Preview

Can prehospital "plasma supplement" neutralize the systemic storm in severe trauma?

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SUMMARY

Severe trauma is a leading cause of mortality. Its pathophysiology, progression, and outcome are complex and heterogenous. In this issue of *Cell Reports Medicine*, Wu et al. from the PAMPer study provide new insights into the potential underlying biology based on multi-omics analysis.[1]

Unintended injuries represent a leading cause of premature death worldwide. In 2020, critical injuries took nearly 200,000 lives in the United States, only behind the heart disease, cancer, and COVID-19.[2] Patients with critical injuries, or severe trauma, have a high mortality rate, and over 50% of them die at the scene of injury or before hospitalization. After hospitalization, the majority of early deaths occurring within the first 2 days can be attributed to traumatic brain injury (TBI) and hemorrhagic shock, while the later deaths were largely due to sepsis and multiple organ failure.[3] Over the last two decades, the mortality rate has significantly improved in the specialized trauma centers.[4] However, the prehospital mortality rate, in other words deaths in minutes to a few hours after injury, has not been improved.[5] Although the coagulopathy and hemorrhagic shock are more approachable to treatment, damage to the central nervous system or TBI still remains a major challenge in patients with severe trauma.[6]

The Prehospital Air Medical Plasma (PAMPer) trial was designed to test the efficacy and safety of prehospital plasma resuscitation in critically injured patients at risk for hemorrhagic shock, through a multicenter phase 3 trial at the University of Pittsburgh Medical Center.[7] During the air medical transport to nine level-I trauma centers, patients were randomized to receive a standard-care or allogeneic thawed plasma resuscitation. Clinical data from 501 patients showed a significant improvement in mortality at

30 days in the plasma resuscitation group.[7] To further understand the complex human response to severe trauma and the potential underlying biological mechanism(s) of plasma-based resuscitation in reducing mortality, the PAMPer study investigators have been analyzing the patient clinical data in relation to serum biomarkers including endotheliopathy biomarkers, cytokines, and lipidomics.[7,8]

In the this issue of *Cell Reports Medicine*, Wu et al. reported the metabolomic and proteomic datasets and completed a 6-layer multi-omic map for the PAMPer cohort.[1] Their metabolomic and proteomic analysis at admission, 24 h, and 72 h after hospitalization revealed an abrupt and massive release of cellular constituents into the circulation. The metabolomic analysis revealed seven metabolite modules that evolved differently between the resolving and non-resolving (severe) conditions across the three time points. These metabolite modules were further validated in the TD-2 cohort of 472 blunt trauma survivors, indicating that the metabolic shift in severe trauma is closely related to clinical outcome. The proteomics analysis in 151 PAMPer patients for 1305 proteins in plasma revealed that the majority of proteins elevated in the serum at hospitalization, particularly in the non-resolving cases, reflect a massive release of cellular constituents caused by injury.

With the integrated 6-layer multi-omic array from 88 patients, the authors pooled 200 variables highly correlating with injury

severity, lactic acidosis, and prothrombin time based on the international normalized ratio (IRN). They further identified two clusters. The first cluster consisting of inflammatory cytokines, endothelial and tissue injury markers, cellular components and stress response, energy substrates, and metabolic intermediates was named "Systemic Storm." The second cluster enriched in lipids, lipid transport proteins, coagulation factors and enzymes was named "Massive Consumption." These two patterns clearly depicted the injury-induced immediate changes in circulating proteins and metabolites, as well as endangering coagulopathy,[1] providing a critical insight to the hyperacute phase of the injury.

