Blood Product Supply for a Helicopter Emergency Medical Service

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Keywords

Transfusion therapy · Clotting factors · Thawed plasma · Helicopter emergency medical service

Abstract

Background: Long patient transport times to trauma centers are a well-known problem in sparsely populated regions with a low hospital density. Transfusion of red blood cell concentrates (RBC) and plasma improves outcome of trauma patients with severe bleeding. Helicopter emergency services (HEMS) are frequently employed to provide early advanced medical care and to reduce time to hospital admission. Supplying HEMS with blood products allows prehospital transfusion and may help to prevent exsanguination or prolonged hemorrhagic shock. We have investigated the maintenance of blood product quality under air transport conditions and the logistical steps to introduce a HEMS blood depot into routine practice. **Methods:** A risk analysis was performed and a validation plan developed. A special, commercially available transport container for blood products was identified. Maintenance of temperature conditions between 2 and 6°C in the box were monitored at ambient temperatures up to 35°C over 48 h. Quality of blood products before and after helicopter air transport were evaluated including (1) for

RBCs: hemoglobin, hematocrit, hemolysis rate; (2) for thawed plasma: aPTT, INR, single clotting factor activities. The logistics for blood supply of the regional HEMS were developed by the transfusion service of the Greifswald University Hospital in collaboration with the in-hospital transport team, the HEMS team, and the HEMS operator. **Results:** The transport container maintained a temperature below 6°C up to 36 h at 35°C ambient temperature. Vibration during helicopter operation did not impair quality of RBC and thawed plasma. To provide blood products for HEMS at least two transport containers and an additional set of cooling tiles is needed as the cooling tiles need a special temperature priming over 20 h. The two boxes were used at alternate days. To reduce wastage, RBCs and thawed plasmas were exchanged every fourth day and reintegrated into the blood bank inventory for further in-hospital use. **Conclusions:** Supplying HEMS with RBCs and plasma is feasible. Helicopter transport has no negative impact on blood product quality. The logistic challenges require close collaboration between the HEMS team and the blood transfusion service.

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Introduction

Bleeding is one of the leading causes of early death in trauma patients [1–3]. In a prospective multicenter cohort study of trauma medical care (PROMMTT) including more than 900 patients 94% of hemorrhagic deaths occurred within 24 h, the majority of these deaths (60%) occurred within 3 h of admission, and the median time to hemorrhagic death was 2.6 h (interquartile range, 1.7–5.4 h) [4]. A transfusion ratio of plasma:RBC $\geq 1:2$ during the first 6 h after arrival at the emergency department (minute 31 to hour 6) was associated with reduced mortality (HR 0.31, 0.16–0.58) [4]. Pre-hospital transfusion can bridge time until hospital admission. The flight time of the helicopter from the scene to the hospital is usually relatively short. Prehospital transfusion is especially relevant if the patient cannot be immediately transported from the scene (e.g., entrapped in a car wreck). Helicopter emergency services (HEMS) and prehospital transfusions can improve the outcome of patients [5, 6]. Recent data also indicate that prehospital transfusion is safe [7–14]. However, it may introduce additional risks for adverse outcomes like induction of hypothermia by non-prewarmed blood [15]. Therefore, it is still under debate whether it improves short-term or long-term survival in civilian settings. The different blood products used by the different rescue services further complicate interpretation and generalization of available data.

In any case, the supply of HEMS with blood products is challenging: a) space and weight limits, no electricity supply on the helicopter; b) influence of vibrations, flight conditions by the helicopter depending on helicopter model [16]; c) variable storage conditions for different blood products; d) variable expiration times of different blood products; e) requests for transfusion safety based on national guidelines for hemotherapy [17].

The implementation of prehospital blood supply for HEMS, locally established for the helicopter Christoph 47 (DRF Stiftung Luftrettung gAG), by the department of transfusion medicine of the University Medicine Greifswald (UMG) is described including risk analysis, validation of the blood product quality, and process organization.

