

Feasibility of prehospital freeze-dried plasma administration in a UK Helicopter Emergency Medical Service

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Background Early transfusion of patients with major traumatic haemorrhage may improve survival. This study aims to establish the feasibility of freeze-dried plasma transfusion in a Helicopter Emergency Medical Service in the UK.

Patients and methods A retrospective observational study of major trauma patients attended by Kent, Surrey and Sussex Helicopter Emergency Medical Service and transfused freeze-dried plasma since it was introduced in April 2014.

Results Of the 1873 patients attended over a 12-month period before its introduction, 79 patients received packed red blood cells (4.2%) with a total of 193 units transfused. Of 1881 patients after the introduction of freeze-dried plasma, 10 patients received packed red blood cells only and 66 received both packed red blood cells and freeze-dried plasma, with a total of 158 units of packed red blood cells transfused, representing an 18% reduction between the two 12-month periods. In the 20 months since its introduction, of 216 patients transfused with at least one unit of freeze-dried plasma, 116 (54.0%) patients received both freeze-dried plasma and packed red blood cells in a 1 : 1 ratio. Earlier transfusion was feasible, transferring the patient to

the hospital before transfusion would have incurred a delay of 71 min (interquartile range: 59–90 min).

Conclusion Prehospital freeze-dried plasma and packed red blood cell transfusion is feasible in a 1 : 1 ratio in patients with suspected traumatic haemorrhage. The use of freeze-dried plasma as a first-line fluid bolus reduced the number of prehospital packed red blood cell units required and reduced the time to transfusion. *European Journal of Emergency Medicine* 00:000–000 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Background

Trauma remains a leading cause of morbidity and mortality [1]. The rationale behind early transfusion of packed red blood cells (PRBC) and plasma is that coagulopathy is lessened, potentially reducing morbidity and mortality [2]. Therefore, the trauma resuscitation protocol is instigated early in the patient's journey to surgical care, bridging the gap to the definitive control of bleeding [3,4].

PRBC do not contain all of the components of whole blood [5]. Importantly, PRBC do not contain clotting factors. It is known that a subset of trauma patients will develop an acute traumatic coagulopathy. Acute traumatic coagulopathy is associated with significantly increased mortality rates [6]. Bleeding patients receiving resuscitation with plasma-poor PRBC are likely to become increasingly coagulopathic, further worsening bleeding and increasing mortality [7,8]. Studies attempt to determine the optimal ratio of blood product components to resuscitate bleeding patients while avoiding worsening of coagulopathy [2,3].

There is reasonable evidence to support the use of PRBC to plasma in a 1 : 1 ratio [9,10]. Major haemorrhage leads to a hypercoagulable state, a consequence of dilution, consump-

tion and inhibition of coagulation. Literature reports that early and aggressive replacement of these clotting factors reduces mortality [8,11], and decreases overall transfusion requirement [12]. The transfusion of fresh frozen plasma (FFP) and PRBCs prevents, rather than treats a dilutional coagulopathy, but may improve survival [13].

In-hospital studies evidence a survival benefit by the introduction of massive transfusion protocol (MTP) that comprised a 1 : 1 : 1 ratio of PRBC, FFP and platelets. Comparing 73 MTP patients to 84 pre-MTP patients with similar demographics and Injury Severity Score (ISS), overall patient mortality improved at 24 h from 36% (pre-MTP) to 17% (MTP), $P=0.008$ and 30 days, $P=0.04$ [14]. Military literature also reports increased survival with plasma and PRBC resuscitation [15].

Retrospective civilian data [9], and more recently a prospective multicentre randomized trial suggests an increased survival at 30 days with early plasma transfusion [8,16]. A systematic review in 2016 questions the current evidence around prehospital blood resuscitation [17]; therefore, the introduction of plasma into a prehospital Helicopter Emergency Medical Service (HEMS) is warranted.

This single centre, retrospective observational study aims to analyse the feasibility of freeze-dried plasma (FDP) by HEMS in the UK, reporting the unique operational and geographical setting. The paper will establish any reduction in prehospital PRBC transfusion, and report any potential time-saving to transfusion in patients with suspected traumatic haemorrhage.

Patients and methods

Study design and prehospital care system

A single centre, retrospective observational analysis of patients requiring a prehospital transfusion of PRBC and/or FDP. The study was registered at the University of Surrey as a Service Evaluation and reported as per Strengthening the Reporting of Observational Studies in Epidemiology Guidelines.