Importantly, a multi-layer analysis in 173 patients at hospitalization identified two endotypes: (1) one mainly representing high levels of endothelial injury markers that were associated with a lower 30-day survival rate, and (2) the other representing lower levels of endothelial injury markers and associated with a significantly higher 30-day survival rate with ~25% net difference. Interestingly, these endotypes particularly influenced differential outcomes in two subgroups of trauma patients that received prehospital plasma resuscitation. Only patients with TBI and high levels of endothelial injury markers responded well to plasma administration, with approximately 70% reduction in mortality, whereas patients without brain injury and lower levels of endothelial injury markers had a marginal response to plasma administration. These
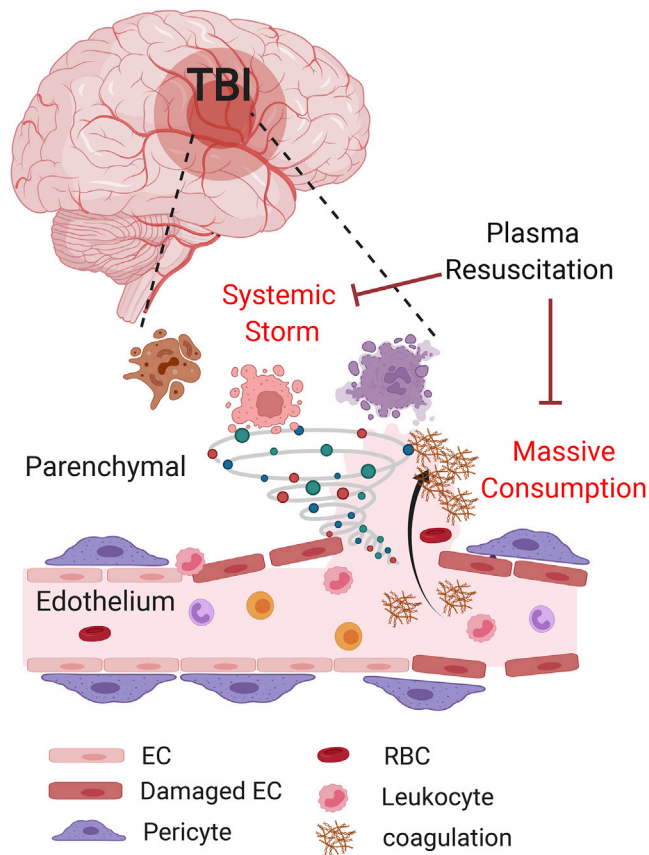
Figure 1. Prehospital plasma resuscitation improves outcome in traumatic brain injury (TBI) patients

Critical trauma leads to a "Systemic Storm" caused by release of several cellular constituents including cytokines and metabolites into the circulation, and a "Massive Consumption" pattern associated with an increase in lipids, coagulation factors, and enzymes in the circulation. Prehospital plasma resuscitation in the PAMPer trial attenuated both the Systemic Storm and Massive Consumption patterns and improved survival in TBI patients with endothelial injuries. EC, endothelial cell; RBC, red blood cell.

injury to plasma administration is consistent with the notion that the blood brain barrier breakdown is likely a key component of its pathogenesis and that preserving the neurovascular function is critical.[10] While the overall survival in hospitalized trauma patients has been improving, the total death toll is still rising in the US every year, which calls for more effective prevention of injuries and violence.

DECLARATION OF INTERESTS

The authors declare no competing interests.

data are very exciting and indicate that prehospital plasma resuscitation could be a promising intervention for patients with severe TBI (Figure 1).[8]

The current findings have provided the needed empirical data on the benefit of plasma-based prehospital intervention for trauma. For the development of point-of-care diagnostics to identify the right endotype subgroup, the authors tested an array of serum biomarkers and found that the combination of a brain injury-specific marker UCHL1 (Ubiquitin C-terminal hydrolase L1), an endothelial injury marker sydencan 1, and inflammatory cytokines IL17A and interferon-inducible protein 10 (IP-10) offer the best predictive value based on 173 studied patients. Therefore, this biomarker panel may provide a practical tool to stratify

trauma patients for effective early treatment.

Overall, the PAMPer study has provided an important evaluation of prehospital plasma resuscitation in the critically injured and demonstrated its efficacy in reducing mortality in TBI patients. This method provides a simple, practical, and likely effective approach that can be easily integrated into the existing prehospital trauma care systems throughout the world.[9] The current study provided not only the two biological signatures, Systemic Storm and Massive Consumption, underlying the early pathophysiological changes upon critical injuries, but also identified a vascular endotype contributing to the outcomes of complex injuries. The selective responsiveness of TBI patients with endothelial

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