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Is prehospital blood transfusion effective and safe in haemorrhagic trauma patients? A systematic review and meta-analysis

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ABSTRACT

Background: Life-threatening haemorrhage accounts for 40% mortality in trauma patients worldwide. After bleeding control is achieved, circulating volume must be restored. Early in-hospital transfusion of blood components is already proven effective, but the scientific proof for the effectiveness of prehospital blood-component transfusion (PHBT) in trauma patients is still unclear.
Objective: To systematically review the evidence for effectiveness and safety of PHBT to haemorrhagic trauma patients.
Methods: CINAHL, Cochrane, EMBASE, and Pubmed were searched in the period from 1988 until August 1, 2018. Meta-analysis was performed for matched trauma patients receiving PHBT with the primary outcomes 24-hour mortality and long-term mortality. Secondary outcome measure was adverse events as a result of PHBT.
Results: Trauma patients who received PHBT with simultaneous use of packed red blood cells (pRBCs) and plasma showed a statistically significant reduction in long-term mortality (*OR* = 0.51; 95% *CI*, 0.36–0.71; $P < 0.0001$) but no difference in 24-hour mortality (*OR* = 0.47, 95% *CI*, 0.17–1.34; *P* = 0.16). PHBT with individual use of pRBCs showed no difference in long-term mortality (*OR* = 1.18; 95% *CI*, 0.93–1.49; *P* = 0.17) or 24-hour mortality (*OR* = 0.92; 95% *CI*, 0.46–1.85; *P* = 0.82). In a total of 1341 patients who received PHBT, 14 adverse events were reported 1.04%, 95% *CI* 0.57–1.75%.
Conclusions: PHBT with simultaneous use of both pRBCs and plasma resulted in a significant reduction in the odds for long-term mortality. However, based on mainly poor quality evidence no hard conclusion can be drawn about a possible survival benefit for haemorrhagic trauma patients receiving PHBT. Overall, PHBT is safe but results of currently ongoing randomised controlled trials have to be awaited to demonstrate a survival benefit.
Study type: Systematic review and meta-analysis

Contents

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Introduction

Worldwide, 5.1 million people die every year as a result of traumatic injuries, of which 1 million are in Europe [1]. These traumatic injuries often result in death by major haemorrhage that could have been prevented in an estimated 29% of the civilian and 24% of the military casualties [2,3]. The introduction of prehospital blood-component transfusion (PHBT) with packed red blood cells (pRBCs), fresh frozen plasma (FFP), freeze dried plasma (FDP), or platelets in addition to the individual use of crystalloids – has improved remote damage control and made haemostatic volume replacement possible early after trauma. It has already been shown that PHBT with only pRBCs resulted in lower prehospital mortality but did not affect in hospital mortality [4]. PHBT reduces the total consumption of blood products during hospital stay and has a positive effect on coagulopathy [5,6].

Decades ago, only fresh whole blood (FWB) was available for transfusion and usage resulted in lower mortality in austere environments such as the battlefield [7]. In the early 1970s, FWB was replaced by blood components because these can be stored for a longer period [8]. The ability to transport oxygen, the haemostatic functions and the retained function of platelets make blood components more suitable for use in civil circumstances or austere environments [7]. However, there only few Helicopter Emergency Medical Services (HEMS) that carry cold stored whole blood, while the United States army uses warm fresh whole blood in combat hospitals by using a walking blood bank [9–11].

The acute traumatic coagulopathy (ATC) is a major threat for each trauma patient and often occurs even before volume resuscitation is initiated, even in the prehospital phase [12]. This coagulopathy in combination with hypothermia and acidosis are referred to as the 'lethal triad' in trauma care [13]. Although the mechanisms of the underlying pathophysiology is only partially clear, its relation to poor survival is evident. Early haemostatic resuscitation addresses ATC and therefore has the potential to improve patient outcome [14].

Despite complex logistics such as storage and preparation, blood or blood components are nowadays generally available in many HEMS as well as a few Ground Emergency Medical Services (GEMS). However, equal administration of components is difficult because most HEMS only carry pRBCs. This is in contrast with in-hospital transfusion where the combined use of pRBCs, plasma and platelets in equal ratios is common practice and is effective in achieving haemostasis [8]. Prehospital transfusion guidelines are not uniform, which results in the initiation of PHBT widespread parameters and clinical experience of the physician. Due to mainly poor quality evidence, there is still no scientific evidence regarding the effectiveness of PHBT on 24-hour and long-term mortality. A systematic review published in 2016 regarding PHBT could not draw conclusions about effectiveness of PHBT and stated that randomised controlled trials (RCTs) had to be awaited [15]. In the past two years, several studies (including two RCTs) have been published. This review gives an overview of the published literature and in addition, for studies with matched cohorts meta-analysis was conducted.

Methods

This systematic review was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (see Appendix S1 for the PRISMA checklist). No protocol was registered for this review. The review is based on a systematic search and predefined inclusion and exclusion criteria. The meta-analysis was performed according to a predefined analysis plan and all methodology was based on guidelines by Cochrane [16].

Comprehensive search

Articles were retrieved from four databases: CINAHL, Cochrane, EMBASE, and PubMed. These sources were systematically searched (by TR) for publications published between 1988 and August 1st, 2018. The search was not restricted by language or publication status. The comprehensive search strategies were created using a step-by-step guide [17] and PRESS [18] as guidance. The search strategy included the following Mesh terms: 'Shock, Hemorrhagic', 'Wounds and Injuries', 'Blood Transfusion', 'plasma', 'Ambulance', and 'Emergency Medical Services'. Corresponding terms were used in the other databases: CINAHL databases (CINAHL-headings), Cochrane (Mesh), and EMBASE (EMTREE terms). A full list of search terms is shown in Appendix S2.

Study selection

All retrieved references were imported into Endnote (X8.0.1, PDF Tron™ Systems Inc. 2001–2014, Canada), and duplicates were removed. The remaining unique references were imported into EROS (Early Review Organizing Software, version 3.0, IECS (Institute of Clinical Effectiveness and Health Policy, Buenos Aires, Argentina) and screened in duplicate for eligibility on title and abstract by at least two of the six independent reviewers (TR, KW, RM, NH, LG, ET). Full texts of eligible references were screened in duplicate for final inclusion by two of the six independent reviewers (TR, KW, RM, NH, LG, ET). In both phases, discrepancies were resolved through discussion. In both screening phases, we used the following predefined exclusion criteria: no blood or blood products administered, no prehospital setting, not a study in humans, no original data available. Studies were selected for meta-analysis when they contained cohorts with matched patients. The study data was retained from the manuscripts only; no authors were contacted to obtain individual patient data. Studies containing inter-facility transports were excluded from all analyses.

Data extraction

One reviewer (TR) extracted the data from the included studies according to a predefined template. The main characteristics of the studies – type of study, author, total number of patients, blood components used, average amount of blood components carried, method of transport, indication for transfusion, injury severity score (ISS) or new injury severity score (NISS), and adverse events – were summarised and attached in appendix S3-S6. For the primary outcomes (24-hour mortality and long-term mortality), meta-analysis was conducted. Twenty-four-hour mortality was defined as patients who died within 24 h after injury, including patients who died in the prehospital setting on scene or during transport. Long-term mortality was defined as 30-day or in-hospital mortality. Our secondary outcome was adverse events resulting from PHBT.