Kent, Surrey and Sussex Air Ambulance Trust (KSSAAT) provides a HEMS service within southeast England, UK. The region has a static population of 4.3 million, and a transient population of ~10 million. The southeast covers a geographical region of ~9000 km², which is predominantly rural, and served by Trauma Units (TU) and Major Trauma Centres (MTCs) in Brighton, London and Southampton. The average primary transfer time to an MTC is 30 min by helicopter, and up to 2 h by ground ambulance. The ground ambulance service does not have the capability to transfuse FDP, and a robust combined dispatch process both anticipates and supports the ambulance service to optimize patient intervention at the point of injury.

Code Red standard operating procedure

In this service, where there is a clinical suspicion of major haemorrhage and signs of haemodynamic compromise 'Code Red' is declared. Code Red is informed by pre-hospital clinical assessment and declared at the discretion of the attending HEMS clinicians. The team of HEMS clinicians differed with regard to prehospital clinical exposure, however, a 24/7 on-call service is provided by HEMS consultants and HEMS paramedic clinical managers, aiming to provide decision-support to any clinical team.

If major haemorrhage is suspected, primary interventions are concurrently managed by the ground ambulance clinicians and HEMS with: (i) control of external haemorrhage, (ii) splinting of limb and pelvic fractures, (iii) packing of facial haemorrhage, and (iv) administration of tranexamic acid (Fig. 1). If hypotension continues [systolic blood pressure (SBP) <80 mmHg or absence of a radial pulse] 'permissive hypotension' is aimed for, targeting an SBP of at least 80 mmHg, or the return of a radial pulse. In patients with polytrauma and suspected traumatic brain injury an SBP of at least 100 mmHg is targeted. Alternative causes of hypotension are excluded, such as tension pneumothorax. Following primary interventions, if hypotension persists a Code Red activation enables titrated transfusion of up to four units of freeze-dried lyophilized plasma (LyoPlas-N-w), and up to four units of O rhesus negative PRBCs from the

Crêdo Cube, Pelican BioThermal, Minnesota, USA. (Series 4, 2-l Insulation 15, VIP Golden Hour) carried 24/7 by KSSAAT clinicians. KSSAAT began transfusing freeze-dried lyophilized plasma (LyoPlas-N-w) on 1 April 2014. FDP has a shelf life of 15 months when stored at 2–25°C. The 200 ml of freeze-dried powder is reconstituted with water for injection (200 ml) by the transfer set included with the product. Following reconstitution, the plasma is gently swirled until all powder is dissolved. At this point, the product is ready for immediate transfusion.

All blood product is warmed utilizing a Belmont Buddy Lite (Belmont Instrument Corporation, Billerica, Massachusetts, USA). Adherence and compliance to the Blood Safety and Quality Regulations (2017) and Medicines and Healthcare Regulatory Agency was ensured [18].

In a patient who is suspected of having major traumatic haemorrhage but is not considered to be peri-arrest an initial bolus of FDP is transfused (Fig. 1). If the patient continues to deteriorate, a further PRBC transfusion is commenced in a 1 : 1 ratio.

Data collection

The KSSAAT database (HEMSbase; Medic 1 Systems Limited, Surrey, UK) was searched to identify all patients transfused with FDP and/or PRBC from 1 April 2014 to 31 December 2016. Further, patients transfused PRBC only (12 months before FDP introduction) were identified. Demographics, mechanism of injury (MOI), ISS, quantity and type of blood product transfused (units), 999 to hospital time and reports of transfusion reaction are recorded. Data were reviewed retrospectively and extracted by the first author (J.O.).

