

# Point-of-injury use of reconstituted freeze dried plasma as a resuscitative fluid: A special report for prehospital trauma care

Elon Glassberg, MD, MHA, Roy Nadler, MD, Todd E. Rasmussen, MD, Amir Abramovich, MD, MPH, Tomer Erlich, MD, Lorne H. Blackbourne, MD, and Yitshak Kreiss, MD, MPA, MHA, Ramat Gan, Israel

This special report describes the broader implications of prehospital fluid resuscitation in the context of what is the first reported case of point-of-injury use of reconstituted, lyophilized single-donor freeze dried plasma (FDP) as a resuscitative fluid.

The Israeli Defense Force Medical Corps (IDF-MC) has deployed FDP as another step in the evolution of casualty care to bring damage-control resuscitation closer to the point of injury as part of the multidisciplinary efforts to improve trauma victims' outcome.

## BACKGROUND

Trauma is the leading cause of death among adults between the ages 18 years and 40 years and the second most expensive public health problem in the United States ahead of cancer, mental illness, and diabetes.<sup>1</sup> Managing the burden of injuries from decades of wars has underscored the importance of trauma research aimed at reducing morbidity and mortality. Seminal reports from this research have shown that more than 80% of deaths on the battlefield occur before patients reach a medical treatment facility. Furthermore, one in four of these "prehospital deaths" have been shown to be potentially survivable, with improved strategies of patient care at the point of injury and en route to a treatment facility.<sup>2</sup>

To date, most advances in prehospital care of dying trauma patients have been aimed at maneuvers to control bleeding at the scene or en route to a hospital. Combat casualty care research in the United States and internationally has demonstrated the lifesaving effectiveness of tourniquets to control hemorrhage in certain patterns of extremity trauma.<sup>2</sup> Topical agents or bandages have also been developed for application by providers at the point of injury to control bleeding from open wounds. The concept of low-volume or hemostatic

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From the Surgeon General Headquarters (E.G., R.N., A.A., T.E., Y.K.), Israel Defense Forces, Ramat Gan, Israel; Department of Military Medicine (E.G., R.N., A.A., T.E., Y.K.), Hebrew University, Jerusalem, Israel; and US Army Institute of Surgical Research (T.E.R.), Joint Base Fort Sam Houston, San Antonio, Texas; The Norman M. Rich Department of Surgery (T.E.R.), The Uniformed Services University of the Health Sciences, Bethesda, Maryland; and US Army Trauma Training Center (L.H.B.), Miami, Florida.

Address for reprints: Elon Glassberg, MD, MHA, Medical Corps, Surgeon General's Headquarters, Military POB 02149, Israel Defense Force, Israel; email: idf\_trauma@idf.gov.il.

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resuscitation has been established to limit overuse of potentially harmful balanced salt solutions such as normal saline, lactated Ringer's solution, and even colloids<sup>3</sup> In a paradigm shift, medics now limit the use of these solutions, which may raise a trauma victim's blood pressure and cause dilution of clotting factors, which together may worsen bleeding.

These and other advances have resulted in lives saved in the prehospital setting. However, the most significant breakthrough in contemporary trauma care, relating to the selective infusion of the components of whole blood, has yet to be made available for routine prehospital use. The singular burden of injury from the wars of the last decade has laid bare the importance of death from hemorrhage, most commonly noncompressible truncal hemorrhage, and led to a reappraisal of dogma pertaining to types of prehospital fluid resuscitation. Largely because of recent military trauma research, the use of packed red blood cells, plasma, and platelets in the prehospital setting for patients having sustained severe injury has been pursued.

