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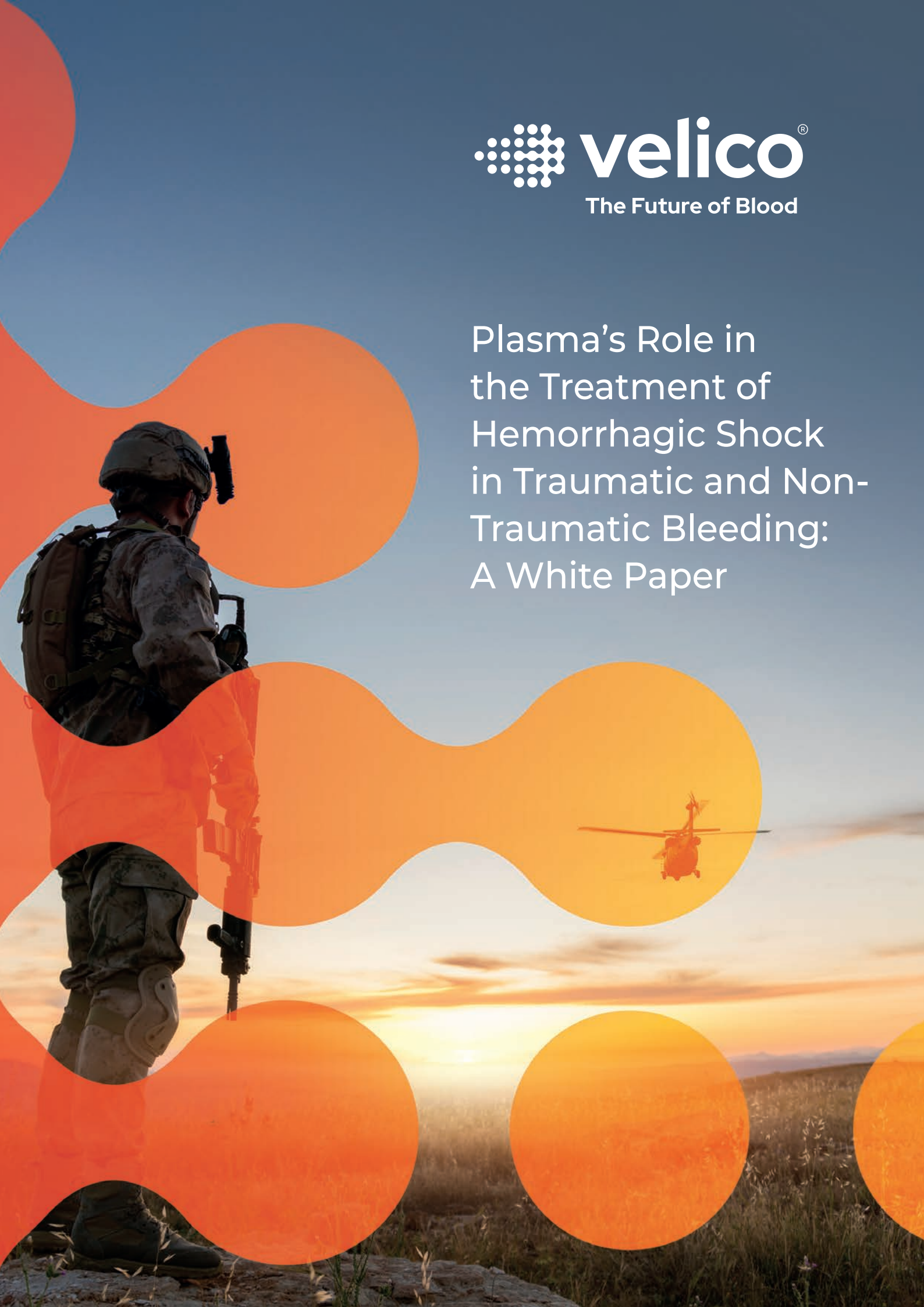
The Future of Blood

Plasma's Role in the Treatment of Hemorrhagic Shock in Traumatic and Non-Traumatic Bleeding: A White Paper



Hemorrhage is the leading cause of death after injury, with the mean time to transfusion of 2.6 hours after admission to an urban level I trauma center. Upon arrival at a trauma center at least 25% of severely injured patients are already coagulopathic (1). In the United States alone there are 30,000 preventable trauma deaths per year. It is estimated that 36% of prehospital deaths are preventable with the use of plasma (2). If hemorrhage due to medical conditions (e.g., gastrointestinal hemorrhage, post-partum hemorrhage, intracerebral hemorrhage) were to be included, this number would be substantially higher, possibly by two times. With the number of deaths due to motor vehicles and firearms rising sharply, the “opportunity pool” for plasma usage will continue to rise.