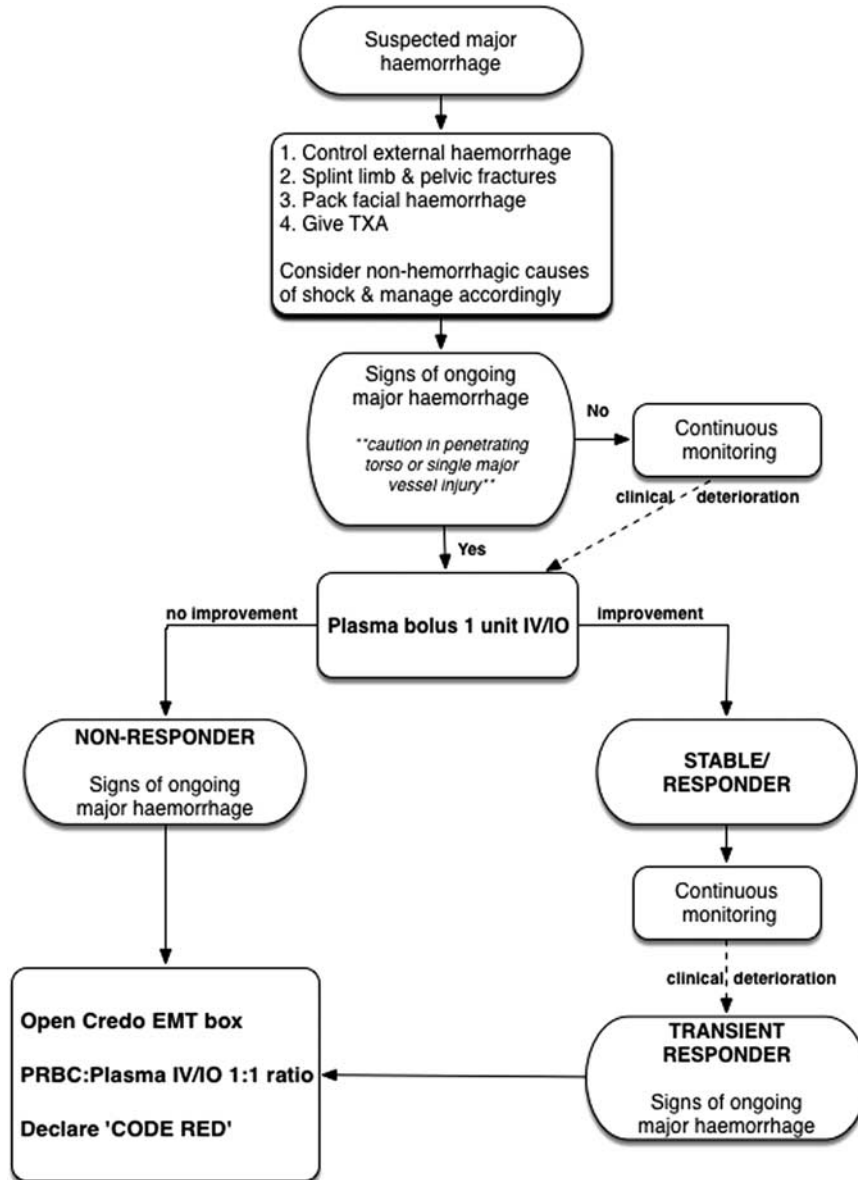
Inclusion criteria

Inclusion criteria comprised the following: (i) blunt and/or penetrating traumatic injury with suspected traumatic haemorrhagic, (ii) prehospital transfusion of PRBC and/or FDP, (iii) patients conveyed to an MTC or TU, (iv) traumatic cardiac arrests (TCAs) and (v) patients who were in TCA, where return of spontaneous circulation was gained, the patient was declared Code Red and conveyed to an MTC. Exclusion criteria comprised (i) interhospital and/or secondary transfers and/or, (ii) patients with suspected medical aetiology.

Statistical analysis

Patients meeting the inclusion criteria were analysed. For demographics, sex frequency, age distribution and median 999 to hospital time, frequency counts and interquartile range (IQR) is reported. The quantity of blood product, MOI and hospital destinations are reported with frequencies (*n*) and percentages (%). Missing data is reported. Data were collated and entered into Microsoft Excel 0.16 Washington, USA. Descriptive statistical analysis was undertaken in Statistical Package for Social Sciences (version 24; IBM).

Fig. 1



Standard operating procedure for blood product transfusion at KSSAAT. i.o., intraosseous; i.v., intravenous; TXA, tranexamic acid.

Ethical approval

National Institute of Health Research criteria for Service Evaluation was met. Internal approval by KSSAAT Research Audit and Development Committee was gained. Formal ethical approval was not required. Patient identifiable data was anonymized and stored on electronic devices with technical encryption (Data Protection Act, 1998).

