In this issue of *JAMA Network Open*, Gruen and colleagues\(^1\) report on the association between prehospital resuscitation with plasma and survival in patients with traumatic brain injury (TBI). The study is a post hoc secondary analysis of a prespecified subgroup from the Prehospital Air Medical Plasma (PAMPer) randomized clinical trial\(^2\), which showed that a resuscitation strategy incorporating plasma substantially reduced 30-day mortality compared with standard care overall in patients with trauma who were at risk for hemorrhagic shock. This outcome appeared particularly robust among patients with TBI in the original trial, although the association was not fully characterized. The goal of the study by Gruen and colleagues\(^1\) was to further explore the association between prehospital plasma resuscitation and the interaction with TBI on outcome. After adjusting for confounders, the authors found that resuscitation with plasma substantially reduced 30-day mortality in patients with TBI. However, no such difference was found in patients without TBI, suggesting that the benefits of prehospital plasma resuscitation may be limited to individuals with head injury. Exploratory analyses indicate that the impact of the treatment is greatest when administered to the most severely injured patients and may be greater when administered soon after injury.

Given the extensive global burden of TBI\(^3\), interventions that improve outcomes have the potential to make a substantial impact on public health. Unfortunately, despite decades of research and promising preclinical studies, few trials have demonstrated meaningful benefits in humans with TBI. The study by Gruen and colleagues\(^1\) is important because it shows that a routinely available intervention may be associated with substantial improvement in TBI survival. The study answers important questions but raises several others.

It is unclear why patients who received plasma were less likely to die. The survival curves of the 2 groups separate early in the first few hours following randomization, and then continue on parallel trajectories. As Gruen and colleagues\(^1\) note, hemorrhagic complications are associated with most deaths within the first few hours, whereas death from TBI tends to occur later in the hospital stay. Does plasma resuscitation reduce deaths attributed to hemorrhage in patients with multiple trauma and TBI? And do patients without TBI truly derive no benefit?

By what mechanism does plasma improve survival? Plasma has long been used to reverse anticoagulation in patients taking vitamin K antagonists, but with fewer than 3% of enrolled patients taking these agents\(^1\), reversal of medication effect cannot account for their results. Plasma is also thought to help maintain endothelial integrity, which may mitigate coagulopathy, thereby slowing intracranial and extracranial hemorrhage.\(^4\) Hypoperfusion, shock, and brain injury can all compromise the endothelium, leading to derangements in hemostasis that may be particularly profound when severe TBI occurs with concomitant extracranial injuries.\(^5\) In line with this idea, Gruen and colleagues\(^1\) found that the survival benefit was most pronounced among patients with severe TBI (Glasgow Coma Scale score <8) and significant extracranial injuries (nonhead Abbreviated Injury Scale score \(\geq 3\)). A complete understanding of the underlying mechanism requires further research.

The study by Gruen and colleagues\(^1\) is the second in recent years to show a benefit from early administration of agents aimed at mitigating coagulopathy in patients with TBI. Published in 2019, CRASH-3 was a randomized clinical trial comparing tranexamic acid (TXA) vs placebo that showed a statistically significant reduction in TBI-related mortality when TXA was administered to patients with mild to moderate injuries.\(^6\) In seeming contradiction to the results of Gruen et al,\(^1\) no treatment...
effect was found in those with severe TBI; this discrepancy may be attributed to the different mechanisms of action in TXA and plasma.

However, both studies appear to show the importance of early treatment. In CRASH-3, the benefit of TXA diminished with time and was no longer statistically significant by 3 hours after injury. Using transport origin as a proxy for time to treatment, Gruen et al found that only patients who were transported directly from the field derived benefit from plasma resuscitation; it had no effect on those who were first triaged to a local hospital before being airlifted to a trauma center (and presumably had longer intervals between injury and plasma resuscitation as a result). However, interventions performed at the referring hospitals prior to randomization may also explain this finding, and, without time measurements, it remains unclear how long after injury plasma administration remains beneficial.

Overall, the study by Gruen et al provides evidence that prehospital plasma resuscitation is associated with improved survival in patients with TBI and multiple trauma, although the study is subject to the usual limitations of secondary analyses of randomized clinical trials. This study also raises several important questions. First, is prehospital plasma resuscitation associated with improved neurologic recovery among survivors? Some interventions that have shown survival benefit in patients with severe head injury do not improve the likelihood of good neurologic recovery, and instead increase the odds of surviving with severe disability. These types of interventions raise ethical and cultural issues that require careful consideration. Second, does plasma truly provide no benefit in patients with trauma without TBI? Third, how soon after injury must plasma be administered to provide benefit? Fourth, given the promising results of CRASH-3, does coadministration of TXA with plasma affect these results? These issues warrant deliberation as trauma systems contemplate the routine use of prehospital plasma in this population.

ARTICLE INFORMATION
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