Material and Methods

Definition of Requirements

As first step the requirements for providing blood products on the helicopter were defined and related risks identified. Requirements were defined by discussion between transfusion medicine staff and the HEMS team of the Department of Anaesthesiology of the UMG together with the HEMS operator. Discussions were performed in formal meetings either in person or via videoconference. The following items were identified:

- 1 The blood product transport container should be able to store 4–6 blood bags (RBCs and plasma) and maintain temperatures between 2 and 6°C, max. 10°C for at least 12 h. The time period of 12 h was necessary because the shift of the helicopter rescue team is 12 h long and an exchange of blood products is only feasible when the shift team is changing.
- 2 The blood product inventory should be able to accommodate thawed plasma (2–6°C) or lyophilized plasma (200 mL glass flasks).
- 3 Air transport should not impair the quality of the blood products, as defined by the national hemotherapy guidelines.
- 4 Blood product quality should allow re-integration of non-used blood products into the regular stock of the blood bank to avoid unnecessary wastage.

Risk Analysis

A risk analysis was performed following the EU-GMP guidelines. A risk priority number (RPN) was calculated based on the Failure Mode and Effects Analysis (FMEA) method [18, 19]. Therefore, the probability of failure occurrence and failure detection was evaluated and the product (RPN) of both calculated (Table 1). An RPN >12 was defined as threshold, which requires validation of the process (Table 1) [20]. As key critical points we identified:

- maintenance of storage temperature between 2 and 6°C for at least 12 h preferentially with additional time buffer
- maintenance of quality of RBC and thawed plasma according to the German hemotherapy guidelines [17].

Validation Plan

As storage container the Credo Cube™ (PELICAN BioThermal™, Plymouth, USA) was identified. The inner wall of this box is covered by 6 special cooling tiles. Before use, these tiles are prepared as follows: storage at $<-18^{\circ}\text{C}$ for 12 h, followed by storage at 2–6°C for 8 h. After this initial temperature priming step the cooling tiles can be stored at 2–6°C for at least 7 days and are ready to use in the Credo Cube™, according to the manufacturer, without electricity.

The temperature was monitored by temperature loggers (elpro, Buchs, Switzerland and TUTELA monitoring systems, Fleet, UK). After temperature priming of the cooling tiles (as described above) the empty Credo Cube™ was stored for 48 h at room temperature and at 35°C, respectively. Temperature was continuously recorded and analyzed by software (elproLOG analyze, Buchs, Switzerland).

Validation of the Blood Product Quality

Quality measurements of blood products were performed before and after transport of the blood products on the helicopter to assess any impact of flight related vibration, acceleration, etc. on product quality.

Samples from the blood bags were drawn by sterile docking before air transport (baseline) and 24 h after the baseline sample was taken (1 day HEMS operation). To test if the blood products can be used for several days, the same blood products were on the helicopter at day 1, day 3, and day 5 (Table 2). Between each operation day the blood products were stored at 4°C in the blood bank. During this time the cooling tiles were re-primed. This evaluation should allow using blood products over 3 days on the helicopter (3 days HEMS operation).

Quality Assessment of RBCs

Hemoglobin concentration and hematocrit were measured by automated cell counter (XN-9000, Sysmex, Norderstedt, Germany). The hemolysis rate was measured by UV spectrophotometer (UV-1700 PharmaSec, Shimadzu Corporation, Kyoto, Japan). Potassium concentration and lactate dehydrogenase levels were mea-

Table 1. Risk analysis to recognize significant processes, which has to be validated following FMEA-criteria (factor 1 = low risk, 5 = high risk)

Risk	Probability of failure occurrence	Severity	Probability of discovery	RPN
Transport container is not sufficiently pre-cooled	2	5	3	30
Temperature increases >6°C during transport	3	5	2	30
Hemolysis of RBCs	4	5	4	80
Clotting factor activity decrease <50%	4	5	4	80
Patient blood is not drawn, post-transfusion compatibility testing in the laboratory after admission of the patient to hospital is not possible	3	5	1	15
Transfusion documents are not returned by the helicopter team to the transfusion medicine laboratory, patient and/or product lookback is not possible	3	5	1	15
Non-authorized access to blood products	2	5	1	10

A risk priority number >12 is the criterion for initiating a validation process.

