Injury, Int. J. Care Injured 50 (2019) 226–234

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Review

What is the impact of prehospital blood product administration for patients with catastrophic haemorrhage: an integrative review☆

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ARTICLE INFO

Article history:
Accepted 29 November 2018

Keywords:
Prehospital
Retrieval
Ambulance
Blood
Plasma
Transfusion
Haemorrhage
Bleeding
Trauma
Shock
Hypovolemia

ABSTRACT

Introduction: Catastrophic haemorrhage is recognised as the leading cause of preventable death in trauma and is also prevalent in medical and other surgical aetiology. Prehospital blood product transfusion is increasingly available for both military and civilian emergency teams. Hospitals have well-established massive transfusion protocols for the resuscitation of this patient group, however the use and impact in the prehospital field is less understood.

Aim: To identify and evaluate the current knowledge surrounding prehospital blood product administration for patients with catastrophic haemorrhage.

Methods: The integrative review method included systematic searching of online databases Medline, EMBASE, SCOPUS and CINAHL alongside hand-searching for primary research articles published prior to 19 November 2018. Papers were included if the population studied patients with catastrophic haemorrhage who received prehospital transfusion of blood products. The level of evidence and quality was evaluated using the NHMRC hierarchy of evidence. All identified full text articles were reviewed by all authors.

Results: Twenty-two papers were included in the final analysis, including both civilian (16) and military (6) practice. The earliest publication for prehospital transfusion was 1999, with increasing prevalence in recent years. Findings were extracted and into two main categories; (1) transfusion processes included team staffing, product selection, and criteria for transfusion and (2) transfusion outcomes; transfusion safety, haemoglobin, hospital intervention and mortality.

Discussion: The level of evidence specific to prehospital blood product transfusion is low, with predominantly retrospective methods and rarely sufficient sample sizes to reach statistical significance. Prehospital research is challenged by clinical and logistical variability preventing accurate cohort matching, sample sizes and inconsistent data collection. Evaluation of prehospital transfusion in isolation is also particularly problematic as multiple factors and developments in clinical practice affect patient outcomes and all samples were subject to survival bias.

Conclusion The volume and strength of the available evidence prevents accurate evaluation of the intervention and definitive practice recommendations however prehospital transfusion is shown to be logistically achievable and without serious incident. The reviewed evidence broadly supports the translation of recent in-hospital studies, such as PROMTT and PROPPR. Further research specific to prehospital practice is required to guide the development of evidence-based protocols.

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https://doi.org/10.1016/j.injury.2018.11.049
0020-1383/

Contents

Introduction

Catastrophic, or life threatening, haemorrhage is recognised as the leading cause of preventable death in trauma patients [1] and is also prevalent in medical conditions such as obstetric complications, gastrointestinal bleeding and surgical patients with intra-operative or post-operative complications [2,3]. Patients are at particular risk of deterioration in the pre-hospital environment. Rapid transport for haemorrhage control intervention is essential [4], however this can be delayed by uncontrollable prehospital factors such as distance, scene accessibility or patient being trapped within a vehicle. Peak incidence of haemorrhagic deaths occurs within the first three hours [5–7]; The early administration of blood products in combination with haemorrhage control strategies such as tourniquets and haemostatic agents can therefore be a lifesaving intervention in this patient group [8–10]. This is of particular significance in the context of rural and remote trauma where transport times are prolonged and reliant on coordinated aeromedical response systems.

Evidence for optimum transfusion protocols within hospitals already exists. The 2013 prospective, observational, multi-centre, major trauma transfusion [6] and later PROPPR study [7] both found transfusion of plasma, platelets and red blood cells [RBC] in balanced ratios early in resuscitation was associated with significantly reduced early trauma deaths and overall bleeding-related mortality. This is of particular relevance when applied to the initiation of transfusion in the prehospital environment where it could enable a patient to survive to definitive intervention. Massive transfusion protocols are common within hospital settings to deliver additional blood products including plasma and platelets in addition to RBC. However the use and impact of blood products in the prehospital field is less understood with limited and conflicting evidence for the best management in this patient group in regard to fluid resuscitation and the use of blood products [11].

Emergency teams commonly undertake both prehospital (primary) and inter-hospital (secondary) missions; the transfusion practice of these teams is explored by Smith et al. [12]. With the development of new technologies such as ROTEM, evidence for haemorrhage control and targeted fluid resuscitation in emergency and trauma are evolving rapidly. This integrative review will review the existing evidence for transfusion during primary ambulance or retrieval service transport prior to arrival at a medical facility. The evidence generated here will guide further research in this area and support the development of models of care to help deliver this important and precious resource to patients who most urgently require it.

Aims

To systematically review the current knowledge in prehospital blood product administration for patients with catastrophic haemorrhage.

