BRIEF RESEARCH REPORT

Freeze Dried Plasma Administration Within the Department of Defense Trauma Registry

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ABSTRACT

Hemorrhage is common among the combat injured, and plasma plays a vital role in blood product resuscitation. Regarding freeze dried plasma (FDP), US forces have had limited access to this product compared with other countries. In 2018, the US Food and Drug Administration provided emergency authorization for Department of Defense (DoD) use through the newly congressionally directed military use pathway. We describe the documented uses of FDP by US forces by performing a secondary analysis of two previously described datasets from the DoD Trauma Registry. In 11 identified cases, the median age was 28; cases were most frequently male, part of Operation Enduring Freedom, with US military affiliation, and injured by explosive or gunshot wound. The median injury severity score was 21; most did not receive a massive transfusion. Most survived to hospital discharge. Ongoing surveillance is warranted to optimize the implementation of FDP into military prehospital guidelines, training, and doctrine.

KEYWORDS: *freeze dried; plasma; combat; military*

Introduction

Hemorrhage is the leading cause of potentially preventable death in US military combat casualties.[1] Prehospital blood products have a demonstrated mortality benefit.[2] Specifically, plasma treats the coagulopathy of trauma, making it a valuable resource for resuscitation.[3] However, the use of blood and plasma products in austere environments is logistically challenging due to weight, volume, and refrigeration requirements. Maintaining an active cooling container in a combat zone is unreliable for long periods of time, and having a reliable refrigeration source near the point of injury is challenging given the often-limited space in vehicles and helicopters.[4] One proposed solution to this problem is FDP, a fluid-extracted resuscitation product that requires reconstitution before use.

Emerging in the 1930s, FDP was originally produced and used by Allied powers during WWII using pooled products from multiple donors.[5–7] As the use of FDP was realized and began to spread, it became apparent that the transmission of hepatitis C virus due to improper donor screening was becoming an issue, resulting in the halt of its use by US forces in 1968.[8] The French Military Blood Institute continued to produce and use FDP in French military forces, but this was ended in 1985 due to risk of HIV infection.[9] FDP was largely abandoned in favor of albumin as a safer alternative for war resuscitation despite its limited use for trauma resuscitation.[10,11] However, as reliable pathogen detection and reduction methods became available in the 1990s, FDP returned as a favorable product is combat resuscitation.[12] The French military resumed production and use of FDP in 1994, and its use has progressively spread among European allies.[9, 13] With the use of FDP becoming more widespread in war resuscitation, it was only time until the United States revisited the approval of its use in combat care.

Due to the lengthy timeline for US Food and Drug Administration (FDA) approval for a US-based FDP product, the US military received FDA approval to collaborate with the French Centre de Transfusion Sanguine des Armées and use their dried plasma products in combat casualty care. The US military has had limited use of the French lyophilized plasma (FLyP) through an expanded access Investigational New Drug (IND) application since 2011. In July 2018, the FDA announced that it had granted emergency use authorization (EUA) to the US DoD to enable the emergency use of FLyP when fresh-frozen plasma (FFP) is not available or practical (Figure 1).[14] However, acquisition efforts for military-wide use are still under way. Despite the use of this life-saving intervention under the IND for several years, its use by US forces has not been examined beyond very limited reports. We are seeking to describe the use of this FDP product under the IND status.

Goal of This Study

We describe the documented uses of experimental freeze-dried plasma use within the DoD Trauma Registry (DoDTR).

Methods

Data Acquisition

We identified cases as part of two studies from the DoDTR, which have been previously described with specific attention to prehospital and emergency department interventions performed

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on trauma patients with data ranging from January 2007 to August 2017.[15–17] The US Army Institute of Surgical Research (USAISR) regulatory office reviewed protocols H-16-005 and H-17-020 and determined they were exempt from institutional review board oversight. We obtained only deidentified data.

DoDTR Description

The DoDTR, formerly known as the Joint Theater Trauma Registry (JTTR), is the data repository of trauma-related injuries for the DoD.[18-22] The DoDTR includes documentation regarding demographics, injury-producing incidents, diagnoses, treatments, and outcomes following injuries. The registry includes US/non-US military and US/non-US civilian personnel from the point of injury to final disposition during war and peacetime. The DoDTR consists of patients admitted to a Role 3 (fixed-facility) or forward surgical team (FST) with an injury diagnosis using the *International Classification of Diseases, 9th Edition* (ICD-9) between 800-959.9, near-drowning/drowning with associated injury (ICD-9 994.1) or inhalational injury (ICD-9 987.9), and trauma occurring within 72 hours from presentation to a facility with surgical capabilities.