Table 2. Validation plan for short-term and long-term evaluation of blood product quality over 3 HEMS operation days

Day 1	Day 2	Day 3	Day 4	Day 5
Baseline sample was taken from the blood products	HEMS in operation, blood products were transported	One-day-operation sample was taken from the blood products	No operation day, blood products stored in the blood bank inventory, re-priming of cooling tiles	HEMS in operation, blood products were transported
				3-day-operation sample was taken from the blood products

sured by automated system (Dimension Vista® 1500 System; Siemens Healthineers, Eschborn, Germany).

Quality Assessment of Thawed Plasma (tFFP)

a) Evaluation of the impact of 1 day HEMS operation: tFFP quality parameters were measured at baseline and 24 h after baseline. b) Evaluation of the impact of 3 days HEMS operation: tFFP bags were divided into two identical units. One unit was stored at 4°C in the blood bank (control unit) and the second was used on the helicopter (air transport units). Samples were drawn and stored at ≤−30°C until measurement (Table 2). For plasma quality assessment global hemostasis parameters prothrombin time (Quick/INR; Dade® Innovin®, SIEMENS Healthcare Diagnostics Products GmbH, Marburg, Germany) and the activated partial thromboplastin time (aPTT; Dade® Actin® FS Activated PTT Reagent, SIEMENS Healthcare Diagnostics Products GmbH, Marburg, Germany) were measured. Further, single clotting factor activities were measured (Table 3).

Development of Logistics for HEMS Blood Supply

To establish the logistics for blood supply several meetings between the HEMS team, in-hospital transport service, the staff of the in-hospital emergency department – as handover point between in-hospital transport team and HEMS team – and the blood bank were performed. The introduction of HEMS blood supply was a stepwise process with continuous monitoring and adjustments if needed. The blood bank team organized the preparation of the Credo Cube™, the logistics of blood product exchange and temperature monitoring. The HEMS team organized the Credo Cube™ transport between blood bank and helicopter port considering the HEMS working shifts. Medical staff of HEMS were edu-

cated for the special conditions of pretransfusional hemotherapy. At the beginning of HEMS blood supply the helicopter worked between sunrise and sunset and was later adopted to a 2-shift/24-h operation.

Results

Temperature Maintenance of the Transport Container

The low-temperature primed (≤−18°C) Credo Cube™ maintained the temperature of 2–6°C for at least 48 h if surrounding temperature was below 24°C, for higher temperatures up to 35°C the inner temperature could be maintained up to 36 h below 6°C ($n = 3$ each) (shown in Fig. 1). After priming of the cooling tiles at 4°C (skipping the −18°C incubation step) the inner temperature of the box crossed the limit of 6°C after 5 h.

Quality Assessment of RBCs

During 1 day HEMS operation (short-term evaluation of the blood product quality) the median helicopter-in-operation time (the helicopter rotor is working) was 219 min per day (range 172–255 min) including 10–12 start and landing procedures per day. During the 3 days HEMS operation cumulative helicopter-in-operation time was 521 min with a median of 181 min per day (range 111–229 min) including 24 start and landing procedures.

Table 3. Single clotting factor activities and their respective reagent are listed

Clotting factor	Analysis by
Fibrinogen	Dade Innovin, SIEMENS Healthcare, Marburg, Germany
Factor II, V, VII, VIII, IX, XII, XIII	Actin FSL, SIEMENS Healthcare, Marburg, Germany
Protein S	Hemoclot Protein S, Coachrom (Hyphen Biomed), Austria
Protein C	Protein C reagent, SIEMENS Healthcare, Marburg, Germany
Von Willebrand factor antigen	WF-Ag, SIEMENS Healthcare, Marburg, Germany
Von Willebrand factor activity	Innovance WF-AC, SIEMENS Healthcare, Marburg, Germany

All analyses were performed on the CS-5100 (Sysmex).

