Current state of transfusion in traumatic brain injury and associated coagulopathy

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Traumatic brain injury (TBI)-induced coagulopathy has long been recognized as a significant risk for poor outcomes in patients with TBI, but its pathogenesis remains poorly understood. As a result, current treatment options for the condition are limited and ineffective. The lack of information is most significant for the impact of blood transfusions on patients with isolated TBI and in the absence of confounding influences from trauma to the body and limbs and the resultant hemorrhagic shock. Here we discuss recent progress in understanding the pathogenesis of TBI-induced coagulopathy and the current state of blood transfusions for patients with TBI and associated coagulopathy.

Patients with severe trauma to the body and limbs often develop hemorrhagic shock due to severe blood loss and the resultant tissue hypoperfusion, leading to secondary ischemic injuries and death. Uncontrolled bleeding (coagulopathy) is a leading cause of preventable death, accounting for 30%–40% of trauma fatalities.[1,2] Bleeding arrest is therefore both a physiological response to trauma and a treatment goal for patients with trauma. The causation of trauma-induced coagulopathy is multifactorial, including blood loss, consumption or dilution of coagulation factors and platelets, dysfunctions of platelets and the coagulation system, enhanced fibrinolysis, hypothermia, and metabolic acidosis secondary to tissue ischemia.[3–6]

Retrospective and observational studies have consistently shown that coagulopathy is also common in patients with isolated TBI,[7–9] which is increasingly common among civilians.[10] A post-hoc outcomes analysis of 670 patients with isolated TBI or with TBI plus hemorrhagic shock enrolled in the Pragmatic Randomized Optimal Platelets and Plasma Ratios

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(PROPPR) trial[11] found that patients with both TBI and hemorrhagic shock had worse coagulopathy than patients with either condition alone before resuscitation, significantly greater odds of respiratory complications, and a higher mortality rate.[12] TBI-induced coagulopathy could result in disseminated intracranial hemorrhage and delayed intracranial or cerebral hematoma[13–15] and is closely associated with poor outcomes for the patients.[10,13,16] More importantly, TBI-induced coagulopathy does not follow the same pathway as coagulopathy induced by trauma-induced hemorrhagic shock, because patients with isolated TBI suffer minimal blood loss and lack systemic tissue hypoperfusion. Instead, laboratory measures suggest that TBI-induced coagulopathy develops rapidly from a hypercoagulable state, as fibrin degradation products and D-dimer are first detectable within minutes of TBI, and this is followed by profound depletion of fibrinogen.[14,17,18] Prolonged prothrombin and partial thromboplastin times usually occur late.[14,17,18] This order of events suggests that TBI-induced coagulopathy is consumptive in nature and differs mechanistically from the deficient or dilutional coagulopathy found in patients with trauma-induced hemorrhagic shock.

We recently demonstrated that brain-derived cellular microvesicles (BDMVs) produced by traumatically injured glial cells and neurons are rapidly released into the circulation.[19] These BDMVs induce a hypercoagulable state that quickly becomes a consumptive coagulopathy in mice subjected to severe TBI.[19] This rapid shift from a hyper- to a hypocoagulable state can be reproduced in non-injured mice infused with purified BDMVs,[19,20] suggesting that BDMVs induce consumptive coagulopathy independent of the confounding condition of TBI. Another key observation made in the mouse study is that more than 50% of circulating procoagulant microvesicles are morphologically intact extracellular mitochondria (exMTs).[20] Both BDMVs and exMTs are highly procoagulant because of the anionic phospholipids that are abundantly expressed on their respective surfaces: phosphatidylserine (PS) on membrane microvesicles and cardiolipin (CL; 1,3-bis(sn-3′-phosphatidyl)-sn-glycerol) on extracellular mitochondria.[19,20] In addition, BDMVs and exMTs have been found to activate endothelial cells in vivo and in vitro, resulting in vascular leakage, endothelial procoagulant activity, and the production of endothelial microvesicles.[21] Finally, morphologically intact exMTs released from injured cerebral cells may also be metabolically viable to generate and release oxidants that become a source of systemic oxidative stress. As a result, these brain-derived cellular microvesicles initiate and propagate key secondary pathological processes of TBI: endothelial injury, coagulopathy, and inflammation. Because of these detrimental activities, removing cellular microvesicles from the circulation by the apoptotic cell-scavenging factor lactadherin (milk fat globule–epidermal growth factor 8)[22] has been shown to accelerate microvesicle clearance, to prevent TBI-induced coagulopathy, and to improve the outcome of TBI in mouse models.[21,23]

