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On the Frontlines of Pre-Hospital Care: The Efficacy of Freeze-Dried Plasma

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ABSTRACT

Despite continued developments made in the field of trauma care, hemorrhagic shock resulting from trauma remains the leading cause of preventable death on the battlefield. The current methods being used for the treatment of patients with acute hemorrhage include dressing the wound in an attempt to stop the bleeding, along with intravenous administration of fluids intended to replace the blood loss and treat the accompanying shock. The question of what kind of fluid to use is one that fascinated many throughout history, consequentially leading to the development of physiological crystalloid based solutions on one hand and isolated blood products on the other. With its introduction, plasma was found to have significant clinical benefits, conceivably because plasma replenishes various coagulation proteins that are consumed during the coagulopathy that often accompanies traumatic injuries. In military and remote settings, the logistical limitations of plasma, namely the need to maintain a comprehensive cold-chain infrastructure and the complicated process of thawing the plasma, restricted the use of plasma in these settings. In World War II, these barriers were lifted as Freeze-Dried Plasma (FDP) was invented, not requiring any freezers and soon available. This product was vastly used during the war with hundreds of thousands treated, but then disremembered because of disease transmission issues such as hepatitis found among recipients in the 1960's. Modern-day advanced techniques have improved the safety and made it possible to produce safe and effective dried plasma solving the previous problems, but still, FDP is currently used by only a few countries worldwide. In line with its unpopularity, little has been published regarding the clinical effects of this product.

***Purpose of this Study**: To shed light on the clinical effectiveness of using freeze-dried plasma as a pre-hospital resuscitation fluid during the treatment of hemorrhagic shock in the pre-hospital setting.*

***Methods**: A retrospective analysis of data collected on trauma patients injured in the Syrian civil war and treated by the IDF from 2014 until 2016. Casualties who required long evacuation time (i.e., over 45 minutes) were chosen. Two groups of casualties were allocated according to weather FDP was used (N=29), or standard-care fluids were given (N=83).*

***Results**: Using FDP as part of the pre-hospital resuscitation was shown to be associated with an improvement in both vital signs and shock index score. Moreover, among these patients, a lower transfusion volume was needed throughout their hospitalization. However, an increased risk for mortality, increased risk of in-hospital blood transfusion, and increased risk of pre-hospital intubation were observed in the FDP treated group.*

***Conclusions**: The effectiveness of FDP presented inconclusive but promising results in lowering the severity of shock and reducing iatrogenic coagulopathy in trauma patients. Further research is needed to disprove the adverse outcomes of this study.*

Background

Epidemiology

Despite extensive developments in the field of trauma care, hemorrhagic shock resulting from trauma remains the leading cause of preventable death on the battlefield [1]. Uncontrolled hemorrhage still accounts for more than 50% of all trauma-related deaths in both civilian and military environments happening within 48 hours of injury [2], with the majority of the patients dying within the first three hours of injury [3]. For this reason, prompt identification and treatment of the hemorrhagic patient are crucial for its survival. The current methods used for treatment and management of patients with acute hemorrhage include dressing the wound (or applying pressure) in an attempt to stop the bleeding and prevent additional blood loss, while supplementary intravenous transfusion of fluids may be necessary to replace the blood loss and treat the accompanying shock [4]. This basic strategy in treating hemorrhagic trauma patients has not changed significantly in the last century. Nevertheless, the 'tactics' being employed in order to reach this goal have gone significant improvements over time [5].

History

The need for blood replacements was realized soon after the discovery of the blood circulation by William Harvey in 1628. Medical practitioners tried numerous substances such as beer, urine, milk, plant resins, and sheep blood as a substitute for blood loss. Of the different materials that were tried as blood substitutes over the years, only a few yielded success. First used in 1832, Robert Lewins described the effects of the intravenous administration of an alkalinized salt solution in treating patients during the cholera pandemic [6]. In 1885 Sidney Ringer developed a physiologic salt solution composed of sodium, potassium, and calcium for rehydration of children with gastroenteritis, which has been modified and further advanced in the modern era by Alexis Hartman [7]. While it is still used today as a blood-volume expander, Ringer's solution does not replace the action of red blood cells, platelets and clotting factors. Furthermore, its use carries additional disadvantages, which will be discussed later. Alogside the search for a blood substitute, there has been a concurrent effort to develop whole blood transfusions. In the early 19th century, it was the British obstetrician Dr. James Blundell who made endeavors to treat hemorrhage by transfusion of human blood using a syringe: In 1829 following experiments with animals, he performed the first successful transfusion of human blood to treat postpartum hemorrhage, using the patient's husband as a donor. Initially, blood transfusion was carried out without any knowledge of blood groups, and not surprisingly, many recipients died. By the end of the 19th-century, blood transfusion was regarded as an unsafe and questionable procedure and was largely shunned by the medical establishment. By the 1920s, blood grouping became universal practice following the discovery of the four distinct blood groups. The first transfusions had to be made directly from donor to receiver before coagulation occurred. Adding anticoagulant and later refrigerating the blood made it possible to store blood for several days, consequently paving the way for the development of blood banks with the first being established in 1921 by the British Red Cross [8]. It was only by 1918 that plasma was recognized by captain Gordon Ward for its possible therapeutic benefit in treating patients with active hemorrhage, with the idea of using plasma as a substitute for whole blood first introduced in 1936 by John Elliot. He used a vacuum bulb-tube with citrated anticoagulant, which had sites for removals of RBCs and ultimately accomplished the separation of plasma from whole blood [9-11].

Meanwhile, Max Strumia, who had been studying plasma as an antimicrobial agent since 1927, was already experimenting with turning Elliott's fractionated plasma into a sterile powder using the process of freeze-drying [10]. World War II reignited interest in the research of blood and blood substitutes granting Strumia enough of both military funding and Red Cross blood to prepare several hundred units of frozen dried plasma (FDP) for trial by the Navy and Army. In July 1940, the war had already begun in Europe, and London was under relentless aerial attack, forcing Britain to request from its American allies for large quantities of plasma to be shipped overseas to aid in the war effort in what was called the "Blood for Britain Campaign."

Manufacturing and Packaging

To ensure the Blood for Britain campaign succeeds, a special FDP package designed for the battlefield was developed, which minimized breakage and made transportation, packaging, and storage much more manageable. The package came in two tin cans containing 500 ml glass bottles: One bottle contained distilled water used to reconstitute the dried plasma contained within the other bottle (Figure 1). With this new configuration, the plasma was ready to be transfused in about 3 minutes and could stay fresh for around 4 hours. The same FDP pre-use reconstitution process is still used today (Figure 3). Between 1942 and 1945, the American National Red Cross collected over 13 million units of blood. Of those, more than 12 million units were converted into plasma, with most RBCs being discarded [10]. During ramp-up to large-scale industrial production, much of the plasma was created using large donor pools. This later lead to the observation that viral hepatitis contaminated donors infected multiple recipients and the cession, resulting in the termination of the widespread use of pooled plasma in the 1960s and 1970s.

