Prehospital Plasma Transfusion: What Does the Literature Show?

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Keywords

Prehospital · Plasma · Transfusion

Abstract

Background: Early initiation of blood products transfusion after injury has been associated with improved patient outcomes following traumatic injury. The ability to transfuse patients' plasma in the prehospital setting provides a prime opportunity to begin resuscitation with blood products earlier and with a more balanced plasma:RBC ratio than what has traditionally been done. Published studies on the use of prehospital plasma show a complex relationship between its use and improved survival. **Summary:** Examination of the literature shows that there may be a mortality benefit from the use of prehospital plasma, but that it may be limited to certain subgroups of trauma patients. The likelihood of realizing these survival benefits appears to be predicted by several factors including the type of injury, length of transport time, presence of traumatic brain injury, and total number of blood products transfused, whether the patient required only a few products or a massive transfusion. When taken as a whole the evidence appears to show that prehospital plasma may have a mortality benefit that is most clearly demonstrated in patients with blunt injuries, moderate transfusion requirements, traumatic brain injury, and/or transport time greater than 20 min, as well as those who demonstrate a certain cytokine expression profile. **Key Messages:** The evidence suggests that a targeted use of prehospital plasma will most likely maximize the benefits from the use of this limited resource. It is also possible that prehospital plasma

may best be provided through whole blood as survival benefits were greatest in patients who received both prehospital plasma and RBCs.

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Introduction

Death due to hemorrhage is a leading cause of mortality worldwide and results in a significant loss of life years [1]. Over the course of time, various resuscitation strategies have been used to address this clinical problem. In the recent past, a resuscitation model based on crystalloid as the main fluid dominated clinical practice. Improved understanding of the risk of crystalloid and the need for early inclusion of blood products has resulted in newer resuscitation practices [2], specifically, Damage Control Resuscitation (DCR), which emphasizes the early inclusion of blood products and focuses on providing the patient with balanced resuscitation in ratios that approximate 1:1 [3].

In addition to the early inclusion of blood products in the resuscitation of injured patients, the overall time to initiation of transfusion has been shown as a critical factor in reducing mortality [4, 5]. The ability to transfuse patients in the prehospital setting provides a prime opportunity to begin resuscitation with blood products earlier and with a more balanced plasma:RBC ratio than what has traditionally been done. It would seem logical that the initiation of blood product transfusion in the prehospital setting would improve patient outcomes. How-

Fig. 1. Identification, review, and selection of included studies.

ever, research on the outcomes and benefits of prehospital plasma transfusion (PHP) in particular has shown that the answer may be much more complex. Studies to date have shown that there are numerous factors that can impact the likelihood that PHP will improve the patient's outcome. In fact, the two largest randomized trials conducted on this topic showed conflicting results [6, 7].

If PHP is to be widely adopted, it is critical to understand and identify the factors that affect its effectiveness in order to target the patients and clinical situations where the benefits of PHP will likely be maximized. Additionally, it is important to understand the outcomes and metrics that should be used to classify the benefits of PHP. As the effects of prehospital plasma are likely multifactorial, understanding its impact will require examination of more nuanced outcomes beyond simple measurements of mortality. To that end, this review aims to analyze the

current evidence for the use of PHP and identify further opportunities for research to provide a level of clarity that can improve clinical decision-making. This review will not address the use of freeze-dried plasma, plasma used in military settings, and papers that examined prehospital transfusion of other blood products without an adjusted analysis for plasma transfusion.

Methods

Articles included in this analysis were identified through a PubMed search using medial subject headings: prehospital, plasma, and transfusion. Studies were included if they reported on transfusion of plasma used in a prehospital civilian setting with the use of plasma as the primary variable and measured safety, feasibility, or a direct clinical outcome. Non-comparative studies, review articles, or articles not available in English were excluded from analysis. Adherence to the inclusion criteria was determined by review of abstracts and/or full text of the articles identified. Additional articles were identified and included through review of the references of previously included articles if they met all inclusion criteria (Fig. 1).

Results

The initial search yielded 158 results. One hundred twenty-nine articles were excluded based on review of the abstract. These studies were excluded because the plasma transfusions were not administered in the prehospital setting, were focused on prehospital transfusion of non-plasma products, used freeze-dried plasma, were performed in a military setting, were animal studies, were limited to description of study design, contained only in vitro studies, or presented methods to implement a prehospital transfusion program without actual transfused patient data. Twenty-nine articles underwent full text review. Sixteen articles were excluded based on full text review for presenting studies of prehospital transfusion of plasma and RBCs without an adjusted analysis for the transfused plasma. The remaining 13 articles were included in the review. Review of the references list of the included articles yielded one additional article that met the inclusion criteria and was therefore included in this analysis for a total of 14 articles [6–19].

