Freeze dried plasma and fresh red blood cells for civilian prehospital hemorrhagic shock resuscitation

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BACKGROUND: The last decade of military trauma care has emphasized the role of blood products in the resuscitation of hemorrhaging patients. Damage-control resuscitation advocates decreased crystalloid use and reintroduces blood components as primary resuscitative fluids. The systematic use of blood products have been described in military settings, but reports describing the use of freeze dried plasma (FDP) or red blood cells (RBCs) in civilian prehospital care are few. We describe our preliminary results after implementing RBCs and FDP into our Helicopter Emergency Medical Service (HEMS).

METHODS: We collected data on the use of FDP (LyoPlas N–w (AB)) during a 12-month period from May 31, 2013, to May 30, 2014, before RBC (0Rh (D) negative) introduction in June 2014. FDP and RBCs were indicated in trauma and medical patients presenting with clinical significant hemorrhage on scene. Data were obtained from HEMS registry and patient records.

RESULTS: Our preliminary results show that FDP was used in 16 patients (88% males) during the first year. Main patient categories were blunt trauma (n = 5), penetrating trauma (n = 4), and nontrauma (n = 7). Ten patients (62%) were hypotensive with systolic blood pressures less than 90 mm Hg on scene. The majority (75%) received tranexamic acid. Of 14 patients admitted to the hospital, 11 received emergency surgery and 8 needed additional transfusions within the first 24 hours. No transfusion-related complications were recorded. Two of the FDP patients died on scene, and the remaining 14 patients were alive after 30 days. Early results from the recent introduction of RBC show that RBCs were given to four patients. Two patients (one penetrating trauma and one blunt trauma patient) died on scene because of exsanguination, while additional two patients (one blunt trauma patient and one with ruptured aortic aneurism) survived to hospital discharge.

CONCLUSION: Our small study indicates that introduction of FDP into civilian HEMS seems feasible and may be safe and that logistical and safety issues for the implementation of RBCs are solvable. FDP ensures both coagulation factors and volume replacement, has a potentially favorable safety profile, and may be superior to other types of plasma for prehospital use. Further prospective studies are needed to clarify the role of FDP (and RBCs) in civilian prehospital hemorrhagic shock resuscitation and to aid the development of standardized protocols for prehospital use of blood products. (*J Trauma Acute Care Surg*. 2015;78: S26–S30.

LEVEL OF EVIDENCE: Therapeutic study, level V.

KEY WORDS: Plasma; shock, hemorrhagic; blood transfusion; emergency medical services; air ambulances.

Military prehospital blood transfusion is described as early as World War I (WWI), and transfusion-based resuscitation continued to be the standard of care throughout WWII as well as the Korean and the Vietnam conflicts. Plasma as replacement fluid for blood loss peaked during WWII, and dried plasma was the dominant source of plasma because of logistical and storage advantages.[1]

Submitted: September 2, 2014, Revised: January 9, 2015, Accepted: February 2, 2015.

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Presented at the 4th Annual Remote Damage Control Resuscitation Symposium of the Trauma Hemostasis and Oxygenation Research Network, June 9–11, 2014, in Bergen, Norway.

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DOI: 10.1097/TA.0000000000000633

Since the Vietnam War, crystalloids and colloids have been the predominant resuscitation fluids in hemorrhaging patients treated by civilian emergency medical services (EMS) worldwide.[2] The last decade of military trauma care has again emphasized the role of blood products in the resuscitation of hemorrhaging patients in the field.[3] The modern use of plasma has also evolved from treating civilian and military combat casualties, recognizing that resuscitation with crystalloids or colloids may contribute to dilutional coagulopathy in trauma patients.[4] The use of lyophilized plasma may be less likely to worsen coagulopathy, although solid outcome data on the prehospital use of plasma are still lacking.[5] In the absence of an ideal resuscitation fluid for hemorrhagic shock patients, the concept described as damage-control resuscitation (DCR) advocates reducing crystalloid use and reintroduces blood components as primary resuscitation fluids.[6]

The systematic prehospital use of blood products like red blood cells (RBCs) and freeze dried plasma (FDP) have recently been described in military settings, but reports describing its use in suspected hemorrhagic shock in civilian EMS are scarce.[7,8] The main objective of this study was to evaluate the

feasibility of introducing RBC and FDP into a civilian Helicopter EMS (HEMS), which includes describing how these products were made available for prehospital use, how we minimize waste, and how we address safety issues.