Because of their distinct pathogenic pathways, coagulopathy induced by trauma to the body and limbs and hemorrhagic shock and that induced by isolated TBI may require different resuscitation strategies. The timely, judicious, and balanced use of blood-component and fluid resuscitations has been the management of choice for coagulopathy associated with body trauma, especially when hemorrhagic shock is present. However, patients with isolated TBI suffer minimal blood loss and are often restricted on fluid resuscitation to prevent secondary cerebral damage induced by high intracranial pressure. Blood transfusion is therefore mostly for reversing trauma-induced or medically induced coagulopathy and for managing comorbidities such as anemia in patients with isolated TBI. There has recently been a demographic shift in occurrence of TBI from generally young adults to older adults (50 years and older).[24] These older patients often suffer from isolated TBI due to falls, are more likely to present with comorbidities such as anemia due to chronic disease or iron deficiency, and are often on antiplatelet medications and/or anticoagulants that cause medically induced coagulopathy in trauma. Here we discuss the current state of blood transfusions in managing patients with TBI.

RED CELL TRANSFUSION

Isolated TBI rarely sustains enough blood loss to require red blood cell transfusion. However, a recent retrospective analysis in adult patients with isolated, severe TBI found that 2% of patients were anemic upon presentation but approximately 50% developed anemia (defined in this study as a hemoglobin level < 10 g/dL) in the intensive care unit within 1 week.[25] A mean 7-day hemoglobin of < 9 g/dL was associated with increased hospital mortality in a retrospective study of 169 patients with severe TBI (risk ratio 3.1, 95% CI 1.5–6.3).[26] Another retrospective study of 80 patients with TBI further showed that a hemoglobin level ≤ 9 g/dL was a risk factor for unfavorable outcomes, but only when the low hemoglobin level was associated with brain tissue oxygen tension <20 mmHg,[27] suggesting that laboratory anemia alone does pose a significant risk of poor clinical outcomes. By contrast, other studies suggest that anemia does not negatively impact on the outcome of patients with TBI,[28,29] indicating that, unlike hemorrhagic shock, the impact of anemia on outcomes of TBI remains to be further defined.

A small-cohort retrospective study of 28 patients with severe TBI found that red cell transfusion worsened the pressure reactivity index (PRI), which is often used to indicate the state of cerebral autoregulation, primarily in patients with brain oxygenation of > 20 mmHg.[30] The multiple organ dysfunction score (MODS) also significantly increased with increasing red cell transfusion in patients with TBI who had hemoglobin levels of > 10 g/dL at

admission, a Glasgow Coma Scale (GCS) score of 8 or less, and no evidence of shock.[31] A recent randomized clinical trial compared neurological outcomes between red cell transfusions and/or erythropoietin therapy and placebo controls for patients with closed TBI whose hemoglobin level was maintained at either > 7 g/dL or > 10 g/dL.[32] The trial found that giving erythropoietin or maintaining a hemoglobin level at > 10 g/dL with red cell transfusion did not improve neurological outcome of the patients at 6 months, and more importantly the use of a hemoglobin level of 10 g/dL as the transfusion threshold was associated with a higher incidence of adverse events, including a significantly higher rate of deep vein thrombosis.[32] Similarly, a recent retrospective outcomes study of 939 patients with TBI (The Abbreviated Injury Scale head >3) stratified by threshold values of initial hemoglobin levels ≤ 7, ≤ 8, ≤ 9, and ≤ 10 g/dL, found that an increase in hemoglobin level of 1 g/dL improved clinical outcomes by 33% for patients with initial hemoglobin level < 8 g/dL,[33] which is consistent with anemia being a risk factor for poor TBI outcome.[26] However, the same study found that red cell transfusion was associated with poor outcomes for patients with hemoglobin levels > 8 g/dL. In a subgroup analysis of patients with closed TBI and initial hemoglobin levels < 9 g/dL from the Transfusion Requirements in Critical Care trial,[34] no significant difference was found in rates of multiple organ dysfunction, length of hospital or intensive care unit stay, and 30-day all-cause mortality between patients who were randomized to a restrictive allogeneic red blood cell transfusion strategy (Hb 7.0 g/dL and maintained between 7.0 and 9.0 g/dL) or to a liberal strategy (Hb 10.0 g/dL and maintained between 10.0 and 12.0 g/dL).[35] Results from this study have led some institutions to recommend a restrictive transfusion trigger of hemoglobin level < 7 g/dL for patients with TBI.

