

Review Article

FREEZE-DRIED PLASMA AT THE POINT OF INJURY: FROM CONCEPT TO DOCTRINE

Elon Glassberg,^{*†} Roy Nadler,^{*†} Sami Gendler,^{*†} Amir Abramovich,^{*†}
Philip C. Spinella,^{‡§} Robert T. Gerhardt,[§] John B. Holcomb,^{||} and Yitshak Kreiss^{*†}

**Surgeon General's Headquarters, Israel Defense Forces, and †Department of Military Medicine, Hebrew University, Jerusalem, Israel; ‡Department of Pediatrics, Division of Critical Care, Washington University in St Louis, Missouri; and §US Army Institute of Surgical Research, Fort Sam Houston; and ||Center for Translational Injury Research, Division of Acute Care Surgery, Department of Surgery, University of Texas Health Science Center at Houston, Houston, Texas*

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ABSTRACT—While early plasma transfusion for the treatment of patients with ongoing major hemorrhage is widely accepted as part of the standard of care in the hospital setting, logistic constraints have limited its use in the out-of-hospital setting. Freeze-dried plasma (FDP), which can be stored at ambient temperatures, enables early treatment in the out-of-hospital setting. Point-of-injury plasma transfusion entails several significant advantages over currently used resuscitation fluids, including the avoidance of dilutional coagulopathy, by minimizing the need for crystalloid infusion, beneficial effects on endothelial function, physiological pH level, and better maintenance of intravascular volume compared with crystalloid-based solutions. The Israel Defense Forces Medical Corps policy is that plasma is the resuscitation fluid of choice for selected, severely wounded patients and has thus included FDP as part of its armamentarium for use at the point of injury by advanced life savers, across the entire military. We describe the clinical rationale behind the use of FDP at the point-of-injury, the drafting of the administration protocol now being used by Israel Defense Forces advanced life support providers, the process of procurement and distribution, and preliminary data describing the first casualties treated with FDP at the point of injury. It is our hope that others will be able to learn from our experience, thus improving trauma casualty care around the world.

KEYWORDS—Plasma, freeze-dried plasma, resuscitative fluid, pre hospital, point-of-injury care

INTRODUCTION

The Israel Defense Forces (IDF) Medical Corps is obligated to an ongoing effort to improve combat casualty care provided to wounded soldiers on the battlefield, with the specific target of eliminating “potentially survivable” deaths. While substantial progress has been made in the field of trauma care, the challenge of improving the care provided before hospital arrival, where most lives could be saved, remains (1). Among military trauma casualties, major hemorrhage, mainly non-compressible and junctional, is the proximate cause of potentially survivable mortality in roughly 90% of cases, the majority of which occur before arriving at a medical facility. Improved point-of-injury care could therefore potentially allow for increased survival (2).

Blood loss leads to decreased circulating volume, oxygen-carrying capacity, clotting factors, and platelets. This, in turn, results in shock and ultimately death if not addressed promptly (3). Restoration of these lost capacities may be achieved by the implementation of damage control resuscitation (DCR), a

balanced transfusion strategy incorporating transfusion of packed red blood cells (RBCs), platelets, and plasma in a 1:1:1 ratio, mimicking whole blood (4, 5). This approach is associated with improved outcomes and reduced mortality (6–9) and has been widely implemented in hospitals by both military and civilian emergency medical systems throughout the world (10, 11).

Although administration of blood, plasma, and platelets has been the standard of care in trauma for many years, technical and logistic constraints have limited their use in the out-of-hospital, preoperative military setting (referred to as NATO Role 1 medical echelon) (3). Red blood cells and fresh frozen plasma (FFP) require refrigeration, whereas platelets require constant agitation and stirring and are thus virtually unavailable within the austere environment of the battlefield. Platelets have short viability, further limiting their availability on the battlefield. Plasma in Israel is currently stored solely in frozen form. Unfortunately, FFP requires a significant amount of time to thaw before it can be made available for use and can suffer from a small but real incidence of bag breakage. Other systems use refrigerated thawed plasma, which too has significant logistical constraints, especially when use is infrequent (12).

