusion strategy can largely be attributed to the findings of Transfusion Requirements in Critical Care trial. This landmark study demonstrated that a restrictive transfusion strategy, targeting a hemoglobin threshold of 7 g/dL, could yield outcomes comparable to or better than a liberal strategy targeting 10 g/dL.[14] Notably, the restrictive approach was associated with a lower incidence of transfusion-related complications, such as infections and acute lung injury, prompting widespread reevaluation of transfusion practices across various medical conditions.

Transfusion strategies in TBI

Several studies have highlighted that restrictive transfusion strategies may be safe and effective for patients with TBI. For instance, Gobatto et al.[11] found that a restrictive strategy did not significantly increase mortality, while reducing the risk of TRALI. Similarly, a meta-analysis conducted by Florez-Perdomo et al.[9] confirmed that a restrictive transfusion approach reduced the risk of transfusion-related complications without significantly affecting overall mortality or neurological outcomes when compared to a liberal strategy.

The HEMOTION trial further supported these findings by showing no significant differences in neurological outcomes or mortality between restrictive and liberal transfusion strategies.[32] This suggests that a restrictive approach may be safer for patients with TBI, particularly by minimizing the risks associated with overtransfusion.

However, it is crucial to recognize the potential risks associated with restrictive strategies in certain patient populations. LeRoux[19] highlighted concerns that a restrictive transfusion strategy might exacerbate hypoxia in patients with severe TBI, indicating that although

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restrictive strategies are generally safe, they may not be suitable for all TBI cases. The study underscores the importance of maintaining adequate cerebral oxygenation, especially in critically injured patients and suggests that transfusion strategies should be tailored to the individual needs of the patient.

With recent advancements in monitoring technologies, real-time cerebral oxygenation can now be monitored, leading to an emerging view that directly assessing and managing cerebral oxygenation may be more effective than merely targeting hemoglobin levels.

CEREBRAL OXYGENATION MONITORING GUIDED TRANSFUSION

Brain tissue oxygen ($PbtO_2$) monitoring

$PbtO_2$ monitoring involves the direct measurement of oxygen levels within the brain tissue, providing real-time assessments of cerebral oxygenation. This technique is particularly valuable in TBI management because it can detect cerebral hypoxia that may not be apparent with only intracranial pressure (ICP) monitoring. Generally, $PbtO_2$ levels <20 mmHg indicate an insufficient oxygen supply to the brain, necessitating immediate therapeutic intervention.

Stiefel et al.[31] reported significantly reduced mortality rates in patients monitored with both $PbtO_2$ and ICP compared with those monitored with ICP alone, suggesting that dual monitoring can improve survival rates. However, Martini et al.[22] found that $PbtO_2$-guided management was associated with a slightly higher mortality and worse neurological outcomes than ICP monitoring alone, raising concerns regarding the widespread use of $PbtO_2$ monitoring.

Recent large-scale randomized controlled trials, such as BOOST-2 and OXY-TC, aimed to evaluate the efficacy of strategies to optimize cerebral oxygenation by maintaining $PbtO_2$ levels >20 mmHg. The BOOST-2 trial demonstrated that $PbtO_2$-guided therapy could reduce the duration of cerebral hypoxia, although it had a limited effect on long-term neurological outcomes.[25] Similarly, the OXY-TC trial found no significant differences in 6-month neurological outcomes between patients managed with both $PbtO_2$ and ICP monitoring and those managed with ICP alone, although $PbtO_2$ monitoring was effective in reducing episodes of cerebral hypoxia.[26] These findings suggest that although $PbtO_2$ monitoring may not be a universal strategy for all patients with TBI, it could be beneficial for specific high-risk individuals.

$PbtO_2$-guided transfusion strategy

Smith et al.[30] observed that $PbtO_2$ increased by an average of 3.2 mmHg following RBCT in 74% of patients,[19] and Zygun et al.[34] found a significant positive correlation between changes in hemoglobin levels and $PbtO_2$. Additionally, patients with low baseline PbtO2 levels (<15 mmHg) showed the greatest improvement.[34] These findings indicate that $PbtO_2$-guided transfusion decisions can optimize oxygen delivery to the brain, potentially reducing unnecessary transfusions while maintaining adequate cerebral oxygenation.