Methods

An integrative review method was selected to ensure a systematic search strategy, rigorous screening process and inclusion of all available evidence from a variety of sources. The review process follows the Whittemore and Knafl [13] framework for integrative review; problem identification, systematic literature search, data evaluation, analysis and presentation of findings.

The research question was developed using the population, intervention, comparison and outcome (PICO) structure [14]. The identified population was patients with catastrophic haemorrhage (P) who received prehospital transfusion of blood products (I). No control or comparator was required (C) and any measured outcome (O) was reviewed.

Search strategy

The Cochrane Library and online databases Medline, EMBASE and SCOPUS were selected to screen worldwide publications across medical disciplines, searching multiple databases reduces the omission of pertinent findings as a result of variances in terminology and indexing [13]. Additional manual searching of reference lists and online search engines was conducted. All literature published prior to 19 November 2018 was included for screening.

The key search terms were identified from the PICO framework; catastrophic haemorrhage, blood product transfusion and pre-hospital. Synonyms applied for each of these terms are detailed in Table 1. Each key word and synonym were combined using the 'OR' before applying 'AND' to the three sets.

Screening process

Articles were included if they were primary research, relating specifically to bleeding patients who received blood products prior

Table 1
Keywords and synonyms used in search strategy to identify evidence for prehospital blood product transfusion.

Catastrophic haemorrhage	Bleeding, Haemorrhage/ Hemorrhage, Trauma, Obstetric, Gynecology, Aneurysm, Gastrointestinal, Surgical/Surgery, Damage Control, Exsanguination, Injury
Blood Product Transfusion	Transfusion, Blood, Red Blood Cells, Platelets, Fresh Frozen Plasma, FFP, Cryoprecipitate, Tranexamic Acid, Resuscitation, Damage Control
Pre-Hospital	Ambulance, Retrieval, Emergency, Helicopter, Air Ambulance, Aeromedical, Prehospital, EMS, EMT

to arrival at a hospital. Articles were excluded if full text was not available in the English language as it was beyond the resource capacity of the study. Many military papers were excluded due to an inability to isolate patients who received blood prior to attendance at a field medical facility or the use of warm fresh whole blood transfusion, which is not commonly practiced in civilian populations. Papers which included both prehospital and inter-facility transfers but analysis did not distinguish between patient groups were also excluded as the prehospital data could not be identified. All full text articles were reviewed by all authors. The search process is summarised in Fig. 1.

The quality of included papers was reviewed using the National Health and Medical Research Council hierarchy of evidence [15]. The methods of the papers were critically appraised and their data extracted and collated. Findings were integrated into two categories relating to clinical practice and evaluation.

Results

The search yielded 5382 papers, following removal of 943 duplicates, the titles and abstracts of 4439 papers were screened to distinguish those which met the inclusion and exclusion criteria. Five additional papers were identified through hand-searching. Full text was retrieved for 212 articles. All full text articles were reviewed by all authors. A total of 22 papers were deemed to meet the inclusion criteria. The search process is summarised in Fig. 1 and a summary of the included articles is shown in Table 2. The earliest identified documentation of prehospital blood transfusion was the 1999 publication by Barkana et al. [16]. No papers were found published between 2000 and 2012 and there has been an increase in research prevalence in recent years; 2013 (2), 2014 (2), 2015 (5), 2016 (2), 2017 (5) and into 2018 (5).

The level of evidence varied, the majority of study designs were retrospective with seven retrospective cohort studies (III-3) and eleven case series (IV). Only four papers were prospective studies, including two prospective cohort studies (III-2) and one randomised control trial (II) published both with early results and at completion.

Military services were reviewed in Afghanistan (3) and Israel (3). In civilian populations the USA hosted the majority of studies (9), with the remaining studies conducted in the UK (3) Australia (2), the Netherlands (1) and Norway (1). Nine services transported their patients by helicopter, three were served only by road vehicles and a combination of both were used in nine settings.

Many studies measured outcomes following hospital admission in addition to prehospital records, this results in a higher prevalence of missing data and is particularly notable in the transfer of civilian patients into local public health systems by military teams.

Transfusion processes

The first category of findings was transfusion processes, this included the qualifications of the staff involved in the initiation of