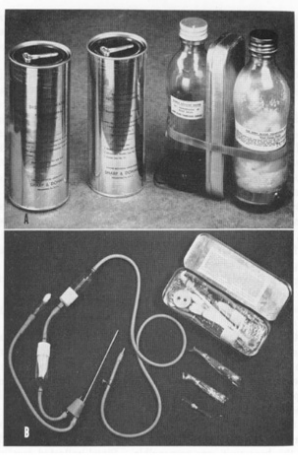


Figure 1. (A) British (right) & US Army dried plasma units. **(B)** British dispensing set for plasma. Available from: http://history.amedd.army.mil/booksdocs/wwii/blood/chapter1.htm, accessed 26 March 2020.

Resurrection of Dried Plasmas Usage

It was only until 2007 that the German Red Cross Blood Service West started producing single-donor lyophilized FDP from quarantined plasma. LyoPlas N-w quarantined plasma is stored and frozen after donation for at least four months and is used only after repeated negative donor tests for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), hepatitis A virus (HAV) and Parvovirus B19- at the time of donation and six months post-donation. Since its introduction in 2007, more than 230,000 LyoPlas N-w (German LPN-W) units have been transfused. The safety profile was determined to be comparable to Fresh frozen plasma (FFP) [12]. Nevertheless, to this day, most countries still do not have commercially available dried plasma products.

Logistical Challenges

Delivering blood products to the battlefield presents a significant challenge. FFP is stored frozen at -18°C and requires thawing before transfusion (a process that takes approximately 30 minutes using designated equipment). This requires maintaining a cold (FROZEN) chain over considerable distances from manufacturing to the point of care. Once thawed, liquid plasma must be administered immediately or (if refrigerated) within five days. These limits and sometimes even prevent the use of FFP in settings where freezers and other support equipment are unavailable (e.g., battlefields and remote locations) [13]. Dried Plasma that can be stored in room temperature offers a solution that could permit advanced damage control resuscitation in the pre-hospital arena and on the battlefield. The Israel Defense Forces has introduced FDP as the resuscitation fluid of choice used by advanced lifesavers (Physicians and paramedics) in 2013 [14,15]. FDP is also used by the national emergency services (MDA) as a result of collaboration with the IDF medical corps. Other dried plasma products are also used by the French Special Forces, in South Africa and Germany (including a very limited use in civilian settings) [12,15,16].

Coagulopathy and Crystalloids based resuscitation

Approximately 25% of all severely injured trauma patients admitted to the hospital have variable degrees of laboratory coagulopathy [17]. Due to logistical restraints listed above, most

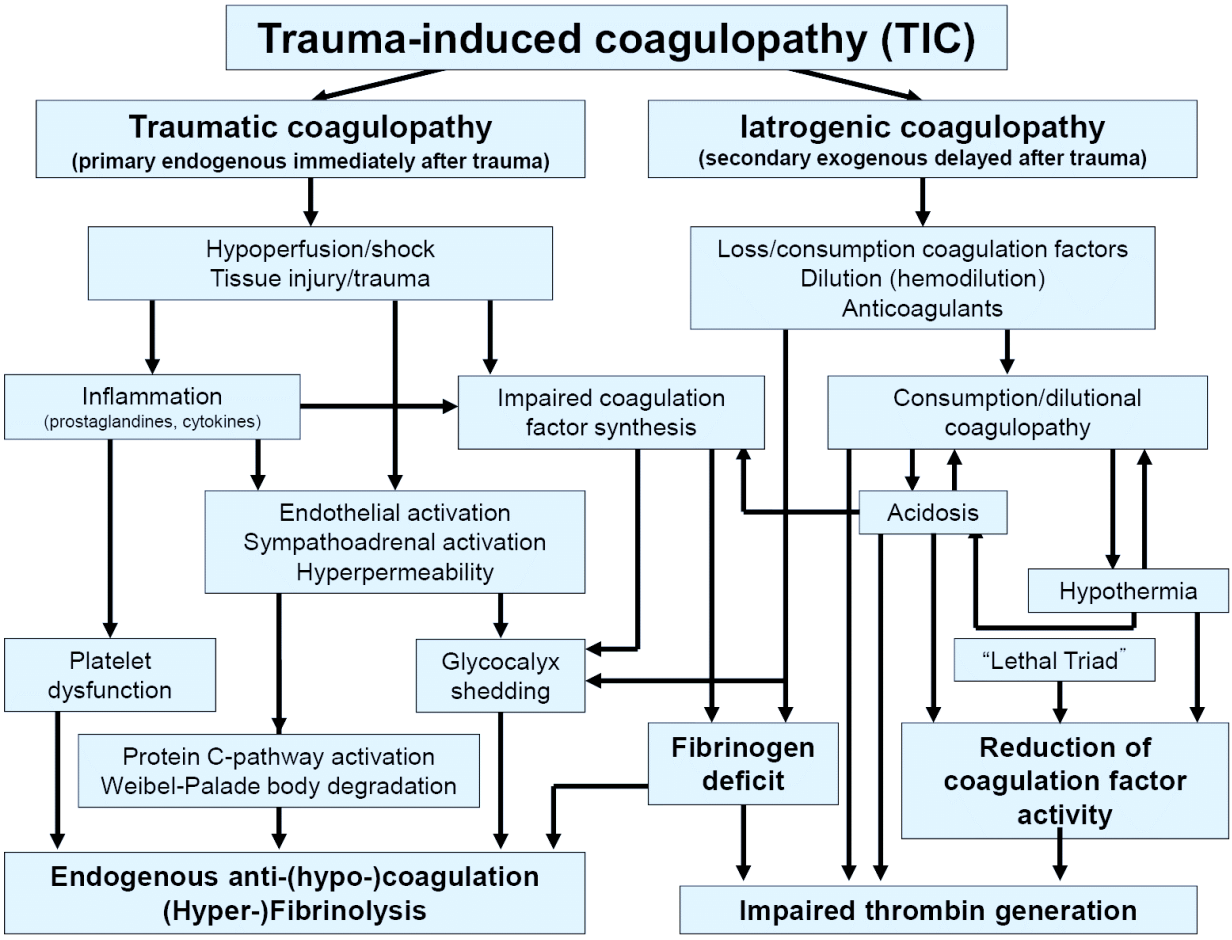


Figure 2: Current concept and understanding of the mechanisms underlying TIC: The current concept of trauma-induced coagulopathy separates traumatic coagulopathy, which is primarily triggered by the traumatic event itself, from iatrogenic coagulopathy, which aggravates traumatic coagulopathy in the further sequel. The iatrogenic arm of TIC includes loss, consumption, and dilution of coagulation factors. Existing traumatic coagulopathy, together with acidosis and hypothermia, creates the "lethal triad" of death, and reductions and/or deficits in coagulation factor activity lead to impaired thrombin generation thereby substantially aggravating traumatic coagulopathy. Source: Updated concepts on the pathophysiology and the clinical management of trauma hemorrhage and coagulopathy. Chinese Journal of Traumatology 20(3):125-132, June 2017.