The 2020 Seattle International Severe Traumatic Brain Injury Consensus Conference algorithm focused on managing patients using both ICP and $PbtO_2$ monitoring. The algorithm recommends a stepwise approach to improve cerebral oxygenation when the $PbtO_2$ falls below 20 mmHg. They specifically suggested considering pack RBCT if the hemoglobin levels dropped below 9 g/dL.[7] Although $PbtO_2$ monitoring may not be universally applicable, further

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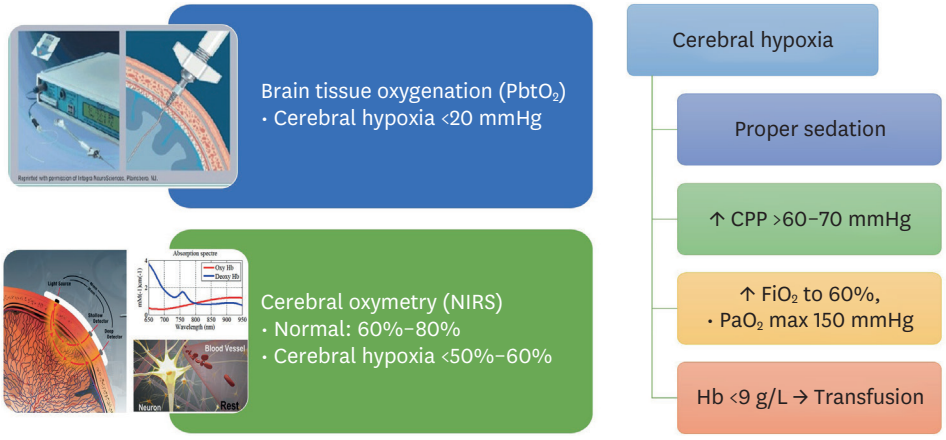

FIGURE 2. Cerebral hypoxia triggered transfusion. This figure illustrates the management protocol when cerebral hypoxia is detected using $PbtO_2$ tension or NIRS. Upon cerebral hypoxia detection, interventions such as sedation, augmentation of CPP, and increasing the FiO_2 are implemented. If Hb levels are <9 g/L, a transfusion should be considered to enhance oxygen-carrying capacity, which allows transfusion decisions to be based on the patient's cerebral oxygenation status, thereby optimizing outcomes while preventing unnecessary transfusions.
$PbtO_2$: brain tissue oxygen, NIRS: near-infrared spectroscopy, CPP: cerebral perfusion pressure, FiO_2: fraction of oxygen, Pao_2: Partial Pressure of Oxygen in Arterial Blood, Hb: hemoglobin.

research is needed to identify patients who would benefit the most from this strategy, and individualized approaches should be emphasized (**FIGURE 2**).

Near-infrared spectroscopy (NIRS) monitoring

NIRS is a non-invasive method for measuring regional cerebral oxygen saturation (rSO_2) by analyzing the absorption of near-infrared light by oxygenated and deoxygenated hemoglobin in the cortical tissue. The normal range of NIRS is generally considered to be an rSO_2 value of 60%–80%. Hypoxemia is typically defined when rSO_2 values is <50%–60%, with values <50% indicating a critical state requiring immediate intervention. Additionally, a 20% decrease from baseline is recognized as the threshold for cerebral ischemia progression (**FIGURE 2**).[6]

NIRS-guided transfusion strategy

Sen et al.[29] demonstrated that NIRS could be useful for detecting intracranial hematomas and assessing ICP and brain oxygenation. Leal-Noval et al.[18] showed that using NIRS to guide transfusion decisions based on rSO_2 levels resulted in fewer transfusions than decisions based solely on hemoglobin levels, without adversely affecting mortality or neurological outcomes. These findings suggest that NIRS-guided transfusion decisions may be more precise and targeted.

However, NIRS has certain limitations. It primarily measures the cortical oxygenation, which may not fully reflect the oxygenation status of the entire brain. Additionally, NIRS signals can be influenced by the surrounding tissues or hematomas, which complicates data interpretation. Although NIRS has the potential to guide transfusion decisions, more research is needed to establish its clinical impact on TBI management and determine its role alongside other monitoring techniques such as $PbtO_2$.

CONCLUSION

An appropriate RBCT strategy is crucial to improve survival and minimize secondary brain injury in patients with TBI. Early resuscitation should focus on restoring the blood

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volume and maintaining blood pressure to ensure adequate oxygen delivery to the brain. While restrictive transfusion strategies have been effective, their application in severe TBI cases requires caution because of the need to manage cerebral perfusion and oxygenation. Advanced monitoring technologies, such as $PbtO_2$ and NIRS, can guide individualized transfusion strategies by providing real-time cerebral oxygenation data. Future research should aim to optimize and integrate monitoring into transfusion protocols to enhance outcomes of patients with TBI.

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