Before arrival at a resuscitative surgical facility, where definitive hemostasis is instituted, circulating intravascular volume must be at least minimally maintained, in an attempt to ensure perfusion to hypoxia-sensitive tissues (i.e., cardiac muscle, central nervous system, kidneys). Historically, crystalloid or colloid fluids have been transfused intravenously as a

Address reprint requests to Elon Glassberg, MD, MHA, The Trauma and Combat Medicine Branch, Medical Corps, Surgeon General's Headquarters, Military POB 02149, Israel Defense Forces, 02149, Israel. E-mail: idf_trauma@idf.gov.il.

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temporizing measure. While they restore intravascular volume transiently, thus supporting blood pressure and tissue perfusion, they provide no oxygen-carrying capacity or replacement of consumed clotting factors and platelets. Furthermore, their use may result in dilution coagulopathy, hyperchloremic acidosis (an induced form of type II renal tubular acidosis), acute respiratory distress syndrome (13, 14), and inflammation (15), exacerbating trauma-induced coagulopathy (TIC) (16–18).

Trauma-induced coagulopathy is part of the lethal triad, along with hypothermia and metabolic acidosis (19). Trauma-induced coagulopathy is the result of complex mechanisms including consumption and loss of coagulation factors, hyperfibrinolysis, release of anticoagulation factors, and dilution of coagulation factors by crystalloid or colloid infusion. The treatment of TIC is a major challenge in combat casualty care, with a reported prevalence of 20% to 30% among combat casualties requiring blood transfusion (20, 21). Coagulopathy is associated independently with an up to a five-fold increase in mortality (7, 22–24). Efforts to mitigate or reverse this injury-associated coagulopathy seem logical.

The previous resuscitation fluid of choice used by medical care providers in the IDF was Hartmann solution. Although probably superior to most other crystalloid-based solutions or colloid-based solutions (25, 26), resuscitation with large volumes of Hartmann solution is still associated with a negative outcome, mainly due to its deleterious effects on coagulation, endothelium function, transient intravascular value, and increase in edema (13). The former IDF fluid resuscitation clinical practice guidelines instructed the use of Hartmann solution in 500-mL boluses to patients suffering from blood loss. With the understanding that Hartmann solution as a resuscitation fluid is far from optimal, the IDF medical corps sought an alternative, with desired attributes to include safety, logistical ease, maintenance of circulating volume, coagulopathy improvement, and availability in NATO Role 1 combat settings, thus allowing point of injury and prehospital advanced field DCR. The term remote DCR (RDCR), already established to describe prehospital (sometimes remote) resuscitation, will be used throughout the article (3). Early use of plasma in the hospital setting is associated with increased survival (4, 27, 28). Radwan et al. (28) have shown that use of thawed plasma in the emergency department, allowing plasma to be used as a primary in-hospital resuscitation fluid, was associated with improved survival. Plasma resuscitation likely has a beneficial effect by avoiding dilutional coagulopathy, replacing both procoagulant and anticoagulant proteins, repairing endothelial function, and producing anti-inflammatory effects (29–31). It is therefore reasonable to assume that plasma infusion as close as feasible to the point of injury in the prehospital setting may augment that effect further. We present the process that has led to the decision to use plasma, in the form of freeze-dried plasma (FDP), as the preferred resuscitation fluid in the IDF for use by physicians and paramedics taking care of severely wounded casualties (allowing the use of Hartmann solution as the resuscitation fluid by basic life support providers), the IDF protocol for plasma administration in the out-of-hospital setting, the implementation of FDP distribution throughout the IDF, and

preliminary data describing our initial experience with FDP transfusion at the point of injury.