Analysis

We performed all statistical analysis using Microsoft Excel (version 10, Redmond, WA) and JMP Statistical Discovery from SAS (version 13, Cary, NC). We used descriptive methods for reporting on the cases. We defined a massive transfusion as at least 10 units of packed red blood cells and/or whole blood within the first 24 hours.

Results

Within our two datasets, we identified 11 cases of FDP use by US forces. The median patient age was 28 years (interquartile range [IQR] 25–31 years), and patients were most frequently male, part of Operation Enduring Freedom, of US military affiliation, and injured by explosive or gunshot wound. The median injury severity score was 21 (IQR 17–33), and most did not receive a massive transfusion and survived to hospital discharge (Table 1).

Discussion

Our study identified 11 cases of reported FDP use by US coalition forces. Expectedly, those receiving FDP were most likely to have been injured by gunshot wound or explosive mechanisms, as that makes up the bulk of combat injuries seen in deployed military treatment facilities.[17] The mortality rate in this cohort was about 1:11, which corresponds to the reported in-hospital mortality rate for transfused and admitted coalition forces in Iraq.[23] In this series of cases, we summarize the history of FDP use by US forces during the chaos of combat.

FIGURE 1 *French FDP kit.*

(Courtesy of USAMMDA Public Affairs.)

Previous studies have examined the effectiveness of FDP to treat coagulopathy as compared with FFP showing similar efficacy.[24] Other studies on the use of FDP in a combat setting are limited, with the only in depth analyses coming from French forces in Afghanistan.[25] However, the results from this study were especially comparable to ours. Although a larger cohort was examined, the mechanisms of injury and rate of mortality examined in the cohort that received FDP were akin to those seen in our study, further contributing to the French summarization of FDP use. Additionally, the ease of use of FDP was reported, attributing this to the short reconstitution time and convenience of the product.[26]

While our study provides early examination into the use of FDP by US forces, most frequently Special Operations Forces (SOF), but by virtue of the access restrictions, these case data are limited, and ongoing surveillance is warranted. Understanding the environments in which FDP is used most often by US forces and medical personnel's familiarity with the product can be used to inform predeployment training as FDP continues to expand in the combat setting. Although the product

TABLE 1 *Description of Casualties Who Received FDP for Trauma-Related Injuries*

Age (y)	Sex	Military Operation	Patient Affiliation	Mechanism of Injury	Injury Severity Score	Massive Transfusion	Outcome
21	Male	OIR	Partner force	GSW	10	No	Alive
26	Male	OEF	US military	Explosive	21	Yes	Alive
25	Male	OEF	Coalition	Explosive	45	Yes	Alive
31	Female	OEF	Humanitarian	GSW	20	No	Alive
31	Male	OEF	US military	GSW	25	No	Dead
24	Male	OEF	US military	Explosive	45	Yes	Alive
30	Male	OEF	Partner force	Blunt NOS	17	No	Alive
27	Male	OEF	Humanitarian	Explosive	17	No	Alive
45	Male	OEF	Humanitarian	GSW	30	No	Alive
45	Male	OFS	US government	Explosive	33	Yes	Alive
28	Male	OFS	US military	GSW	17	No	Alive

OIR, Operation Inherent Resolve; OEF, Operation Enduring Freedom; OFS, Operation Freedom's Sentinel; GSW, gunshot wound; NOS, not otherwise specified.

has shown to be safe in trauma resuscitation, its benefit to US military forces will not be fully realized until its use become more widespread among non-SOF medical personnel in the combat environment.

Study Limitations

There are several limitations of this study. First, the observational nature of our investigation limits the conclusions that can be drawn. Second, for an encounter to be generated within the DoDTR, casualties must arrive at the forward surgical team or fixed-facility alive or with ongoing interventions; thus, we do not have data on casualties who may have received FDP and died on the battlefield. Last, and most important, the data within the registry require accurate documentation so casualties in which FDP was administered but without the intervention documented would have been missed. Previous publications have demonstrated poor data capture in the deployed setting.[27]

Conclusions

We report on 11 cases of FDP use within the registry. With the recent FDA approval of FDP for military use, ongoing surveillance is warranted to optimize its implementation into prehospital guidelines, training, and doctrine.