Among the included studies were two randomized controlled trials [6, 7], a single-center prospective observational study [18], and one single-center retrospective observational study [19] (Table 1). The remaining studies were secondary analyses of data from either the Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock (PAMPer) trial [8–12, 14, 17] or a combined data set from COMBAT and PAMPer [13, 15, 16]. All studies included analysis of a cohort of adult trauma patients who were transfused with

Table 1. Study design

	Study type/data source	Intervention	Primary outcome
<i>Primary study</i>			
Kim 2012	Retrospective observational	Two units of thawed plasma	Hemostatic function measured by INR
Henriksen 2016	Prospective observational	Two units of thawed plasma	Hemostatic function measured by rTEG
Moore 2018	Randomized controlled trial	500 mL of plasma thawed immediately prior to use	24-h and 28-day mortality
Sperry 2018	Randomized controlled trial	Two units of thawed plasma	24-h and 30-day mortality
<i>Secondary analysis</i>			
Anto 2020	PAMPer		Mortality in patient requiring an MT vs. no MT
Gruen JAMA 2020	PAMPer		Mortality with TBI vs. no TBI
Gruen JTACS 2020	PAMPer		Unexpected survival
Gruen JCI 2020	PAMPer		Expression of biomarkers
Guyette 2021	PAMPer		Mortality based on products transfused (RBCs + plasma, plasma, RBCs, or crystalloid)
Moore 2020	PAMPer plus COMBAT		Risk of hypocalcemia
Pusateri 2020	PAMPer plus COMBAT		Mortality based on transport time greater or less than 20 min
Reitz 2020	PAMPer plus COMBAT		Mortality: blunt vs. penetrating injury
Reitz 2021	PAMPer		Mortality based on age of plasma
Sim 2020	PAMPer		Mortality based on achievement if various CAT

MT, massive transfusion; CAT, critical administration threshold.

either prehospital plasma or the center's standard of care treatment as the control group. Adult was defined as 18 and older in all studies except in Henriksen et al. [18], where it was defined as greater than 16 years of age. Henriksen et al. [18] included all trauma patients that were transfused either in the prehospital setting or within 6 h of admission. Kim et al. [19] included all patients that met institutional guidelines for activation of a massive transfusion event. PAMPer and COMBAT included trauma patients with systolic blood pressure (SBP) <70 mm Hg or SBP between 70 and 90 mm Hg and heart rate greater than 108 [6, 7].

The PAMPer study (and all secondary analyses) and Kim et al. [19] both used plasma that had been thawed in the blood bank, while COMBAT provided plasma that was thawed immediately prior to transfusion while the patient was in the ambulance [6–12, 14, 19]. Henriksen et al. [18] did not specify when the plasma was thawed. All studies used group AB or A plasma with PAMPer indicating that the group A plasma featured a low titer of anti-B. Across all studies, patients could receive a maximum of two units or 500 mL of plasma in the prehospital setting. In addition to plasma, prehospital RBCs and crystalloid could also have been transfused if they were part of the center's standard of care to the patients who were in the standard of care arm in all studies except for the COMBAT trial where the control arm received only crystalloid. COMBAT specified the use of normal saline, while the other studies did not specify the type of crystalloid used

[6, 7, 18, 19]. Tranexamic acid was used in the COMBAT study, but the frequency of its use was not significantly different between the two groups, and no specific analysis was performed regarding its use. The other primary studies did not provide information on the use of TXA [6, 7, 18, 19].