of the world still uses crystalloid and colloid based resuscitation fluids for pre-hospital treatment of hemorrhaging trauma patients. Of these, current treatment protocols for the restoration of circulatory volume mainly include the use of crystalloids (water-based salt solutions) mostly due to financial considerations, along with the unnecessity of relying on blood donors: Saline (0.9% NaCl solution) and Hartmann's solution (Lactated Ringers: a mixture of sodium chloride, sodium lactate, potassium chloride, and calcium chloride in water). While the apparent contribution to the pre-load (and blood pressure) to ensure perfusion to critical hypoxia-sensitive tissues such as cardiac muscles and CNS may be life-saving, these solutions lack any oxygen-carrying capacity, nor clotting factors or platelets. Furthermore, saline and Hartman's are very acidotic (with a pH of 5.4 and 6.2, accordingly). During massive transfusion for hemorrhage, this may result in dilution coagulopathy and worsen the acidosis, ultimately aggravating the trauma-induced coagulopathy (TIC). This is not surprising, given that these solutions have been initially formulated for conditions other than the replacement of blood, that these solutions have been useful to treat dehydration. When they are used judiciously in relatively small volumes, they are well tolerated and relatively harmless. However, over the years, they have attained widespread use for the treatment of hemorrhagic shock. Current updated guidelines state that treatment of hemorrhage with IV crystalloid increases the risk of TIC from dilution of clotting factors and platelets, and possibly hypothermia. Moreover, in order to avoid these complications in injured patients, the recommendation is that treatment with IV fluid should be avoided whenever possible and, if unavoidable, given in the smallest volumes necessary, until blood products become available [18]. One prospective observational study looking at goal-directed resuscitation in the pre-hospital setting found that infusions of more than 500 mL of isotonic crystalloid were associated with worse outcomes in patients without hypotension (defined as systolic blood pressure < 90), but not in patients with hypotension, suggesting that resuscitation should be goal-directed based on the presence or absence of hypotension [19]. A retrospective study of just over 3000 trauma patients resuscitated with isotonic crystalloid found no adverse effect in patients given one liter of fluid or less but reported a two-fold increase in mortality among patients who received 1.5 liters or more [20]. There have been many theories regarding the underlying mechanism of TIC, but not one, in particular, is agreed upon. The current understanding of TIC is summarized in Figure 2 [5].

While the contentious issue of colloid versus crystalloid solution in fluid resuscitation is continued to be debated, on June 2013 the US Food and Drug Administration added a black boxed warning to HES, a colloid solution previously used for volume replacement in several clinical settings including sepsis, trauma, and cardiopulmonary bypass. The black box warning deals with increased mortality and severe renal injury in critically ill adult patients as well as an increased risk of bleeding in the setting of HES use in cardiopulmonary bypass. This was based upon the publication of three randomized controlled trials in 2012 indicating an increased risk of mortality and renal injury requiring renal replacement therapy in critically ill adult patients with sepsis and those admitted to the ICU. Similarly, the European Medicines Agency followed claiming that HES should no longer be used in patients with sepsis or burn injuries or in critically ill patients, banning the colloid based solution from Europe as well.

Plasma

Plasma accounts for up to 55% of the overall blood volume and consists of hundreds of dissolved proteins, coagulating factors, electrolytes, hormones, carbon dioxide, and glucose [21]. During the treatment of hemorrhagic shock, early pre-hospital administration of plasma may offer several advantages over current resuscitation fluids being used in the military setting worldwide. These benefits firstly include avoidance of crystalloid transfusion, hence preventing dilution coagulopathy contributing to the formation of TIC. Also, studies have shown that early treatment with plasma achieved improved maintenance of intravascular volume, possibly by improving endothelial function or by being a potent volume expander due to its oncotic properties [21]. Furthermore, being at a physiological pH, plasma administration may diminish the acidosis often present during the resuscitative phase of hemorrhagic shock, and that plays a role in the lethal triad (acidosis, hypothermia, and coagulopathy). It might be argued that treating the pH has advantages because the enzymes necessary for the coagulation cascade work better at an optimal temperature and optimal pH.

Nevertheless, some claim that the acidotic state is not necessarily undesirable because the body tolerates acidosis better than alkalosis, but this is yet to be farther elucidated [22]. Lastly, plasma contains clotting factors that are depleted in trauma and hemorrhage, and that are much needed for its treatment [22]. It is important to remember that despite all its advantages, plasma lacks any oxygen-carrying capacity, so in that sense, it is inferior to fresh whole blood (FWB).

Current Study

Studies aiming to mitigate potentially survivable deaths from hemorrhage focus on rapidly stopping the bleeding and then the early use of blood products. As described above, this can potentially be achieved using plasma as a resuscitation fluid in the pre-hospital setting. For the last century, logistic considerations have significantly limited the treatment options in the pre-hospital scenery, especially in the military arena, and this is true even today. The present use of crystalloid and colloid based solutions as a resuscitation fluid for reasons of logistic difficulties holds many clinical disadvantages to the patient as compared to FFP and FWB. Although FWB is probably preferred as it contains all blood components and oxygen-carrying capacity, it is not always feasible in the military environment, and the same is true for FFP, which necessitates a challenging cold chain to be constructed and implemented and a rigorous thawing process before infusion.

In contrast to blood, plasma can be preserved in a freeze dried form (i.e., FDP). With this product, the logistical benefits for the military are tremendous as FDP is not required to be stored

at freezers or refrigerators and is easily prepared minutes before transfusion. Even with its associated benefits, the widespread use of FDP both inside and outside of the hospital setting is scarce, mainly due to historical safety concerns that have been solved since then. In 2013 the Israel Defense Forces Medical Corps adopted FDP as the resuscitation fluid of choice to be used by its' advanced lifesavers (physicians and paramedics). Replacing the Hartman's solution in the hand of the advanced life savers, FDP is expected to offer a significant advantage to the bleeding casualties. Unfortunately, little has been published regarding the clinical effect and practical experience from the use of FDP in the pre-hospital setting. The IDF has been one of the frontrunners in the field, while others are beginning to follow [23]. As of December 2019, the FDA has given only preliminary approval for the use and manufacturing of FDP in the United States. Even so, the few case series published provide only limited relevant clinical data (such as laboratory tests) and focus on the hospital phase of care. The information regarding the outcome of these casualties is lacking. The purpose of this study is to shed light and provide quantitative data concerning the pre-hospital usage of FDP and its clinical benefits. The clinical characteristics of prolonged evacuation trauma patients, treated with FDP, will be described. This study may provide much-needed data regarding the use of FDP and its' possible benefits and will allow evaluating FDPs' adaptation as the fluid resuscitation of choice in the pre-hospital setting. Our results will hopefully also assist our colleagues in treating trauma patients worldwide in their efforts to consider similar policies.