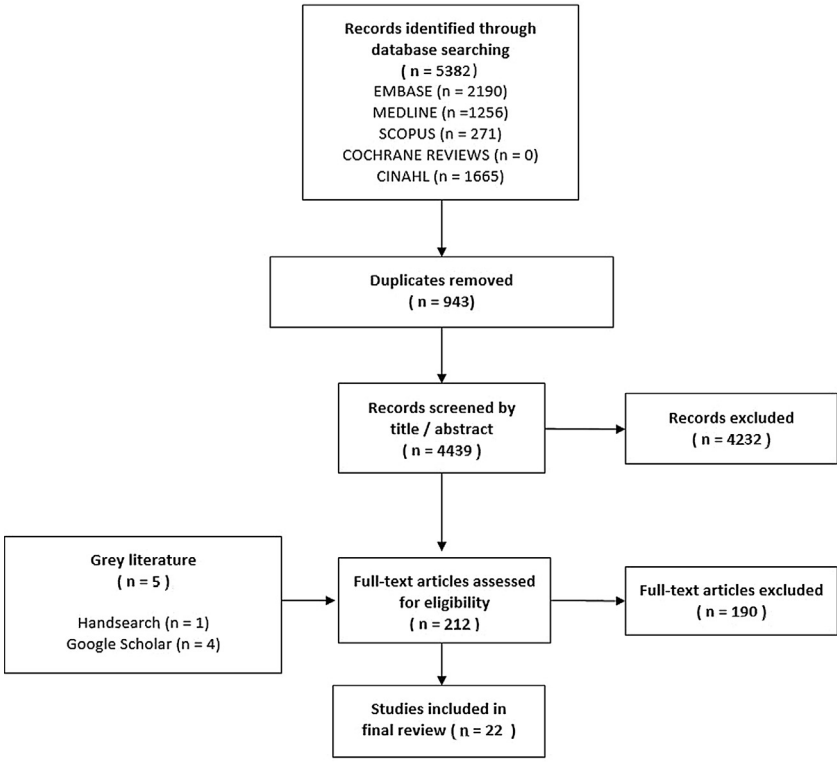

Fig. 1. PRISMA diagram showing search strategy.

Table 2
Summary of articles which met inclusion criteria and were selected for review.

YEAR	AUTHORS	TITLE	COUNTRY	LEVEL	POPULATION	STAFF	TRANSPORT	TIME PERIOD	COHORT SIZE	PRODUCT TYPES	INDICATIONS FOR TRANSFUSION	MEAN INJURY TO HOSPITAL	HB ON ARRIVAL (g/dL)
1999	Barkana et al.	Prehospital blood transfusion in prolonged evacuation	MILITARY, Israel	IV	Trauma	Military	Road / Helicopter	30 Months, 1994-1996	40	RBC	Haemodynamic instability after 2 l crystalloid	120 mins	Median 9.6, Range 2.4 - 14.3
2013	Malsby et al.	Prehospital Blood Product Transfusion by U.S. Army MEDEVAC During Combat Operations in Afghanistan: A Process Improvement Initiative	MILITARY, USA (Afghanistan)	IV	Trauma	Military	Helicopter	May 2012 - July 2012	15	RBC and Plasma	BP unpalpable or <90, HR > 120. SpO2 < 90 (later removed). Multiple amputations added	Not Discussed	Range 9.2 - 14.5.
2013	Wheeler et al.	Blood Administration in Helicopter Emergency Medical Services Patients Associated With Hypothermia	New England, USA	III-3	Trauma	Civilian	Road / Helicopter	1 January 2005 - 30 September 2009	30	RBC	Not Discussed	Not Discussed	Not Discussed
2014	Bodnar et al.	Characteristics and outcomes of patients administered blood in the prehospital environment by a road based trauma response team	Queensland, Australia	IV	Trauma	Doctor & Paramedic	Road	1 January 2011 - 30 June 2012	71	RBC	Haemorrhagic shock with severe haemodynamic compromise - nil radial pulse / hypoperfusion or suspected ongoing haemorrhage	24.3 km, 64 minutes	Not Discussed
2014	O'Reilly et al.	Prehospital blood transfusion in the en route management of severe combat trauma: a matched cohort study	MILITARY, UK (Afghanistan)	III-3	Trauma	Military	Helicopter	May 2006 - March 2011 (blood from 2008)	97 Matched Cohort	RBC and Plasma	No palpable radial pulse or BP <80 mmHg	Range 50-171 mins. Medians 68 min. (transfused), 109.5 min. (non-transfused).	Not Discussed
2015	Benov et al.	Augmentation of point of injury care: reducing battlefield mortality - the IDF experience	MILITARY, Israel	IV	Trauma	Military	Road / Helicopter	8 July 2014 - 26 August 2014	25 Transfused	Plasma	Haemorrhagic shock.	Not Discussed	Not Discussed
2015	Brown et al.	Pre-Trauma center red blood cell transfusion is associated with improved early outcomes in air medical trauma patients.	Pittsburg, USA	III-3	Trauma	Paramedic & Nurse	Helicopter	2008- 2013	71 Transfused, matched to 142 Control	RBC	>15 years old. Decreased tissue perfusion	19-20 mins transfer time	Medians. 11.4 (transfused), 11.35 (non-transfused)
2015	Chapman et al.	COMBAT: initial experience with a randomized clinical trial of plasma-based resuscitation in the field for traumatic hemorrhagic shock	Denver, USA	II	Trauma	Paramedic	Road	Not Specified	16 Plasma v. 14 NaCl	Plasma	BP<70 mmHg or <90 mmHg + HR>108	29 minutes injury to ED	Not Discussed
2015	Holcomb et al.	Prehospital transfusion of plasma and red blood cells in trauma patients	Texas, USA	III-3	Trauma	LifeFlight	Helicopter	20 months, 2011 - 2013	137 Transfused v 169 without Transfusion Capacity	RBC and Plasma	>12 years old. 2 of: penetrating truncal mechanism, BP < 90 mmHg, HR > 120, FAST+	68 minutes	Medians. 13.5 (transfused), 13 (non-transfused)
2015	Sunde et al.	Freeze dried plasma and fresh red blood cells for civilian prehospital hemorrhagic shock resuscitation	Bergen, Norway	IV	Trauma (9) & Medical (7)	Doctor & Paramedic	Road / Helicopter	May 2013 - May 2014 FDP (6 months RBC)	16 Plasma (4 RBC)	RBC and Plasma	Clinical assessment of significant haemorrhage. BP <90 mmHg with minimal response to fluids.	50 min. blunt, 114 Penetrating, 55 Medical	9.8-16.6 range.