The total number of subjects included in the primary studies ranged from 59 to 501. The number of subjects in the combined PAMPer and COMBAT analyses ranged from 160 to 626 and ranged from 166 to 501 in the secondary analyses of the PAMPer study. Patients were transported by air medical transport in two of the primary analyses [7, 19] and in all of the secondary analyses of the PAMPer study [8–12, 14, 17]. In the COMBAT trial patients were transported via ground medical transport. Patients in Henriksen et al. [18] and the combined PAMPer/COMBAT analyses [13, 15, 16] were transported via either ground or air medical transport as specified by the trial in which they were enrolled. Median transport times from the scene of the accident to the hospital were reported in all primary analyses with the exception of Henriksen et al. [18]. The median transport time was not significantly different between the prehospital plasma group and control in those studies where these data were reported; however, there was a major difference between patients in the COMBAT and PAMPer trials (Table 2). The proportion of patients with blunt injuries was higher in the PAMPer study. Patients in the PAMPer trial also tended to be older and have lower injury severity scores

Table 2. Primary analysis studies

	PAMPer		COMBAT		Henriksen		Kim	
	FFP	Standard care	FFP	Standard care	FFP	Standard care	FFP	Standard care
<i>Patient characteristics</i>								
Number	230	271	65	60	75	182	9	50
Age (median)	44	46	33	32.5	34	39	54	41
Injury severity score	22	21	27	NR	29	26	27	23
Blunt injury, %	81.3	83.4	46	53	54.7	74.7	67	82
Transport type	Air	Air	Ground	Ground	Air	Air	Air	Air
Transport time	42	40	19	16	NR	NR	40	39
<i>Primary outcomes</i>								
Mortality, %								
24-hour	13.9	22.1	12	10	16	10.4	44	10
28/20-day	23.2	33	15	10				
rTEG MA, mm					62.55 (2 units)	58.73		
Change in INR							0.9	0.2

as well as more frequently required massive transfusion than those in COMBAT [6, 7].

Mortality (30- or 28-day, respectively) was the primary outcome for the PAMPer and COMBAT studies [6, 7]. The primary outcome in Henriksen et al. [18] and Kim et al. [19] was hemostatic function assessed by thromboelastography (TEG) and INR, respectively. Other non-mortality outcomes were measured as the primary outcome in Moore et al. [15] (risk of hypocalcemia) and Gruen et al. [11] (expression of biomarkers for inflammation and endothelial function/damage) and are shown in Table 1.

Among studies with mortality as the primary outcome, PAMPer demonstrated lower 30-day mortality in the group of patients who received PHP compared to those in the standard of care arm (23.2% vs. 33.0%, respectively, $p = 0.02$) [7], while the COMBAT trial showed no significant difference in mortality between the plasma versus standard of care recipients (15% vs. 10%, respectively, $p = 0.37$) [6] (Table 2). In a combined analysis of PAMPer and COMBAT, Reitz et al. [13] showed a mortality benefit in patients with blunt injury (32% lower independent hazard for 28-day mortality, HR 0.68, 95% CI 0.47–0.96, $p = 0.03$), but not in those with penetrating injuries (HR 1.16, 95% CI 0.4–3.1, $p = 0.78$). In a separate combined analysis, Pusateri et al. [16] showed a mortality benefit in prehospital patients who received plasma and who had a transport time greater than 20 min compared to those with a similar transport time but without PHP (HR 0.78, 95% CI 0.40–1.51, $p = 0.46$) where prehospital time is defined as arrival on scene to arrival in ED.

In secondary analysis of PAMPer data, Gruen et al. [9] showed PHP was associated with improved survival in patients with traumatic brain injury (TBI) (HR 0.56, 95% CI 0.35–0.91) and polytrauma (HR 0.50, 95% CI 0.28–0.89)

compared to those without those conditions. In another secondary analysis of the PAMPer study, Sim et al. [17] showed that mortality varied based on the definition of massive transfusion applied to the study cohort with overall study mortality rates of 13.1%, 17.4%, and 10.0% based on CAT1hr (≥ 3 units per hour in the first hour), CAT4hr (≥ 3 units per hour in any of the first 4 h), and historic massive transfusion definitions (≥ 10 units of RBCs in 24 h), respectively. Anto et al. [8] showed lower mortality in patients who required a massive transfusion, defined as receipt of more than 10 RBC units in 24 h, compared to those who did not require a massive transfusion (42% vs. 26%, respectively, $p = 0.001$). Reitz et al. [12] demonstrated that the age of the thawed plasma, i.e., the number of days post-thaw before it was transfused, did not impact mortality or biomarker expression in a secondary analysis of PAMPer data. Guyette et al. [14] demonstrated that the greatest mortality reduction was seen in patients who received both plasma and RBCs in the prehospital setting (HR 0.38, 95% CI 0.26–0.55, $p < 0.001$). This analysis also showed that PHP alone (HR 0.57, 95% CI 0.36–0.91, $p < 0.001$) produced the second lowest mortality rate followed by the prehospital transfusion of RBCs alone (HR 0.68, 95% CI 0.49–0.95, $p < 0.001$). In this analysis, the patients who received only saline had the highest 30-day mortality (HR 1.65, 95% CI 1.17–2.32, $p < 0.001$) [14].