Materials and Methods

A retrospective analysis of data regarding trauma patients injured in the Syrian civil war and treated by the IDF and the northern Israeli hospitals from 2014 until 2016. Patients were treated at the northern Israeli border by the IDF and then transferred to one of the Northern Israeli hospitals. Syrian citizens were chosen for this study simply because they represent the largest cohort of trauma patients treated by the IDF during these years. Casualties who required longer evacuation time (i.e., over 45 minutes) were chosen in order to concentrate on those suffering prolonged consequences of shock and hypo-perfusion. Two groups of casualties were allocated according to weather FDP was used (N=29), or not (N=83) based on administration indications: According to IDF guidelines in place during the study period, the indication for administration of FDP during resuscitation was an injury mechanism indicating massive hemorrhage along with signs of hemodynamic compromise seen as either SBP<90 and HR>130 or an absent radial pulse. During our evaluation, we compared several clinical aspects (detailed below), as recorded in the different hospitals, between the two groups. These clinical findings served us as the outcome measure for each one of the treatments.

The FDP product used by the IDF Medical Corps is the German-made LyopPlas. Each unit is prepared from a single donor and requires blood type compatibility. It can be stored in temperatures up to 25°C for up to 15 months and is reconstituted in 200- mL of sterile water in 10 minutes (Figure 3). After preparation, it is best used within the first 6 hours. Detailed information regarding the product is summarized in Table 1 & Table 2. LyoPlas was the only FDP product used during the study period.

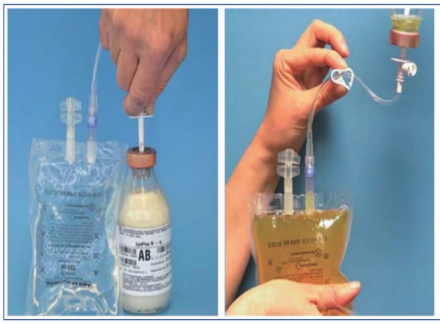


Figure 2. Reconstitution of LyoPlasN-w before use. Source: Plasma Transfusion: History, Current Realities, and Novel Improvements Shock46(5):468-479, November 2016.

t tests – Means: Difference between two independent means (two groups)

Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	One
	Effect size d	=	0.6
	α err prob	=	0.05
	Power (1−β err prob)	=	0.8
	Allocation ratio N2/N1	=	2
Output:	Noncentrality parameter δ	=	2.5376170
	Critical t	=	1.6646246
	Df	=	78
	Sample size group 1	=	27
	Sample size group 2	=	53
	Total sample size	=	80
	Actual power	=	0.8080281

The sample size was calculated using the POWER*G 3.1.7 software. When the minimum level of significance required is 5%, and the power of the test is 80%, the effect size is 0.6 (medium level).

The quantitative data were described using central tendencies and measures of variability (average & standard deviation for quantitative data which is typically distributed as opposed to median & interquartile range for quantitative data which is not normally distributed). Categorical data is be presented using frequency distribution tables and percentages. Student's t-test was used to compare independent samples, which are typically distributed, and the Mann Whitney U test was used for independent samples, which are not normally distributed. Fischer Exact test and $\chi 2$ test were used to examine the dependence and correlation between the categorical data. The Kolmogorov-Smirnov test was be used for testing if a variable follows a normal distribution. Following IRB approval ("Helsinki Committee," clinical information regarding the allied casualties, was extracted by the lead investigator from the medical records. The relevant clinical data gathered from each patient were recorded and analyzed anonymously and included:

Delta - The change in the vital signs that were observed throughout the transportation, calculated by subtracting the pre-hospital vital signs from those measured at the time of hospital admission. The %delta was also presented as the percent of change, calculated for each group by subtracting each measure in the field by the corresponding measure in the hospital, divided by the first measure in the field.

Shock Index (SI) –defined as heart rate divided by the systolic blood pressure. While heart rate and systolic blood pressure independently are inaccurate at identifying hemorrhagic shock (an increase in heart rate does not always accompany a decrease in systolic blood pressure), SI- which uses these two variables together- is a better marker for assessing the severity of shock.

Modified Shock Index (MSI) – SI does not take into account the diastolic blood pressure, so a modified shock index was created. MSI is defined as heart rate divided by the mean arterial pressure (MAP). High MSI indicates high stroke volume and low systemic vascular resistance, a sign of hypodynamic circulation. In contrast, low MSI indicates a hyperdynamic state. MSI is considered a better marker than SI for the prediction of mortality.

Delta SI and MSI - From these two measures, a delta SI & delta MSI was deduced, which accounts for the difference between these scores before and after treatment with plasma or standard-care fluids (i.e., the change in SI and MSI after initial treatment).

Outcomes measures

In order to describe the clinical characteristics of prolonged evacuation trauma patients, treated with FDP and to evaluate its clinical effectiveness the outcome measures used in this study consisted of the following: Blood workup (laboratory tests) and coagulation studies during hospital admission (PLT, PT, PTT, INR). Vital signs at the time of arrival to hospital vs. vital signs in the field. Shock Index & Modified Shock Index at point of hospital admission vs. in the field. Data regarding pre-hospital treatments (intubation and mechanical ventilation, administration of blood products, and resuscitation fluids) was also collected. As well as additional information regarding the injuries themselves, the pre-hospital transportation times, length of hospitalization, and 24-hours and 30 days mortality.

Results

Patients Characteristics

Between March 2014 through May 2016, a total of 112 trauma patients, transported from the Syrian border to Northern Israel Hospitals with an evacuation time that was greater than 45 minutes, were investigated. These patients were then divided and assigned into two groups depending on whether they received FDP in the pre-hospital setting: Plasma group (n=29) & Standard-Care group (n=83). Most of these patients (97.3%) were men, and most (90.2%) had an injury caused by penetrating trauma, with a median Shock Index & Modified Shock Index scores of 0.98 and 1.26 respectively (a SI >0.9 or <0.5 & MSI >1.3 or <0.7 are indicative of significant trauma and higher mortality rates). The overall 30-day mortality rate was 6.1% (1.5% within the first 24-hours of admission). Pre-hospital intubation was performed on 16 patients (18.4%), with 11 patients (16.9%), not neccesserity the same, needing further mechanical ventilation during their hospitalization. 31.3% of the patients received blood transfusions (FFP, Packed RBC's, FWB) during their hospitalization, whereas 81.8% required crystalloid transfusion. Urgent operative procedures were performed in 69.2% of the patients upon arrival. Additional data regarding the patients' injuries are summarized in Table 3.