PATIENTS AND METHODS

Design and Ethics

This study was designed as a retrospective observational study and was performed at the Helicopter EMS in Bergen, Norway. HEMS-Bergen operates 24/7/365 and responds to both medical and trauma cases with a 60:40 ratio. Our HEMS is staffed by an experienced prehospital anesthesiologist, a flight paramedic (HEMS crew member), and a pilot. The Privacy Protection Supervisor at Haukeland University Hospital approved the study as quality assurance in the health service, and this is not subject to approval from the Regional Committees for Medical Research Ethics in Norway.

RBC Onboard HEMS

RBC was introduced on our HEMS on June 25, 2014, and is available to bring onboard 24/7. Prehospital transfusion of RBCs is indicated in patients with clinical significant hemorrhage on scene, based on clinical assessment by the attending physician. Additional indications are systolic blood pressure less than 90 mm Hg and minimal response to initial fluid resuscitation. Two units of fresh RBCs (0Rh (D) negative) are supplied every seventh day from Haukeland University Hospital's blood bank (delivered close to the day it is produced) and stored in a refrigerator at 4°C next to the helicopter in a transportable "golden hour box." The boxes were pretested and validated for the storage of RBCs, for example, temperature stability. If not used by HEMS within a week, the RBCs are returned to the blood bank and can be used in the university hospital for an additional 28 days. Supplying the prehospital chain with fresh RBCs stored for less than 8 days is less likely to cause wastage and also provides prehospital hemorrhaging patients with RBCs with minimum "storage lesions." RBC and/or FDP transfusions are documented in hospital records with product information inclusive of batch number, and a corresponding transfusion record is sent to the Department of Immunology and Transfusion Medicine at Haukeland University Hospital.

FDP (LyoPlas)

LyoPlas N-w (Deutsches Rotes Kreuz–Blutspendedienst West, Hagen, Germany) is quarantined single-donor plasma from male donors or donors tested negative for human leukocyte antigen antibodies. We currently use only AB plasma, but it is available in all blood groups: O, A, B, AB. Being an EU-approved blood product and based on specifications and documentation by Deutsches Rotes Kreuz, the Norwegian Directorate for Health and Social Affairs approved the import of LyoPlas N-w to Norway by the Department of Immunology and Transfusion Medicine at Haukeland University Hospital, Norway. Our HEMS may request LyoPlas N-w through our Department of Immunology and Transfusion Medicine. Criteria for prehospital transfusion of FDP are the same as those stated for RBCs earlier. FDP is stored at room temperature in the fast-response car and in the helicopter, making it readily available. LyoPlas N-w powder dissolves in 200 mL of sterile water and is ready for injection in 3 minutes to 6 minutes, depending on water temperature. All HEMS crew, including flight paramedics and pilots, were trained in preparing and administering LyoPlas on physician's orders. It can be administered through intravenous or intraosseous vascular routes. After the recent introduction of RBC, we seek a "plasma first" transfusion policy. Alternative resuscitation fluids in our service are crystalloids (Ringer's acetate).

Data Acquisition

All patients receiving FDP by our HEMS during a 12-month period from May 31, 2013, to May 30, 2014, were retrospectively identified and included in the study. Patients receiving RBCs during a 6-month period following its implementation were also identified. Our HEMS covers a population of approximately 500,000 people. Data were obtained from HEMS and patient medical records at Haukeland University Hospital. The severity of illness or trauma in patient groups was scored according to The National Advisory Committee on Aeronautics (NACA) severity score.[9] We collected baseline characteristics from prehospital and in-hospital treatments (e.g., systolic blood pressure, heart rate, and respiratory rate), along with data on transfusions, surgery, and outcome. In case of missing data, the attending prehospital HEMS anesthesiologists provided details to supplement and clarify the data.

Statistical Analysis

We evaluated the characteristics and clinical progress in transfused patients between prehospital and in-hospital phases. Shock characteristics and interventions were analyzed. Continuous variables are expressed as median (range), and categorical variables are expressed as numbers (percentage). The statistical package for the IBM SPSS statistics (SPSS, version 21, IBM Corporation, Armonk, NY) was used to analyze the data.

RESULTS

Patients Receiving FDP

We included 16 consecutive patients receiving FDP on HEMS missions during the 12-month study period. All patients were included before RBC was available on HEMS. Two patients died on scene, and the remaining 14 were admitted to the emergency department (ED) at Haukeland University Hospital. Of all the patients, 62% were transported to the final hospital on helicopter, 25% were on ground ambulances accompanied by an HEMS physician, and 13% were not transported. Patient categories were blunt trauma (31%), penetrating trauma (25%), and nontrauma (44%). Median NACA severity score for all patients was 5 (range, 3–7). The majority of patients (88%) were male. Median age was 36 years (range, 22–82 years). Patient baseline characteristics are shown in Table 1, including physiologic parameters.