Fig. 1. Reports of temperature monitoring recorded by temperature logger in the empty Credo Cube™ stored at surrounding temperature 20–24°C (**a**) and at 35°C (**b**) for more than 48 h. Temperatures up to 35°C limited the working time of the Credo Cube™ with inner temperature condition <6°C to a maximum of 40 h (red line indicates the time when the inner temperature of the box exceeded 6°C).

The Credo Cube™ was loaded with three RBCs and three tFFP. For 1 day HEMS operation 12 RBCs were assessed. For 3 days HEMS operation 3 RBCs were assessed over 5 days as described in Table 2. After return to the blood bank no signs of hemolysis were observed. Hemo-

globin concentration and hematocrit did not deviate from the requested specifications (Tables 4, 5) [17]. Potassium levels slightly increased but did not exceed the limit of 60 mmol/L (approved by the drug authority for RBCs of our institution; Human-Erythrozytenkonzentrat PAGGSM, leukozytendepletiert/HGW) (Tables 4, 5).

Quality Assessment of tFFP

For 1 day HEMS operation 12 tFFPs were assessed. For 3 days HEMS operation 3 tFFPs were assessed and compared with their biologically identical split units stored at 4°C in the blood bank. Four of the FFPs already showed decreased clotting factor activities <50% immediately after thawing: FVII activity of 41% and 46%, FVIII activity of 44%, and FXII activity of <5% (this tFFP was excluded from the analysis of FXII). After short-term HEMS operation clotting factor VIII showed the most pronounced decrease during 24 h after thawing (by median 13%). All other clotting factors decreased by less than 5% (Table 6). After 3 days HEMS operation the decrease of clotting factors in the air transport units was comparable to the control units stored in the blood bank. In tFFPs most pronounced decrease in clotting factor activity was observed for clotting factor VIII (by mean 37%, final levels 36–57%), protein S (by mean 24%, final levels 55–103%), and clotting factor XI (mean 11%, final levels 89–119%). The changes of global coagulation parameters PT (Quick) and aPTT, and single clotting factors fibrinogen, factors II, V, VII, IX, X, XII, XIII, vWF-Ag and -activity, and Protein C were less than 10% after 3 flight days. The changes of all coagulation parameters of the tFFP air transport units were in the same range as in the respective control units stored in the blood bank at 4°C: clotting factor VIII (by mean 39%, final levels 36–61%), protein S (by mean 19%, final levels 60–97%), and clotting factor XI (by mean 11%, final levels 96–129%) (Table 7). The only exception was seen for factor V where the decrease in the air transport units was slightly larger than in the control units (–7.3% vs. –1.7%; Table 7).

Table 4. RBC quality measurements before/after 1 day HEMS operation (mean, range; *n* = 12)

	Baseline	24 h after baseline	Specification	Δ before and after 1 day HEMS operation
Hb/unit, g	45.35 (35.6–53.8)	46.29 (36.3–55.8)	≥40.0	0.94
HK, L/L	0.522 (0.465–0.561)	0.531 (0.494–0.567)	0.50–0.70	0.010
Rate of hemolysis, %	0.282 (0.176–0.495)	0.261 (0.171–0.450)	<0.8	–0.021
Potassium, mmol/L	16.10 (9.50–30.10)	18.04 (11.60–31.50)	<60	1.94

Table 5. RBC quality measurements before/after 3 days HEMS operation (mean, range; *n* = 3)

	Baseline	After 3 days HEMS operation (day 5 after baseline)	Specification	Δ before and after 3 transport days
Hb/unit, g	45.8 (44.3–8.1)	49.5 (45.0–53.0)	≥40.0	3.7
HK, L/L	0.51 (0.46–0.54)	0.55 (0.54–0.57)	0.50–0.70	0.041
Hemolysis rate, %	0.32 (0.23–0.45)	0.21 (0.15–0.27)	<0.8	–0.102
Potassium, mmol/L	12.4 (9.5–15.9)	20.8 (17.0–25.8)	<60	8.5

Hb, hemoglobin; HK, hematocrit.