PLASMA AS THE PRIMARY RESUSCITATION FLUID IN MILITARY PREHOSPITAL SETTING (ROLE 1)

A special task force, organized by the IDF Medical Corps and composed of the country's leading trauma surgeons and hematologists, examined the full arena of advanced field RDCR in early 2011 to determine future priorities. It was the board's recommendation that the first change to be implemented would be the use of point-of-injury tranexamic acid, which was embedded in the IDF clinical practice guideline for all advanced life support (ALS) medical personnel by mid-2011. The second priority set by the task force was the early use of plasma as soon and as close as possible to the point of injury.

Published data further support this recommendation, although it describes the use of thawed plasma, as a dried product is not currently approved in the United States (32). Dried plasma products are in use in German, French, and Norwegian militaries; the Norwegian civilian emergency aeromedical services; and the US army Special Operations Forces. Plasma infusion is considered to be the standard of care for treating TIC. Plasma has demonstrated superiority over colloid fluids at reversing coagulopathy secondary to trauma and improving survival in animal models, even in the absence of transfused RBCs (33, 34). Furthermore, a high (>1:2) plasma-to-RBC ratio was associated with improved survival and decreased death from hemorrhage in patients requiring massive transfusion or with significant bleeding (6, 8, 11, 35, 36). In addition, it was established that earlier administration of plasma is associated with improved survival, an effect that diminished with delayed infusion (8, 28, 37, 38). Although earlier studies concerning plasma-to-RBC ratios probably suffer from some degree of survival bias (resulting from early death occurring after administration of RBCs but before administration of plasma) (39), several recent studies that were designed to address this bias also demonstrate the benefits of early plasma transfusion (28, 40, 41).

Other studies demonstrated that the use of prehospital thawed plasma, compared with control, is associated with significant improvement of the international normalized ratio on arrival, lower volume of crystalloid infusion, and elimination of plasma deficit at 24 h (32). The rapid availability of plasma as close as possible to the point of injury appears to be of increasing importance (42).

Most hospitals utilize thawed FFP for the correction of TIC, usually in conjunction with packed RBCs (pRBCs). Fresh frozen plasma is stored in temperatures approximating -20°C and requires a long thawing process, thus making its use unfeasible in the far-forward military settings. Because FFP is not suitable for use in NATO Role 1 conditions, alternatives to FFP for field use were needed.

USE OF FRESH FROZEN PLASMA ALTERNATIVES AS RESUSCITATION FLUID AT OR NEAR THE POINT OF INJURY (NATO ROLE 1)

Dried plasma, which can be stored at ambient temperatures, will enable early treatment in out-of-hospital setting, such as

on the battlefield, thus allowing earlier correction of coagulopathy. Possible plasma preparations include FDP and lyophilized plasma and spray-dried plasma (43–45).

The use of dried plasma is hardly innovative. Dried plasma was used by the US Armed Forces to treat the wounded in World War II. Modern data exist regarding the use of dried plasma including *in vitro* data, animal model, and clinical data. *In vitro* analysis of FDP has demonstrated a small decrease in factors V and VIII (ranging from a 25% decrease to no decrease) when compared with fresh plasma. The global capacity to induce clot formation *in vitro* seems to be preserved (46). Storage for 24 months at room temperatures led to a total reduction of approximately 30% in factors V and VIII concentration and to a total reduction of 45% in fibrinogen concentration, compared with fresh plasma (45).

Several animal models comparing FFP and FDP have not demonstrated any difference in respect to coagulation parameters (44, 47).