Type of Injury or Illness

Hemorrhaging trauma patients (n = 9) included those who were involved in fall from heights, motor vehicle collisions, closed head or open head injuries, and knife stab wounds. Nontrauma patients (n = 7) included those who experienced gastrointestinal hemorrhage, ruptured abdominal aortic aneurisms, postpartum hemorrhage, and posttonsillectomy bleedings. Younger

TABLE 1. Baseline Characteristics for Patients Receiving FDP

Patient Category	Blunt Trauma	Penetrating Trauma	Nontrauma
No. patients	5 (100)	4 (100)	7 (100)
Male	4 (80)	4 (100)	6 (86)
Age, y	26 (23–51)	34 (27–46)	70 (22–82)
NACA severity score	5 (4–6)	5 (4–7)	5 (3–7)
Prehospital			
Systolic blood pressure, mm Hg	90 (50–141)	100 (0–170)	76 (0–150)
Heart rate, beats/min	100 (60–170)	90 (0–147)	60 (0–140)
Respiratory rate, breaths/min	16 (6–30)	16 (0–30)	14 (0–40)
Pulse oximetry, %	100 (99–100)	99 (0–100)	100 (0–100)
Glasgow Coma Scale (GCS) score	8 (3–14)	11 (3–15)	15 (3–15)
Timeline			
Injury to hospital, min	50 (28–109)	114 (54–290)	55 (43–166)
On-scene time, min	10 (2–15)	25 (8–45)	13 (5–36)
On scene to hospital arrival, min	23 (10–58)	23 (10–30)	24 (20–50)
ED			
Systolic blood pressure, mm Hg	105 (68–140)	120 (50–150)	113 (95–160)
Heart rate, beats/min	100 (65–150)	80 (70–150)	82 (55–116)
Respiratory rate, breaths/min	25 (20–30)	22 (16–28)	16 (12–32)
Pulsoxymetri, %	100 (83–100)	100 (92–100)	98 (95–100)
GCS score	12 (10–15)	13 (12–15)	15 (15)
Surgery			
Emergency surgery* < 24 h	4 (80)	3 (75)	4 (57)
Hemostatic surgery** < 24 h	3 (60)	1 (25)	4 (57)
Survival			
Dead on scene or < 24 h	0 (0)	1 (25)	1 (14)
Survival > 30 d	5 (100)	3 (75)	6 (86)

Data presented as number of patients (percentage) or median (range) per patient category.

*Emergency surgery includes all types of surgery performed to address acute injury and illness.

**Hemostatic surgery includes all types of surgery specifically performed to stop loss of blood.

patients dominated the trauma groups, while older patients represented the majority of nontraumatic hemorrhages (Table 1).

Prehospital Volume Replacement

The majority of patients (87%) received 200 mL of dissolved FDP in the field. Two patients (13%) received between 100 mL and 150 mL of FDP before arrival at the hospital. Pretransfusion hypotension was seen in 62% of the patients, but only 12% were still hypotensive at the time of admission. Median systolic blood pressure increased after prehospital FDP transfusion in all patient categories. Along with the FDP, 75% of the patients received tranexamic acid (1g intravenously), but only 29% of the patients received a follow-up dose after hospital admission. Only 19% of the patients received any prehospital crystalloids by the HEMS (median, 0-mL Ringer's acetate; range, 0–2,000 mL), and none received prehospital colloids. However, 64% of the patients received crystalloids upon admission to the ED (median, 575-mL Ringer's acetate; range 0–1,000 mL). One patient received colloids (mannitol, 300 mL) in the ED. Overall, 57% of the patients admitted to the hospital received additional blood component transfusions during the first 24 hours. Hemoglobin (Hb) measurements from the first arterial blood gas in the ED was available in all patients admitted, showing a median Hb of 12.9 mg/dL (range, 9.8–16.6 mg/dL). In-hospital volume therapy is described in Table 2.

Adverse Events

No transfusion reactions or complications were recorded with FDP or tranexamic acid given by the HEMS.

Surgery

Overall, 68% of the patients received emergency surgery after arrival at the hospital, including laparotomy, splenectomy, intracranial pressure monitoring, suture of various skin and soft tissue lacerations, emergency thoracotomy, varying surgery for bone fracture repair, endovascular stent graft implantation, curettage of the uterus, and nasal tamponade. One patient had an emergency thoracotomy performed on scene after cardiac tamponade by stabbing.