Table 6. tFFP quality measurements before/after 1 day HEMS operation (mean, range; *n* = 12); decrease of activity >10% is marked in grey

	Baseline	24 h after baseline, 1 day HEMS operation	Δ before and after transport
Prothrombin time, %	77.0 (59.0–103.0)	75.4 (58.0–101.0)	–1.6
Activated partial prothrombin time, s	29.0 (23.0–34.0)	29.9 (24.0–36.0)	0.9
Fibrinogen, g/L	2.3 (1.6–3.4)	2.4 (1.7–3.3)	0.1
Factor II, %	92.7 (76.0–134.0)	92.3 (76.0–136.0)	–0.3
Factor V, %	81.8 (54.0–114.0)	78.8 (50.0–111.0)	–3.0
Factor VII, %	76.3 (46.0–108.0)	76.7 (41.0–140.0)	0.3
Factor VIII, %	81.6 (44.0–116.9)	68.8 (33.7–92.2)	–12.8
Factor IX, %	90.3 (72.0–118.0)	89.6 (73.0–128.0)	–0.7
Factor X, %	96.9 (79.0–114.0)	99.3 (72.0–131.0)	2.3
Factor XI, %	89.8 (66.0–136.0)	87.8 (62.0–138.0)	–2.1
Factor XII, %	77.9 (41.0–112.0)	78.9 (41.0–118.0)	1.0
Factor XIII, %	101.8 (71.0–143.0)	103.0 (68.0–143.0)	1.2
Von Willebrand factor antigen, %	106.3 (62.0–164.0)	106.1 (57.0–163.0)	–0.2
Von Willebrand factor activity, %	95.1 (52.0–158.0)	94.3 (47.0–154.0)	–0.8
Protein C, %	93.9 (75.0–115.0)	95.9 (76.0–119.0)	2.0
Protein S, %	91.6 (55.0–121.0)	87.7 (47.0–123.0)	–3.9

Logistic Process for Providing Blood Products for HEMS

The final logistical process has been established: two transport containers and three sets of cooling tiles are in use. While one Credo Cube™ is on the helicopter, the second with cooling tiles is reactivated. A third set of cooling tiles is stored at 2–6°C as backup system.

The Credo Cube™ is loaded by the blood bank staff with three tFFPs blood type AB or A (in case of AB shortage) and three RBCs of blood type O Rh positive or two lyophilized plasmas (Lyoplas®, DRK Blutspendedienst West) and two RBCs and issued in the morning (shown in Fig. 2a, b). To avoid shortage of AB plasma, we also use blood type A plasma for the Credo Cube™ as it was shown

Table 7. tFFP quality measurements of split tFFP ($n = 3$) before/after 3 days HEMS operation (air transport) or storage in parallel in the blood bank at 2–6°C (control, $n = 3$) (mean, range); decrease of activity >10% is marked in grey

