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Literature Review

Articles That May Change Your Practice: Prehospital Plasma

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Patients with severe traumatic injuries require time-sensitive correction of blood loss to improve outcomes. If not managed promptly and appropriately, uncontrolled hemorrhage may lead to a lethal triad of coagulopathy, acidosis, and hypothermia. Hypoperfusion leads to cellular hypoxia, anaerobic metabolism, and worsening hypothermia, which further worsen coagulopathy. Unless resuscitation is initiated, the hemorrhage is stopped, and the coagulopathic state is reversed, death will ensue. The acute management of these patients has evolved significantly in recent years because of new knowledge of the pathophysiology that takes place after acute blood loss.

The initial treatment is no longer a matter of repeat crystalloid boluses before considering blood products. Crystalloid alone, or in large volumes before the administration of blood products, results in dilutional anemia, dilutional coagulopathy, and a reduction in the blood's oxygen-carrying capacity. The evidence now supports conservative use of crystalloids, with small amounts pending the prompt administration of blood products.

Previous "articles[1]" reviewed the advances in prehospital use of blood products in patients with hemorrhagic shock. At that time, benchtop and clinical evidence[2-8] suggested early transfusion of packed red blood cells (PRBCs) after trauma resulted in favorable outcomes for patients with hemorrhagic shock because of acute traumatic blood loss. This concept of "damage control resuscitation[9]" is believed to benefit the patient by potentially reducing downstream complications caused by hemorrhage by intervening soon after the time of injury, before the development of irreversible shock, coagulopathy, and inflammatory response that occur after injury. The previous review[1] concluded that although evidence exists for prehospital use of blood products, rigorously designed prospective trials were needed to clarify the beneficial roles of this therapy in the prehospital setting and to identify which of the various blood components have a key role.

At the time the previous review was published in this journal, a group of investigators at the University of Pittsburgh published the design and rationale for a randomized clinical trial to determine the effect of prehospital plasma transfusion during air medical transport on mortality in patients at risk for traumatic hemorrhage.[10] Their hypothesis was that plasma transfusion mitigates the coagulopathy that can complicate traumatic hemorrhage, alters the inflammatory response, and reduces permeability of endothelial cells after hemorrhagic shock. This would have a net benefit in patient outcome. Their trial, the Prehospital Air Medical Plasma (PAMPer) trial, was designed to determine the efficacy and safety of prehospital plasma resuscitation compared with standard care resuscitation in severely injured patients at risk for hemorrhagic shock. This issue of "articles" focuses on the results of this clinical trial because it provides key evidence regarding the role of blood products in the prehospital management of shock caused by acute, life-threatening hemorrhage.

Sperry JL, Guyette FX, Brown JB, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. *N Engl Med J.* 2018;379:315-326.

The authors conducted a pragmatic, multicenter, cluster randomized trial involving injured patients who were at risk for hemorrhagic shock during air medical transport to a trauma center. The authors hypothesized that prehospital administration of plasma would reduce 30-day mortality in this patient population.

Patients were eligible if they were transported from the scene of their injury to a participating trauma center or from a referral emergency department to a participating trauma center. Eligible patients had at least 1 episode of hypotension (systolic blood pressure $<$ 90 mm Hg) and tachycardia (heart rate $>$ 108 beats/min) or they had severe hypotension (systolic blood pressure $<$ 70 mm Hg), either before the arrival of air medical transport or any time before arrival at the trauma center. Patients were excluded if they were younger than 18 or older than 90 years of age, vascular access could not be established, they had an isolated fall from standing, they had a documented cervical cord injury, they were known to be a prisoner, they had a cardiac arrest lasting longer than 5 minutes, they had a penetrating brain injury, they had an isolated drowning or hanging incident, they had burns covering greater than 20% of the body surface area, or they were being admitted as an inpatient from an outside hospital.

Air medical bases were randomly assigned to the "plasma" (intervention) group for 1 month. In addition to standard care, those in the intervention group administered 2 units of thawed plasma to eligible patients before any other resuscitation fluid was given. As part of their standard resuscitation practice, 13 of the 27 air medical bases participating in the trial also carried 2 units of PRBCs on all of their flights. The primary outcome of the trial was mortality at 30 days. Secondary outcomes included mortality at 24 hours and in hospital, volumes of blood component and resuscitation fluid administered within 24 hours of enrollment, incidence of multiorgan failure, acute lung injury, transfusion-

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related lung injury, nosocomial infections, and indices of coagulopathy.

