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Does Administration of Prehospital Plasma Improve Survival Rates in Injured Adults at Risk for Hemorrhagic Shock?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether administration of prehospital plasma will improve survival rates in injured adults at risk for hemorrhagic shock.

Study Design: A systematic review of two randomized controlled trials (RCT) and one retrospective cohort study

Data Sources: All three studies were identified using PubMed and selected based on their ability to answer the clinical question while including patient-oriented outcomes (POEMs). All articles were peer-reviewed, published in English, and published on or after 2011.

Outcomes Measured: The outcomes addressed were survival rates, calculated using mortality rates based on if the patient was alive or not at the time of follow up. This includes 30-day, 28-day, and in-hospital mortality rates.

Results: An RCT by Sperry et al. showed improved survival rates of 75.9% in those who received plasma versus 65.9% in those who received standard care ($p=0.03$). Moore et al. showed a survival rate of 90% in the control group versus 85% in those who received fresh-frozen plasma ($p=0.37$). Shalifer et al. looked at freeze-dried plasma and found that 91.5% of patients who received it survived versus 93.8% who did not ($p=0.17$).

Conclusion: Evidence between all three studies was conflicting. Future studies should investigate further the forms of plasma for maximum benefit and logistic ease.

Key Words: prehospital plasma, trauma, hemorrhagic shock

INTRODUCTION

Hemorrhagic shock is a type of hypovolemic shock that is characterized by severe blood loss. Initially, the body compensates through various mechanisms such as tachycardia and vasoconstriction. Beginning at 15% volume loss, hypotension, hypoxia, and eventually, death ensues.[1] Signs of hemorrhagic shock include obvious traumatic bleeding; however, will not be present in all patients. Patients in hemorrhagic shock may be altered, lethargic, or comatose. On physical exam, they can be cool, pale, and diaphoretic. Vital signs may show a narrow pulse pressure or decreased venous pressure.[1]

Injury is a common cause of hemorrhagic shock, so common that it is the leading cause of death in patients up to 45 years old and is the 4th leading cause of death for all ages.[2] It is estimated that 30 to 40 percent of trauma deaths are due to hemorrhage, with up to 56% occurring during the prehospital period.[3] An exact cost estimate for hemorrhagic shock has not been identified, but it is estimated that the lifetime cost of overall injury in the US is $406 billion.[4] The total cost of injury in 2019 alone was $4.2 trillion.[5] Further, injury accounts for an extensive amount of healthcare visits each year. In 2020, there were an estimated 23 million non-fatal injury ER visits and approximately 279,000 injury deaths in the US.[6]

Fatal consequences from hemorrhagic shock stem from inadequate perfusion to organs. To compensate, catecholamines are released and cause vasoconstriction, increased contractility, and tachycardia.[7] Eventually, compensatory mechanisms cannot keep up with metabolic demands, contributing to coagulopathy, activation of inflammatory cascades, and metabolic acidosis which ends in organ failure and death.[7] This triad is associated with increased mortality in trauma patients. While the mechanisms of shock are understood, the types and amounts of fluids to

interfere with the unruly pathway are up to debate.[8] Common treatment methods include crystalloid fluids such as normal saline or lactated ringers in the prehospital setting.

Utilizing blood products in the prehospital setting allows for early intervention, though they are not commonly used due to the specific conditions required to store them. Plasma, however, offers logistical advantages such as coming in freeze-dried or fresh-frozen forms. It is thought that plasma may benefit by mitigating coagulopathy, restoring the endothelial matrix, reducing permeability, and lessening the inflammatory response.[9,10] It also has the benefit of a high oncotic pressure to expand volume and can replenish coagulation factors rather than diluting them as with clear fluids.[11] This paper evaluates two randomized control trials and one retrospective cohort study comparing the effects of intravenous plasma administration versus standard resuscitation on injured adults at risk of hemorrhagic shock in the prehospital setting.

OBJECTIVE

The objective of this selective EBM review is to determine, “Does administration of prehospital plasma improve survival rates in injured adults at risk for hemorrhagic shock?” It is hypothesized that the use of prehospital plasma will increase survival rates in trauma patients compared to standard resuscitation.

METHODS

Articles were selected based on ability to answer the clinical question while including patient-oriented outcomes (POEMs). Additionally, studies must have met criteria based on population, intervention, comparisons, and outcomes. Articles referenced in this EBM review were found through PubMed using keywords “hemorrhagic shock” and “prehospital plasma.” All articles selected were in English language. Articles were required to be published data in peer-

reviewed journals. Other inclusion criteria include primary research, only researching adult patients, and being published on or after 2011. Studies with children, published before 2011, or secondary research were excluded.