Table 2 (*Continued*)

YEAR	AUTHORS	TITLE	COUNTRY	LEVEL	POPULATION	STAFF	TRANSPORT	TIME PERIOD	COHORT SIZE	PRODUCT TYPES	INDICATIONS FOR TRANSFUSION	MEAN INJURY TO HOSPITAL	HB ON ARRIVAL (g/dL)
2016	Henriksen et al.	Pre-hospital transfusion of plasma in haemorrhaging trauma patients independently improves hemostatic competence and acidosis	Texas, USA	III-2	Trauma	LifeFlight	Road / Helicopter	October 2012 - November 2013	75 Prehospital Blood v. 182 In-Hospital Blood	RBC and Plasma	Not Discussed	Not Discussed	Medians. 12.4 (transfused), 13.1 (non-transfused)
2016	Thiels et al.	Prehospital blood transfusions in non-trauma patients	Minnesota, USA	III-3	Trauma (549) & Medical (308)	Not specified	Road / Helicopter	2012-2014	549 Trauma and 308 Non-Trauma	RBC and Plasma	2 of: BP < 90 mmHg, HR > 120, Penetrating Mechanism, POC Lactate >5, POC INR > 1.5, BE > -5, StO2 < 65%	Not Discussed	Medians. 9.5 (nontrauma), 11.3 (trauma)
2017	Heschl et al.	Prehospital transfusion of red cell concentrates in a paramedic-staffed helicopter emergency medical service	Victoria, Australia	IV	Trauma (136) & Medical (6)	Paramedics. Doctor consulted to approve blood	Helicopter	July 2011 - December 2015	142	RBC	refractory hypovolemic shock after 40 ml/kg crystalloid	Medians: Scene time 76 min., transport time 38 mins	Not Discussed
2017	Holcomb et al.	Multicenter observational prehospital resuscitation on helicopter study	Texas, USA	III-2	Trauma	Not Specified	Helicopter	January 2015 - November 2015	43 Transfused v. 66 Not Transfused	RBC and Plasma	Not Discussed	58 mins from activation. 18 min. transfer time.	Not Discussed
2017	Lyon et al.	Pre-hospital transfusion of packed red blood cells in 147 patients from a UK helicopter emergency medical service	Kent, England	IV	Trauma (142) & Medical (5)	Doctor & Paramedic	Road / Helicopter	February 2013 - December 2014	147	RBC	Retrospective only: No palpable central (38%) or peripheral (9.1%) pulse, drop in BP (39.9%), tachycardia (2%), loss of verbal contact (1.4%). Combination (9.6%)	114 mins from 999 call. 30 min. transfer time (44 km average)	Not Discussed
2017	Shackelford et al.	Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30 day survival.	MILITARY, USA (Afghanistan)	III-3	Trauma	Military	Helicopter	April 2012 - August 2015	55 transfused. 345 matched cohort	RBC and Plasma	Traumatic limb amputation above knee/elbow OR shock defined as BP < 90 mmHg or HR>120	48 mins	Not Discussed
2017	Shlaifer et al.	Prehospital administration of freeze-dried plasma, is it the solution for trauma casualties?	MILITARY, Israel	IV	Trauma	Military	Not Discussed	January 2013 - June 2016	109	RBC and Plasma	Penetrating Mechanism plus one of: no radial pulse, HR > 130, BP < 90, GCS < 8	Not Discussed	Not Discussed
2018	Mix et al.	Prehospital blood product administration opportunities in ground transport ALS EMS - A descriptive study	Minnesota, USA	IV	Trauma	Not Specified	Road / Helicopter	1 January 2011 - 31 December 2015	28	RBC and Plasma	HR > 120 and/or SBP < 90 mmHg	Not Discussed	Not Discussed
2018	Moore et al.	Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial	Denver, USA	II	Trauma	Paramedic	Road	1 April 2014 -31 March 2017	Plasma 65 v Control 60	FFP	Adult trauma, BP < 70 or < 90 mmHg + HR > 108	Not Discussed	Medians. Plasma Group 12.6, Control 13.5
2018	Moors et al.	Prehospital Blood Transfusions in Pediatric Patients by a Helicopter Emergency Medical Service	Netherlands	IV	Trauma (9) & Medical (1)	Doctor - nurse or Paramedic	Helicopter	1 January 2007 - 30 November 2015	10	RBC	"blood loss or nonresponsive to fluid therapy with signs of haemorrhagic shock"	Not Discussed	5.2-10.7
2018	Raitt et al.	A report of two years of prehospital blood transfusions by Thames Valley Air Ambulance	Thames Valley, England	IV	Trauma (59) & Medical (4)	Paramedic & Doctor present or consulted	Road / Helicopter	3 January 2014 - 12 February 2016	63	RBC	Not Specified	Not Discussed	Not Discussed
2018	Rehn et al.	Pre-hospital transfusion of red cells in civilian trauma patients	London, England	III-3	Trauma	Doctor & Paramedic	Helicopter	January 2009 - February 2012 v. April 2012-February 2015	137 Pre-Transfusion v. 128 Transfusion	RBC	Suspicion of major harmorrhage and haemodynamic compromise (SBP <90 mmHg)	73.5 Minutes (No Transfusion) v. 78 Minutes (Transfusion)	Not Discussed

