COMMENTARY

Prehospital fresh frozen plasma: Universal life saver or treatment in search of a target population?

Michael Makris MD[1] | Alfonso Iorio MD, PhD[2]

[1]Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK

[2]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

Correspondence
Michael Makris, Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK.
Email: m.makris@sheffield.ac.uk

Recently within 2 days of each other, two of the leading medical journals published trials on the use of prehospital fresh frozen plasma (FFP) for trauma patients, reaching apparently different conclusions. In the *New England Journal of Medicine* article reporting on the Prehospital Air Medical Plasma (PAMPer) trial, Sperry et al[1] found that two units of prehospital FFP was associated with an almost 10% survival advantage. In the Control of Major Bleeding After Trauma Trial (COMBAT) reported in the Lancet, Moore et al[2] found that the same volume of plasma had no survival advantage.

The concept of prehospital plasma is in theory attractive. You have an injured individual who is likely to need plasma in the next few hours, so why not preemptively reduce the bleeding by administering plasma first? An important issue to consider, however, is that at the injury scene the patient is not likely to be deficient in clotting factors yet. The prehospital transfusion of blood products has been shown to improve survival in US military combat casualties injured in Afghanistan.[3]

The normal range for clotting factors measured as percent of normal is approximately 50-150 with a mean of 100. It follows, that the average individual can lose half their plasma volume and still have clotting factor levels in the normal range even after reconstitution of blood volume. A major reduction in clotting factors can occur in two relevant settings, firstly when there is marked hemodilution such as that following major fluid resuscitation and secondly due to consumption in the presence of disseminated intravascular coagulation (DIC). With the exception of obstetric DIC at the time of delivery, this consumption is not usually so rapid to become a major issue in the prehospital management of trauma.

Fresh frozen plasma is obtained from whole blood donation or plasmapheresis. While in the COMBAT trial they specify that they gave two units of approximately 250 mL each of FFP, the PAMPer investigators do not specify the volume of the two units they administered. The PAMPer FFP was prethawed and could be up to 5 days since thawing, while the COMBAT product was collected by plasmapheresis, frozen within 24 hours and thawed rapidly in special equipment before administration. In a study one of us was involved in, measuring clotting factor levels before and after administration of four units of optimally thawed FFP just before infusion, the increase in clotting factor levels was 9%-14%.[4] Based on the volume of FFP infused in the PAMPer and COMBAT studies, the increase in factor levels would be 7% at best. This suggests that if prehospital FFP provides benefit, it is unlikely that this is through the substitution of coagulation factors. Other modes of FFP benefit include protecting the endothelial glycocalyx and reducing vascular permeability and inflammation.[5,6]

We compared the PAMPer and COMBAT trials looking for differences in their design and conduct to shed light on the true effect of FFP, if any (Table 1). Of course, the simplest explanation for the difference in results could well be a combination of chance and low power for the COMBAT study, due to low event rate and small sample size. The contribution of the COMBAT trial under a fixed effect meta-analysis approach would have been <10%, and the pooled estimates, driven by the larger PAMPer study, would have shown a significant benefit for plasma administration at both 24 hours (OR = 0.64, 95% CI 0.42-0.98) and 1 month (OR = 0.67, 95% CI 0.46-0.98). Even under the more conservative random-effect approach, the visual inspection of the forest plot (Figure 1) would support both the hypothesis the two trials observing a different effect (as their effect sizes lie on opposite sides of the identity line) and instead representing random variation of the same effect (as the confidence intervals do overlap). However, there are clear differences between the trials, starting from the choice of results to report and the modality used to report them. The entry criteria for the two trials were the same in terms of blood pressure and heart rate measurements, but