Together, clinical and mostly retrospective studies have identified anemia as a potential risk factor for poor clinical outcomes in patients with TBI. However, red cell transfusion does not appear to mitigate the risk, and in some reports it is associated with poor outcomes for these patients.[26,27,36–39] The exact reasons for this apparent discrepancy remain to be investigated, but there are several possibilities. First, substantial red cell transfusion may alter brain vessel hemodynamics by increasing blood viscosity and thus reducing blood flow and tissue perfusion.[40] Second, the efficacy of red cell transfusion may be affected by storage lesions.[41–44] For example, a left shift of the hemoglobin-oxygen dissociation curve of stored red cells increases the affinity of hemoglobin to oxygen, making the oxygen release in hypo-oxygenated tissues difficult and slower.[45,46] Third, stored red cells contain large quantities of cellular microvesicles,[47–49] which could be detrimental.[48,50–52] For example, these cellular microvesicles express anionic phospholipids such as phosphatidylserine, making them highly procoagulant,[48,51] and could carry hemoglobin, which induces oxidative stress, promotes inflammation, and reduces nitric oxide.[50,53] They can also stimulate inflammation through their cytokine cargos and by regulating the immune response of the host.[54,55] Larger, prospective, and controlled clinical trials with the power to detect the best trigger for red cell transfusions and possible negative or positive effects of them are required to develop red cell transfusion strategies that specifically target patients with isolated TBI. Basic science and mechanistic studies are also needed to delineate the host responses to red blood cell-derived microvesicles.

PLASMA TRANSFUSION

Patients with isolated TBI receive plasma transfusions primarily to revers trauma-induced or medically induced coagulopathy. In a provider-profiling survey that included 66 centers from 20 European countries, fresh frozen plasma was transfused to treat hemostatic abnormalities in 73% of patients with TBI.[56] A small retrospective study found that plasma transfusion before hospital admission reduced the average international normalized ratio (INR) upon admission from 3.1 to 1.9 in patients with TBI on warfarin, but the clinical outcomes for these patients were not reported.[57] The transfusion of fresh or lyophilized fresh frozen plasma (FFP) has been reported to reduce neurologic impairment and accelerate the recovery of Yorkshire swine subjected to TBI and controlled hemorrhagic shock as compared to those receiving normal saline.[58,59] The cerebral lesion also appears to be smaller in FFP-treated swine. However, it is not clear whether FFP directly improved TBI or indirectly improved it by correcting hemorrhagic shock thus improving tissue perfusion. Nevertheless, plasma transfusion to correct mild laboratory coagulopathy (INR 1.4–2) in patients with TBI remains controversial and can lead to a delay in neurosurgical intervention.[60] In a retrospective study, patients with moderate coagulopathy who received FFP and packed red cells were likely to have a lower Glasgow Outcome Score-Extended (GOSE, odds ratio 7.17 [95% CI 2.12–24.12]), but no significant correlation was found between plasma transfusions and 6-month mortality.[61] A recent retrospective, multicenter study of 618 patients with TBI found significant higher mortality among those who received plasma regardless of TBI severity, due in part to a high overall rate of complications such as acute respiratory distress syndrome (ARDS) and pneumonia.[62] Counterintuitively, a prospective observational study of 101 severely injured pediatric patients with and without TBI found that plasma transfusions and TBI were two independent predictors of fibrinolysis shutdown, and they were associated with poor prognosis in a regression model that included all transfusion products and was controlled for confounding factors.[63] These findings led the study's authors to suggest that plasma transfusions should not be used to target INR thresholds but rather to target parameters of rapid thromboelastography and clinical signs of bleeding.

Taken together, retrospective studies with very limited sample sizes and adjustments for confounding variables do

not support routine plasma transfusion to reverse TBI-induced coagulopathy, especially for moderate cases. There are insufficient data to evaluate the efficacy of plasma transfusion to reverse the effect of warfarin or other anticoagulants. Large, prospective, randomized, controlled trials are again needed to address the potential benefits in this clinical situation.

At Harborview Medical Center University of Washington, which is the only level-1 trauma center in the five Northwest states, the standard practice for reversing the effect of anticoagulants is to use pro-thrombin complex concentrate (PCC). For patients on warfarin, the PCC dosage is determined by the presenting INR with a target of 1.5 or less posttransfusion. PCC is also used for patients on factor X inhibitors, as previously reported,[64] with the treatment goal of modified partial thromboplastin time< 90. Direct thrombin inhibitors such as dabigatran are not effectively reversed by PCC, but could be reversed by the targeted antidote idarucizumab.