Table 3: Patient's Injury Data.

		n	%
Mechanism of Injury	Unknown	21	18.8%
	Firearm	30	26.7%
	Blast	41	36.6%
	Fragmentation	20	17.9%
Body Regions Injured	Head & Neck	48	42.9%
	Chest	20	23.0%
	Abdomen	21	24.1%
	Torso	3	3.4%
	Upper Limbs	36	41.4%
	Lower Limbs	37	42.5%

Note - the percentages for the subcategories of the above/below variables are based on the number of patients assessed for this variable rather than on the total number of patients in each trial group. It is notable that most of the patients were involved in a blast mechanism of injury and that the most commonly affected body regions were the head & neck (42.9%) and the limbs (41.1% and 42.5% for the upper and lower limbs respectively). Additionally, the median number of total body regions injured was 2. In regards to the continuous data gathered, the median age of a patient in this study was 25 years old, hospitalization time stood at a median of 18 days, interquartile range (IQR) 6 to 35 days, and the transport time to the hospital was at a median of 149 minutes (IQR 121 to 184 minutes). Vital signs were taken once in the field by the evacuating unit and once more in the hospital during admission. The corresponding data is presented in Table 4.

Table 4: Vital Signs.

	Mean	SD	Percentile 25	Median	Percentile 75
HR - Field	101.92	25.58	85.00	98.00	120.00
SBP - Field	115.33	18.89	110.00	120.00	129.50
DBP - Field	75.23	10.59	70.00	75.00	80.00
Sat (O_2) - Field	96.83	1.88	96.00	97.00	98.00
HR - Hospital	90.70	27.28	72.00	85.00	110.00
SBP - Hospital	118.29	19.91	111.00	120.00	129.00
DBP - Hospital	68.67	15.63	61.00	70.00	79.00
Sat (O_2) - Hospital	98.05	5.94	98.00	99.00	100.00

HR – Heart Rate; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; Sat(O_2) – Oxygen saturation; SD- Standard deviation.

Table 5: Lab Results.

	Mean	SD	Percentile 25	Median	Percentile 75
PT	13.82	1.91	12.60	13.60	14.70
PTT	29.67	7.96	26.00	28.90	31.30
INR	1.15	.16	1.04	1.10	1.23
Platelets	250.41	115.29	180.00	233.00	299.00
pH	7.30	.09	7.25	7.32	7.36
PCO_2	45.60	8.03	40.20	44.60	50.40
HCO_3^-	22.34	4.61	19.70	22.90	25.60
BE	-3.93	4.75	-6.40	-2.80	-.70
Lactic Acid	8.10	15.79	1.62	2.40	4.72
HGB	12.58	2.50	10.90	12.70	14.20
Glucose	126.84	39.91	101.00	114.90	146.00

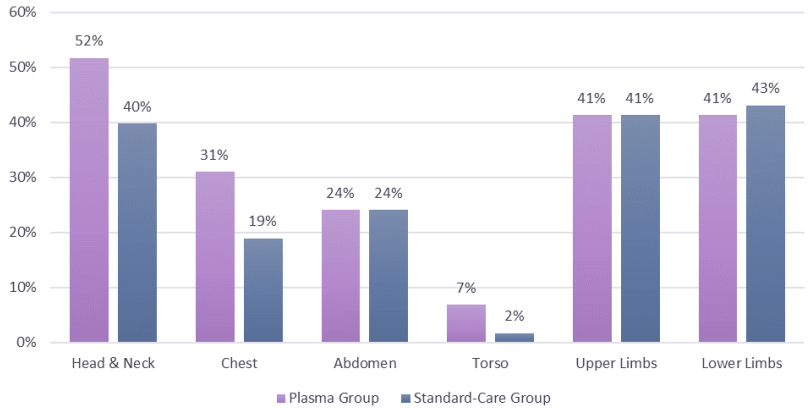
PT – Prothrombin time; PTT - partial thromboplastin time; INR - international normalized ratio; HCO_3^- - Bicarbonate; BE – Base excess; HGB – Hemoglobin. Platelets – Numbers presented in thousands.

Median blood pressure measures were nearly identical at the field and the hospital (115/75 and 118/69 respectively), but the heart rate observed decreased by nearly 15% from the pre-hospital arena

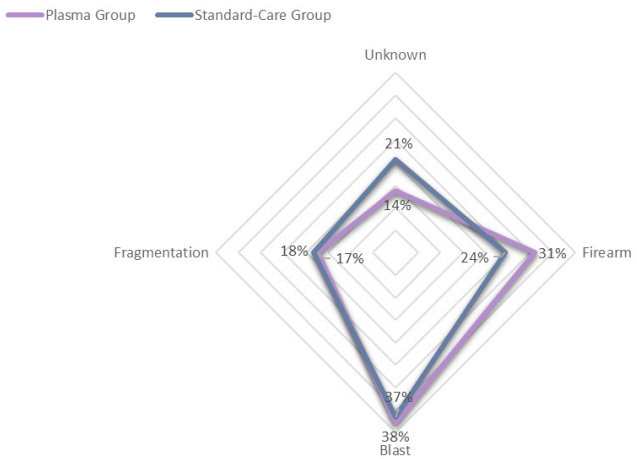
(98 beats/min) to hospital arrival (85 beats/min). Laboratory blood testing results taken in the ER unit upon arrival of the patients are listed in Table 5. As expected when dealing with hemorrhagic trauma patients, the hemoglobin documented at the point of admission was somewhat low, with a median of 12.7 (IQR 10.9 to 14.2) combined with a median lactic acid of 2.4 and a median pH of 7.32 meets the criteria of lactic acidosis and anemia. Coagulation studies upon arrival (PT, PTT, INR) were within normal ranges across all tests, including the average level of platelets (median 233,000; IQR 180,000 to 299,000).

Primary Outcomes

The demographic characteristics and injury characteristics were similar in the two trial groups (Figure 4). Patients in the standard care group, who were not transfused with freeze-dried plasma, received more significant volumes of crystalloid based solutions during their hospitalization than the patients in the plasma group. Furthermore, the number of patients who acquired crystalloids infusion was also higher in the standard-care group, as opposed to the plasma group [36] patients (75%) vs. nine patients (33%); P=0.03]. Also, a significantly higher percentage of patients in the plasma group (78%) received an addition of at least one type of blood product (FWB, FFP, packed RBCs) during their stay, in contrast to the standard-care group (8%); P<0.001. The time of hospitalization in the two groups was also not significantly different. A roughly 40-minute difference was observed in the median transportation time of the two groups, with significantly shorter times in the standard-care group (135 min; IQR 120 to 177 vs. 177 min; IQR 147 to 229 in the plasma-treated group P=0.002). There were four deaths in the plasma group within the first 30 days of hospitalization versus no deaths in the standard-care group [P<0.001]. Of those deaths, one had died during the first 24 hours of admission [P=0.026]. Pre-hospital intubation was performed in 41.4% of patients of the plasma group and 6.9% of patients of the standard-care group [P<0.001]. In the hospital, additional mechanical ventilation during hospitalization was needed in 63.6% of the patients in the plasma group, whereas only 7.4% in the standard-care group [P<0.001]. The need for surgery after enrollment was not significantly different among the two groups (Table 7).