The beneficial effect of fresh whole blood as a resuscitative fluid to expand a patient's circulatory volume following trauma and shock has been observed for more than a century.<sup>4</sup> In addition to restoring circulatory volume, whole blood provides oxygen carrying capacity, vitally important clotting factors, platelets, and a buffering capability. Impracticality and safety issues have led to a disassembly of whole blood into its components to allow storage, shipment, safety assurance, and selective or targeted transfusion. In fact, one of the most significant lessons stemming from the wars in Afghanistan and Iraq has been that life saving was associated with balanced, component-based resuscitation, namely, platelets, plasma, and packed red blood cells,<sup>5</sup> in what is effectively a reassembly of the whole blood.<sup>6</sup>

Coagulopathy induced by trauma develops in 20% to 30% of combat casualties requiring blood transfusion, with a rise in prevalence with increasing injury severity,<sup>7</sup> and is associated independently with an up to a fivefold increase in mortality.<sup>6,8,9</sup> Rapid and aggressive treatment of coagulopathy induced by trauma (including prompt transfusion of plasma and platelets) was shown to reduce mortality in hemorrhaging patients,<sup>10,11</sup> therefore representing a major challenge for point-of-injury/combat casualty care phase, as recognized by providers around the world.<sup>12,13</sup>

Plasma infusion is considered to be the standard of care for treating trauma-induced coagulopathy. Plasma has demonstrated superiority over colloid fluids at reversing coagulopathy secondary to trauma and improving survival in animal models, even without transfusing red blood cells.<sup>13-15</sup> Furthermore, high

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plasma-to-red blood cell (RBC) ratio was found to be correlated with improved survival in trauma patients, with ratios approaching 1:1 demonstrating the most prominent effect.<sup>10,16,17</sup> This effect is further emphasized in the subgroup of patients requiring massive transfusion (defined as the infusion of >10 U of blood in 24 hours).<sup>18</sup> Early administration of fresh frozen plasma (FFP) was associated with increased survival, an effect diminished with delayed infusion, as demonstrated in a prospective study.<sup>10,17</sup> Recent studies have also demonstrated that the use of plasma in the prehospital setting, compared with control, was associated with significant improvement in the international normalized ratio on arrival, lower volume of crystalloid infusion, and elimination of plasma deficit at 24 hours.<sup>19</sup> The rapid availability of plasma is thus of increasing importance.<sup>10,20</sup> It is important to note that some of the advantages offered by the plasma are not fully understood at this time.<sup>21</sup> Unfortunately, FFP is not available in the prehospital setting, owing to the necessity to store the plasma at  $-18^{\circ}\text{C}$  to maximize its shelf life, mandating a thawing process that requires both equipment not available in the field and approximately 30 minutes to complete.

FDP, introduced in 1941, offers potential to serve as a resuscitation fluid in the field, requiring no refrigeration, simple, and safe. Used in the battlefields of the World War II and Korea, early dried plasma was pooled from as many as 1,000 donors, introducing a substantial risk for a blood-borne infections.<sup>22</sup>

FDP use was subsequently abandoned by the US blood bank owing to the risk of hepatitis,<sup>22</sup> with the thought being that with the introduction of helicopters and shorter evacuation times, the need for field resuscitation will diminish in a way that will not justify the risks involved in the plasma administration. Production continued in France, and during the Indochina war (1946–1979), almost 40,000 U of dried plasma was produced by the French Military Blood Institute.<sup>23</sup>

The German Red Cross produces a similar freeze dried and lyophilized plasma, collected from a single donor, offering an even more improved safety profile owing to a quarantine period of 4 months and a shelf life of 15 months.

Risks commonly associated with plasma transfusion (as with other blood products) include transfusion-associated lung injury, allergic transfusion reactions, and transfusion-associated volume overload, which are more common with massive transfusions of ABO-incompatible plasma.<sup>24–26</sup> Less common risks are infectious disease transmission, white blood cell-associated risk, and alloimmunization-related risks.<sup>24</sup> It is worth noting that to date, all reports regarding major adverse reactions were related either to the use of fresh plasma or FFP. The French Hemovigilance system has recorded more than 1,000 administrations of dried plasma, with no documentation of any significant adverse effect.<sup>23</sup> The German Red Cross reports the cumulative use of several hundred thousand units, with no major adverse effects attributed to the FDP recorded.<sup>13,27</sup> This improved safety profile is probably related to the removal of residual cells through filtration and using only those that come from male donors or those examined for leukocyte antibodies.