TABLE 1 Comparison of the PAMPer and COMBAT trials

	PAMPer trial		COMBAT trial	
	FFP	Standard care	FFP	Saline
Patient characteristics				
Number	230	271	65	60
Age median (y)	44	46	33	32.5
Male (%)	71.3	73.8	80	85
Blunt injury	81.3	83.4	46	53
Prothrombin time ratio or INR on arrival at hospital	1.2	1.3	1.27	1.15
Injury severity				
Prehospital intubation (%)	50	52	Not given	
Prehospital red cells (%)	26.1	42.1	Not given	
Transfused red cells in first 24 h (%)	Not given		55	58
Injury severity score (median)	22	21	27	
Operations in first 24 h (%)	71.7	80.1	Not given	
Setting	US air medical transport		Denver, US ground transport	
Median prehospital transfer time (min)	42	40	19	16
Entry qualification	BP <90 mm Hg plus pulse >108 or BP <70		BP <90 mm Hg plus pulse >108 or BP <70	
Randomization	Cluster randomization to plasma or standard care at monthly intervals. Treating staff not blinded.		Individual randomization by the content of coolers. Treating staff not blinded	
Intervention	2 units pre-thawed up to 5-day-old plasma	Standard care no fluid volume stipulated	2 units apheresis FFP approx 500 mL	Normal saline as per standard care (volume not same)
Prehospital crystalloid (mL)	500	900	150	250
Outcome				
24-h mortality (%)	13.9	22.1	12	10
28- or 30-day mortality (%)	23.2	33	15	10

COMBAT, Control of Major Bleeding After Trauma Trial; FFP, fresh frozen plasma; PAMPer, Prehospital Air Medical Plasma.
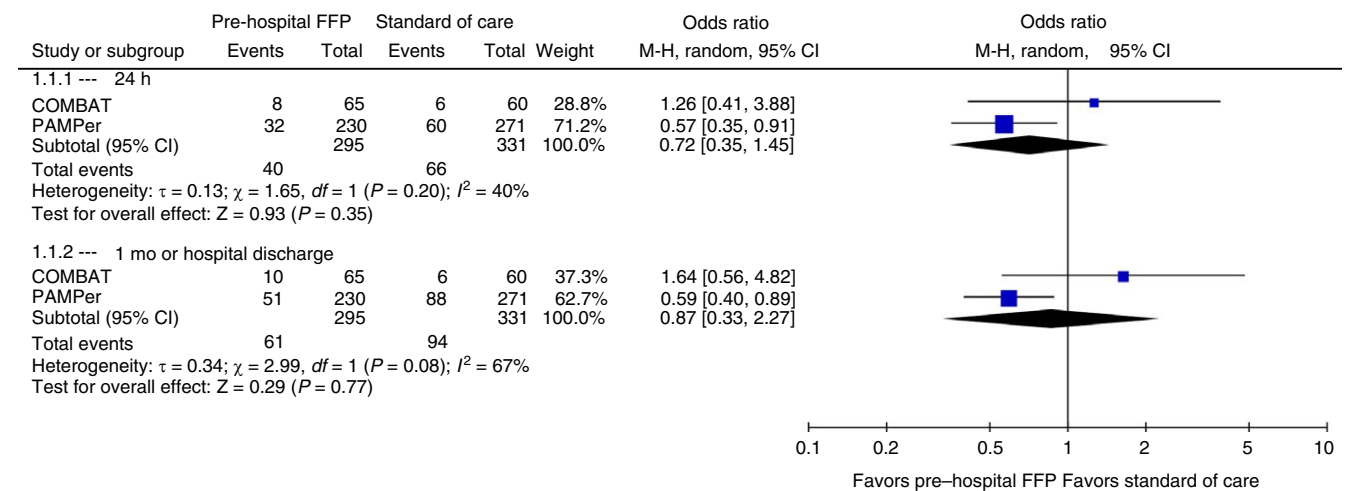

FIGURE 1 Random effect meta-analysis of mortality data from the PAMPer and COMBAT trials. CI, confidence interval; COMBAT, Control of Major Bleeding After Trauma Trial; PAMPer, Prehospital Air Medical Plasma trial

the PAMPer trial patients were older, more likely female and much more likely to have sustained a blunt injury. In terms of severity of the injury, as defined by the injury severity score, the COMBAT trial patients were more severely affected—unfortunately, we do not have the data on prehospital intubation and interventions in the first 24 hours for the COMBAT trial.