A. Body Regions Injured



B. Mechanism of Injury

Figure 4: Injury characteristics of the two trial groups. No significant differences were observed. **[A]** – Body regions injured; upper & lower limbs were equally involved with head & neck being stood out; the sum adds up to more than 100% because some patients suffered from multi-trauma. **[B]** – Mechanism of injury; the leading cause of injury for both groups were a blast mechanism.

As shown in figure 4, the mechanisms of injury among the two groups were similar, and no substantial differences were observed as regards the body regions injured.

In terms of the lab results, no significant difference between the groups were noted concerning the first coagulation studies (PT, PTT, INR) performed in the hospitals. However, the median number of platelets was significantly [P=0.001] lower in the plasma group (186,000) when compared to the standard-care group (250,500). Additional differences noted between the two groups, particularly in the chemistry panel, and are summarized in Table 6.

Table 6: Lab Results.

Variable	Plasma Group (N=29)	Standard-Care Group (N=83)	P-Value
PT – sec	14.35 (12.9-14.7)	13.40 (12.5-14.7)	0.135
PTT – sec	27.25 (24.65-32)	29.00 (26.1-31.3)	0.272
INR	1.10 (1.0-1.28)	1.10 (1.06-1.20)	0.295
Platelets*†	**186.00 (148-248)**	**250.50 (218-316.5)**	**0.001**
pH*₮	**7.30 (7.25-7.34)**	**7.34 (7.30-7.38)**	**0.026**
PCO_2	45.40 (41.9-50.4)	43.65 (39.1-50.05)	0.251
$HCO3^-$*₮	**20.35 (16.2-23.3)**	**23.80 (22.1-26.2)**	**0.018**
BE*₮	**-3.70 (-6.6—2.1)**	**-1.75 (-5.2-0.2)**	**0.031**
Lactic Acid	2.15 (1.47-3.30)	2.62 (1.66-18)	0.100
HGB*₮	**12.00 (9.6-13.2)**	**13.20 (11.7-14.55)**	**0.010**
Glucose	132.00 (102-152)	109.95 (101-144)	0.096

* No significant differences were observed between the two groups in the above characteristics except where noted with '*' and bolded. (x-y) refers to the interquartile range of Q1-Q3 representing 25%-75% percentile of each variable. PT – Prothrombin time; PTT - partial thromboplastin time; INR - international normalized ratio; HCO_3^- - Bicarbonate [P=0.018]; BE – Base excess [P=0.031]; HGB – Hemoglobin [0.01]; Platelets – Numbers presented in thousands [P=0.001]; pH – normal range of 7.35-7.45 [P=0.026]; † - P=0.001; ₮ - 0.01<P<0.05;

Pre-hospital vital signs were not significantly different between the two groups, except the overall median systolic blood pressure that is relatively lower in the plasma group (104 mm Hg) than the standard-care group (122 mm Hg) [P=0.001]. In particular, the median systolic blood pressure and heart rate observed in the plasma group at the time of hospital arrival were 110 mm Hg and 100 beats/min, respectively, indicating a worse homodynamic condition than that of the standard-care group. In those casualties not receiving plasma, a higher median systolic blood pressure (121 mm Hg; P=0.041(and a lower heart rate (82 beats/min; P=0.029) were measured. The delta (change) in the vital signs, (calculated by subtracting the pre-hospital vital signs from those measured at the time of hospital admission) is of greater interest when examining the benefits of one resuscitation fluid over another (Figure 5). In contrast to using the vital signs solely, this measure shows superiority to the plasma-treated group over the standard-care group. The change in the vital signs during transport was improved in the plasma group, as seen in the positive Delta and %Delta showed in the plasma group as opposed to the negative Delta in the standard-care group.

The DELTA of each group was calculated by subtracting each measure in the field by the corresponding measure in the hospital, divided by the first measure in the field.

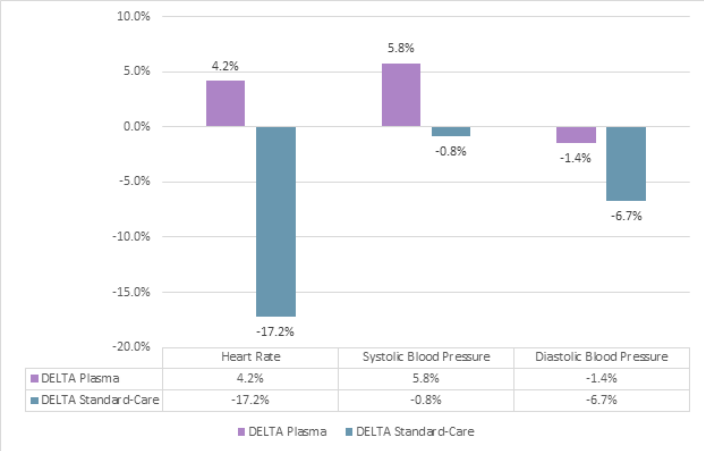


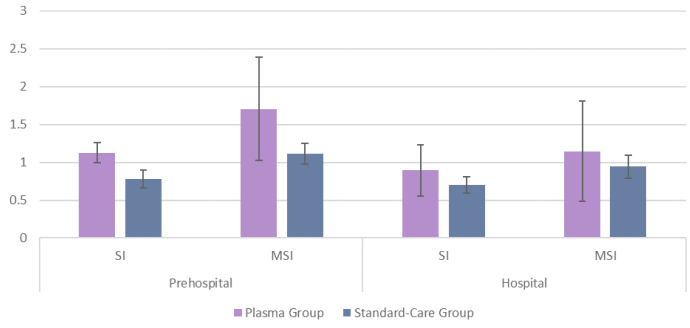
Figure 5: The difference in the vital signs measures between hospital and field.

The shock index (SI) and modified shock index (MSI), were calculated twice: based on the pre-hospital vital signs measurements and once more using the measures taken upon arrival at the hospitals. From these two measures, a delta SI & delta MSI was deduced, as described in the Methods section. The delta SI & delta MSI had seen a more significant reduction in the plasma group as opposed to the standard-care group (Figure 6).