Recently, French-made FDP has been used for taking care of wounded soldiers admitted to intensive care units in Afghanistan.<sup>28</sup> To the best of our knowledge, point-of-injury

(i.e., use as primary resuscitation fluid) plasma use has not been reported since the 1950s, and point-of-injury single-donor plasma was not previously reported.

Modern data exist regarding the use of dried plasma, including in vitro data, animal model, as well as clinical data concerning its qualities and efficacy compared with that of fresh plasma and FFP. In vitro analysis of FDP has demonstrated a decrease of factor V and VIII by 80% and 75%, respectively, when compared with fresh plasma. However, the global capacity to induce clot formation in vitro was shown to be preserved.<sup>29</sup> Several animal models comparing FFP and FDP have not demonstrated any difference with respect to coagulation parameters,<sup>30,31</sup> and some have demonstrated a coagulation profile similar to that of fresh plasma and superior to the coagulation profile of FFP.<sup>32</sup> Several authors have already advocated the use of dried plasma in the battlefield as the next generation of damage-control resuscitation.<sup>12,13,33</sup>

As of now, owing to the years that have passed since the use of FDP by US providers, the Food and Drug Administration now requires reevaluation of the Food and Drug Administration before approving its use in the United States.<sup>34</sup>

The IDF-MC has embraced the concept of eliminating preventable deaths as part of the next 10-year force build-up plan and emphasizes point-of-injury care. As most trauma deaths occur in the prehospital setting and in the first hour after injury, this is where most lives can be saved.<sup>2</sup>

These efforts include deploying advanced lifesavers to the front lines; the use of effective tourniquets; resuscitation fluids that ameliorate the trauma-induced coagulopathy and acidosis; haemostatic agents and more, along with constant feedback from rapid and professional investigations of incidents involving casualty care; as well as a detailed trauma registry and goal-directed research efforts, to found the basis for our clinical practice guidelines.

Included in the attempts to optimize the care provided to the wounded before reaching the advanced care facilities (whether civilian trauma centers or deployed military medical units), great emphasis is on applying damage-control resuscitation principles that call for limiting intravascular volume replacement to the minimum required to perfuse vital organs and the use of blood products for resuscitation, as part our resuscitation protocols. Thus, IDF-MC advanced lifesavers (physician and EMT paramedics) limit the volume of crystalloids administered and carry tranexamic acid (TXA).<sup>3,35</sup>

As of January 2013, FDP was introduced to the IDF-MC as the advanced resuscitation fluid for trauma casualties, under a protocol developed by the Trauma and Combat Medicine Branch of the IDF-MC, with the help of leading trauma and hematology experts, both in Israel and in the United States. The FDP, which every physician and paramedic in the IDF is equipped with, is meant to serve forth and for all as a resuscitation fluid, a volume expander, excellent buffering capacity, and a source for coagulation factors, taking into account some obvious advantages such as being initially pH balanced (unlike the saline or lactated Ringer's solutions with a pH of 5.4 and 6.2, respectively).

The product chosen by the IDF-MC was LyoPlas (DRK-Blutspendedienst West, German Red Cross) owing to the qualities mentioned previously, the improved safety index and

record, the simple and rapid reconstitution process, along with the advantage of its being a commercial product stored at ambient temperature of 2°C to 25°C. The reconstitution process involves infusion of the supplied water for injection via a supplied transfer set to the bottle containing the powdered plasma, which completely dissolves within a few minutes. Transfusion of the plasma then takes place through a 170- $\mu$ m to 230- $\mu$ m standard filter. The use of type AB male or those examined for leukocyte antibodies ensures the product to be suitable for all blood types.