Survival

All 14 patients receiving FDP and admitted to the hospital were alive after 30 days, while 2 patients died on scene following cardiac arrests caused by massive gastrointestinal hemorrhage and cardiac tamponade.

Patients Receiving RBCs

Early results from the recent introduction of RBC show that RBCs were given to four patients so far. Two patients (one penetrating trauma and one blunt trauma patient) died on scene because of exsanguination, while additional two patients (one blunt trauma patient and one with ruptured aortic aneurism) survived to hospital discharge. Further analysis of the RBC use is premature because of the small numbers. However, no transfusion-related reactions or complications were recorded in these four patients.

TABLE 2. In-hospital Volume Replacement

Patients Transfused	Blunt Trauma	Penetrating Trauma	Nontrauma
No. patients	5 (100)	3 (100)	6 (100)
Transfusions < 24 h	4 (80)	1 (33)	3 (50)
ED first Hb	14.2 (9.8–16.6)	12.5 (11.9–14.7)	12.5 (9.8–13.7)
Lowest Hb < 24 h, g/dL	12.7 (8.8–13.4)	11.0 (8.2–14.7)	10.5 (7.4–12.6)
Received crystalloids in ED	3 (60)	2 (67)	4 (67)
Received colloids in ED	1 (20)	0 (0)	0 (0)
Received packed RBCs < 24 h	4 (80)	1 (33)	3 (50)
Received thawed FFP < 24 h	4 (80)	1 (33)	2 (33)
Received platelet concentrate < 24 h	2 (40)	1 (33)	0 (0)

Data presented as number of patients (percentage) or median (range) per patient category.

DISCUSSION

Main Findings

Our small study indicates that introduction of FDP into civilian HEMS seems feasible and may be safe and that logistical and safety issues for implementing RBCs are solvable.

Remote DCR Paradigm Shift and Current Transfusion Guidelines

During resuscitation of critically ill patients with major blood loss, there has been a shift toward the use of blood component therapy also in the prehospital arena.[10] Prehospital providers frequently start resuscitation with crystalloids because of its ready availability. However, the disadvantages of crystalloids such as saline and lactated Ringer's solution for the management of hemorrhagic shock patients are well-known.[11] Current recommendations from the American College of Surgeons and European guidelines favor early transfusion of blood products instead of large-volume resuscitation with crystalloids.[2,12]

Plasma and the ''Endotheliopathy of Trauma''

Primary coagulopathy of trauma is a recognized process, which may occur in as many as 25% to 30% of patients after major trauma.[13–15] The term *endotheliopathy of trauma* has been used to describe systemic endothelial injury and dysfunction that can lead to coagulation disturbances, inflammation, vascular leak, edema, and tissue injury.[15] Resuscitating with plasma seems to help repair the endotheliopathy in vitro.[16,17]

Plasma May Also Be Indicated in Nontrauma Patients

A large part of our patients were in need of volume replacement because of ongoing bleeding from medical or surgical causes (e.g., gastrointestinal hemorrhage or ruptured aortic aneurisms) and received prehospital FDP transfusion and tranexamic acid. FDP ensures both coagulation factors and volume replacement, has a potentially favorable safety profile, and may be superior to other types of plasma for prehospital use.[7] Moreover, in most civilian urban settings, transport times from point of injury or illness to a surgical facility may be relatively short (<30 minutes). Nonetheless, early treatment of hemorrhagic shock by addressing both coagulopathy and oxygen debt may be important in preventing death of exsanguination.[15] An initial restoring of the circulation by using a maximum of 2 U (400 mL) of FDP in adults seems reasonable.

Rationale for Adding RBCs

Shock is well-known to occur when oxygen delivery does not meet the tissues need for oxygen consumption, and in hemorrhaging patients, an oxygen debt may start to develop, and the tissues start to become ischemic and convert to anaerobic metabolism.[15] Now, most guidelines for the prehospital treatment of hemorrhagic shock favor permissive hypotension. This describes a resuscitation approach, which limits the administration of fluids (crystalloids/colloids) until surgical hemorrhage control can be achieved. Small volumes (e.g., 250 mL) administered may increase the cardiac output and hence the blood pressure since the circulation is severely constricted, with a reduced circulating blood volume after hemorrhage. This approach accepts a low flow state (low cardiac output) before surgical control, and this may require a higher threshold for RBC transfusion to avoid oxygen debt development. Thus, the innate response in many EDs to immediately administer crystalloids or colloids to trauma patients on arrival is questionable.