transfusion, the criteria or observation parameters for transfusion and the fluids or products chosen.

Staffing

In the research undertaken in the civilian environment, the prehospital staff had a range of professional qualifications, but most commonly the team comprised a doctor and paramedic [17–22]. Four studies had paramedic-only teams [23,24] although two [25,26] required approval for transfusion from a doctor by telephone. Brown [27] was the only service to identify a paramedic and nurse team however, according to their website, LifeFlight™, the helicopter medical service studied in Henriksen [28] and Holcomb [29], is staffed by either an EMT or nurse with a paramedic [30]. The clinical governance, training and experience of these practitioners to facilitate this advanced scope of practice was not reported.

Transfused products

Nine studied services administered only red blood cells (RBC), three gave plasma only and ten transfused a combination of both. Where both were transfused, two papers [31,32] specified that plasma would be given first and one [33] RBC first, the remaining do not specify. Five papers discuss the active warming of RBCs for transfusion [17,18,32]. Wheeler et al. [20] found that patients who received un-warmed blood transfusion were six times more likely to suffer hypothermia, than those who were not transfused at all, however it should be noted that this is when compared with the administration of warmed fluids. The majority of studies had one or two units of RBC or plasma available and therefore a mean number of units transfused between one and two for each RBC and plasma. The highest documented mean was 2.4 in a study where teams carried four units of RBC [18]. The earliest paper in this review was published in 1999, early in the journey of damage control resuscitation strategies, as evidenced in the protocol of 2 litres of crystalloid administration prior to transfusion, with an average crystalloid transfusion volume of 4400mls [16] transfused prior to hospital arrival compared to 1650mls in 2017 [34]. Moors et al [21] studied paediatric patients only and report 7–29 ml s/kg of PRBC transfusion prior to arrival at hospital.

Blood transfusion criteria

Factors influencing the decision to initiate transfusion included the mechanism of injury, physical observations and clinical assessment. Four studies [20,26,28,29] did not identify the criteria used to initiate transfusion. Six studies [16,17,21,25,27,35] do not quantify their criteria for transfusion, stating haemodynamic shock or instability as indication for transfusion.

Table 2 shows the identified indications for transfusion as quoted in the literature. The most common single measured criteria for transfusion was a blood pressure <90 mmHg (10) while other blood pressure criterion included <80 mmHg (1), <70 mmHg (1), no central pulse (1), no radial pulse (5) or a drop in blood pressure (1). Where tachycardia was an identified parameter, a rate of >120 was the most commonly stated figure [31,32,36–38], however >130 [34] and >108 [23] were identified in one study each. Unquantified hypoperfusion [39], GCS < 8 (1) and a loss of verbal contact (1) were also cited as indications. The guidelines for initiation of transfusion for doctors reflected clinical assessment as hypoperfusion or haemodynamic instability where more prescriptive guidelines were utilised for paramedics or nurses, with defined parameters for blood pressure or heart rate.