Risk of bias assessment

Risk of bias assessment was performed for all studies included in the meta-analysis. The Cochrane risk of bias tool version 5.1.0 was used to access the risk of bias in RCTs [16]. The tool consists of seven signalling questions with which the risk of selection, performance, detection, attrition, reporting and other biases can be assessed using a three-grade scale: (low, high, or unclear risk of bias (see Appendix S8) The risk of bias in retrospective cohort studies was evaluated using the ROBINS-I (Risk Of Bias In Non-randomised Studies of Interventions; [19]. ROBINS-I covers the following domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurements of outcomes, selection of the reported result, and overall bias. Using this tool, retrospective cohort studies were classified using a five-grade scale: low, moderate, serious or critical risk of bias, or no information (see Appendix S7). All assessments were performed in duplo by two independent authors, who resolved discrepancies through discussion.

Data synthesis and analysis

We used Revman 5.3.5 (The Cochrane Collaboration, Oxford, United Kingdom) to perform meta-analysis. Studies with matched cohorts reporting 24-hour mortality, long-term mortality, or both were included for meta-analysis. The studies contained a 'standard care' group (infusion with crystalloids, no transfusion, unknown or combination with blood components) and an intervention group (transfusion with blood or blood components). We performed separate analyses for patients receiving only prehospital pRBCs, patients receiving both prehospital pRBCs and plasma and patients receiving plasma only, versus standard care. The Mantel-Haenszel random effects model was used for all the studies with matched cohorts, and effect sizes were calculated as odds ratio (*OR*) and corresponding 95% confidence intervals (95% *CI*). Heterogeneity was assessed using the I^2 statistic.

Results

Literature search and study selection

The search identified 3475 references from four databases (Fig. 1). After removing 471 duplicates, 3004 references were screened based on their title and abstract, of which 263 were eligible for inclusion and underwent subsequent full-text screening. Based on full-text assessment, 49 studies were included of which 9 were included for meta-analysis.

Study characteristics and quality assessment

Baseline characteristics of the 49 included studies are summarized in appendix S3 (case reports), S4 (case series), S5 (cohort studies) and S6 (RCTs). Most studies were retrospective, including five case reports [20–24] case series [25–48] and 18 case-control or matched cohort studies [4–6,49–63]. Two studies were RCTs [64,65]. Studies were performed in the United States (n = 25), Afghanistan (n = 6), Israel (n = 4), United Kingdom (n = 4), Australia (n = 3), the Netherlands (n = 2), Austria (n = 2), or Iraq, Norway or France (each n = 1). Severity of injury was reported in 31 studies (63%). In total, 5159 patients received PHBT. In studies reporting the gender of the patients, the majority were male (median 73% range 19%–100%; n = 54 study groups). The individual use of pRBCs was reported in 24 studies, followed by the individual use of FDP in five studies. Sixteen studies reported a combined usage of pRBCs and FFP, and two studies reported the combined usage of pRBCs and FDP. Two studies transfused only FFP. Patients were transported by HEMS in 33 studies and by ground ambulances in four studies. In nine studies, there was a combination of air and ground transport. HEMS crews had an average of two to four bags of O-Negative pRBCs (250–300 mL) on board. For plasma, this standard was up to 4 units of FFP. The long-term mortality rate varied between 6% and 62.3%.

32 studies described the indications used for initiating blood or blood-component transfusion [51,52,58,54,49,56,55,6,60,62,27–33,42,41,44,46,47,36,39,37,22,23,48,34,43,64,65].

In most of the larger studies (> 100 patients), the systolic blood pressure and heart rate were used as part of the indication to start PHBT. However, the threshold for transfusion of the systolic blood pressure varied between the studies (80–90 mmHg). Parameters such as prehospital lactate > 5, Hb < 7 g/dl, penetrating mechanism, estimated blood loss > 500 mL, capillary refill > 2 s, and clinical gestalt were less used.

Risk of bias was assessed for the nine studies included in the meta-analysis (seven cohort studies and two RCTs; see appendix S7 and S8). For the two RCTs, we judged the risk of bias in each domain to be the same for all outcomes in the study, and therefore present only one score per domain, except for detection bias where we judged the risk of bias to differ between the primary and secondary outcomes. Both studies were at high risk of performance bias, because (full) blinding of personnel and patients could not be performed. One study appeared to be at risk of reporting bias, since data for two secondary outcomes mentioned in the study protocol were not reported. One study was at unclear risk of selection bias and reporting bias because of missing information regarding

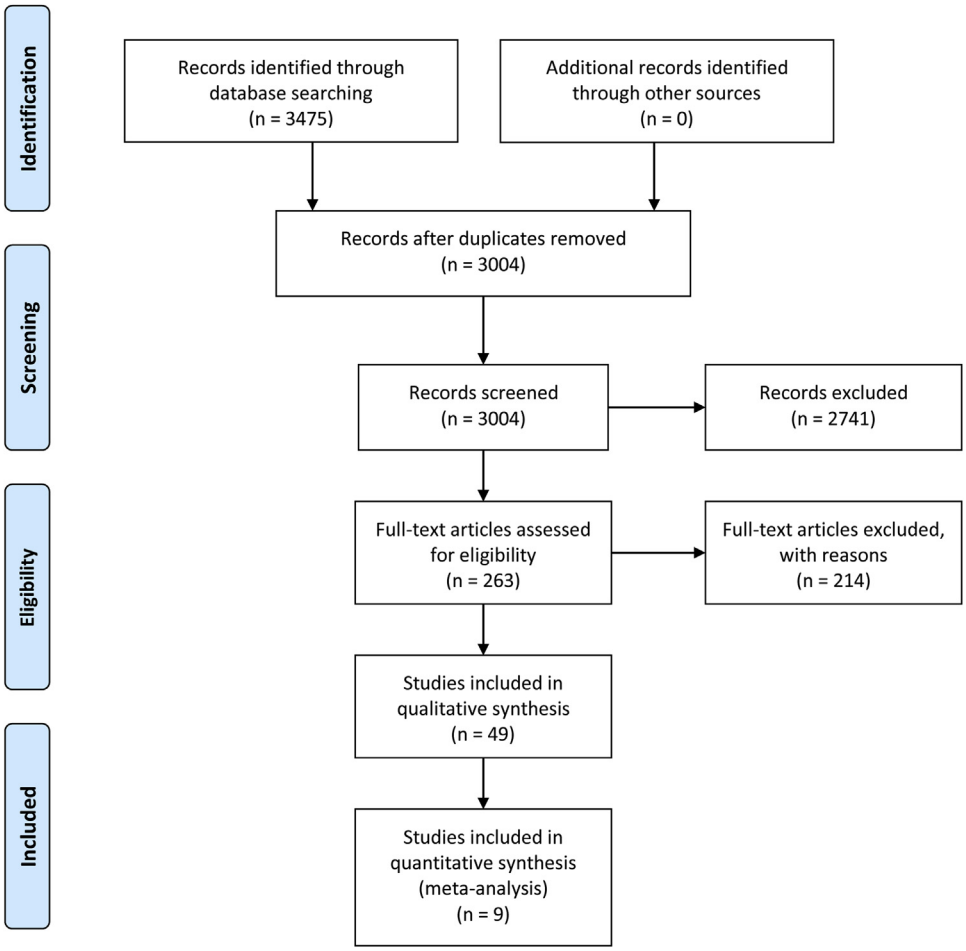

Fig. 1. Prisma study flowchart of included studies.

random sequence generation and the a priori definition of primary and secondary outcomes. The studies were judged to be at low risk of bias for all other bias domains.