Henriksen et al. [18] did not show a difference in in-hospital mortality between patients who received PHP and those treated with standard of care (26.7% vs. 20.9%, $p = 0.313$). The study did show that when adjusted for prehospital RBC transfusions, the administration of prehospital plasma was associated with a significantly higher rTEG MA (58.73 vs. 62.55 mm, $p = 0.012$) at the time of admission compared to those treated with standard care.

Kim et al. [19] demonstrated a greater correction of coagulopathy as measured by the INR in the patients who received PHP at the initiation of transport versus arrival at trauma center, which was not statistically significant (0.9 vs. 0.2, $p = 0.078$). This analysis also showed that the transfusion of prehospital plasma was associated with a plasma:RBC ratio that more closely approximated 1:1 at 30 min and at 24 h after admission compared to those treated with standard of care [18].

In a combined analysis of PAMPer and COMBAT data, Moore et al. [15] showed an increased risk of hypocalcemia in patients who received prehospital plasma compared to those who did not (53% vs. 36%, adjusted relative risk 1.48, 95% CI 1.03–2.12, $p = 0.03$). This study also showed that after adjusting for confounders, severe hypocalcemia was associated with decreased survival and the need for massive transfusion [15]. In an analysis of the most severely injured patients, Gruen et al. [11] showed that prehospital plasma was associated with an increase in adiponectin, IL-1 β , IL-17A, IL-23, and IL-17E upon admission, and a reduction in syndecan-1, TM, VEGF, IL-6, IP-10, MCP-1, and TNF- α , and an increase in IL-33, IL-21, IL-23, and IL-17E 24 h later.

Discussion

On the surface, it would appear that the ability to transfuse blood products, specifically plasma, in the prehospital setting would have obvious clinical benefits in the treatment of trauma patients. However, examination of the published studies on the use of prehospital plasma show a more complex relationship between its use and improved survival. Examination of the literature shows that there may be a mortality benefit, but that it may be limited to certain subgroups of trauma patients. The likelihood of realizing these survival benefits appears to be predicted by several factors including the type of injury, length of transport time, presence of TBI, and total number of blood products transfused, whether the patient required only a few products or a massive transfusion. The practical application of the existing data must be evaluated in the context of study size and design and the subsection of trauma patients included in the respective studies.

To understand the circumstances where PHP is most likely to have an impact it is important to understand the mechanisms by which it is expected to impact mortality. Among the theorized mechanisms of action for PHP are treatment of coagulopathy [20], changes in the inflammatory response to injury [21], and repair of the endothelial lining [22].

It is important to keep in mind that of the 14 studies analyzed herein, only 4 presented primary data and the remainder performed secondary analyses of the primary data and must be viewed with the understanding that the

original study was not always designed to facilitate the detection of a difference in these secondary analyses. This is the nature of performing a secondary analysis. The overwhelming number of subjects and the only randomized controlled trial data come from the COMBAT and PAMPer trials. These two studies present conflicting conclusions with PAMPer showing a mortality benefit from PHP while no difference was seen in COMBAT. There are several factors that may explain why these two trials with similar inclusion criteria and treatment protocols reached different conclusions. One possible explanation for the difference is chance and the lower power of the COMBAT study due to its smaller sample size (125 patients in COMBAT vs. 501 in PAMPer). There were also differences in patients' demographics with PAMPer patients tending to be older, more likely to be female, more likely to have a blunt injury, have a lower injury severity score and longer median transport times compared to the patients in COMBAT. Given the shorter median transport time in COMBAT (19 min vs. 41 min in PAMPer), it is possible that the difference in time to initial transfusion between the PHP and control groups was not sufficient to show a mortality benefit in COMBAT as the control patients did not have to wait for long to receive their plasma when they arrived at the hospital. It should also be noted that there was a difference in the relative amount of crystalloid administered in the standard of care and PHP groups between the studies with the standard care group in PAMPer receiving an average of 400 mL more crystalloid compared to the standard of care group in COMBAT who received only 100 mL more when compared to their respective PHP groups. Given the known association of higher volumes of crystalloid with worse outcomes this could also have contributed to the difference in observed results [2].