In conjunction with abnormal vital signs including heart rate, systolic blood pressure and altered level of consciousness as detailed in Table 2, a penetrating mechanism was recognised as an indication for transfusion in three papers [32,34,36] and traumatic limb amputations in two [31,37]. A suspicion of ongoing haemorrhage was sufficient indication in two studies, and despite three papers discussing the use of FAST scans, only one listed a positive finding as criteria for transfusion [26]. Point of care blood results were utilised in one study. Two studies required a combination of two criteria [29,36] while one abnormal physiological observation was sufficient when in the context of penetrating trauma [34].

All studies discussed transfusion in the context of trauma, five studies also discussed medical aetiology for haemorrhage [18,19,25,26] although only one [36] compared transfusion outcomes between these two groups.

The Assessment of Blood Consumption (ABC) [40] scoring system was identified in the transfusion criteria of Holcomb et al [32]. Components defined in the ABC Scoring are also reflected in the criteria of many of the identified studies, for example blood pressure <90 mmHg, heart rate >120 beats per minute, a positive FAST scan or penetrating mechanism. Other published tools to predict transfusion include the Trauma Associated Severe Haemorrhage [41] and McLaughlin scores however these both require laboratory data, preventing their application in the prehospital environment without point of care blood testing capacity.

Transfusion outcomes

Transfusion outcomes were evaluated using the reported outcome measures of transfusion safety, haemoglobin measurement, hospital interventions and mortality.

Transfusion safety

Two studies each had one incidence of a minor transfusion reaction, a mild rash [16] and the sensations of chills [34]. Thiels et al. [36] documented one unspecified mild reaction during plasma transfusion during a later transfusion in hospital. Many services acted to reduce waste by rotating blood products back into the hospital system, Holcomb et al. [29] declare a wastage rate of 1.9%, Heschl et al. [25] a rate of 0.5% following power failures and broken bags. Lyon et al. [18] identified eight units, approximately two per cent, which were wasted in the early stages of the programme due to user error.

Hb on arrival at hospital

Seven papers measured haemoglobin [Hb] on arrival to hospital as a reflective measure of prehospital transfusion, the range across all papers was 2.4 g/dl [16] to 16.6 g/dl [19]. Two studies comparing Hb on arrival between patients who did and did not receive prehospital transfusion [27,32] found those that had received prehospital transfusion had higher Hb levels, however the results were not significant. Conversely, Henriksen et al. [28] found those who had been transfused prehospital arrived to the hospital with a lower Hb than those whose transfusions were later initiated in hospital. Patients with a medical aetiology presented to hospital with a lower Hb than victims of trauma [36]. Penetrating trauma resulted in greater blood loss than blunt trauma [16,19].

Hospital intervention

Between 36% [34] and 89% [18] of patients received additional blood products once in hospital [Table 2]. The definition of massive transfusion was agreed across the literature at >10 units of blood products. In the ATLS guidelines (2018) this refers to the first 24 h of care, however in the reviewed studies it is unclear if this includes prehospital transfusion or in what time frame. O'Reilly [33] reports the lowest incidence of massive transfusion at 12%, this is of particular interest as it is the only study reporting on this outcome which strictly transfused both RBC and plasma in a ratio of 1:1 which could reflect the in-hospital evidence [7]. Brown et al [27] and Holcomb et al. [32] identified a lower mean number of

RBC units infused in hospital when initiated prehospital [p = 0.66; p = 0.261].

Seven papers reported the need for surgical or radiological intervention in large numbers of their populations, as shown in Table 2. One paper [16] was nonspecific overall however 35% of patients were treated with surgery for abdominal wounds. For medical patients, Thiels et al. [36] report 32% of patients had surgery and 47.5% were treated in endoscopy. The only paper to record surgical intervention in a non-transfused population was Brown et al. [27] at 28% p < 0.01.

Injury severity and mortality

Three tools were used to measure injury severity as a predictor of mortality; Injury Severity Score (ISS), Revised Trauma Score (RTS) and the Trauma Mortality Prediction Model (TMPM). Nine studies recorded injury severity score (ISS). All populations suffered severe injuries, with median ISS values ≥16. Raitt et al [26] and Bodnar et al. [17] recorded the highest ISS with a median of 34 and a mean of 32 respectively among their transfused patients.

ISS scores were similar between prehospital transfusions and non-transfused patients in both O'Reilly et al. [33] and Henriksen et al. [28] but Holcomb et al. [29] found a statistically higher ISS (ISS = 25) among those who received prehospital transfusion than those who did not (ISS = 17). Despite this, three [29,33,37] of the five [27,28] studies which document long term mortality for matched patients without prehospital transfusion record lower mortality rates among patients who received prehospital transfusion than those who did not. Brown et al [27] identify a 95% confidence interval 1.88–21.14 for 24 h survival following adjusted odds ratios for prehospital transfusion. The only result of statistical significance [p = 0.013] was identified by O'Reilly et al. [33].