As previously mentioned, dried plasma was already used in World War II by the US Armed Forces; however, early dried plasma was pooled from as many as 1,000 donors, introducing a substantial risk for blood-borne infections in the survivors (48). Significant advancements were made in the 1990s, when the French Blood Bank, which had been producing dried plasma since World War II, produced dried plasma pooled from under approximately 10 donors. Since then, advanced medical units of the French Army as well as the German Armed Forces have used FDP (49). Recently, French FDP was approved by the Food and Drug Administration for US Special Operations Forces use under limited contingency circumstances. Development, regulatory approval, and deployment of a dried plasma product for point-of-injury resuscitation are a high priority for the US Military. In a review of dried plasma use by the French Army in a field hospital in Afghanistan, no adverse events were reported (49). Several authors have already advocated the use of dried plasma on the battlefield as the next generation of DCR (3, 42, 50, 51). However, clinical data regarding field (at or near the point of injury) usage of all plasma preparations (both freeze dried and fresh frozen) are limited (32, 52).

Risks commonly associated with plasma transfusion (as with other blood products) include transfusion-related acute lung injury (TRALI), allergic transfusion reactions, and transfusion-associated volume overload. Less common risks include infectious disease transmission and white blood cell-associated risks. Conversely, becoming more widely appreciated are the similar deleterious effects of crystalloids and artificial colloids in severely injured patients (13, 14–18). The incidence of plasma-related adverse reaction varies and probably lies between 1:300 and 1:1,700 events per transfusion (53). Minor allergic reactions, including urticarial, pruritus, flushing, and so on, are the most common adverse reaction with an estimated incidence of 1% to 3% of transfusions (54). Severe adverse reactions, however, are much less frequent. The incidence of TRALI, probably the most significant adverse reaction associated with blood products transfusion probably, lies between 1:66,000 and 1:285,000 and the incidence of severe allergic reaction between 1:18,000 and 1:172,000 transfusions (54–57).

Notably, Starkey et al. (58) have shown that hemostatic resuscitation using high ratio of FFP to pRBCs was not associated with TRALI or acute respiratory distress syndrome, even in non-massively transfused patients. The incidence of blood-borne infections is rare, with reported incidence of less than 1:1,000,000 for hepatitis C and HIV and around 1:280,000 for hepatitis B transmission (59, 60). It is worth noting that most reports regarding major adverse reactions are related to the use of FFP, whereas less documentation exists regarding acute adverse reactions associated with FDP. The French Haemovigilance system has recorded more than 1,000 administrations of dried plasma, with no documentation of any significant adverse effect (50). The German Red Cross has recorded more than 200,000 U of their freeze-dried single-donor plasma (LyoPlas) with no evidence of a higher incidence of major adverse reaction compared with that of FFP with a 0.023% published incidence of anaphylactic shock and bronchospasm (45).

PRODUCT SELECTION

Several attributes are essential in a field deployable product. The reconstitution of the product had to be a fast and simple process, as its use is expected to be urgent and under austere conditions. The dried plasma had to be heat-stable and stored in field-compatible containers. Because rapid means to identify blood type at the point of injury are not available, we sought a product that would not need blood type matching, thus minimizing the risk for blood type incompatibility and alleviating the need for carrying multiple plasma types.

To date, efforts to develop Israeli FDP continue, forcing us to rely on commercially available foreign products. Flyp is a preparation manufactured by the French Blood Bank, from approximately 10 donors, whereas LyoPlas, manufactured by the German Red Cross, is a single-donor product. Both were considered by the IDF special task force. The main characteristics of these products are described in Table 1.

TABLE 1. Main characteristics of two dried plasma products

Product	LyoPlas (39)	Flyp (5, 7, 10)
Manufacturing country	Germany	French
Reconstitution time	Up to 10 min	Up to 5 min
Storage	Up to 25°C	Up to 25°C
Compatibility	Blood type-specific*	Universal ABO compatibility
Donor profile	Single donor (men or nulliparous women)	Up to 11 donors
Infection prevention	Repeated donor serologic testing, following a 4-mo quarantine	Amotosalen photoactivation
Container	Glass bottle	Glass bottle
pH	7–7.2	8
Reconstitution fluid	200 mL of sterile water	200 mL of sterile water
Shelf life	15 mo	24 mo

*Plasma from type AB donors enables universal compatibility.