The population selected for this EBM review was injured adults at risk for hemorrhagic shock. Any type of IV plasma must have been the intervention within chosen studies and given in the prehospital setting. The comparison must have been standard resuscitation, occasionally recognized as other IV fluids. The outcomes measured were survival rates. Two randomized control trials and one retrospective cohort study were included in this selective EBM review. Statistical analysis reported within these articles includes NNT, OR, RR, and p values. Demographics and characteristics of studies selected can be found in Table 1.

Table 1. Demographics and Characteristics of Included Studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Sperry 2018 (9)	RCT	501	Adults 18-90 years old	Injured adults with at least one episode of hypotension (SBP <90mmHg) and tachycardia (>108 bpm) OR any severe hypotension (SBP <70mmHg) before arrival of air medical or arrival to trauma center	Pts >90 or <18 years old, IV or IO access could not be established, isolated fall from standing, documented cervical cord injury, prisoner, pregnant, traumatic cardiac arrest >5 minutes, penetrating brain injury, isolated drowning or hanging, burn >20% BSA, family objects, opt-out bracelet, or admitted as inpatient at an outside referral hospital	42	2 units IV of thawed plasma (group AB or group A with a low anti-B antibody titer) vs IV crystalloid solution
Moore 2018 (10)	RCT	144	Adults >18 years old	Injured adults with SBP ≤70mmHg or 71-90mmHg and HR 108 bpm	Prisoner, pregnancy, isolated GSW to head, asystole or CPR before randomization, known objection to blood products, opt out bracelet/necklace, family objection	19	IV thawed plasma vs IV normal saline
Shlaifer 2019 (11)	Retrospective cohort	96	Adults 18-43 years old	Casualties treated with prehospital freeze-dried plasma between 01/2013-12/2016	Patients outside the age range or treated outside the timeframe	0	IV freeze-dried plasma versus not being treated with freeze-dried plasma

OUTCOMES MEASURED

The outcomes addressed were survival rates which were measured based on whether the patient was alive or not at time of follow up. Follow up was obtained from researchers contacting patient or their family regarding the status of the patient. Time of follow up varies between studies. Sperry and colleagues measured 30-day mortality rate.[9] Moore et al. measured 28-day mortality rate.[10] In contrast, Shlaifer et al utilized in-hospital mortality rate.[11]

RESULTS

Sperry et al. conducted a randomized control trial throughout the United States including KY, TX, PA, TN, and OH.[9] A total of 27 air medical bases were assigned an intervention using computer-generated block randomization.[9] Patients were then grouped based on which air medical team responded to their incident. There were 501 participants in total with 230 that received plasma in the prehospital setting versus 271 that received standard care (IV crystalloid solution).[9] No significant demographical variance was noted between participants; however, the majority were male.[9] At 30 days, trial personnel contacted patients or family of the patient in order to assess mortality.[9] A total of 42 patients were lost to follow up between groups (<20%) owing to lost contact, withdrawn consent, or imprisonment.[9]

Blinding medical personnel involved in patient care was unfeasible in the study, although treatment assignment was concealed to those who assessed outcomes. A modified intention-to-treat analysis was performed using multiple imputation.[9] Table 2 outlines the difference in 30-day mortality rates between interventions. Mortality was approximately 34% for trauma patients in the standard care group, therefore 65.9% survived.[9] In the plasma group, 30-day mortality was 24.1% and thus the survival rate was 75.9%.[9] Odds ratio for the overall mortality rate was 0.61

(0.42-0.92) with p=0.03 when including missing data analysis.[9] A total of 10 adverse events were recorded (2 in standard care group, 6 in plasma group).[9] Documented adverse events in the standard group included respiratory distress, fever, and sepsis.[9] In the plasma group, allergic reaction, hypotension, transfusion reaction, and urticaria were noted.[9] Between both groups, 3 were events deemed serious (1 in plasma group and 2 in the standard care group).[9]

Table 2. 30-day Mortality and Survival Rates Between Plasma and Standard Care Groups with Statistical Significance[9]

Standard Care Group Mortality	Standard Care Group Survival	Plasma Group Mortality	Plasma Group Survival	OR (95% CI)	P-value
34.1%	65.9%	24.1%	75.9%	0.61 (0.42-0.92)	0.03