Regarding the cohort studies, the overall risk of bias was critical in six studies and serious in one study. For most studies, this critical risk of bias was the result of confounding and selection bias (e.g. in many studies the intervention was administered to patients whose ISS was substantially higher than of the control group, which influenced the outcome), or missing data.

Meta-analyses of primary outcomes

A brief overview of the characteristics of the studies included for quantitative (meta-analyses) are summarized in Table 1. Nine studies were included with a total of 3078 patients, of which 1214 (39.4%) were in the intervention group [64,65,4,51–53,49,6,61]. Five studies were performed in the United States, two in the United Kingdom, one in the Netherlands and one in Afghanistan. Median age was ranged 24–49 in the intervention group compared to 23–49 in the standard care group. Eight studies reported on 24-hour mortality that ranged from 6% to 30% in the intervention group and 10%–42% in the standard care group. Long-term mortality was reported in all studies and ranged from 8.2%–59.8% in the intervention group and 10%–62.3% in the standard care group. Only one study reported transfusion with only plasma [65]. The rate of severe injury was reported using ISS in nine studies (range 17–35) or NISS in two studies (range 21–27). One study did not describe injury severity [4]. It is challenging to compare the demographics, and haemodynamic instability because individual patient data was lacking. The following outcome measures were analysed by meta-analysis: 1) effect of pRBCs only on 24-hour mortality, 2) effect of pRBCs only on long-term mortality, 3) effect of pRBCs and plasma on 24-hour mortality and 4) effect of pRBCs and plasma on long-term mortality. The effect of prehospital transfusion with plasma on 24-hour mortality and long-term mortality was analysed by narrative synthesis.

Effectiveness of pRBCs on 24-hour mortality

Three studies with matched civilian trauma patients reported 24-hour mortality [49,51,4]. A total of 484 civilian trauma patients received pRBCs, which were compared to 545 patients receiving only standard care. The total number of events in the pRBCs group was 124, compared to 173 in the control group. Pooled data showed no difference in 24-hour mortality (*OR* = 0.92; 95% *CI,* 0.46–1.85; *P* = 0.82; Fig. 2a). Study heterogeneity was high (I^2 80%).

Effectiveness of pRBCs on long-term mortality

A total of four studies reported long-term mortality in patients who received PHBT with pRBCs only [6,51,49,4]. In total, 723 patients were transfused compared with 1025 patients receiving only standard care. All studies were performed in a civilian setting. The total number of events in the pRBCs group was 298, compared to 370 in the standard care group. Heterogeneity was low (I^2 18%). Pooled data showed no difference in long-term mortality between the standard care and PHBT groups (*OR* = 1.18; 95% *CI*, 0.93–1.49; *P* = 0.17; Fig. 2b).

Table 1
Characteristics for studies included in meta-analysis.

Reference	Group	Study Design (Period)	Setting (mechanism)	Type of transport	Patients (% male)	Age (range)	Cause of injury	Injury burden (ISS/ NISS)	Indications for PHBT	Prehospital intervention	24-hour mortality n (%)	Long-term mortality n (%)	Adverse events by transfusion
Moore et al. (65) *(United States)*	Plasma	RCT (04-2014-03-2017)	Civilian Trauma	GEMS	65 (80)	33 (25-51)	Blunt 46%	NISS 27.0 (10.0-41.0)**	SBP $\leq$ 70 mmHg or SBP 71-90 mmHg + HR $\geq$ 108 bpm	4 units of plasma during transport (37%) 3 units of plasma during transport (31%) Saline 150 (0-300)	8 (12%)	10 (15%)	No differences in adverse events
	Standard care		Civilian Trauma	GEMS	60 (85)	32.5 (25.5 – 42.0)	Blunt 53%	NISS 27.0 (11.5-36.0)**	See above	Saline 250 (100-500)	6(10%)	6 (10%)	No differences in adverse events
Sperry et al. (64) *(United States)*	pRBCs + plasma	RCT (05-2014 – 10-2017)	Civilian Trauma	HEMS	230 (71.3)	44 (31-59)	Blunt 81.3% Penetrating 20 %	ISS 22 (14-33)**	RBC transfusion should be administered after 1 L of crystalloid total has been received by an injured patient and any one of the following are present: Hypotension with SBP <90mmHg Changes in mental status Changes in skin color (pallor, mottling or cyanosis) Tachycardia with HR > 120 beats per minute CR >2 seconds Urine output 0.9 9. RBC transfusion initiated at a referring facility (inter-facility transports) Lactate level $\geq$4 mmol/L Shock index (HR/SBP) >0.9 RBC transfusion initiated at a referring facility (inter-facility transports) In cases of penetrating wounds or clinical evidence of active bleeding, RBC may be initiated earlier through consultation with a medical command physician.	2 units of plasma (89.1%) 1 unit of plasma (9.1%) no plasma (1.7%) pRBCs 42.1% Saline 500 (0-1250)	32 (13.9%)	62 (26.9%)	6 / 230 (2.6%)
	Standard care		Civilian Trauma	HEMS	271 (73.8)	46 (28-60)	Blunt 83.4% Penetrating 18.1%	ISS 21 (12-29)**	See above	pRBCs 42.1% Saline 900 (0-1500)	60 (22.1%)	99 (36.5%)	4 / 271 (1.5%)
Subgroup Sperry *et al.* [64] *(United States)*	pRBCs + plasma	RCT (05-2014 – 10-2017)	Civilian Trauma	HEMS Scene patients	170 (unknown)	Unknown	Unknown	Unknown	See above	Not specified	unknown	40 (23,5%)	Unknown
	Standard care		Civilian Trauma	HEMS	203 (unknown)	Unknown	Unknown	Unknown	See above	Not specified	Unknown	76 (37.4%)	Unknown
Rehn et al. (4) *(United Kingdom)*	Post-pRBCs	RMC (01-2009 – 02-2012)	Civilian Trauma 100%	HEMS Scene: 100%	239 (77)	32 Range [24–45]	Blunt 57.7%	Unknown	Unknown	Median 2 units of pRBCs	66 (27.6%)	143 (59.8%)	Unknown
	Pre- pRBCs	RMC (04-2012 – 02-2015)	Civilian Trauma 100%	HEMS Scene: 100%	300 (80)	31 Range [23–50]	Blunt 62.1%	Unknown	Unknown	Only crystalloids	126 (42%)	187 (62.3%)	Unknown
	pRBCs				50 (90)						19 (30%)	22 (45%)	

Table 1 (*Continued*)