Specifically, the infection risk reduction processes differ, as the production of the German Red Cross LyoPlas mandates all donors to undergo a second serologic screening 4 months following the initial plasma donation, thus making the final shelf life of the product somewhat shorter. The French blood bank produces dried plasma that undergoes a chemical process utilizing Amotosalen and UV radiation to minimize the risk for infection. Unlike the French product, which requires no blood type matching, the German LyoPlas requires ABO compatibility. Because of the IDF requirement for an ABO universal product that does not require blood type matching, the desired FDP is type AB male plasma.

Storage is another important factor to consider, as both the German LyoPlas and the French Flyp are to be stored at temperatures between 2°C and 25°C. Laboratory testing of LyoPlas demonstrated a decline in fibrinogen activity after storage for 34 days at 38°C to 42°C to 64% (45), indicating that the product can probably be used even after short periods of storage at high temperatures. At times of routine security missions, the majority of the IDF medical teams are mounted or forward operations base-based and are thus able to store FDP at moderate room temperatures. High-intensity conflicts and special operations will probably involve carrying plasma (by armored vehicles and foot-bound medical teams) at higher ambient temperatures. Consideration should then be given to discarding the FDP units after prolonged exposure to high temperatures.

The number of donors required for the production of an FDP unit is an important attribute. The single-donor LyoPlas probably offers a good safety profile with regard to the transmission of infectious diseases both known (e.g., prions) and unknown (61). On the other hand, being a single-donor product exposes the plasma units to a higher risk of specific clotting factor deficiencies due to the known high variability of clotting factor activity between individual donors (up to 100%) and antibody-mediated adverse events.

Therefore, both products met the main requirements we set and were both valid options, with the main differences being pooled versus single-donor products (each having both merits and drawbacks) and costs, which proved a significant consideration due to the intention for wide distribution.

The final choice of LyoPlas over the alternatives was made because of the documented and published safety profile, the preference for a single-donor product, and a somewhat simpler reconstitution process. The more compact glass bottle and significantly lower costs were considered as well.

SCENARIO, INDICATIONS, AND CLINICAL GUIDELINES FOR USING FDP AT THE POINT OF INJURY

The IDF Medical Corps policy is that plasma is the resuscitation fluid of choice for selected, severely wounded trauma patients, rather than crystalloid solutions, and should be transfused as near to point of injury as practicable. In accordance with this policy, FDP was distributed to all the IDF active duty medical teams on call, and the purchasing and distribution process continues, with the aim of equipping all ALS providers in the IDF. Being a blood product with limited

availability, a cost of hundreds of dollars per unit and a relatively short shelf life, the widespread distribution of FDP has substantial logistical and operational implications. The IDF has thus begun the distribution of FDP to ALS providers in the active component, relying on future development of a centralized, just-in-time supply for much larger reserve component medical units.

We assume that similar to its use in the hospital settings, the early prehospital use of plasma as a resuscitation fluid will eventually replace crystalloid solutions in patients with major hemorrhage, thus minimizing deleterious effects associated with crystalloids. Because of logistical difficulties (mainly those involved in the thawing process of FFP), a 1:1 ratio of FFP to pRBCs is rarely achieved unless thawed or liquid plasma is placed in the emergency department. Use of prehospital FDP to initiate transfusion will allow a balanced plasma-to-RBC ratio from the initial resuscitation. Furthermore, a reconstituted dried product that is similar in efficacy to day 0 thawed plasma would be preferable compared with days 3 to 5 thawed plasma unit (29).