Moore et al. conducted a randomized control trial investigating the effects of prehospital plasma use on trauma patients using ambulance transport. In this study, 33 ambulances were randomly loaded with plasma or frozen water based on a block schedule generated by the researchers.[10] These interventions were delivered in sealed packaging by staff that were not involved in enrollment or data analysis. After determining eligibility on scene, paramedics would open the cooler with the package. If the cooler had plasma, it was thawed and immediately administered to the patient.[10] If it was frozen water, patients were given 0.9% normal saline (standard of care).[10] In all, 144 patients participated in the study.[10] Of those, 19 were lost to follow up or excluded from analysis due to ineligibility (age less than 18, ineligible vitals, no trauma, no consent) or being transferred to another facility.[10] Both intention-to-treat and as-treated analyses were completed. 125 patients were included in as-treated analysis (65 received plasma, 60 received normal saline).[10] To note, 2 patients meant to receive plasma were incorrectly treated with saline and thus analyzed in the saline group.[10] ITT safety analysis

included all 144 patients deemed potentially eligible (73 received plasma, 71 received normal saline including 2 by error).[10] Demographics were similar among patients, although there were more men than women enrolled. At 28 days, research personnel contacted patients in the hospital or via telephone if they had been discharged to assess mortality status.[10]

As-treated analysis data is highlighted. Table 3 depicts mortality and survival rates between both interventions. Of those who received plasma, 85% survived.[10] In the standard care group, 90% had survived.[10] Calculated risk ratio for mortality rate was 1.54 (0.60-3.98), although results between interventions were not statistically significant (p=0.37).[10] Table 4 depicts calculated treatment effects using RBI, ABI, and NNT. The calculated NNT was -20, suggesting less clinical effect. No increase in adverse events were associated with either intervention, however the study concluded early due to futility.[10] The ITT analysis found no significant differences in survival, 84% in the plasma group versus 91% standard care (p=0.19), compared to the as-treated analysis.[10]

Table 3. 28-day Mortality and Survival Rates Between Plasma and Control Groups with Statistical Significance[10]

Control Group Mortality	Control Group Survival	Plasma Group Mortality	Plasma Group Survival	RR (95% CI)	P-value
10%	90%	15%	85%	1.54 (0.60-3.98)	0.37

Table 4. Calculations for Treatment from Moore et al.[10]

RBI	ABI	NNT
-0.056	-0.050	-20

Shlaifer et al. performed a retrospective cohort study comparing trauma patients treated with freeze-dried plasma (FDP) in the prehospital setting between January 2013-December 2016 to those not treated with freeze-dried plasma between January 2006-December 2015.[11] Using the IDF Trauma Registry and National Israel Trauma Registry, patients treated with FDP were

selected and matched with a control based on age, sex, injury severity, and mechanism of injury.[11] After matching, identification details were removed for analysis. In-hospital mortality rate was measured. There were 96 patients total, 48 of those received FDP and 48 did not.[11] Patients were characteristically similar and almost all were male sex.

Table 5 outlines the in-hospital mortality rates. In the control group, those who did not receive FDP, 93.8% had survived.[11] Of those who did receive FDP, 91.5% survived.[11] Results were not statistically significant (p=0.17).[11] Table 6 depicts calculated treatment effects including RBI, ABI, and NNT. The NNT was -44, indicating low clinical significance. There was no mentioning of adverse effects or tolerability within this study.

Table 5. In-hospital Mortality and Survival Rates Between FDP and Control Groups with Statistical Significance[11]

Control Group Mortality	Control Group Survival	FDP Group Mortality	FDP Group Survival	P-value
6.2%	93.8%	8.5%	91.5%	0.17

Table 6. Calculations for Treatment from Shlaifer et al.[11]

RBI	ABI	NNT
-0.025	-0.023	-44

DISCUSSION

The goal of this EBM review was to determine if early administration of plasma can improve survival rates in injured patients at risk for hemorrhagic shock. Varying results were found across all 3 studies.

Sperry et al. showed that those given thawed plasma in the prehospital setting via air medical transport were more likely to survive compared to those who received standard care (75.9% versus 65.9% seen in those given standard care).[9] The results were statistically

significant (p=0.03) with a protective odds ratio (0.61) and narrow confidence interval (0.42-0.92) as shown in Table 2.[9] The study was portrayed across the United States and included a large sample size making it highly generalizable.