An important difference between the trials emerges on looking at the control arms, both receiving standard care. These individuals had identical entry criteria and in theory similar management plans after reaching the hospital facility. However, the 24-hour mortality was 10% in the COMBAT trial and 22% in PAMPer, while the respective 28- to 30-day mortality was 10% and 33%. Such large differences must relate to differences in severity of the injury in the two groups, which unfortunately is not reported with sufficient details to allow a direct comparison. As these data must have been collected, the authors should be encouraged to publish data allowing direct comparison between the two trials, especially detailing the injury severity. It would also be good to see retrospective data from both research networks showing whether the mortality figures observed in the two trials are representative of their previous experience or they happened to select a more (PAMPer) or less (COMBAT) severe population.

Since both trials were randomized, one would expect the two arms to be comparable in every aspect except for the intervention. In the PAMPer trial, however, 42.6% of the standard care patients received prehospital red cells (vs 26.1% in the FFP arm) and an average 400 mL more crystalloid before reaching hospital. Both of these features could contribute to the higher mortality in the standard care group of the PAMPer study.

The transfer times from the scene of injury to hospital were longer at 40-42 minutes when performed by helicopter (PAMPer) while only 16-19 minutes by road ambulance (COMBAT). It can be argued that for road transfers, the interval is so short that it is unlikely that any prehospital intervention will make much difference, and intervention driven differences would be more likely seen as the transfer time increases.

Irrespective of all the above issues, we believe the two studies show that if there is a benefit for prehospital FFP, this is not due to the clotting factors in the product. The coagulopathy of the patients in both trials on arrival to hospital was very mild, with a median prothrombin time ratio or INR of 1.3 or less. Furthermore the COMBAT trial investigators report that the median levels for fibrinogen and factors II, V, VII, IX, XI, and XIII on arrival to hospital were normal in both groups and indeed were higher in the non-FFP group.

No adverse events in relation to the administration of the FFP were observed but three important issues need to be considered before implementing prehospital FFP as a policy:

(A) The FFP used was a not virally inactivated blood product and can in theory transmit infections. This can be due to the donors being viremic shortly after infection (before the development of antibodies), due to currently unknown infections, or due to prions.

(B) The delay in getting the injured individual to hospital whist trying to thaw and administer the FFP outside a clinical trial setting.

(C) The fact that if all emergency ambulances and helicopters carry thawed universal donor blood group AB plasma, the already known frequent shortages of this product will be exacerbated. Lyophilized FFP may overcome this limitation in the future but it is not currently routinely available.[7]

Our conclusion reflecting on these two randomized clinical trials is that the case for universal use of prehospital FFP is not yet made. Until further results from these trials are published to guide interpretation of current evidence and planning of future large pragmatic trials, it would be better for first response teams to concentrate on getting the injured individual to the controlled hospital environment as soon as possible, rather than investing precious time in administering FFP before transfer. Indeed, even assuming plasma can benefit a subgroup of more severely injured patients, it might be difficult to stratify them with the little time and few tools available at the injury site.

RELATIONSHIP DISCLOSURE

The authors declare that they have nothing to disclose in relation to this manuscript.

AUTHOR CONTRIBUTIONS

Both authors contributed to the preparation of the manuscript and met all the required conditions for authorship.

ORCID

Michael Makris https://orcid.org/0000-0001-7622-7939
Alfonso Iorio https://orcid.org/0000-0002-3331-8766

REFERENCES

1. Sperry JL, Guyette FX, Brown JB, et al. Prehospital plasma during air medical transport in trauma patients at risk of hemorrhagic shock. N Engl J Med. 2018;379:315–26.
2. 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;392:283–91.
3. Shackelford SA, del Junco DJ, Powell-Dunford N, et al. Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. JAMA. 2017;318:1581–91.
4. Makris M, Greaves M, Phillips WS, Kitchen S, Rosendaal FR, Preston FE. Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. Thromb Haemost. 1997;77:477–80.
5. Barelli S, Alberio L. The role of plasma transfusion in massive bleeding: protecting the endothelial glycocalyx? Front Med. 2018;5:91.
6. Pati S, Peng Z, Wataha K, Miyazawa B, Potter DR, Kozar RA. Lyophilized plasma attenuates vascular permeability, inflammation and lung injury in hemorrhagic shock. PLoS ONE. 2018;13(2): e0192363.
7. Carrigue D, Godier A, Glacet A, et al. French lyophilized plasma versus fresh frozen plasma for the initial management of trauma induced coagulopathy: a randomized open label-trial. J Thromb Haemost. 2018;16:481–9.