Plasma was introduced in several forms as a therapeutic modality during World War II for the treatment of hemorrhage caused by battlefield injury. While medics and other medical staff observed that this intervention was beneficial, complications, primarily transfusion-associated viral hepatitis due to pooling of plasma from multiple donors led to the demise of this approach. Between the Korean and Vietnam wars, crystalloid infusion became the preferred treatment of hemorrhagic shock. While crystalloids were thought to have benefits, they only supply volume and are associated with risks, primarily adult respiratory distress syndrome. Depending on the study, the observed increase in ARDS and organ failure is 9-40% (3) As a result, clinicians sought a better solution.

The pathophysiologic consequences of major hemorrhage are hypothermia, acidosis and resuscitative hemodilution, which, if allowed to progress, results in trauma-induced coagulopathy (TIC). In the 1990s it was found that early resuscitation is crucial for preventing coagulopathy, exsanguination, and cardiac arrest. During the wars in Iraq and Afghanistan clinicians learned that in the prehospital and hospital environment, a “balanced” transfusion strategy which approximates whole blood, with a 1:1:1 ratio of packed red blood cells to platelets to plasma provides a survival benefit (4). While crystalloid has continued to be used over the last 2 decades, its role as the standard of care has been eclipsed by blood products. From 2016 to 2023 at least 13 guidelines were issued in the United States or abroad which recommend the use of blood products including plasma (5,6). However, such a strategy is constrained by blood product availability and logistical considerations. As of late 2023 less than 1% of prehospital emergency medical vehicles routinely carry blood products. Clearly, products which reduce or eliminate these constraints are highly desirable.

In the setting of hemorrhagic shock, plasma provides the full spectrum of essential coagulation factors and increases intravascular volume by enhancing colloidal osmotic pressure. Logistical considerations and cost influence the availability of plasma-derived products. The most widely used product today is thawed plasma (FP-24). It must be stored at refrigerated temperatures and has a 5-day expiration period. Lyophilized plasma is not approved in the US, stored in glass bottles, is prone to significant breakage and degrades rapidly after thawing. Spray-dried plasma (Frontline ODP) can be stored at both refrigerated and room temperature and has a targeted shelf life of 6 months (room temperature) to 2 years (refrigerated). The product (a dry powder) is stored in a rugged pouch and therefore can withstand tough conditions. Rehydration is accomplished with sterile water and the powder goes into solution in approximately 3 minutes..

Clinical Studies of Plasma

Much of the literature is supportive of prehospital plasma in the treatment of hemorrhagic shock. The two most important studies are the Pragmatic, Randomized Optimal Platelet and Plasma ratios (PROPPR) and Prehospital Plasma During Air Medical Transport (PAMPer). Both studies demonstrated a survival benefit. The PROPPR study supported the use of 1:1:1 resuscitation ratio in hemorrhagic shock. (7) The PAMPer study was randomized to either thawed plasma or saline to patients being transported by air ambulance to a trauma center (8). In a post-hoc analysis the survival benefit was greatest with transport times longer than 20 minutes. The plasma arm was associated with a 10% survival advantage (9). In the United States there are “care deserts” created by the closure of rural hospitals, the implications of which are longer transport times from points of injury to the nearest trauma center (10). High-risk pregnancies in rural settings increase the odds of post-partum hemorrhage; long transport times increase the chances of maternal mortality. These conditions underscore the value of FrontlineODP, by having plasma available at the pointof-care without the limitations of other liquid blood products.

In a 2021 review article prehospital plasma was shown to have a mortality benefit in patients with blunt trauma, moderate transfusion requirements, traumatic brain injury and/or transport times of greater than 20 minutes, as well as those with specific cytokine profiles (11). To underscore the importance of point-of-care resuscitation, a recent study concluded that for every 1-minute delay in prehospital resuscitation and administration of blood products, there was a 2% increase in the odds of 30-day mortality (12).

The Take-Home Message

Early administration of blood products saves lives.

Not all studies of plasma have had positive outcomes. In a randomized study by Moore et al (2018; The Lancet: 392; 283-291) prehospital administration of plasma provided no survival advantage vs. saline (13). However, this study was done in an urban environment and the transit time was only 19 minutes for the plasma-first arm.

Cost-Effectiveness of Early Administration of Plasma

In a secondary analysis of the PAMPer trial, thawed plasma demonstrated a cost benefit with an incremental costeffectiveness ratio of $50,467 per Quality Adjusted Life Year (QALY) compared with standard of care (Hrebinko et al. JAMA Surgery. 2021; 1131-1139)(14). When considering only patients injured by a blunt mechanism, the incremental cost-effectiveness ratio decreased to $37, 735 per QALY. Therefore, thawed plasma was lifesaving and cost-effective compared with standard of care.