Reference	Group	Study Design (Period)	Setting (mechanism)	Type of transport	Patients (% male)	Age (range)	Cause of injury	Injury burden (ISS/ NISS)	Indications for PHBT	Prehospital intervention	24-hour mortality n (%)	Long-term mortality n (%)	Adverse events by transfusion
Peters et al. (51) *(Netherlands)*		RMC (01-2007 – 11-2015)	Civilian Trauma 100%	HEMS Scene 100%		33 (18-70)	MVA 35 (70%) Penetrating 7 (12%) Fall from height 5 (10%) Other 3 (6%)	ISS 34 (9-75)** n = 45	HEMS physician based on clinical parameters in combination with trauma mechanism	pRBCs 750 ml (250-5000) Crystalloids 1500 mL (0-9250)			1 mild reaction possible the result of administration of in hospital FFP
	Standard Care				50 (90)	33 (18-63)	MVA 34 (68%) Penetrating 3 (6%) Fall from height 6 (12%) Other 7 (14%)	ISS 35 (18-75)** n = 40	See above	Crystalloids 1750 mL (250-5000)	16 (32%)	20 (40%)	
Shackelford et al. (52) *(Afghanistan)*	PHBT	RMC (04-2012 – 09-2015)	Military Trauma 100%	MEDIVAC Scene 100%	55 (unknown)	26 [23–29]**	GSW: 9 (16%) Explosives 46 (84%)	ISS 29 (17-36)**	At least 1 established criterion for prehospital transfusion for severe trauma: ≥1 traumatic limb amputation with at least 1 located above the knee or elbow SBP <90 mm Hg or a HR > 120 beats per minute) documented on initial transport from point of injury.	38 patients pRBCs 7 plasma only 10 pRBCs and plasma	3 (6%)	6 (11%)	Unknown
	Standard care			MEDIVAC Scene 100%	345 (unknown)	25 [22–29]**	GSW: 101 (29%) Explosives 244 (71%)	ISS 28.6 (24.0-33.2)**			67 (20.2%)	76 (22.9%)	
Holcomb et al (53) (*United States*)	PHBT	RMC (01-2015– 11-2015)	Civilian Trauma 100%	HEMS Scene: 100%	43 (67,4)	Median (48 (27,62)*	Any penetrating injury 9 (20,9%)	ISS 24 (10-34)*	Unknown	Plasma only (24%) pRBCs only (7%) Plasma + pRBCs (69%)	5 (11.6%)	8 (18.6%)	Unknown
	Standard care				66 (72,7)	Median 39 (26,56)*	Any penetrating injury 18 (27,3%)	ISS 22 (10-34)*	Unknown		10 (15.2%)	14 (21.2%)	Unknown
Miller et al. (49) (*United States*)	pRBCs	RMC (2007-2013)	Civilian Trauma 100%	HEMS Scene: 100%	195 (70)	35.6 (25.0-54.2)	Penetrating 39 (20%) Other 156 (18%)	ISS 22.0 (34.0-42.5)**	Bloodloss >500 mL	Up to 2 u O- pRBCs	39 (20%)	59 (30.2%)	Unknown
	Standard care			HEMS	195 (65)	38.3 (25.8-56.9)	Penetrating 36 (82%) Other 159 (82%)	ISS 22.0 (34.0-43.0)**		None	31 (15.8%)	48 (24.6%)	
Brown et al (6) (*United States*)	PHBT	RMC (2007-2012)	Civilian Trauma 100%	HEMS	240 (69)	49 (28-71.5)	Blunt 191 (80%) Penetrating 49 (20%)	ISS 18 (10-29)**	After infusion of 1 to 2 l crystalloids: SBP <90 mmHg Changes in mental status Changes in skin color CR > 2 s	pRBC 300 mL (200-500) crystalloids 500 mL (100-1000)	54 (22.5%)	74 (30.8%)	No reported complications
	Standard care		Civilian Trauma 100%	HEMS	480 (67)	49 (31-68)	Blunt 395 (82%) Penetrating 85 (18%)	ISS 17 (9-27)**	Lactate > 4 mmol/L Urine output <30 ml/h for > 4h SI >0.9 Penetrating wounds or active bleeding RBC can administered earlier.	Crystalloids 400 ml (100-1000)	unknown	115 (23.9%)	No reported complications

O'reilly et al. (61) (*Afghanistan*)	PHBT	RMC (07-2008 – 03-2011)	Military Trauma 100%	MERT-E Scene: 100%	97 (97.9)	24 (20-28)	Blunt 1 (1%) Explosive 50 (51.5%) GSW 46 (47.4%)	NISS 22 (15-33)** ISS 16 (9-25)**	Unknown	pRBCs 1 median [1,2] range [0-4] FFP 2 median [1,2] range [0-4]	unknown	8 (8.2%)	No serious adverse events or complications
	Standard care				97 (100)	23 (21-28)	Blunt 3 (3.1%) Explosive 48 (49.5%) GSW 46 (47.4%)	NISS 21 (14-34)** ISS 16 (9-24.5)**	Unknown		unknown	19 (19.6%)	

Legend: RCT, randomized controlled trial; RMC, retrospective matched cohort; NISS, new injury severity score; ISS, injury severity score; PHBT, pre-hospital blood transfusion; GEMS, ground emergency medical Service; HEMS, helicopter emergency medical service; SBP, systolic blood pressure; HR, heart rate; MVA, motor vehicle accident; GSW, gunshot wound; MERT-E, medical emergency response team enhanced; FFP, fresh frozen plasma; INR, international normalized ratio; CR, capillary refill; MEDEVAC, medical evacuation; Hb, haemoglobin * (P25,P75) ** (IQR, interquartile range).

Effectiveness of pRBCs and plasma on 24-hour mortality

Two retrospective studies with matched cohorts were included. One was performed in civilian [53] and one in military setting [52]. A total of 97 trauma patients received the combination of pRBCs and plasma compared with 398 matched control patients who only received standard care. The total number of events in the pRBCs and plasma group was 8, compared to 77 in the standard care group. Pooled data showed no difference in the odds for 24-hour mortality (*OR* = 0.47, 95% *CI*, 0.17–1.34; *P* = 0.16; Fig. 3a). Heterogeneity was defined as moderate (I^2 48%).

Effectiveness of pRBCs and plasma on long-term mortality

Three retrospective studies and one RCT reported long-term mortality in patients who received combined transfusion with pRBCs and plasma [52,53,61,64]. Two studies were conducted in a civilian setting [53,64] and two studies in a military setting [52,61]. In total 364 patients received PHBT compared to 698 patients receiving only standard care. The total number of events in the intervention group was 62, compared to 185 in the standard care group. Heterogeneity was defined as low (I^2 0%). Pooled data showed a 49% reduction in the odds for long-term mortality in the intervention group (*OR* = 0.51; 95% *CI*, 0.36–0.71; $P < 0.0001$) (Fig. 3b).

Narrative synthesis of primary outcomes

Effectiveness of plasma on 24-hour and long-term mortality

One RCT reported the outcome after prehospital administration of plasma in trauma patients [65]. The study contained only civilian trauma patients who were transported by GEMS. A total of 65 patients received prehospital thawed plasma compared with 60 patients receiving standard care. The total number of events in the plasma group was 8 compared with 6 in the control group who only received standard care. Data showed no difference in the odds for 24-hour mortality (*OR* = 1.26, 95% *CI*, 0.41–3.88; *P* = 0.68) and long-term mortality (*OR* = 1.64, 95% *CI*, 0.56–4.82; *P* = 0.37).