A total of 564 patients were eligible for enrollment in the prehospital setting. Of these, 230 were eligible and randomly assigned to the plasma group and 271 to the standard care group. Most patients (82.4%) had an injury caused by blunt trauma, with a median Injury Severity Score of 22 (interquartile range, 13-30). The overall 30-day mortality was 29.6%. Prehospital treatment teams administered the assigned treatment in 496 of the 501 participants (99.0%). Those assigned to the plasma group received a near 1:1 ratio of prehospital plasma to PRBCs, consistent with the principles of damage control resuscitation. The study intervention did not delay the transport time to the trauma center (42 minutes in the plasma group and 40 minutes in the standard care group).

The primary outcome data were available in 481 patients (96.0%). The authors found that mortality at 30 days was lower in the plasma group than in the standard care group (23.2% vs. 33.0%, $P = 0.03$). When adjustments were made for the volume of prehospital crystalloid solution administered and the percentage of patients who received prehospital PRBCs, the administration of prehospital plasma was associated with a risk of death within 30 days after randomization that was 39% lower than the risk with standard care (adjusted odds ratio = 0.61; 95% confidence interval, 0.40-0.91; $P = 0.02$). The Kaplan-Meier survival curves showed an early separation of the 2 groups, with a survival benefit in the plasma group beginning 3 hours after randomization.

Prehospital plasma administration was also beneficial in secondary outcomes. Mortality at 24 hours and in-hospital mortality were lower in the plasma group. Patients in the plasma group also received fewer units of blood component overall and fewer units of PRBCs within 24 hours after enrollment. They also had a lower median prothrombin time ratio at the time of the first blood sampling. There were no significant differences between groups in other resuscitation variables at 24 hours or the incidence of multiorgan failure, acute lung injury, transfusion-related lung injury, or nosocomial infections. Five patients (2.2%) in the plasma group had transfusion-related reactions that were considered to be related to the trial treatment, all of which were minor.

The authors concluded that in injured patients with hemorrhagic shock the prehospital administration of thawed plasma was safe and resulted in lower 30-day mortality and a lower median prothrombin time ratio than standard care resuscitation, irrespective of whether or not PRBCs were administered.

This study is notable for a number of reasons. The study's pragmatic design reflects real-world situations in a heterogeneous patient population with a broad mix of injuries and severities. The results are also consistent with in-hospital studies showing the benefit of incorporating plasma into resuscitation of a trauma patient experiencing hemorrhagic shock. The intervention is also simple to deliver in the prehospital setting. Although the study was unable to determine the independent or additive effects of prehospital administration of plasma and PRBCs, the survival benefits attributable to plasma persisted after adjustment for prehospital PRBC administration. The number of adverse events identified in the intervention group is quite small, but it is not possible to determine the risk associated with this intervention given the data presented. Most importantly, given the differences in mortality between the 2 treatment groups, only 10 patients meeting these study criteria would need to receive prehospital plasma (in addition to standard care resuscitation) for 1 additional patient to survive.

The use of thawed plasma in the prehospital setting, as was done in this trial, poses several challenges. It requires proper refrigerated storage and has a shelf-life of only 5 to 7 days. The logistics of maintaining a supply without wasting product is a logistical challenge, requiring a good partnership with a blood supply agency and local hospitals. Never-frozen liquid plasma is a potential alternative because it retains the majority of its clotting factors and inhibitors at 26 days.[11] Although availability is not widespread and not approved by the Food and Drug Administration (United States) or Health Canada (Canada), freeze-dried plasma can potentially overcome issues with storage and shelf-life. It has shown promise as part of the resuscitation of patients with hemorrhagic shock in military and civilian settings.[12,13] If freeze-dried plasma becomes more widely available, it would overcome the storage and shelf life issues present with current forms of plasma.

If the ultimate goal is to restore circulating volume with a comparable fluid, whole blood may be the most effective option. It has the benefit of having oxygen-carrying red blood cells and clotting factors and platelets to enable and promote the formation of a clot. It has a typical shelf life of 21 days and would be an ideal prehospital resuscitation product if it were more widely available. Although theoretically promising, further study would be needed to compare it with existing resuscitation therapies, including those that involve blood components such as PRBCs and plasma.

The prior “articles[1]” addressing prehospital blood products concluded that rigorously designed prospective trials were needed to determine the beneficial roles of blood component therapy in the prehospital setting and identify the ratios of various components in this therapy. The PAMPer trial is precisely the type of study needed to help clarify the role of prehospital blood products. The trial shows the benefits of prehospital plasma administration, with or without PRBCs, and should prompt air medical programs to consider adding plasma to their prehospital resuscitation regimen for patients with hemorrhagic shock.

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