Prehospital Vitals as Transfusion Criteria

Although deranged patient's vitals (e.g., decreased systolic blood pressure, increased heart rate, and reduced cerebral function indicating low perfusion states) traditionally may have been regarded as legitimate starting criteria for the transfusion of blood components in hemorrhaging patients, the ATLS [Advanced Trauma Life Support] classification and interpretation of hypovolemic shock may need a critical revision in favor of modern DCR thinking.[12,18] In our study, median systolic blood pressure in penetrating and blunt trauma patients were in the subnormal but not hypotensive range, while nontrauma patients were in the hypotensive range. On scene, the attending physicians assessed all these patients as having ongoing significant hemorrhage and in need of FDP. Interestingly, both Apodaca et al.[19] describing MERT, PEDRO, and DUSTOFF MEDEVAC platforms in Afghanistan and Kim et al.[20] describing plasma use in MAYO-HEMS (United States) described their transfused patients being far from hypotensive. This may suggest that our trauma patients were in a compensatory phase of hemorrhage and the physician's decision to transfuse was based on clinical assessment of the patient's circulatory status as deteriorating and in need of intervention. Many of the nontrauma patients had probably been bleeding for a prolonged time (e.g., gastrointestinal bleeding) and were more decompensated on scene. Nonetheless, because only little more than half of our patients required additional transfusions and all admitted patients survived 30 days, this may suggest that their degree of hemorrhage was moderate or that plasma transfusion stabilized these patients as judged by the improvements in circulatory status or a combination of both.

Practical Issues in Making FDP and RBC Available Prehospital

The "sine qua non" in making prehospital use of blood products possible is a good working relationship with a major blood bank. In our case, all applications to governmental departments, the registered import of LyoPlas N-w AB from Germany, the production of fresh RBCs, and the testing and approval of our golden hour boxes was conducted by the Department of Immunology and Transfusion Medicine at Haukeland University Hospital. Overall, the blood banker's perspective on the implementation and the use of blood products in prehospital emergency care are of vital importance in making these products available to prehospital patients.[21] We have developed a system that makes fresh RBCs available for prehospital hemorrhaging patients, along with the rotation of unused RBCs back to the hospital to ensure minimal wastage.

When FDP is stored at room temperature with a long shelf-life, its main advantage is that it does not need to be thawed before administration, making it readily available on scene after dissolving the plasma powder. Our practice with preparing the FDP en route to the patient (or the pilot preparing it on scene simultaneously to ongoing medical treatment) transforms into short turnaround times, thereby minimizing on-scene times and prioritizing

rapid transport to hospital and surgical control. FDP seems to be the product of choice for future prehospital EMS providers.[22]

Adverse Events

No transfusion-related complications were recorded in our patients. As with all products derived from human blood, risks may include circulatory overload, ABO incompatibility, transmission of infectious diseases, and allergic reactions. Complicating this is the fact that transfusion reactions (e.g., tachycardia or hypotension) may mimic the clinical status of a hemorrhaging patient or vice versa. As a rule, when in doubt, we recommend abortion of transfusions when this becomes an issue.

Strength and Limitations

The strength of our clinical study is that we have included all patients receiving FDP and RBCs during the study period. Limitations are the small number of patients, the retrospective design, and the risk of missing or incomplete data. Our procedure to ask the attending prehospital anesthesiologists to provide details to supplement and clarify missing patient data maintained the integrity of our study.

Implications and Future Studies

Because only half of our patients needed additional transfusions after hospital arrival, although the majority received emergency surgery, our results indicate the need for more stringent starting criteria for prehospital plasma and RBC transfusions. Further studies are needed to clarify the role of FDP and other blood components such as RBCs or whole blood, in civilian prehospital hemorrhagic shock resuscitation, and to aid the development of standardized transfusion protocols for prehospital use.

CONCLUSION

Our small study indicates that the introduction of FDP into civilian HEMS seems feasible and may be safe and that logistical and safety issues for the implementation of RBCs are solvable. FDP ensures both coagulation factors and volume replacement, has a potentially favorable safety profile, and may be superior to other types of plasma for prehospital use. Further prospective studies are needed to clarify the role of FDP (and RBCs) in civilian prehospital hemorrhagic shock resuscitation and to aid the development of standardized protocols for prehospital use of blood products.

AUTHORSHIP

G.A.S., J.-K.H., B.V., and G.S. conceived the study. G.A.S. and K.-C.F. performed the data collection from patient and HEMS records. G.A.S. and K.-C.F. performed the statistical analysis. G.A.S., J.-K.H., B.V., K.-C.F., and GS wrote the first draft. All authors revised subsequent drafts for intellectual content. All authors have read and approved the final version of the manuscript.

DISCLOSURE

The authors declare no conflicts of interest.

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