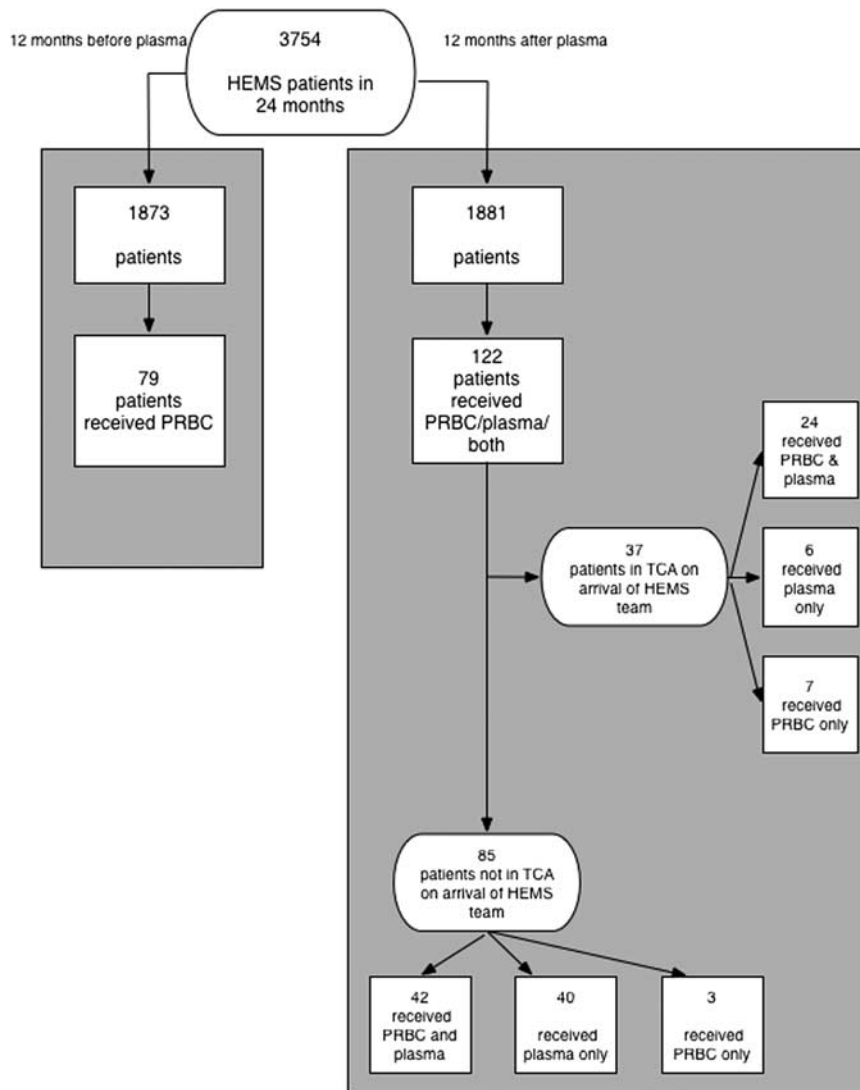
Results

In the 12 months before the introduction of FDP, 1873 patients were identified, of which 79 received PRBC (4.2%) and a total of 193 PRBC units were transfused

(Fig. 2). In the 12 months with FDP availability, of 1881 patients, 85 patients received FDP. Of this, three patients received PRBC only, 42 received both FDP and PRBC, and 40 received FDP only. A total of 158 units of PRBC were transfused, representing a 35-unit (18%) reduction in PRBC unit quantity. There were no reports of adverse reactions, and 100% traceability was achieved.

In the first 20 months following the introduction of FDP, 216 patients received at least one unit of FDP. Of the patients meeting the inclusion criteria the mean age was 46 years (4–90 years) and 73% were male. In 68 (32%) of patients, ISS was recorded, the average ISS was 32.

Fig. 2



Patient inclusion 12 months before and 12 months after freeze-dried plasma introduction. HEMS, Helicopter Emergency Medical Service; PRBC, packed red blood cells; TCA, traumatic cardiac arrest.

The MOI was predominantly road traffic collisions involving cars, motorcycles or pedestrians. When categorized by MOI, only 17 (7.9%) of patients had sustained penetrating trauma, compared with 199 (92.1%) with blunt trauma. Of 216, 93 (43.0%) were declared Code Red at scene (Table 1).

Of these 216 patients, 116 (54.0%) received FDP and PRBC in a 1 : 1 ratio, 74 (34.3%) received only one unit of FDP (note only 12 months depicted in Fig. 2). Of this study population, 49 (22.7%) received FDP as part of the TCA algorithm, of these 37 were pronounced life extinct at the scene. In 12 patients return of spontaneous circulation was achieved and the patient was subsequently conveyed to an MTC. The majority of patients were conveyed to an MTC [164 (75.9%)], only three (1.4%)

were conveyed to a TU. In a further nine patients' destination was not recorded. Earlier transfusion of FDP and PRBC was feasible; median 999 time to arrival at hospital was 111 min (IQR: 95–138 min). Transferring the patient to the hospital prior to transfusion would have incurred a further delay of 71 min (IQR: 59–90 min).