Narrative synthesis of secondary outcomes

Adverse events

The absence or presence of adverse events of PHBT in trauma patients was reported in 14 studies [24,23,28,29,51,6,32,34,38,61,37,44,47,64]. In the studies reporting adverse events, a total of 1341 trauma patients were transfused, and 14 of them developed a complication which was possibly related to the transfusion (1.04%, 95% *CI* 0.57–1.75%). Complications were directly after admission an allergic reaction with rash (n = 5), a possible breathing depression (n = 1), anaphylaxis (n = 1), hypotension (n = 1) and urticaria (n = 1). In 4 patients the authors could not conclude whether the complication was a direct result of the transfusion. During the administration of FDP, there was one complication after infusion. One patient developed chills and shivering, what was not evidently the result of the transfusion, but rather from the sepsis she developed [29].

Discussion

The objective of this systematic review was to determine the effectiveness and safety of PHBT for haemorrhagic trauma patients. Although there was a significant reduction in the odds for long-term mortality when receiving both pRBCs and plasma simultaneously, no hard conclusions can be drawn regarding effectiveness. This is a result of the fact that the majority of literature provided mainly poor quality evidence and was retrospective. Two recently published RCTs provide high quality evidence regarding the use of plasma in haemorrhagic shock.

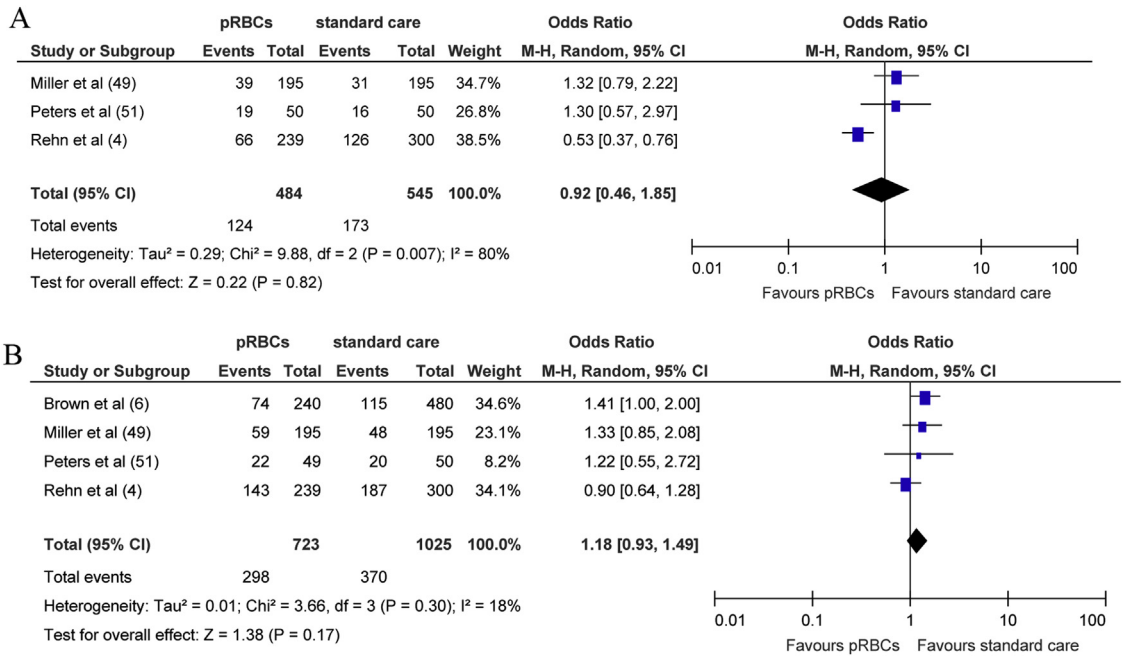

Fig. 2. (a) Comparison of prehospital transfusion with packed red cells only vs. standard care on 24-hour mortality. The studies are shown by name with point estimates of the odds ratios and 95% confidence intervals. (b) Comparison of prehospital transfusion with packed red cells only vs. standard care on long-term mortality. The studies are shown by name with point estimates of the odds ratios and 95% confidence intervals.

However, one of the two RCTs contained inter-facility transports and was therefore excluded from 24-hour mortality meta-analysis [64]. The other RCT showed no survival benefit, which could be explained by the low number of included patients which resulted in early termination of the study [65]. Regarding safety, only 14 adverse events of PHBT (1.04%) were reported, which confirms the safety of PHBT. However, not all included studies reported adverse events, which means that this number may be an underestimation of the actual number.

There are several other factors that could have influenced the results found in this meta-analysis and which make the extrapolation of the findings to clinical practice challenging. First of all, among included studies there is a lack of uniform guidelines for initiating PHBT. Although it is best practice to use uniform guidelines or cut-off points, in practice, the clinical condition of the patient will often determine as the most important factor in treatment. Overall, the criteria for initiating PHBT were evident blood loss (all studies) and clinical signs of shock (systolic blood pressure < 90 mmHg in combination with heart rate > 120 beats per minute). Secondly, the liberal use of crystalloids in both intervention and standard care groups makes it difficult to determine the individual effect of PHBT. Although infusion of crystalloids is still common practice in prehospital care, the use of crystalloids should be limited to a maximum of 1.5 litres per adult patient due to the harmful effects when administered in larger quantities [66]. Thirdly, it is hard to compare military patients versus civilian patients just soldiers often have a lower age than the civilian population in general, are generally at excellent baseline health and are also better trained in the treatment of severe blood loss through 'self-help' (tourniquet use). Tourniquets use enables them to be capable of acting quickly and effectively at arresting haemorrhage, which could result in a higher chance of survival [67]. In addition, there is a difference between the studies as to whether they reported ISS or NISS, which makes comparisons unreliable. in ISS or NISS, which makes it unreliable to compare the studies. Also, the whole trauma system needs to be considered (the 'Chain of Survival'). A recently published study showed that PHBT only resulted in lower prehospital mortality but did not affect in-hospital mortality [4]. It is therefore necessary to also optimize in-hospital care to treat this type of patient, who may previously have deceased at the scene or on route to hospital.

Finally, transfusion strategies are different among studies. The current in-hospital guideline is that massive transfusion should be performed early, with components (pRBCs/plasma/platelets) in equal ratio (1:1:1), supplemented with medication (tranexamic acid, fibrinogen) to treat induced coagulopathy [8]. However, plasma and platelets are not always available in prehospital setting, and if it is, in insufficient quantities. (60)

In addition to availability, storage and transportation of blood components is challenging. It requires a refrigerator, with continuous temperature monitoring and an active cooler box on-board. The use of a fluid warmer to warm the blood is advised because administration of cold fluids or blood components will worsen hypothermia and increases the total amount of the in-hospital transfused blood products and the risk of complications such as pneumonia, renal failure, cardiac arrest, and ATC [68]. The use of FDP offers solutions to these logistic problems. FDP can be stored at room temperature, is available in less than 10 min has comparable haemostatic functions to FFP, and its anticoagulant function is ensured [34]. In contrast, FFP has a thawing time of 20 min [69]. FDP has already been used in prehospital settings by both military and civilian agencies, such as the French (French FLYP), the United Kingdom, Norwegians, the Germans (LyoPlas N-w), the South Africans and the Israeli Defence Force [69,29]. In the US, FDP is recently approved by the Food and Drug Administration (FDA) as a transfusion product.