Two distinct scenarios exist for prehospital infusion of plasma: (1) as a primary resuscitation fluid when RBC infusions are not available and (2) transfusion concurrent with RBCs, where available, serving as a procoagulant agent and intravascular volume replacement, consistent with the RDCR paradigm. The second scenario represents the classic indication. As mentioned, there is substantial evidence supporting plasma transfusion along with pRBCs transfusion (4). The first scenario (Fig. 1) depicts the IDF clinical practice guideline regarding dried plasma transfusion as a resuscitation fluid replacing the use of crystalloid solutions. While others have

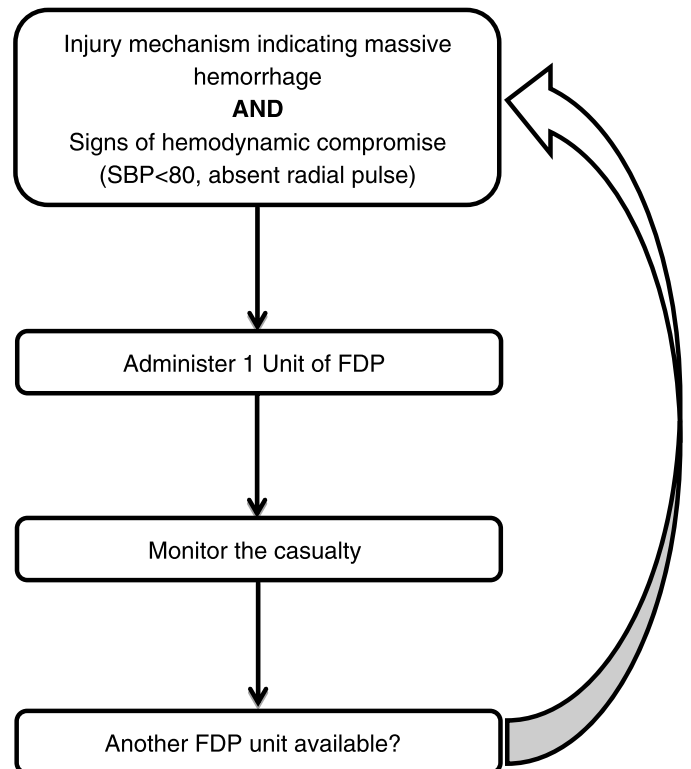


FIG. 1. The IDF dried plasma transfusion protocol. SBP indicates systolic blood pressure.

deployed thawed and liquid plasma in the prehospital settings, to the best of our knowledge we described the implementation of the first system-wide prehospital dried plasma transfusion protocol.

The criteria for plasma transfusion near the point of injury are similar to prehospital RBC transfusion and consist of a combination of injury mechanism and the patient's hemodynamic status. Clinical consideration is given to the mechanism of injury, which must indicate a massive hemorrhage (either noncompressible hemorrhage or a substantial compressible hemorrhage, i.e., penetrating injury, amputation, or explosion injury). Hemodynamic status must indicate hemodynamic shock defined as systolic blood pressure of less than 80 mmHg or nonpalpable radial pulse.

These treatment criteria are designed to avoid overtreatment. Being a blood product and not without risks, plasma transfusion should be used only in patients in whom a significant benefit would be achieved, setting a high threshold for treatment aimed to ensure that only patients with substantial bleeding and at a significant risk of developing coagulopathy would receive the plasma transfusion. In effect, a trauma casualty who met criteria for plasma transfusion and has received plasma on the battlefield will likely go on to receive continued blood component transfusion at the next level of care (NATO Role 2 or 3 facility, or initiated during tactical air evacuation).

Our protocol sets the resuscitation goal at a systolic blood pressure of greater than 80 mmHg or the return of palpable radial pulse. After transfusion of 3 U of FDP, providers are instructed to carefully consider further administration of FDP units. The rationale for this approach is the higher incidence of adverse reaction associated with large volumes of plasma administration. Furthermore, providers are encouraged to weigh the benefits of further plasma transfusions against the possible futility of such treatment for casualties who remain hemodynamically unresponsive to 3 U of plasma whose evacuation is still delayed. This is especially true for scenarios involving multiple casualties.