Only Bodnar [17] discusses RTS, where no patients with RTS < 2 survived, despite receiving blood products sooner (p = 0.13). Survival to discharge was found to be 3.6% higher than TRISS prediction, suggesting survival benefit with prehospital transfusion [17]. Brown et al. [27] were the only paper to apply the trauma mortality prediction model (TMPM), a less commonly used [42] tool used to predict mortality following trauma. Brown found that patients who received prehospital transfusion had a higher median TMPM score (p = 0.05) and therefore had a greater predicted mortality rate although this was not reflected in survival at either 24 h (p = 0.16) or in-hospital deaths (p = 0.03).

Not all papers specified a timeframe for in-hospital deaths. Combining statistics for mortality rates among transfused patients found a range of 12% [34] to 45% [17]. A mean calculated across the 12 papers with data available is a mortality rate of 24%. The two papers with the highest overall mortality are the two oldest papers, Barkana et al. [16] at 38% and Bodnar et al. [17] at 45%. Raitt et al. [26] note that no patients with prehospital cardiac arrest survived to discharge. No significant results were identified in reporting six or 24-hour survival. With the exception of Holcomb et al. [29], where at both three and 24-hours half the number of patients who received prehospital transfusion had died, all other trends suggest higher mortality rates among patients who received prehospital transfusion. Shackelford et al. [37] found that patients who had transfusions initiated within 15 min of MEDEVAC arrival had a significantly higher (p = 0.02) chance of survival. Late mortality was commonly recorded at 30 days.

Discussion

This review demonstrated that the number of published studies investigating prehospital transfusion is small and overall the level of evidence is low, affecting the accurate clinical evaluation of prehospital transfusion and the recommendations which can be drawn from the evidence base. The predominantly retrospective study designs are less robust, limiting both clinical impact and applicability [15].

Research in the pre-hospital environment

Conducting research in the prehospital environment is challenged by multiple factors including cohort matching, sample sizes and data collection. A particular complexity of prehospital research is the extensive clinical, ethical and logistical factors limiting clinical trials and accurate data collection. Data collection can be complicated by the nature of the dynamic prehospital environment, particularly in military settings. Despite this, military research has dominated the trauma evidence base in recent years with survival rates for those wounded in combat at an all-time high [43]. Cohort matching is particularly complex in the prehospital environment, allowing for mechanism, circumstance and injuries sustained.

Randomised controlled trials (RCT) in the prehospital environment are rare due to the logistical and ethical challenges. The COMBAT trial [23] explored the effects of plasma first transfusion and did not find any reportable survival benefit. However as a metropolitan service, the transport times from scene of injury to hospital were predominantly under twenty minutes which would significantly impact upon the volume of plasma transfused and its measurable effect upon arrival to hospital [44]. This paper is one of seven reviewed studies which reports survival 28 or 30 days [18,19,23,29,32,36,37], while haemorrhagic trauma deaths most commonly occur in the first three hours [6,7].

Prehospital research over time has also been confounded by changes in hospital care associated with haemorrhage control. This ongoing development in clinical practice is demonstrated in O'Reilly et al. [33] where observed improved patient outcomes cannot be attributed entirely to prehospital transfusion due to the concurrent practice developments including the use of tranexamic acid, viscoelastic-directed therapy (thromboelastography [TEG], ROTEM), hybrid suite intervention and trauma system development including the introduction of air transport assets. This progress also confounds the amalgamation of evidence collected across the eighteen-year span of this literature review.

Broxton et al. [45] acknowledged that no formal evaluative tool specific to massive transfusion protocols exists. Reported outcome measures such as product requirements, haemoglobin on arrival and mortality were reviewed throughout the literature, however these each carry complexities as evaluative tools due to the nature of prehospital care and variability of circumstance and injury. For example, the measurement of haemoglobin seems a reasonable outcome measure in catastrophic haemorrhage however, on further exploration, this is recognised as an imperfect evaluative tool for prehospital transfusion. Firstly, none of the reviewed patients had pretransfusion measurement, preventing comparison. Secondly, patients who received large volumes of crystalloids, particularly those studied by Barkana et al. [16] or only plasma would encounter haemodilution. This could be relevant for Henriksen et al. [28], who found a lower Hb on arrival to hospital in patients who received prehospital transfusion than those who did not. However, this could also represent a cohort suffering more acute blood loss as recognised by treating teams and therefore more likely to initiate prehospital transfusion.

Another key complexity in this field of research is that prehospital transfusion is the difficulty in establishing causal associations with the outcome of interest. For example, in the 2017 study by Shackelford et al. [37], the treating team with the capacity to offer transfusion were also able to provide a higher level of care, which could reasonably contribute to the better patient outcomes reported. Also, as previously discussed, O'Reilly et al. [33] study

spanned five years, 2006–2011, and reported outcomes before and after blood transfusion practices were introduced in 2008. During this time significant practice developments occurred including the introduction of air transport which dramatically reduced prehospital times, therefore it is impossible to evaluate the impact of blood transfusion upon these patient outcomes. This is further evidenced by the highest mortality rates documented in the two studies of earliest undertaking [16,17].