Parameter	Air transport units/ control units	Baseline	After 3 days HEMS operation (5 days after baseline)	Δ before and after 3 transport days
Quick, %	Air transport	81.3 (63.0–103.0)	74.3 (59.0–89.0)	–7.0
	Control	85.7 (68.0–107.0)	78.0 (63.0–95.0)	–7.7
aPTT, s	Air transport	24.7 (23.0–27.0)	27.7 (25.0–31.0)	3.0
	Control	23.7 (22.0–26.0)	26.7 (25.0–29.0)	3.0
Fibrinogen, g/L	Air transport	2.2 (1.8–3.0)	2.2 (1.8–2.9)	0.0
	Control	2.4 (2.0–3.3)	2.4 (1.9–3.2)	–0.1
Factor II, %	Air transport	112.0 (95.0–134.0)	110.0 (90.0–136.0)	–2.0
	Control	122.3 (102.0–140.0)	121.7 (104.0–140.0)	–0.7
Factor V, %	Air transport	99.3 (80.0–114.0)	92.0 (74.0–101.0)	–7.3
	Control	102.3 (75.0–123.0)	100.7 (74.0–117.0)	–1.7
Factor VII, %	Air transport	65.0 (46.0–88.0)	56.7 (40.0–74.0)	–8.3
	Control	70.3 (45.0–101.0)	63.7 (43.0–85.0)	–6.7
Factor VIII, %	Air transport	84.3 (64.2–97.8)	47.3 (36.1–56.7)	–37.0
	Control	89.9 (65.3–107.7)	51.1 (35.7–61.3)	–38.8
Factor IX, %	Air transport	94.7 (91.0–100.0)	91.7 (88.0–98.0)	–3.0
	Control	106.0 (104.0–109.0)	102.0 (99.0–108.0)	–4.0
Factor X, %	Air transport	101.7 (79.0–114.0)	100.0 (72.0–120.0)	–1.7
	Control	115.7 (85.0–133.0)	116.3 (87.0–133.0)	–0.7
Factor XI, %	Air transport	112.0 (94.0–136.0)	100.7 (89.0–119.0)	–11.3
	Control	121.0 (104.0–146.0)	109.7 (96.0–129.0)	–11.3
Factor XII, %	Air transport	89.0 (73.0–112.0)	92.7 (75.0–119.0)	3.7
	Control	98.7 (81.0–122.0)	99.0 (82.0–121.0)	0.3
Factor XIII, %	Air transport	114.0 (103.0–123.0)	116.3 (103.0–126.0)	2.3
	Control	118.3 (108.0–130.0)	118.3 (109.0–127.0)	0.0
vWF antigen, %	Air transport	85.7 (74.0–92.0)	85.3 (81.0–89.0)	–0.3
	Control	81.3 (68.0–89.0)	82.7 (74.0–87.0)	1.3
vWF activity, %	Air transport	96.3 (76.0–115.0)	68.0 (60.0–75.0)	–4.0
	Control	70.0 (67.0–75.0)	67.0 (64.0–72.0)	–3.0
Protein C, %	Air transport	96.3 (76.0–115.0)	103.3 (83.0–122.0)	7.0
	Control	97.7 (76.0–117.0)	102.3 (82.0–121.0)	4.7
Protein S, %	Air transport	103.0 (76.0–121.0)	79.0 (55.0–103.0)	–24.0
	Control	98.3 (78.0–109.0)	79.0 (60.0–97.0)	–19.3

that low volumes of blood type A plasma are not harmful in emergency transfusion of a patient of unknown blood type [21, 22]. In case of transfusion no more than three units of AB0 incompatible plasma would be transfused. In addition, empty blood tubes for blood drawing before transfusion, needed for subsequent blood group typing after hospital admission, a transfusion protocol, and two bedside AB0 typing cards (Medtro®, Medtro, Bammmental, Germany) are included into the box (shown in Fig. 2a). If Lyoplas is provided, the box contains additionally two reconstitution fluid bags and two transfer sets (shown in Fig. 2b). This reduces the space and allows to transport

two RBC units only. We provide all documentary material in the same box as the blood products to reduce the risk of missing documentation.

Two cooling containers are used in the routine on alternate days. The Credo Cube™ is issued early in the morning before the day HEMS shift starts. It is carried to the in-hospital emergency department by the in-hospital transport team and is picked up there by the helicopter team at the beginning of the day shift. The Credo Cube™ is placed into the helicopter (shown in Fig. 2c) together with a blood warming device (Quinflow Warrior lite™). When the night shift is finished (24 h later), the Credo

Fig. 2. Packing of the Credo Cube™: a small bag with bedside ABO typing cards, blood drawing material, a min-max thermometer, 3 RBC and 3 tFFP units (a) or alternatively 2 RBC units and two bottles of lyophilized plasma (b), two bags of reconstitution fluid for the lyophilized plasma, and two transfer sets. A transfusion protocol and 5 patient identifier bracelets are placed at the inner side of the cover. For air transport the Credo Cube™ is tied to a helicopter seat (c).