Moore et al. and Shlaifer et al. both demonstrated that giving plasma in the prehospital setting did not improve survival rates. Moore et al., looking at fresh-frozen plasma given, found that 85% of those who received it survived versus 90% of those who received standard care.[10] The RR for 28-day mortality was 1.54, indicating those who received plasma had 1.54 times the chance of dying versus those who received standard care.[10] The 95% CI was wide and the p-value was not statistically significant (p=0.37) implying that the results could be due to chance.[10] Based on an NNT of -20, for every 20 people treated with prehospital plasma, one less person is going to survive compared to being treated with standard care. Shlaifer et al., looking at freeze-dried plasma, also showed a higher survival rate of 93.8% in the control group versus 91.5% in the plasma group.[11] The data, however, were not statistically significant (p=0.17).[11] The data is supported with NNT -44 which says that for every 44 people treated with prehospital plasma, one less person is going to survive compared to those not treated with it.

It is important to address the limitations that exist within these studies. Moore et al. attribute the lack of treatment effect possibly due to inclusion criteria of one episode of hypotension and tachycardia which may or may not be due to hemorrhage.[10] The study was also conducted in Denver, an urbanized area, so is less generalizable to rural populations. Similarly, Shlaifer et al. was conducted in Israel so is less generalizable to larger countries with differences in population health and medical standards. Those in the plasma group were treated in a later timeframe (2013-2016) than the control period (2006-2015) allowing for some bias due to

possible modernized changes in medicine.[11] Further, Sperry et al. did not blind emergency workers or receiving hospital providers also possibly contributing to bias.

CONCLUSION

The evidence analyzed from all 3 studies is conflicting when trying to answer if giving plasma in the prehospital setting will improve survival rates in injured adults at risk for hemorrhagic shock. Sperry et al. found that it did with statistically significant data, however, Moore et al. and Shlaifer et al. found the opposite although the data was not statistically significant. Future studies are warranted to evaluate the benefit of prehospital plasma on trauma patients at risk for hemorrhagic shock and if it ultimately outweighs the strain of costs and resources. It would be valuable to further investigate thawed plasma given the logistical success as seen in Sperry et al. Additionally, it may be useful to further investigate the advantages of incorporating plasma within air medical services given higher patient acuity and being well-equipped to handle the needs of carrying plasma.

REFERENCES

1. Gasper WJ, Iannuzzi JC, Johnson MD. Chapter 12-9: Shock. In: Papadakis MA, McPhee SJ, Rabow MW, McQuaid KR, eds. *Current Medical Diagnosis & Treatment 2022.* New York, NY; McGraw-Hill Education; 2022.

2. Centers for Disease Control and Prevention. Injury Prevention & Control. https://www.cdc.gov/injury/wisqars/animated-leading-causes.html#print. Updated 2022. Accessed October 4, 2022

3. Kauvar D, Lefering R, Wade C. Impact of hemorrhage on trauma outcome: An overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma.* 2006;60(6 Suppl):S3-S11. doi:10.1097/01.ta.0000199961.02677.19

4. Corso P, Finkelstein E, Miller T, Fiebelkorn I, Zaloshnja E. Incidence and lifetime costs of injuries in the United States. *Injury Prevention.* 2006;12(4):212-218. doi:10.1136/ip.2005.010983

5. Peterson C, Miller GF, Barnett SBL, Florence C. Economic Cost of Injury - United States, 2019. *Morbidity and Mortality Weekly Report.* 2021;70(48):1655-1659. doi:10.15585/mmwr.mm7048a1

6. Centers for Disease Control and Prevention. Fatal injury reports, regional and state, 1981-2020. https://wisqars.cdc.gov/fatal-reports. Updated 2020.

7. Kreimeier U. Pathophysiology of fluid imbalance. *Critical Care.* 2000;4 Suppl 2(Suppl 2):S3-S7. doi:10.1186/cc968

8. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database of Systematic Reviews.* 2018;2018(8):CD000567. doi:10.1002/14651858.CD000567.pub7

9. Sperry JL, Guyette FX, Brown JB, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. *N Engl J Med.* 2018;379(4):315-326. doi:10.1056/NEJMoa1802345.

10. 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;392(10144):283-291. doi:10.1016/S0140-6736(18)31553-8

11. Shlaifer A, Siman-Tov M, Radomislensky I, et al. shlai *J Trauma Acute Care Surg.* 2019;86(1):108-115. doi:10.1097/TA.0000000000002094

12. Jost D, Lemoine S, Lemoine F, et al. Prehospital lyophilized plasma transfusion for trauma-induced coagulopathy in patients at risk for hemorrhagic shock: A randomized clinical trial. *JAMA Netw Open.* 2022;5(7):e2223619. doi:10.1001/jamanetworkopen.2022.2361