Limitations

In this review, studies were included that date from 1988 to August 1, 2018. The risk of bias between these studies is large

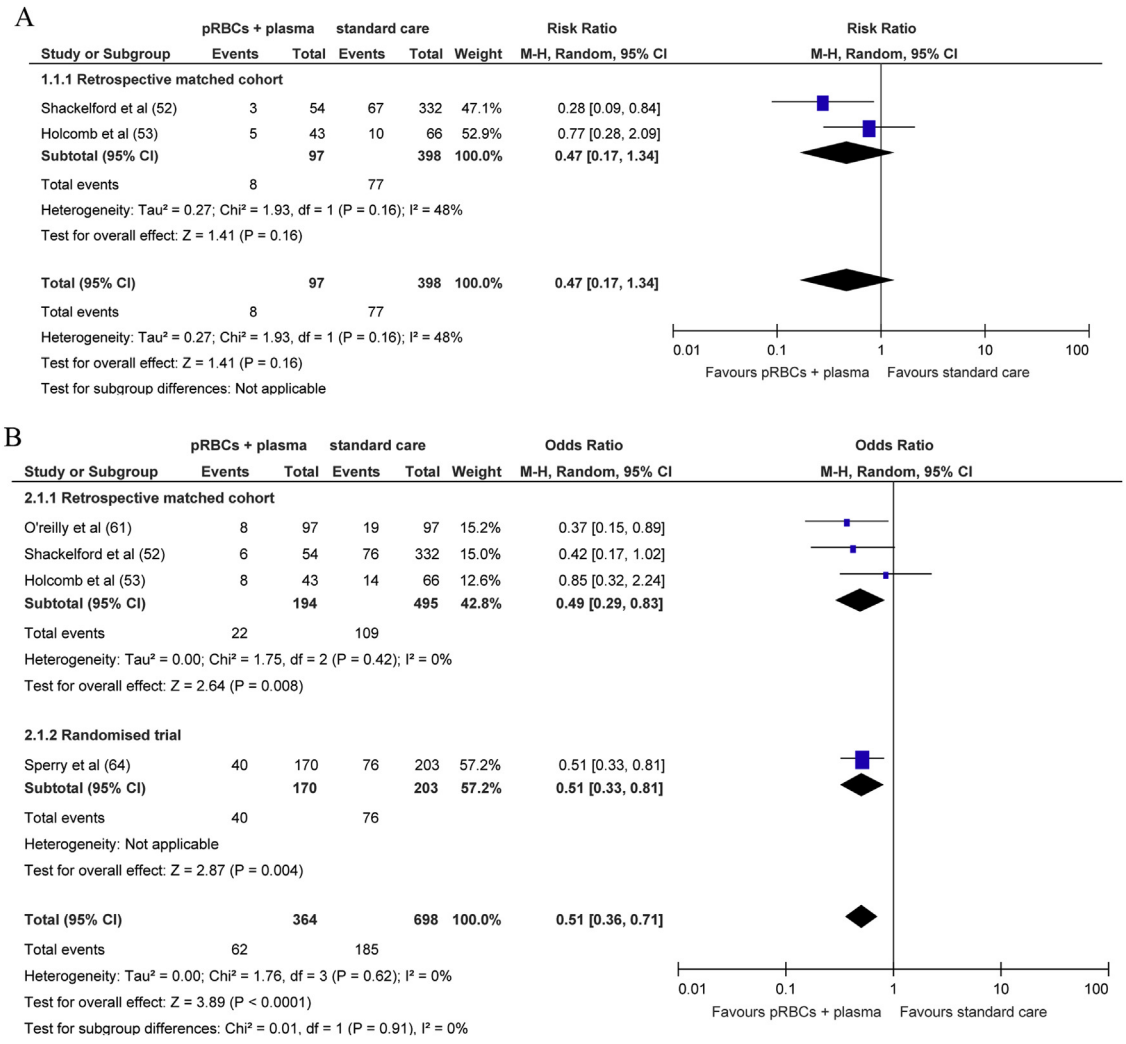

Fig. 3. (a) Comparison of prehospital transfusion with combined use of both packed red cells and plasma vs. standard care on 24-hour mortality. The studies are shown by name with point estimates of the odds ratios and 95% confidence intervals.
(b) Comparison of prehospital transfusion with combined use of packed red cells and plasma vs. standard care on long-term mortality. The studies are shown by name with point estimates of the odds ratios and 95% confidence intervals.

considering the 30-year time span of the literature. Studies are hardly comparable because there is no standard indication for transfusion; some protocols are even outdated. The majority of studies consisted of low patient numbers. Other lifesaving interventions – such as emergency thoracotomy, clamshell thoracotomy, advanced airway management, or the administration of crystalloids before PHBT– can distort the data. The lack of a uniform guideline could influence our conclusion because over- or under-transfusion could lead to a poorer chance of survival. The high heterogeneity observed in our meta-analysis of the effect of pRBCs versus standard care on 24-hour mortality is likely a result of these variations in study design and quality. The study by Rehn et al 2018 shows a positive effect of treatment which was not observed in the other two studies, but we could not readily explain this difference based on a difference in the studies' characteristics [4]. Unfortunately, some of the key study characteristics were not reported, e.g. the ISS, which may have influenced the outcome. The study of Sperry et al included both scene and inter-facility transports. In this meta-analysis only the scene transports were included [64]. Until additional evidence becomes available, the outcome of this meta-analysis should be interpreted with care.

The current literature provides mostly low-quality evidence from retrospective studies. Two RCTs were published recently [64,65]. In a large, ongoing, RCT, 'Resuscitation with Pre-Hospital Blood Products' (RePHILL), trauma patients are randomly exposed to crystalloids, packed red cells, and plasma; it is currently ongoing and recruiting will finish at the end of 2020 [70]. Other studies currently including patients are Prehospital Administration of Lyophilized Plasma for Post-traumatic Coagulopathy Treatment (PREHO-PLYO) ***ClinicalTrials.gov Identifier: NCT02736812***, Rapid Administration of Blood by HEMS in Trauma (RABBIT) ***ClinicalTrials.gov Identifier: NCT03522636*** and Prehospital Pragmatic Group O Whole Blood Early Resuscitation Trial (PPOWER) ***ClinicalTrials.gov Identifier: NCT03477006.*** It is assumed that these trials provide high-quality evidence according to the efficacy and safety of use of prehospital blood products [70,15].

Conclusions

Carrying and administering blood components by (H)EMS is feasible and safe. PHBT with simultaneous use of both pRBCs and plasma resulted in a reduction in the odds for long-term mortality. However, no hard conclusion could be drawn as most studies contained only low quality evidence. Future results of currently ongoing RCTs have to be awaited.

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Authorship

All authors contributed to the acquisition and analysis of data and writing of this article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.injury.2019.03.033.