Cube™ is returned to the blood bank. After return the logger records are checked. If temperature is maintained below 6°C, the blood products are stored in the blood bank for 1 day and are used again for the next HEMS operation day. After 3 days, new RBCs and tFFPs are issued with the Credo Cube™. The RBCs and tFFPs from the previous transport days are visibly checked for hemolysis or abnormalities and returned into the blood bank inventory until their expiration (RBCs 49 days, tFFP 7 days after thawing at 2–6°C in the thawed plasma bank) [23].

In case of transfusion, a pretransfusion blood sample is drawn and the transfusion protocol is filled in. Patient blood samples, the transfused empty blood bags, and the transfusion protocol are returned to the blood bank. In the blood bank tube segments of the RBCs issued in the Credo box are stored in the fridge and are used for retrospective compatibility testing. Data on the transfusion protocol are stored for lookback events. The empty Credo Cube™ is newly packed using the backup cooling tiles and new blood products and returned to the helicopter.

To prevent unauthorized opening, the Credo Cube™ is sealed and the seal must be broken before the box can be opened (shown in Fig. 2b, right picture).

Legal Requirements

The hospital transfusion service is a different legal entity than the HEMS operator. Both institutions have to establish their own quality management system according to the local requirements. In Germany these are defined by the transfusion law and the hemotherapy guidelines [17, 24]. To be able to re-integrate the blood products into the blood bank inventory, we have defined the sealed Credo Cube™ as sub-depot of the transfusion service of the University Medicine Greifswald. If the seal is broken the blood products are issued to the HEMS operator and cannot be re-integrated into the in-hospital blood bank.

Responsibility for the transfusion process is with the HEMS operator, the DRF Luftrettung. They have set up a hospital-like transfusion system with board, quality management, and physician in charge, which enables the company to use blood products according to German regulation. Any other agreement between the blood service and the HEMS operator, which includes transfer of patient data after transfusion from the helicopter team to the blood bank requires appropriate contracts according to the local regulations of patient data protection.

Discussion

The Credo Cube™ allows storage of blood components at 4°C ± 2°C for up to 36 h even at ambient temperatures of 35°C. RBC and tFFP quality were maintained

after 3 days of HEMS. The helicopter is equipped with blood products in Greifswald since June 2019 and up to now none of the returned products showed obvious quality impairment. Changes in clotting factor activities did not differ from aliquots of the same product stored in the blood bank at 2–6°C after thawing and were in the same range as described previously for the storage of thawed plasma at 2–6°C for up to 7 days [25].

Critical for planning of the logistic sequence is the appropriate preparation of the cooling tiles of the Credo Cube™. After the deep freeze period at ≤−18°C the tiles have to be stored at 2–6°C for at least 12 h. Otherwise the tiles might be too cold for the blood products and potentially harm red cells. If the tiles are prepared at 4°C only, the period during which temperature is maintained below 6°C decreases rapidly (data not shown).

At least two blood transport containers and three sets of cooling tiles are required to ensure a 24-h supply including the possibility to rapidly reload the Credo Cube™ in case of transfusion. In line with prior reports, which used other transport boxes [26], we observed a minor increase of potassium concentration in red cells, which however, maintained within the RBC specification.