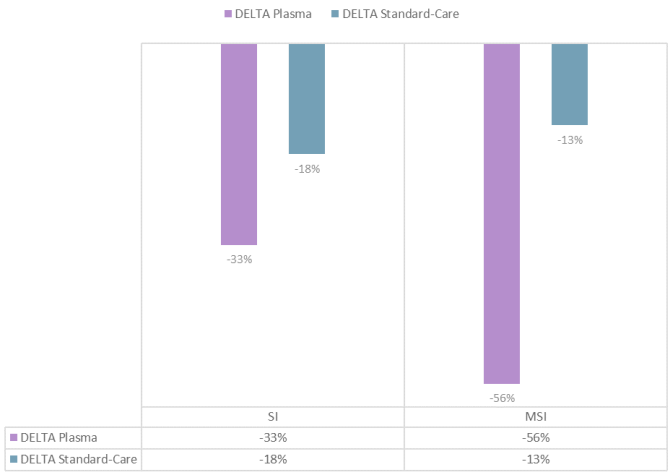
Table 7: Primary and Secondary Outcomes.

Variable	Plasma Group (N=29)	Standard-Care Group (N=83)
Median age (IQR) - yr	25 (20-30)	25 (21-31)
Male sex – no. (%)	27 (93.1)	82 (98.8)
Injury caused by blunt trauma – no. (%)	1 (3.4)	10 (12)
Injury caused by penetrating trauma – no. (%)	28 (96.6)	73 (88)
Median body regions injured (IQR) – no.	2 (1-2)	1 (1-3)
Median prehospital transport time (IQR) – min*‡	**177 (147-229)**	**135 (120-177)**
Pre-hospital intubation – no. (%)*Δ†	**12 (41.4)**	**4 (6.9)**
Median pre-hospital systolic blood pressure (IQR) – mm Hg*†	**104 (80-110)**	**122 (115-130)**
Median pre-hospital diastolic blood pressure (IQR) – mm Hg	70 (70-80)	75 (70-80)
Median prehospital heart rate (IQR) – beats/min	96 (85-120)	99 (87-118)
Median hospitalization (IQR) – days	28 (4-56)	17 (6-30)
Median blood products transfusion – no. (%)*Δ†	**21 (78)**	**4 (8)**
Median crystalloid transfusion – no. (%)*Δ₮	**9 (33)**	**36 (75)**
Median hospital systolic blood pressure (IQR) – mm Hg*‡	**110 (72-132)**	**121 (115-129)**
Median hospital diastolic blood pressure (IQR) – mm Hg	69 (47-80)	70 (62-79)
Median hospital heart rate (IQR) – beats/min* ‡	**100 (81-130)**	**82 (70-104)**
Median prehospital SI (IQR) Ł	1.13 (1.07-1.38)	0.78 (0.76-1.00)
Median prehospital MSI (IQR) Ł	1.71 (1.51-2.51)	1.11 (0.98-1.27)
Median hospital SI (IQR) Ł	0.89 (0.57-1.17)	0.70 (0.56-0.81)
Median hospital MSI (IQR) Ł	1.14 (0.87-1.65)	0.94 (0.82-1.14)

Continuous variables were compared with the use of the Mann–Whitney U test, and categorical variables were compared with the use of Fisher's exact test. IQR denotes interquartile range.
* - No significant differences were observed between the two groups in the above characteristics except where noted with '*' and bolded out.
Δ - The percentages for the subcategories of this variable are based on the number of patients assessed for this variable rather than on the total number of patients in each trial group.
† - P=0.001
‡ - 0.001<P<0.01
₮ - 0.01<P<0.05
Ł - Normal score range from 0.5 to 0.9 with anything else indicating major trauma and increased mortality
Ł - Normal score range from 0.7 to 1.3 with anything else indicating major trauma and increased mortality



A. Shock Index & Modified Shock Index



B. Difference in the SI & MSI measures between hospital and field

Figure 6: Shock index and Modified shock index scores. Both scores were calculated as listed in the Materials & Methods section. **[A]** – SI, MSI at field and hospital. **[B]** – Difference between hospital and field scores.
SI – Shock index. MSI – Modified shock index

Discussion

Currently, the use of freeze-dried plasma is limited to only a few countries worldwide, with the Israeli Defense Force Medical Corps being amongst them. It has been reported in previous studies that the early use of plasma during the treatment of hemorrhagic shock resulting from trauma holds several clinical advantages over the current crystalloid-based resuscitation fluids popularly used in the military setting. These include improving the survival, decreasing the total blood product requirements, limiting iatrogenic crystalloids use, and therefore correcting coagulopathy, ultimately reducing complications in patients undergoing massive transfusion. All these advantages have been reported in studies that were conducted using a fresh frozen plasma product. However, to date, the amount of data available regarding the clinical outcomes from the use of freeze-dried plasma, in the same manner, is scarce. It has been historically demonstrated during World War II that in the remote military setting, FDP grants logistical superiority over FFP and other blood products requiring a cold chain infrastructure. The only thing left to unveil was the clinical benefits of this product. In this study, we hoped to shed some light on this matter. In the military scenario, it may be impossible to move patients to hospital facilities within the first few hours of injury. Therefore, our primary inclusion criteria for this study were prolonged evacuation time trauma patients. Before assessing our results, one particular bias must be addressed. During this retrospective study, the division to the plasma group vs. standard-care group was based on whether FDP was used or not. The decision to administer FDP in the field was based on the IDF's resuscitation guidelines at the time of the study which state the administration in case of an injury mechanism indicating massive hemorrhage along with signs of hemodynamic compromise seen as either SBP<90 and HR>130 or an absent radial pulse. This initial discrimination based on vital signs indicating shock can be an important predictor factor for the outcome of a patient in each group regardless of the type of treatment received. With that in mind, we examined and tried to better understand our conclusions. Concerning the advantages reported by our colleagues in previous studies with FFP, indeed one of them was observed in this study: Fewer patients in the plasma group received crystalloid based fluids during their hospitalization than the standard-care group. This finding could imply that the early use of FDP during the pre-hospital treatment of hemorrhagic shock could have possible long-term beneficial effects well beyond the first few hours of treatment. For example, using more crystalloids may result in dilution coagulopathy, which, in turn, can worsen the acidosis and aggravate TIC (Figure 2). Based on our results, using FDP has been shown to reduce this risk by preventing unnecessary crystalloid use, thus halting the progression of TIC and possibly even preventing it. However, further research is needed for this to be confirmed. It could be argued that the lower followed administration of crystalloid fluids in the plasma group occurred because this group had received more blood products during hospitalization, namely fresh frozen plasma and packed red blood cells. While this might be true, the result of less crystalloid use is still met, and the greater use of blood products could be for the reason that the initial condition of the plasma group was more severe than that of the standard-care group, and not because the former had received FDP. Although FDP has been reported to be reconstituted in only a matter of minutes, it was an intriguing finding to see that the group treated with plasma had a longer transport time with a median of the 40-minutes difference between the two groups. This can be explained by the presumption that the plasma group most likely required additional life savery interventions during initial