PLATELET TRANSFUSION

In the same provider-profiling survey of 66 centers from 20 European countries, platelets were transfused to treat hemostatic abnormalities in 52% of patients.[56] There have been consistent reports that platelets undergo significant phenotypic changes over the course of TBI, but their causes are less understood than the causes of the consumptive coagulopathy and hyperfibrinolysis.[14,65] Platelets have moderately low counts and enhanced activation and express procoagulant activity in patients with TBI as well as in rats subjected to TBI.[66–70] A consistent but not fully explained observation is that platelets from patients with TBI[67–69,71] and from experimental TBI rats[68,72,73] and swine[74] respond poorly to adenosine diphosphate and to arachidonic acid. This poor response is independent of platelet counts, hemorrhagic shock, and tissue hypoperfusion.[67,68,72,73] More importantly, it does not appear to be caused by granule depletion of activated platelets.[75] Despite this reported platelet dysfunction in patients with TBI, and the increase in elderly patients on anti-platelet medications, platelet transfusions have not consistently been found to improve outcomes in patients with TBI in the limited number of clinical studies reported in the literature. A recent large, multicenter, retrospective study found that platelet transfusion was among the best variables for predicting volume expansion ("blossoming") of traumatic cerebral intraparenchymal hemorrhage following TBI.[76] Even for TBI patients with mild thrombocytopenia (50-107x10^9/L), platelet transfusion does not appear to improve clinical outcomes for the patients.[61]

Inconsistent results were also reported for platelet transfusion to control medically induced bleeding tendencies in older patients who are on anti-coagulants and anti-platelet medications. A retrospective study of 328 patients with TBI found that platelet transfusion did not reduce mortality in older patients (≥ 50 years of age) on aspirin or clopidogrel,[77] and it was even trending for worse medical declines in another similar study.[78] Using the VerifyNow assay, which is widely used to detect platelet response to anti-platelet drugs, a retrospective cohort analysis detected a similar trend toward higher mortality in patients with TBI who were on aspirin preinjury and failed to improve platelet function after transfusion (non-responders).[79] Consistent with these reports, Hendrickson et al.[80] identified platelet transfusion as an independent and modifiable risk factor for the development of ARDS. A systematic review of seven retrospective cohort studies since 2015 found that platelet transfusions were associated with an elevated pooled odds ratio of 1.77 (95% CI 1.00–3.13) for in-hospital mortality of patients with TBI and primary intracranial hemorrhage.[81] But the study's authors concluded that the methodological limitations of these studies were too severe to draw definitive conclusions.[81] One small but prospective study using whole blood aggregometry found that platelet transfusion reversed aspirin-induced platelet inhibition but not TBI-induced platelet inhibition,[82] highlighting the impact of different pathophysiologic mechanisms on the efficacy of platelet transfusion in TBI.

In addition to individual blood components, the ratio in which transfusion products are given may also influence the outcome of TBI.[83] In a retrospective observational study of 385 patients with isolated and blunt TBI, transfusion in a plasma-to-red cell ratio of > 1 was an independent predictor for reduced in-hospital mortality, but the same was not true for transfusion of platelet and red cells at a ratio > 1.[84] Brasel et al.[85] conducted an outcome study of severe TBI recruited from 22 level-1 trauma centers and reported that transfusion with a high platelet-to-red cell ratio was independently associated with improved survival in patients with TBI, whereas transfusion with a high plasma-to-red cell ratio was independently associated with improved survival of trauma patients without TBI. Another retrospective study, in which the survival benefits were compared between TBI patients who received plasma, red cells, and platelets in a 1:1:1 ratio (ratio-based group) and those who received non-ratio-based transfusions found significantly improved survival among the patients receiving the ratio-based transfusion in a multivariate logistic regression analysis.[86]

In summary, TBI-induced coagulopathy is a common and well-known condition, but we have just begun to understand its pathogenesis, especially its consumptive nature. The distinctive pathways of coagulopathy derived from traumatic hemorrhagic shock and from TBI require differential therapeutic strategies. Although patients with isolated TBI do not have an intrinsic need for blood transfusion, they are routinely transfused with various blood components to treat coagulopathy, to reverse the effects of anticoagulant and antiplatelet medications, and to correct comorbidities. While the findings reported in the literature are overwhelmingly negative or ineffective, the efficacy of

blood transfusions has so far been evaluated in only a limited number of clinical outcome studies, which are mostly retrospective and very limited in sample sizes, patient stratifications, and confounding adjustments. Basic and translational studies at cellular levels are also needed to understand the impact of transfusions on endothelial injury, coagulopathy, hyperfibrinolysis, and platelet dysfunction. Information from these basic and translational studies could help us develop well-targeted therapies, which could then be evaluated for efficacy in large, randomized, prospective, and controlled clinical trials.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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