After thawing of FFP the most sensitive clotting factor is factor VIII for which the most pronounced loss of activity occurred within the first 24 h, but mean activity was maintained higher than 50%. After 3 days HEMS operation (5 days after thawing) factor VIII further decreased to a mean level of 47%. This loss of FVIII activity is in the expected range: Buchta et al. described a factor VIII decrease to 0.53 (0.51–0.54 U/mL) [27], and von Heymann described a decrease of the factor VIII activity by 43% after storage of thawed plasma at 4°C for 6 days [28]. In general, the helicopter transport did not affect clotting factor activities any different compared to aliquots of the same plasma stored at the blood bank under regular conditions. We have previously shown that the loss of procoagulatory activities of clotting factor VIII and IX in plasma stored at 4 ± 2°C did not impair its thrombin generation potential as also anticoagulatory clotting factors are decreased [29]. In this regard the present study also observed a parallel decrease in factor VIII and protein S activities. This adds relevant information. We systematically validated tFFP using plasmapheresis plasma [25], while we used source plasma for the current study. Source plasma might have less well preserved clotting factors compared to apheresis plasma due to longer storage of whole blood before fractionation. It is therefore encouraging that we found no quality impairment of thawed tFFP obtained from whole blood donations in the current analyses.

As discussed before in detail [25], in case of massive transfusion the follow-up blood products will be freshly thawed plasma, maintaining clotting factor levels in the patient.

An alternative to thawed plasma is lyophilized plasma, which we also use in the Credo Cube™, but the size of the plasma bottles and the water bags needed for reconstitution only allow transport of two lyophilized plasma units together with two RBCs. Further disadvantage is that manipulation and time for reconstitution is needed to get a ready-to-transfuse product.

The decision to establish a blood inventory on HEMS has to be made in regard to the HEMS operating area, local hospital density, the risk of major trauma e.g. by difficult traffic conditions and the associated obstacles for ground emergency medical service. Mecklenburg-Vorpommern is an area with large distances between hospitals and large distances between blood suppliers and hospital blood banks. The possibility to start transfusions within 30 min after trauma helps to bridge the time for large distance transport to the next hospital/trauma center.

While our study shows the feasibility to carry an emergency blood depot on the helicopter, we did not perform any outcome studies. Up to now eight patients received blood transfusion during HEMS operation in Greifswald. We did not observe any major deviations or major adverse events, but the number of patients is too small to draw any meaningful conclusions on clinical efficacy. This will require to combine the results of all patients receiving prehospital transfusions on the helicopter in Germany during the last 2 years.

Conclusion

The present study shows the feasibility of supplying the helicopter emergency medical service with RBCs and plasma. Helicopter transport has no negative impact on blood product quality. The logistic challenges require close collaboration between the helicopter team and the blood transfusion service.

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Statement of Ethics

The prospective observation of the patients who received prehospital blood transfusion from the HEMS blood container is approved by our local ethical committee (reg. No. BB020/20). The data presented for validation of storage and transport conditions

monitoring the blood product quality by HEMS transport were collected based on “Arzneimittel- und Wirkstoffherstellungsverordnung – AMWHV” §7 by German legislature.

Conflict of Interest Statement

M.B. and K.-C.T. are members of the scientific working group of the DRF Luftrettung. M.R., F.R., J.B. are employees of the DRF Luftrettung. K.S. received research funding from Immucor, traveling support from SOBI and consultant fees from Aspen. A.G. received research funding from Ergomed, Boehringer Ingelheim, Rovi, Sagent, Macopharma, Portola, Biokit, Blau Farmaceutics, Prosensa/Biomarin, DRK-BSD NSTOB, DRK-BSD Baden-Württemberg/Hessen, travel support, speakers and consulting fees from Roche, GTH e.V., Sanofi-Aventis, Macopharma, Chromatec, Instrumentation Laboratory, Bayer Vital and Aspen. B.H., G.J., M.H., T.W., K.H. declare no conflict of interest.

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Author Contributions

M.B., G.J., K.-C.T., K.S., and A.G. designed the validation plan. M.B. organized the logistics of the laboratory measurements. G.J., K.-C.T., K.H. organized the transport logistics between the hospital blood bank and helicopter port. M.R., F.R., J.B. provided the storage containers and developed the quality management structure and policies for hemotherapy under HEMS conditions. M.B., M.H., T.W. performed RBC and tFFP quality assessment. M.B. and K.S. analyzed the results. M.B., K.-C.T., B.H., K.S., and A.G. wrote the manuscript. All authors finally approved the submitted version of manuscript.

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