Manufacturing of Spray-Dried Plasma: Frontline ODP (On Demand Plasma)

A de-centralized model of manufacture, by regional blood centers, is envisioned, with FrontlineODP produced from single-donor plasma (whole blood or apheresis-derived). The product will be made in blood centers alongside routine blood component operations. Component laboratory staff are typically able to operate the Frontline system with minimal training. Blood centers-based production has the advantage of enabling the availability of dry plasma that can be inventoried anywhere-blood centers, hospitals, emergency medicine services or military bases. The product can be made available in urban, suburban, rural, austere and wilderness settings. If desired, autologous plasma products can be supplied to populations at risk of severe injury (military, EMS' law enforcement). Additionally, the product can be part of a national stockpile of essential medicines, available as a vital link in preparedness for a national emergency, including a nuclear accident or nuclear explosion. Decentralized manufacture reduces risk of a centralized, single-site approach which is vulnerable to a number of potential threats including acts of terrorism, climatic or regulatory stoppages. Such a situation was noted in 2017 when Hurricane Maria devastated the pharmaceutical and medical device industry in Puerto Rico, resulting in shortages of essential medicines and other products for the next 2 years. The 2023 tornado destruction of a pharmaceutical manufacturing plant in North Carolina reinforces that risk.

Characterization

Coagulation factor levels are comparable to conventional plasma products. There is no evidence of factor activation by the process. Residual moisture is about 1%. Testing for functionality, either through thromboelastography, thrombin generation or microfluidic measurement of clot generation demonstrate no significant differences with fresh frozen plasma.

Clinical Performance

In a dose-response study of autologous ODP in healthy subjects, no adverse events have been reported.

Summary

Frontline ODP is a spray-dried plasma product derived from volunteer blood donors. All essential coagulation factors remain intact and in physiologic concentrations. FrontlineODP is optimized for rapid response at the point of injury and has the logistical advantage of flexible storage options including It is stored refrigerated or room temperature conditions. In a doseresponse, randomized controlled study, no adverse effects have been observed. It is bioequivalent to FFP or FP24.

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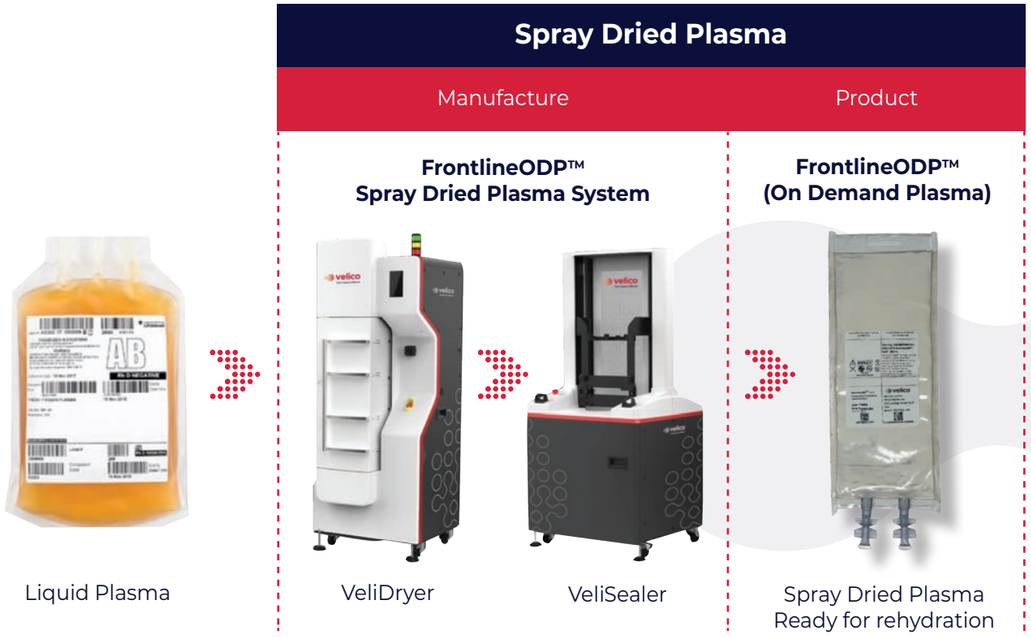

FrontlineODP™ System

- Decentralized manufacturing
- Integrates into blood bank labs
- Designed for ease of use and operation

FrontlineODP™ (On Demand Plasma)

- Rehydrates in 2.5 minutes
- Comparable Factor Activity
- Ultra Lightweight PVC Bag
- Optimized for Extended Shelf Life

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The Future of Blood

Together, we can make a real difference

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