Critical Review Form
Therapy

PGY-1

HYPERLINK "http://pmid.us/30032977"Moore HB, Moore EE, Chapman MP, et al. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. Lancet. 2018 Jul 28;392(10144):283-291.

Objectives: **To determine "whether plasma-first resuscitation affected trauma-induced coagulopathy and adverse outcomes after injury in patients with haemorrhagic shock. We tested the hypothesis that mortality would be lower among patients who received plasma before arrival at a level 1 trauma facility than among those who received standard care with normal saline." (p. 3)**

Methods: **This pragmatic, randomized controlled trial was based at the Denver Health Medical Center (DHMC) in Denver, CO between April 1, 2014 and March 31, 2017. Injured adults (age > 18 years) with systolic blood pressure (SBP) ≤ 70 mmHg or with SBP 71-90 mmHg AND heart rate ≥ 108 thought to be due to blood loss were eligible for enrollment. Exclusion criteria were pregnancy status, pregnancy, isolated gunshot to the head, ongoing cardiopulmonary resuscitation prior to randomization, known objection to blood products, opt-out bracelet/necklace, or family objection to patient's enrollment.**

DHMC has 33 ambulances which were loaded with prepackaged coolers containing plasma or frozen water, which were randomly assigned in a 1:1 fashion to eligible patients. For patients randomized to a plasma cooler, two units of AB plasma were immediately removed, thawed, and administered; for patients in whom the cooler contained water, normal saline (0.9%) was administered "based on hemodynamic need."

The primary outcome was 28-day mortality. A secondary composite outcome including multiple organ failure (Denver MOF Score), death, or both by day 28 was also measured, as were laboratory indicators of trauma-induced coagulopathy, time from injury to first red blood cell transfusion, number of ventilator-free days, number of intensive-care free days, and development of multiorgan failure.

A total of 144 patients were randomly assigned to study groups by paramedics during the study period. After exclusion of patients for age < 18 (4), withdrawal of consent (9), lack of trauma (2), ineligible vitals (3), and transfer to another facility (1), the as treated analysis included 125 patients, with 65 randomized to the plasma group and 60 to placebo.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized in a 1:1 fashion in blocks of 20.
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "Plasma and dummy (frozen water) loads for the coolers were randomly assigned 1:1 in blocks of 20 according to a schedule generated by the research coordinators. These were delivered to the DHMC Paramedic Division in sealed aluminium cassettes by study staff not involved in enrolment or data analysis, to mask allocation." (p. 4)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. Although the primary analysis was an as-treated analysis, "We did an intention-to-treat (ITT) safety assessment to allow unbiased assessment of the risk associated with randomisation assignment, and an as-treated analysis to assess the effects of the intervention on the proposed outcomes." (p. 6)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, BMI, presence of medical comorbidities, blunt injury as etiology of trauma, injury severity score, presence of traumatic brain injury, and vital signs.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Unclear. While blinding was not attempted, it is unclear if patients were truly aware of what treatment they received.
2.	Were clinicians aware of group allocation?	Yes. The investigators were reluctant to use frozen saline given concerned about thawing this and inducing hypothermia. Additionally, administration of a similar volume of saline (< 800 mL) was felt to not meet standard of care. There is some risk of performance bias on the part of clinicians.
3.	Were outcome assessors aware of group allocation?	Uncertain. The authors make no mention of blinding of outcomes assessors, putting the study at some risk of observer bias.
4.	Was follow-up complete?	Yes. Following exclusion of patients who did not give consent or who were transferred, outcome results were available for all remaining patients.
II.	**What are the results ?**	

1.	How large was the treatment effect?	• There was no statistically significant difference in the rates of 28-day mortality between the plasma group (15%) and the control group (10%): relative risk [RR] 1.54 (95% CI 0.60 to 3.98).
		  ○ There was similarly no significant difference in the ITT analysis: RR 1.79 (95% CI 0.71 to 4.50).
		• No significant difference was seen for:
		  ○ The composite outcome (RR 1.85, 95% CI 0.80 to 4.26)
		  ○ Development of acute lung injury at 28 days (RR 0.86, 95% CI 0.59 to 1.26)
		  ○ Development of multiorgan failure within 28 days (RR 3.69, 95% CI 0.42 to 32.11)
		  ○ Ventilator free days (median 26 days in both group)
		  ○ ICU free days (median 23 vs. 24 days)
		• Median time from injury to first RBC infusion was 46.6 minutes (IQR 32.0 to 55.5) in the plasma group and 37.0 minutes (IQR 24.0 to 46.0) in the control group.

2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Yes. This study was conducted in a large, urban EMS system in Denver, CO with a diverse population. It is likely that patients, transport times, injuries, and medical practice would be similar to those in our system.
2.	Were all clinically important outcomes considered?	Yes. The authors considered multiple outcomes including mortality, need for mechanical ventilation, need for ICU admission, acute lung injury, number of units of each blood product needed, and adverse events.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. Based on this study, administration of plasma during ground transport by EMS in an urban system did not result in any improvement, in mortality, development of acute lung injury, development of multiorgan failure, or transfusion needs. These results may not apply to rural EMS systems with longer transport times or military transport, and should not be generalized to these situations.

Limitations:

1. **There was no blinding of clinicians (performance bias) or outcome assessors (observer bias).**

2. **While a secondary safety intention to treat analysis was performed, the primary analysis was as treated and limited to those patients who did not withdraw consent.**

3. **The study was stopped early as no benefit (or harm) was seen at the interim analyses; this practice has the potential to miss a potentially significant benefit if the study had been allowed to obtain its planned enrollment (Guyatt 2012).**

Bottom Line:

This single-system randomized controlled trial comparing administration of plasma versus saline (control) in the prehospital setting for hemorrhagic shock in trauma found no significant difference in the rates of 28-day mortality between the plasma group and control groups (relative risk [RR] 1.54; 95% CI 0.60 to 3.98). There was also no difference in any of the secondary outcomes, including development of acute lung injury, ventilator-free days, ICU-free days, or volume of various blood products ultimately administered.