Taken as a whole these data support a mortality benefit of PHP that is most clearly seen in trauma patients with certain characteristics. When the COMBAT and PAMPer data sets were combined, the analysis showed the mortality benefit associated with PHP was seen primarily in patients with blunt injuries and not those with penetrating injuries [13]. The difference in outcomes observed between these two groups may have resulted from the sample size of patients with penetrating injuries being too small to show a potential mortality difference. It is also possible that if the benefit of PHP is related more to the proposed inflammatory benefits, particularly endothelial lining protection, it would likely provide greater benefit in a patient with a multisystem blunt injury pattern [23–25]. Alternatively, the use of PHP may have counteracted the benefits of permissive hypotension that have been shown in patients with penetrating injuries [2, 26]. There is also the potential of survivor bias resulting from patients with the earliest deaths more likely to have penetrating injuries and therefore unable to be enrolled before death.

The literature demonstrates that transport time appears to be an important factor in identifying which patients will benefit from PHP. The combined analysis of PAMPer and COMBAT showed that transport times longer than 20 min were associated with a mortality benefit from receipt of PHP [16]. The selection of the 20-min time point was supported by a sensitivity analysis that showed a change in response to PHP was evident for prehospital times longer than 20 min ($p = 0.003$ vs. $p = 0.007$ for 17 min, $p = 0.006$ for 22 min, $p = 0.01$ for 25 min, and $p = 0.02$ for 30 min) [16]. This distinction could potentially explain the results of the initial analyses whereby COMBAT patients had shorter median transport times and no mortality benefit was observed. With shorter transport times it is possible that in-hospital transfusion was not delayed to a degree that would allow for observation of the negative effect resulting from delayed time to transfusion as was apparent in the control arm patients in the PAMPer study [27]. This difference also persisted when adjusted for injury severity which was higher in the PAMPer cohort.

The presence or absence of TBI was associated with a difference in the observed benefit of PHP. In patients with TBI, early interventions that reduce hypoxia, hypotension, and hypocarbia have been shown to improve outcomes [28–31]. There was also a pair of observational studies that suggested a benefit of early in-hospital plasma transfusion in patients with TBI [32, 33]. It would seem logical that this benefit from early in-hospital transfusion could be extrapolatable to the benefit observed from PHP transfusion in injured patients with TBI. In line with this expectation, a secondary analysis of the PAMPer data demonstrated improved survival among patients with TBI (GCS less than 8) and those with polytrauma [9]. The association of benefit in TBI with polytrauma may also suggest that other systemic benefits may contribute to the observed difference in mortality.

When considering the effect that receipt of a massive transfusion might have on the benefit of PHP receipt, the definition of massive transfusion used may be an important factor to consider. This definition was not the same for all studies and depended on the respective inclusion criteria for each study. The results suggest that the benefit of PHP is associated with the overall volume of transfusion. Separate analyses demonstrated that the mortality benefit of PHP was strongest in patients with moderate transfusion needs defined by sub-MT red cell requirements (4–7 units in 24 h) [8] and adjustment of the critical administration threshold (CAT) (≥ 3 units of RBCs transfused in any of the first 4 h) [17]. The idea that patients with moderate transfusion requirements would benefit most from PHP is both logical and in line with existing data. It may be the case that patients with small transfusion requirements either died soon after admission without time to reach the CAT or were not severely injured enough to require enough blood prod-

ucts to meet CAT at any time. Alternatively, patients who reached the CAT at 1 h would likely be more severely injured and have a higher risk of death. This logic is supported by the finding in Anto et al. [8] where a survival benefit in massively transfused patients (greater than 10 RBCs in 24 h) or patients who received fewer than 4 units of RBCs in 24 h was not found. This suggests there may be an optimal patient population with injuries that meet a CAT while not requiring a massive transfusion that would benefit from PHP. PHP may not be optimal for patients with a low chance of survival based on high early transfusion requirements. There is also the question of what impact the PHP had on transfusion requirements. It is unclear if the PHP prevented patients from requiring a massive transfusion who would have if not for the prehospital intervention. Predicting the risk of massive transfusion may be a better assessment tool than who actually received a massive transfusion. It is also worth considering more broadly if the historic definitions of massive transfusion are best suited for this type of analysis or if there should be a focus on smaller transfusion volumes over shorter periods of time [34]. In either case, the challenge will still be predicting which patients are likely to fall into the moderate transfusion group particularly in the prehospital environment when decisions about administering PHP are being made.