### The First Use of FDP at the Point of Injury

An IDF paramedic responded to the scene of a motor vehicle crash, which injured an individual who sustained severe blunt abdominal, pelvic, and head trauma (Glasgow Coma Scale [GCS] of 8). The patient had a systolic blood pressure of 80 mm Hg and a heart rate of 110 beats per minute. More than an hour drive from the nearest hospital, the team of first responders called for rotary wing evacuation and began resuscitation efforts while awaiting the arrival of the evacuation platform. Interventions included orotracheal intubation, placement of two peripheral intravenous lines, and TXA administration. FDP (distributed as a powder) was reconstituted and then administered as the resuscitation fluid. Within 30 minutes of the first responders' arrival, the patient was airlifted to the nearest trauma center (25-minute flight), sedated, and ventilated with a blood pressure of 110/80.

Upon arrival to the trauma center, 94 minutes after injury, the casualty was admitted to the trauma intensive care unit. Admission heart rate was 86, blood pressure was 140/100, saturation was 100%. Emergency department computed tomography demonstrated a bilateral ischial open pelvic fractures, vertebrae (L3, L4) compression fractures, and perineal hematoma. Brain tomography result was normal. The patient's admission hemoglobin was 13.7 g/dL, platelets count of 267 K, lactate of 3.74 mmol/L (range, 0.5–2.4 mmol/L), international normalized ratio of 1.11, and pH level of 7.34. The patient (with an Injury Severity Score [ISS] of 22) did not require subsequent blood product administration or surgical intervention. After an uncomplicated course of observation in the intensive care unit, the patient was extubated within 12 hours and was eventually transferred to a secondary hospital, walking and under antibiotic therapy.

### DISCUSSION

While the favorable response to the point of injury care in this case cannot be attributed to the administration of FDP, we chose to report this first use of FDP at the point of injury because we believe that it assists in restoring perfusion while avoiding unnecessary and possible harmful effects of crystalloid administrations and, when administered as early as possible, offers potential for increasing the survival of casualties by minimizing trauma induced coagulopathy and acidosis, bearing in mind that administration of blood products should be performed with appropriate caution. FDP use may be further beneficial because it allows for earlier plasma administration that could be followed by packed RBCs upon arrival to the next level of care, achieving the desired ratio for blood products

(1:1:1 of packed RBCs, plasma, and platelets), which has been shown to carry a survival benefit.<sup>16</sup>

To the best of our knowledge, this special report is the first and only documented use of single-donor FDP at the point of injury. The case demonstrates the possibility of overtreatment and the need for better monitoring systems for diagnosing shock and guiding prehospital resuscitation. Injury patterns and modeling with vital signs will help guide plasma therapy in the short term. As experience with FDP administration continues to accumulate within the IDF-MC and others around the world, lessons learned and after-action reports may help to update and tune our clinical practice guidelines for FDP administration, as needed.

This landmark case described here is not the trigger to change policies but rather to describe our efforts to implement new modalities of therapy in the prehospital settings and generate hypotheses for trauma research. It is another important step in the continuous effort to improve prehospital resuscitation paradigm by focusing on forwarding relevant technologies established in fixed medical facilities to the point of injury, especially those coping with hemorrhage control. In this report, we shed some light on an international collaboration process among United States, Israel, and others, aimed to alter the outcome in a structured trauma care system in terms of safety and efficacy as occurred with other clinical practice guidelines constructed as a joint effort, such as for the use of TXA. This effort needs further study, and it is our hope that this special report will form the foundation for future clinical experience and case series. It is highly probable that future advances, which are currently happening, will affect the way trauma patients are treated. It is our view that in trauma patients experiencing extensive hemorrhage, plasma should be the resuscitation fluid of choice, in both military and civilian scenarios, both in rural and in urban point-of-injury care, thus offering potential for increasing the survival of casualties and saving lives around the world.

### AUTHORSHIP

E.G. drafted the paper. All authors have contributed significantly to article preparation, literature review, data acquisition and interpretation and critical revision of the manuscript.

### DISCLOSURE

The authors declare no conflicts of interest.

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