DISTRIBUTION

Freeze-dried plasma has been used in selected military care facilities worldwide, principally in Role 3 facilities. To the best of our knowledge, the IDF is the first to instruct the widespread use of plasma at the point of injury, by the entire ALS providers' population. Our medical personnel consist of a very wide spectrum of caregivers with varied clinical skills. The unified protocol is appropriate for paramedics, young general practitioners, anesthesiologists, and surgeons in far-forward intensive care and surgical units.

The prehospital use of FDP went through the Israeli regulatory process and was approved by the Surgeon General in November 2012 and presented to the Advisory Transfusion Committee to the Ministry of Health, with procurement and distribution beginning in December 2012.

Being an innovative treatment, we currently mandate a special training program conducted by the Trauma & Combat Medicine Branch to the first groups of relevant caregivers. In addition to widespread Role 1 distribution, FDP was provided

to both Role 2 facilities and to the IDF aerial evacuation unit; both of which have RBCs transfusion capabilities, thus allowing early 1:1 RBC-to-plasma ratio. Apart from evacuation of those wounded in action, the IDF aerial evacuation unit provides nationwide SAR (search and rescue) capabilities; therefore, FDP usage by this unit is expected to improve casualty care for both civilian and military population.

THE WAY AHEAD

Up to the date of this submission, we have successfully transfused a few dozen units of LyoPlas to trauma casualties at the point of injury. Preliminary data of the first 10 casualties treated by FDP transfusion at the point of injury are shown in Table 2.

No adverse events were documented or reported following the administration of FDP. Similarly, no difficulties were experienced with the reconstitution process of FDP, with a reported time of no more than several minutes from the decision to transfuse FDP to infusing the product.

Although this experience is naturally insufficient to definitively confirm clinical efficacy, it does reassure us that FDP administration at the point of injury is possible. All data concerning FDP administration, both clinical and operational, are collected in the form of mandatory after-action reports, which are then recorded and analyzed using the IDF trauma registry as part of an ongoing effort to learn and improve combat casualty care. Prehospital data may also have the benefit of being less affected by the well-described survival bias associated with transfusion ratios in the hospital settings (39). However, as the most severely injured casualties may die during initiation of point-of-injury advanced resuscitation attempts, some bias is still a concern.

The distribution of FDP throughout the IDF is a substantial step forward in RDCR implementation. Considerable challenges remain, including logistical, operational, and clinical, as well as the costs and the short shelf life that further limit the availability. Efforts to develop simple-to-use, cheap, and safe dried blood products should continue.

TABLE 2. Characteristics of casualties receiving FDP

Point-of-injury data	
n	10
ISS, median (IQR)	19 (17.5–23.5)
Mechanism of injury, % penetrating	80%
Heart rate, median (IQR)	112.5 (110–122)
Systolic BP, median (IQR)	88 (80–90)
Diastolic BP, median (IQR)	50 (26–58)
GCS, median (IQR)	12.5 (8–15)
FDP units per patient, median (IQR)	1.5 (1–2)
Mortality	20%
	1—KIA
	1—DOW

BP indicates blood pressure; GCS, Glasgow Coma Scale; IQR, interquartile range; ISS, Injury Severity Score; KIA, killed in action; DOW, died of wounds.

CONCLUSIONS

In carefully selected patients experiencing uncontrolled major hemorrhage, plasma is probably the optimal primary intravascular resuscitation fluid compared with colloids and crystalloids. Substantial evidence supports the use of plasma at a 1:1 ratio with pRBCs and the benefit of early administration of plasma in the hospital settings. Extrapolating from these data, prehospital use of plasma as close as possible to the point of injury may provide an important contribution to the care given to the hemorrhaging patient. Because of the inherent risks of blood product usage, we took great care to try and identify the subgroup of patients who will benefit most from plasma transfusion at the point of injury, while keeping crystalloid solution as the mainstay of treatment in others.

It is our hope that lessons learned from the full spectrum of the process undergone by the IDF Medical Corps, from concept, through doctrine to implementation in the field, will help others take this big leap in casualty care, thus improving the care provided to the wounded throughout the world.

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