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Disclosures

The authors have nothing to disclose.

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Disclaimer

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Author Contributions

CMC performed the data interpretation and manuscript drafting/development. GC performed data interpretation and manuscript development. SGS is the principal investigator for the overall study and performed data analysis, data interpretation, and critical revisions as the senior author. All authors contributed significantly to this study.

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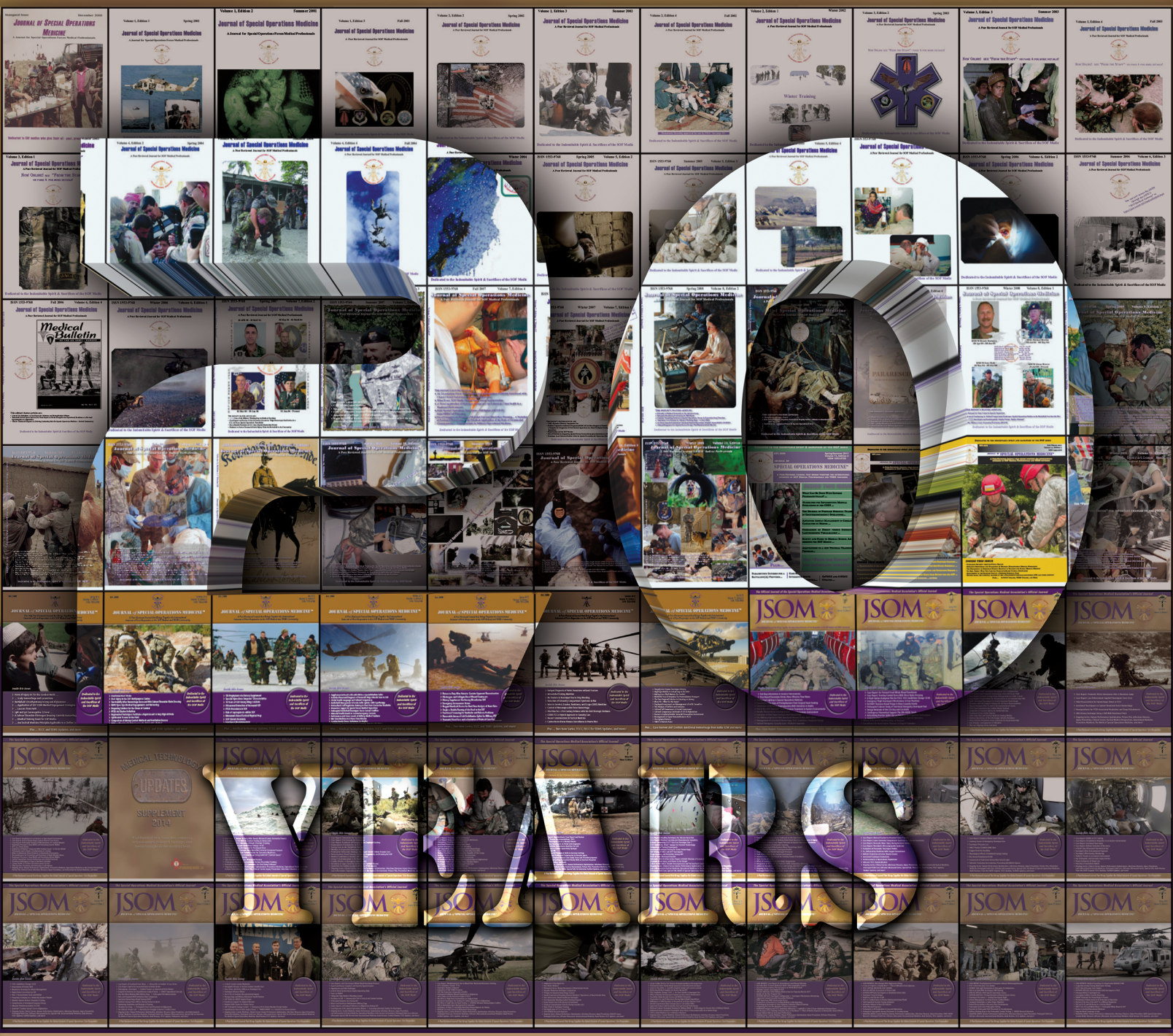

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