Discussion

The introduction of FDP is feasible in a UK HEMS service, allowing timely transfusion of blood product to patients in TCA or those with suspected traumatic haemorrhage. Of those patients who survived to the hospital this resulted in an earlier transfusion at the point of injury. KSSAAT current protocol advocates FDP as a first-line fluid bolus, but clinical discretion can result in

Table 1 Mechanism of injury in the 20 months after the introduction of freeze-dried plasma

Mechanisms	<i>n</i> (%)
Car RTC	59 (27.3)
Motorcycle RTC	40 (18.5)
Pedestrian RTC	37 (17.1)
Fall	25 (11.6)
Intentional self-harm	16 (7.4)
Assault	14 (6.5)
Pedal cyclist	7 (3.2)
Sports injury	4 (1.9)
Crush injury	4 (1.9)
HGV RTC	3 (1.3)
Agricultural accident	2 (0.9)
Struck by falling object	2 (0.9)
Van RTC	1 (0.4)
Animal injury	1 (0.4)
Aircraft accident	1 (0.4)
Total	216 (100)

HGV, heavy goods vehicle; RTC, road traffic collision.

PRBC being transfused first. The results show a decrease in the total volume of prehospital PRBC transfused in patients with suspected traumatic haemorrhage following the introduction of FDP.

Other studies describing the use of FDP in civilian patients included a smaller patient cohort [19]; however, also conclude that FDP is safe and logistically feasible for civilian prehospital HEMS. In the absence of prehospital FDP, patients frequently arrived at the hospital having received up to four units of unopposed PRBCs. Earlier treatment with products containing clotting factors has been suggested to reduce the likelihood of developing a coagulopathy [14].

A randomized controlled trial, The Control of Major Bleeding After Trauma Trial (COMBAT) analyses 144 patients, consistent with previous studies the administration of prehospital plasma (FFP) was safe and feasible [2]. However, due to a consistent lack of differences and no survival benefit between the two randomized groups the trial was stopped for futility. Importantly COMBAT shows a short median time from injury to arrival at hospital (28 min, IQR: 22–34 min) for the plasma group and 24 min (IQR: 19–31 min) in the control group, which shortens time to haemorrhage control and therefore impacts on any survival benefit [2]. Despite ‘unfavourable’ clinical parameters, such as hypotension and tachycardia, haemorrhage was not confirmed in all patients. For example, approximately 50% received no further blood product in-hospital.

By comparison another randomized controlled trial, Prehospital Air Medical Plasma, found prehospital plasma (FFP) to confer a significant 30-day survival benefit from 3 h since the point of injury (plasma group mortality, 23.2% compared with the crystalloid group, 33%) [8]. With a comparable proportion of blunt trauma and transfer times to KSSAAT, these findings support the use of prehospital plasma in such a setting. Future research regarding prehospital blood product is impending, and other work should

target clinical tools to accurately identify the patient with suspected traumatic haemorrhage [2].

Retrospective observational studies hold inherent methodological limitations. First, incomplete data for patient characteristics in this study, in particular, ISS scores skew the data analysis. Second, the study examined only patients who had received FDP from a single UK HEMS service, therefore is not representative of the transfusion protocol across UK HEMS or internationally. Also, the decision to commence the of transfusion blood product is led by the clinicians on the scene with consultant-on-call advice, leading to appreciable variability.

Future work may focus on UK mortality outcomes for civilian patients transfused prehospital plasma with longer prehospital times. Similarly, European literature comparing prehospital FDP to FFP has highlighted between-group differences in time to transfusion, coagulation parameters and fibrinogen concentration requirements [20]. Currently, UK services transfuse either FDP or FFP, and further research into a patient benefit is warranted.

This retrospective review has showed that prehospital FDP and PRBC transfusion in a 1 : 1 ratio is feasible in UK HEMS. The use of FDP as a first-line fluid bolus reduced the volume of prehospital PRBC required, and reduced time to FDP transfusion in patients with suspected traumatic haemorrhage.

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Authors’ contributions: All authors were involved in the implementation of the prehospital transfusion protocol and data collection. J.O. collated the data. Data analysis was performed by J.O., R.L. and J.G. All authors were involved with the preparation of the manuscript. All authors approved the manuscript before submission.

Conflicts of interest

J.O., J.G., G.W. and R.L. are all employees of Kent, Surrey & Sussex Air Ambulance Trust.

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