Another important consideration is the inclusion of RBCs and crystalloid in the prehospital regimen. The evidence against copious crystalloid resuscitation has been well established [3, 35], but it is less clear if RBCs or plasma alone would be superior to the other if only one product could be made available. The inclusion of RBCs as part of the standard of care at some of the PAMPer sites permitted a stratification and comparison of groups that received plasma + RBCs, plasma, RBCs, or crystalloid. The conclusion that the combination of plasma and RBCs provided the greatest survival benefit is logical given it provides a resuscitation that would more closely resemble what the patient is bleeding, and it is similar to whole blood [36, 37]. Plasma alone was shown to be superior to RBCs alone and this would suggest that if only one blood product can be provided plasma should be given priority [14]. This data also points towards serious consideration for the use of whole blood as a way to provide both plasma and RBCs with the added benefit of platelets in one product.

Moving beyond mortality, the literature also provides some insight into some additional clinical considerations. One of these is the observation of hypocalcemia in patients receiving PHP in a combined analysis of COMBAT and PAMPer [15]. Hypocalcemia has been shown to be a sequelae of transfusion and moreover severe hypocalcemia has been associated with increased risk of death in massively transfused patients [38–40]. This relationship may be relevant as it informs our interpretation of the current data and also to how to practically address the is-

sue moving forward. It is important to consider that the hypocalcemia associated with the use of PHP may have dampened the observed benefit of PHP across all included studies. It also suggests that calcium supplementation in massively transfused patients is a topic that deserves further consideration and additional research.

In animal and in vitro studies, the beneficial effects of plasma on endothelial permeability and vascular stability have been shown to be independent of hemostasis and also to decrease with storage [41]. The results of Reitz et al. [12] suggest that while the age of the thawed plasma transfused showed no impact on mortality there were some changes in inflammatory and endothelial lining biomarker expression in severely injured patients. Specifically, old (day 2–5) plasma was associated with increased adjusted inflammatory and decreased adjusted endothelial biomarkers. More extensive analysis of biomarker expression showed PHP patients had lower levels of proinflammatory mediators and markers of endothelial lining damage regardless of plasma storage duration [12]. This suggests the effects of PHP may impact the underlying physiology of trauma beyond simply the replacement of clotting factors.

While the underlying impact of plasma is important to understand there are also clinical markers that are impacted by the use of PHP. In the two studies with coagulation parameters as the primary outcome [18, 19] there was a demonstrated improvement in INR correction or TEG MA in patients who received PHP. Henriksen et al. [18] was limited as the two groups had notable differences in pH and platelet count that may have independently predicted reduced hemostatic competence and future analysis should consider adjusting for pH and platelet count. It should be noted that the difference in INR correction observed in Kim et al. [19] was not significant and was based on a PHP sample size of 9 patients. Both functional and non-functional measures were studied and showed improvement but were not without significant limitations in study design. Henriksen et al. [18] also suggested a role of PHP in early correction of acidosis which could further mitigate the traumatic coagulopathy.

The plasma product and dose are factors that could potentially impact the effect observed in the use of PHP. In the studies examined, the dose of plasma was limited to approximately two units or 500 mL. The normal recommended dose of plasma to correct a coagulopathy has been suggested to be 10–15 mL/kg. In a study that measured clotting factors before and after receipt of four units of FFP there was an increase in clotting factor levels that ranged from 9 to 14% [42]. Given the doses used in the included studies it is likely that clotting factors were increased by less than 10%. This supports the idea that the impact of PHP where observed was not strictly a function of correcting a coagulopathy.

Conclusion

When taken as a whole the evidence appears to show that the PHP may have a mortality benefit that is most clearly demonstrated in patients with blunt injuries, moderate transfusion requirements, TBI, and/or transport time greater than 20 min, as well as those who demonstrate a certain cytokine expression profile. These conclusions were based heavily on the evidence provided in the data from two randomized controlled trials. What remains to be clearly elucidated is the precise mechanism by which PHP produces its benefit. Given the variety of patients and doses used it appears likely that the mechanism of benefit is multifactorial and may in fact be different in different subpopulations of trauma patients. There is a need for more studies focused on identifying the mechanisms of plasma's activity and correlations made with various trauma patient populations. The evidence suggests that a targeted use of PHP will most likely maximize the benefits from the use of this limited resource. It is also possible that PHP may best be provided through whole blood as survival benefits were greatest in patients who received both PHP and RBCs.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

B.P.J., J.L.S., and M.H.Y. contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

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