It should also be noted that all of the reviewed papers are subject to the incidence of survival bias, as all of the patients who received transfusions had by definition survived long enough to receive the intervention. Where specified, between 9.6% [25] and 26% [18] of patients receiving prehospital blood transfusion did not survive to hospital, which may perhaps be explained by longer prehospital times [18].

Recommendations for clinical practice

The service providers each managed the logistical challenges of supplying and storing blood products [38] with minimal wastage. Unused products were consistently returned to higher use areas prior to expiration.

Factors such as the reduced number of staff present, the necessity for multitasking in an acute situation and communication difficulties in a potentially noisy environment are recognised risks for transfusion in the prehospital environment. However, there were only mild transfusion reactions reported, with no adverse events as a result of prehospital blood transfusion. Without detailed revision of each individual case, it is impossible to accurately evaluate the decision for prehospital transfusion. However, the high incidence of both additional transfusions, often reaching massive transfusion status and surgical intervention supports the appropriate identification of catastrophic haemorrhage by prehospital practitioners, with no demonstrated variance between professions. Schroll et al. [46] reported that the simple calculation of shock index by division of heart rate over blood pressure is an accurate predictor for requiring massive transfusion, which could therefore be considered in future protocol development.

Prehospital emergency care is dominated by paramedics and EMTs, for whom blood product transfusion is not common practice. Additional education and training is required to support these professionals to expand their scope of practice, the training and qualifications of the practitioners in the reviewed services is not discussed. While the non-physician teams had more defined initiation criteria, transfusion practices and outcomes were similar for all professions in the reviewed literature. The literature reviewed supports non-physician practitioners to safely provide prehospital blood transfusion, however additional research is required to make profession-specific recommendations.

Crystalloid fluid resuscitation remains an issue of contention in some quarters. One ongoing trial is noted to be in progress in the United Kingdom, Resuscitation with Pre-Hospital Blood Products [RePHILL], with data collection anticipated to be complete in 2020 [47]. However, like COMBAT [23] this trial is set to compare crystalloid resuscitation with transfusion of plasma, which has most recently been reported in favour of transfusion following the Prehospital Air Medical Plasma (PAMPer) Trial [48]. This trial conducted in a regional aeromedical service in the United States of 230 transfused patients found a mortality benefit associated with prehospital transfusion of fresh frozen plasma in trauma patients in haemorrhagic shock. This trial was not included in meta-analysis as data included interfacility transfers and the effect of crystalloid volume appeared to differ substantially with the control arm receiving more, potentially confounding results. The principles of damage control strategies continue to support permissive hypotension in bleeding trauma patients and limited use of crystalloid fluid with a preference for early transfusion of warmed blood products recommended in both American and European guidelines [19].

Research undertaken within the hospital environment has identified statistically significant mortality benefits from transfusion of mixed products, including plasma and platelets, in increased ratios with additional advantage when applied in the first six hours of treatment [6]. Further evidence suggests optimum outcomes are achieved with a ratio of 1:1:1 for red blood cells, plasma and platelets [7]. Specific research for prehospital transfusion is limited, as evidenced in this review, however it is reasonable to assume these findings and the support of early transfusion would be reflected in prehospital practice. While multiple studies demonstrated a preference for 1:1 ratios where dual products were available, none of the reviewed prehospital literature administered three blood product components.

There is increasing interest in the field of prehospital transfusion and haemostatic control. Concurrent research is emerging in relation to the prehospital administration of fibrinogen concentrates, prothrombin, tranexamic acid, whole blood and warm fresh whole blood or 'buddy' donation, as well as the introduction of prehospital TEG and ROTEM. This evidence will continue to guide the developing future of prehospital transfusion practice. Further, the reviewed evidence broadly supports the translation of recent in-hospital studies, such as PROMMT and PROPPR, with regard to early and combined transfusion practices reflected in the prehospital environment. However, further research specific to prehospital practice is required to guide the development of evidence-based protocols.

Conclusion

Robust hospital-based research broadly supports multi-product transfusion, however evidence specifically relating to prehospital blood transfusion is limited. Systemic challenges and ethical considerations complicate the execution of the large randomised trials that would be necessary to achieve significant outcomes. Logistically prehospital transfusion is achievable and has been undertaken without significant adverse incident or excessive product waste, however more robust research is required to determine clinical benefit. Additional research should also address the profession specific education requirements for prehospital practitioners such as paramedics, nurses and EMT's undertaking transfusion.

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