References

[1] Spinella PC, Cap AP. Prehospital hemostatic resuscitation to achieve zero preventable deaths after traumatic injury. Curr Opin Hematol 2017;24 (6):529–35.
[2] Eastridge BJ, Mabry RL, Seguin P, Cantrell J, Tops T, Uribe P, et al. Death on the battlefield (2001-2011): implications for the future of combat casualty care. J Trauma Acute Care Surg 2012;73(6 Suppl 5) S431-7.
[3] Davis JS, Satahoo SS, Butler FK, Dermer H, Naranjo D, Julien K, et al. An analysis of prehospital deaths: who can we save? J Trauma Acute Care Surg 2014;77 (2):213–8.
[4] Rehn M, Weaver A, Brohi K, Eshelby S, Green L, Roislien J, et al. Effect of pre-hospital red blood cell transfusion on mortality and time of death in civilian trauma patients. Shock (Augusta, Ga) 2018.
[5] Brown JB, Cohen MJ, Minei JP, Maier RV, West MA, Billiar TR, et al. Pretrauma center red blood cell transfusion is associated with reduced mortality and coagulopathy in severely injured patients with blunt trauma. Ann Surg 2015;261(5):997–1005.
[6] Brown JB, Sperry JL, Fombona A, Billiar TR, Peitzman AB, Guyette FX. Pre-trauma center red blood cell transfusion is associated with improved early outcomes in air medical trauma patients. J Am Coll Surg 2015;220(5):797–808.
[7] Spinella PC, Cap AP. Whole blood: back to the future. Curr Opin Hematol 2016;23(6):536–42.
[8] Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. Jama 2015;313(5):471–82.
[9] Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. J Trauma 2009;66(4 Suppl) S69-76.
[10] Grosso SM, Keenan JO. Whole blood transfusion for exsanguinating coagulopathy in a US field surgical hospital in postwar Kosovo. J Trauma 2000;49(1):145–8.
[11] Nessen SC, Eastridge BJ, Cronk D, Craig RM, Berseus O, Ellison R, et al. Fresh whole blood use by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets. Transfusion 2013;53(Suppl 1) 107s-13s.
[12] Floccard B, Rugeri L, Faure A, Saint Denis M, Boyle EM, Peguet O, et al. Early coagulopathy in trauma patients: an on-scene and hospital admission study. Injury 2012;43(1):26–32.
[13] Mitra B, Tullio F, Cameron PA, Fitzgerald M. Trauma patients with the' triad of death'. Emerg Med J 2012;29(8):622–5.
[14] Simmons JW, Powell MF. Acute traumatic coagulopathy: pathophysiology and resuscitation. BJA: Br J Anaesthesia 2016;117(suppl_3):iii31–43.
[15] Smith IM, James RH, Dretzke J, Midwinter MJ. Prehospital blood product resuscitation for trauma: a systematic review. Shock (Augusta, Ga) 2016;46 (1):3–16.
[16] Higgins JPT GSe. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The cochrane collaboration. Available from. 2011. www.cochrane-handbook.org.
[17] Leenaars M, Hooijmans CR, van Veggel N, ter Riet G, Leeflang M, Hooft L, et al. A step-by-step guide to systematically identify all relevant animal studies. Lab Anim 2012;46(1):24–31.
[18] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol 2016;(75):40–6.
[19] Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ (Clinical research ed) 2016;355:i4919.
[20] Garner AA, Bartolacci RA. Massive prehospital transfusion in multiple blunt trauma. Med J Aust 1999;170(1):23–5.
[21] Meyer P, Lamour O, Caussanel JM, Marland J, Moreau F. Crush injury of the lower limbs. Use of anti-shock trousers. Annales francaises d'anesthesie et de reanimation 1988;7(5):412–4.
[22] Augustine JJ. Man vs. machine. A farm accident leads to devastating injuries and a tough extrication. EMS Mag 2010;39(6)20–1 18.
[23] Gokhale SG, Scorer T, Doughty H. Freedom from frozen: the first British military use of lyophilised plasma in forward resuscitation. J R Army Med Corps 2016;162(1):63–5.
[24] Gellerfors M, Linde J, Gryth D. Helicopter in-flight resuscitation with freeze-dried plasma of a patient with a high-velocity gunshot wound to the neck in Afghanistan - a case report. Prehosp Disaster Med 2015;30(5):509–11.
[25] Miller BT, Lin AH, Clark SC, Cap AP, Dubose JJ. Red Tides: mass casualty and whole blood at sea. J Trauma Acute Care Surg 2018;85(1S Suppl 2) S134-s9.
[26] Kotwal RS, Scott LLF, Janak JC, Tarpey BW, Howard JT, Mazuchowski EL, et al. The effect of prehospital transport time, injury severity, and blood transfusion on survival of US military casualties in Iraq. J Trauma Acute Care Surg 2018;85 (1S Suppl 2) S112-s21.
[27] Maher P, Utarnachitt R, Louzon MJ, Gary R, Sen N, Hess JR. Logistical concerns for prehospital blood product use by air medical services. Air Med J 2017;36 (5):263–7.
[28] Heschl S, Andrew E, de Wit A, Bernard S, Kennedy M, Smith K. Prehospital transfusion of red cell concentrates in a paramedic-staffed helicopter emergency medical service. Emerg Med Australas 2018;30(2):236–41.
[29] Shlaifer A, Siman-Tov M, Radomislensky I, Peleg K, Shina A, Baruch EN, et al. Prehospital administration of freeze-dried plasma, is it the solution for trauma casualties? J Trauma Acute Care Surg 2017;83(4):675–82.
[30] Vartanian LN. Wren; Uhl, Norm. Blood use in the field. EMS World 2017;6(3).
[31] Chen J, Benov A, Nadler R, Darlington DN, Cap AP, Lipsky AM, et al. Prehospital blood transfusion during aeromedical evacuation of trauma patients in Israel: the IDF CSAR experience. Mil Med 2017;182(S1):47–52.
[32] Lyon RM, de Sausmarez E, McWhirter E, Wareham G, Nelson M, Matthies A, et al. Pre-hospital transfusion of packed red blood cells in 147 patients from a UK helicopter emergency medical service. Scand J Trauma Resuscit Emerg Med 2017;25(1):12.
[33] Mena-Munoz J, Srivastava U, Martin-Gill C, Suffoletto B, Callaway CW, Guyette FX. Characteristics and outcomes of blood product transfusion during critical care transport. Prehosp Emerg Care 2016;20(5):586–93.
[34] Sunde GA, Vikenes B, Strandenes G, Flo KC, Hervig TA, Kristoffersen EK, et al. Freeze dried plasma and fresh red blood cells for civilian prehospital hemorrhagic shock resuscitation. J Trauma Acute Care Surg 2015;78(6 Suppl 1) S26-30.
[35] O'Reilly DJ, Morrison JJ, Jansen JO, Nordmann G, Rasmussen TE, Midwinter MJ, et al. Initial UK experience of prehospital blood transfusion in combat casualties. J Trauma Acute Care Surg 2014;77(3 Suppl 2) S66-70.
[36] Potter DD, Berns KS, Elsbernd TA, Zietlow SP. Prehospital use of blood and plasma in pediatric trauma patients. Air Med J 2015;34(1):40–3.
[37] Malsby 3rd RF, Quesada J, Powell-Dunford N, Kinoshita R, Kurtz J, Gehlen W, et al. Prehospital blood product transfusion by U.S. army MEDEVAC during combat operations in Afghanistan: a process improvement initiative. Mil Med 2013;178(7):785–91.
[38] Sherren P, Burns B. Prehospital blood transfusion: 5-year experience of an Australian helicopter emergency medical service. Crit Care 2013;17(Suppl 2) P295-P6.
[39] Bodnar D, Rashford S, Williams S, Enraght-Moony E, Parker L, Clarke B. The feasibility of civilian prehospital trauma teams carrying and administering packed red blood cells. Emerg Med J 2014;31(2):93–5.
[40] Weaver AE, Eshelby S, Norton J, Lockey DJ. The introduction of on-scene blood transfusion in a civilian physician-led pre-hospital trauma service. Scand J Trauma Resuscit Emerg Med 2013;21(Suppl 1) S27-S.
[41] Glassberg E, Nadler R, Gendler S, Abramovich A, Spinella PC, Gerhardt RT, et al. Freeze-dried plasma at the point of injury: from concept to doctrine. Shock 2013;40(6):444–50.
[42] Higgins GL, Baumann MR, Kendall KM, Watts MA, Strout TD. Red blood cell transfusion: experience in a rural aeromedical transport service. Prehosp Disaster Med 2012;27(3):231–4.
[43] Badjie KSB, Button LM, Stubbs JR. The impact of thawed plasma usage during emergency medical helicopter transport. Transfusion 2012(52) 197A–8A.
[44] Barkana Y, Stein M, Maor R, Lynn M, Eldad A. Prehospital blood transfusion in prolonged evacuation. J Trauma 1999;46(1):176–80.
[45] Prause GD, Gimpl R, Vadon M, Lanzer G. Prehospital use of packed red cells - Preparation, storage and first experience. [German]. Notarzt. 1999;15(1):9–12.
[46] Berns KS, Zietlow SP. Blood usage in rotor-wing transport. Air Med J 1998;17 (3):105–8.
[47] Dalton AM. Use of blood transfusions by helicopter emergency medical services: is it safe? Injury 1993;24(8):509–10.
[48] Moors XRJ, Bouman SJM, Peters JH, Smulders P, Alink MBO, Hartog DD, et al. Prehospital blood transfusions in pediatric patients by a helicopter emergency medical service. Air Med J 2018;37(5):321–4.
[49] Miller BT, Du L, Krzyzaniak MJ, Gunter OL, Nunez TC. Blood transfusion: in the air tonight? J Trauma Acute Care Surg 2016;81(1):15–20.
[50] Kyle T, Greaves I, Beynon A, Whittaker V, Brewer M, Smith J. Ionised calcium levels in major trauma patients who received blood en route to a military medical treatment facility. Emerg Med J 2018;35(3):176–9.
[51] Peters JH, Smulders PSH, Moors XRJ, Bouman SJM, Meijs C, Hoogerwerf N, et al. Are on-scene blood transfusions by a helicopter emergency medical service