treatment, which in turn, could have further delayed transport. The difference between the initial conditions of the groups may even account for the higher mortality rates (both at 30 days and 24 hours), pre-hospital intubation, and quantities of mechanical ventilation observed in the plasma group as a result of their initial condition. The same is true for the lab results, which demonstrated an advantage to the standard-care treatment. In line with this, we would have expected to see the coagulation tests showing somewhat of superiority to the standard-care treatment, but this was not the case as no significant differences were found between the two groups. The most used tests for coagulopathy are prothrombin time, partial thromboplastin time, and international normalized ratio. However, these tests have been shown to be somewhat inaccurate in detecting coagulopathy in surgical patients [3]. One of the major reasons is that coagulopathy is a dynamic state that evolves through different stages of hypocoagulability, hypercoagulability, and fibrinolysis. The traditional tests of blood clotting cannot detect the evolution of coagulopathy through these stages. Moreover, these tests are performed at normal pH and temperature, so they cannot consider the effects of hypothermia and acidosis on coagulation. The traditional tests of coagulation are performed on serum and not on whole blood, so they are unable to measure the interaction of coagulation factors with platelets [22]. To conclude, when testing the potential use of a certain substance as a volume expander – coagulation tests can not serve as a good outcome parameter to assess the benefits of one fluid over the other. When looking at the plasma group, most have arrived at the hospital in a state of metabolic acidosis, with such an increase in acidity that is expected to damage tissues and organs of the body, reducing heart muscle contractility, thus reducing the stroke volume and ultimately lowering the cardiac output. The drop in the stroke volume could explain the compensatory 4.2% rise of the heart rate that was observed in the plasma group and the faster heart rates that were measured at the hospital as opposed to the standard care group. However, it does not explain the 5.8% rise in systolic blood pressure seen in the plasma group. Despite the many potential methods of monitoring shock, only a few are as clinically useful as blood pressure; this surprising increase in blood pressure in the plasma group could support the fact that plasma is a complex solution, containing hundreds of biologically active proteins, with beneficial effects not yet fully understood but surely extend well beyond correction of coagulopathy. This was shown to be further validated when looking at the delta shock index scores of both groups. Both SI and MSI have been suggested to be better markers for the severity of hemorrhagic shock than blood pressure and heart rate when used independently. A retrospective study by Cannon et al., performed at a single level I trauma center, identified 2,445 patients admitted over five years. Patients with SI >0.9 were found to have a significantly higher mortality rate (15.9%) when compared with patients with normal SI (6.3%) [24]. In another retrospective study that examined 8,111 trauma patients over eight years, it was concluded that patients with SI>0.9 were found to have a 1.6-fold higher risk of massive transfusion [25]. In the largest one of these studies, 21,853 patients were identified in a trauma registry, and SI was calculated based on emergency department arrival vital signs. The degree of shock was found to correlate with increasing SI value [26]. In the current study, the median SI calculated from pre-hospital vital signs was 1.13 for the plasma group and 0.78 for the standard care group, indicating greater severity of shock and greater expected mortality rate for the plasma group, and indeed this was the case. What was arousing curiosity was that when calculating the SI for the same patients using the vital signs measures taken at the ER upon arrival to the hospital, a 33% decrease of the median SI was noted in the plasma group. In contrast, only 18% decrease was noticed in the standard-care group. The greater decrease of the SI in the plasma group is crucial as it brought the median SI to a score of 0.89, possibly diminishing the risks associated with a SI score of above 0.9. When looking at the MSI, we find similar differences with an even greater reduction of a remarkable 56% of the score in the plasma-treated group as opposed to only a 13% reduction of the standard-care group. This, too, has lowered the MSI from a high median of 1.71 to a normal range median of 1.14, thus potentially lowering mortality rates. These findings appear very promising and should be further tested in future studies with a greater number of patients in order to be fully confirmed. In conclusion, the use of FDP as a resuscitation fluid in long evac-time trauma patients has benefits over crystalloids in reducing the degree of shock (assessed by vital signs), but further research is needed, as it was found to cause increased mortality in this study [27-30].

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Appendix

Plasma formulation	Abbreviation	Processing	Preparation time, min	Storage, °C	Shelf life, days	Primary benefits	Primary drawbacks
Fresh frozen plasma	FFP	Frozen within 8 h	45	−20	365	Frequently prepared	Frozen storage, preparation time
Thawed plasma	TP	Thawed FFP	0	1–6	5	Decrease waste of thawed FFP	5-day shelf life, refrigeration
Liquid plasma	LQP	Refrigerated	0	2–6	28	Decreased preparation time	28-day shelf life, refrigeration
Plasma frozen Within 24 h	FP24	Frozen within 8–24 h	45	−20	365	Decreased TRALI incidence	Frozen storage, preparation time
German LyoPlas N-w	LPN-W	Freeze-drying	10	23	456	Austere environs, long shelf life	New processing equipment
French FlyP	FlyP	Freeze-drying	6	23	730	Austere environs, long shelf life	New processing equipment
Types of processing							
Lyophilized plasma	LP	Freeze-drying					
Spray-dried plasma	SD	Spray-drying					
Solvent detergent plasma	SDP	Solvent washed					

Table 1: Logistical comparisons of plasma formulations & types of processing.

	FLYP	LyoPlas N-w	Bioplasma FDP
Use	1994-present—French Military 2011-present—Civilian (austere)	General population—Germany	General population—South Africa & neighboring countries
Processes	• Lyophilized • Pooled apheresis FFP <11 donors • All volunteer donors • Donor screening • Testing—disease & factors • Hemovigiliance program • 2003—Leukoreduced • 2010—No HLA Ab+ women • 2010—Amotosalen PR	• Lyophilized • 1990-2006: Pooled S/D • 2007-present—Single Donor • Donor screening • Hemovigilance Program • Frozen >/= 4 mos for donor retest • Leukoreduced • No HLA Ab+ women	• Lyophilized • Pooled (up to 1,500 donors) • All volunteer donors • Donor screening • Comprehensive testing • Hemovigilance program • S/D treatment for PR
Characteristics	• Normal factor levels • ABO-universal	• Normal factor levels • ABO type specific	• Factor levels: >/= 0.40 IU • ABO-universal plasma
Shelf-life	2 years at room temperature	15 months at 2°C-25°C	Store below 25°C
Reconstitution	<6 minutes	A few minutes	<10 minutes
Indication	As sole source of plasma where used	Same as frozen plasma	Where plasma and/or coagulation factors are required
Safety	No adverse events reported (including TRALI) since 1994 start of hemovigiliance program	• >300,000 U S/D LyoPlas • >230,000 U LyoPlas N-w (2007-2013) • Hemovigilance program reported no increase incidence of adverse events	Contraindicated: Severe Protein S deficiency • Hemovigilance program—no increase in adverse events
Efficacy	Clinical use reports support efficacy as part of a 1:1 DCR approach[12]	No restrictions related to clinical efficacy have been identified	No restrictions related to clinical efficacy have been identified

Table 2: Characteristics of commercially available dried plasmas.