useful and safe? A multicentre case-control study. Eur J Emerg Med 2017;17 (November).
[52] Shackelford SA, Del Junco DJ, Powell-Dunford N, Mazuchowski EL, Howard JT, Kotwal RS, et al. Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-Day survival. Jama 2017;318(16):1581–91.
[53] Holcomb JB, Swartz MD, DeSantis SM, Greene TJ, Fox EE, Stein DM, et al. Multicenter observational prehospital resuscitation on helicopter study. J Trauma Acute Care Surg 2017;83(1 Suppl 1):S83–s91.
[54] Fahy AS, Thiels CA, Polites SF, Parker M, Ishitani MB, Moir CR, et al. Prehospital blood transfusions in pediatric trauma and nontrauma patients: a single-center review of safety and outcomes. Pediatr Surg Int 2017;33(7):787–92.
[55] Holcomb JB, Donathan DP, Cotton BA, Del Junco DJ, Brown G, Wenckstern TV, et al. Prehospital transfusion of plasma and red blood cells in trauma patients. Prehosp Emerg Care 2015;19(1):1–9.
[56] Thiels CA, Aho JM, Fahy AS, Parker ME, Glasgow AE, Berns KS, et al. Prehospital blood transfusions in Non-Trauma patients. World J Surg 2016;40(10):2297–304.
[57] Henriksen HH, Rahbar E, Baer LA, Holcomb JB, Cotton BA, Steinmetz J, et al. Pre-hospital transfusion of plasma in hemorrhaging trauma patients independently improves hemostatic competence and acidosis. Scand J Trauma Resusc Emerg Med 2016;24:145.
[58] Hernandez MC, Thiels CA, Aho JM, Habermann EB, Zielinski MD, Stubbs JA, et al. Prehospital plasma resuscitation associated with improved neurologic outcomes after traumatic brain injury. J Trauma Acute Care Surg 2017;83 (3):398–405.
[59] Price DD, Norton RL, Zechnich AD, Eldurkar J, Chok J, Mann NC. Out-of-hospital blood administration for critically injured patients transported by helicopter. Ann Emerg Med 1999;34(4) S50-S1.
[60] Kim BD, Zielinski MD, Jenkins DH, Schiller HJ, Berns KS, Zietlow SP. The effects of prehospital plasma on patients with injury: a prehospital plasma resuscitation. J Trauma Acute Care Surg 2012;73(2 Suppl 1) S49-53.
[61] O'Reilly DJ, Morrison JJ, Jansen JO, Apodaca AN, Rasmussen TE, Midwinter MJ. Prehospital blood transfusion in the en route management of severe combat trauma: a matched cohort study. J Trauma Acute Care Surg 2014;77(3 Suppl 2): S114–20.
[62] Sumida MP, Quinn K, Lewis PL, Jones Y, Barker DE, Ciraulo DL, et al. Prehospital blood transfusion versus crystalloid alone in the air medical transport of trauma patients. Air Med J 2000;19(4):140–3.
[63] Wheeler R, von Recklinghausen FM, Brozen R. Blood administration in helicopter emergency medical services patients associated with hypothermia. Air Med J 2013;32(1):47–51.
[64] Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. N Engl J Med 2018;379(4):315–26.
[65] Moore HB, Moore EE, Chapman MP, McVaney K, Bryskiewicz G, Blechar R, et al. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. Lancet (London, England) 2018;392(10144):283–91.
[66] Ley EJ, Clond MA, Srour MK, Barnajian M, Mirocha J, Margulies DR, et al. Emergency department crystalloid resuscitation of 1.5 L or more is associated with increased mortality in elderly and nonelderly trauma patients. J Trauma 2011;70(2):398–400.
[67] Beekley AC, Sebesta JA, Blackbourne LH, Herbert GS, Kauvar DS, Baer DG, et al. Prehospital tourniquet use in Operation Iraqi Freedom: effect on hemorrhage control and outcomes. J Trauma 2008;64(2 Suppl) S28-37; discussion S.
[68] Lehavi A, Yitzhak A, Jarassy R, Heizler R, Katz YS, Raz A. Comparison of the performance of battery-operated fluid warmers. Emerg Med J: EMJ. 2018;35 (9):564–70.
[69] Nguyen C, Bordes J, Cungi PJ, Esnault P, Cardinale M, Mathais Q, et al. Use of French lyophilized plasma transfusion in severe trauma patients is associated with an early plasma transfusion and early transfusion ratio improvement. J Trauma Acute Care Surg 2018;84(5):780–5.
[70] Smith IM, Crombie N, Bishop JR, McLaughlin A, Naumann DN, Herbert M, et al. RePHILL: protocol for a randomised controlled trial of pre-hospital blood product resuscitation for trauma. Transf Med (Oxford, England) 2018;28 (5):346–56.