REUE | Review Article

Out-of-hospital blood component transfusion: a systematic review

Laura Fernández-Naranjo, Ana Magdalena Vargas-Martínez

BACKGROUND AND OBJECTIVE. On average 45 units of blood components per 1000 population were transfused in Europe in 2019, a year when Spain registered a total of 856 473 units transfused. A high percentage of trauma cases attended by emergency responders involve patients with massive bleeding, and such patients are the ones who receive most of the out-of-hospital transfusions. Our purpose was to analyze available evidence on out-of-hospital blood component transfusions.

METHODS. Systematic review of the literature in the following databases up to February 2023: Web of Science, the Cumulated Index in Nursing and Allied Health Literature, PubMed, and Scopus. Search terms were chosen from among the English Medical Subject Headings and descriptors the parallel Spanish health sciences list (DECS). To evaluate article quality we used checklists from several sources (Cochrane, STROBE [Strengthening the Reporting of Observational Studies in Epidemiology], CHEERS [Consolidating Health Economic Evaluation Reporting Standards], and PRISMA [Preferred Reporting Items for Systematic Reviews]).

RESULTS. Thirty-two articles were reviewed. The main causes of hemorrhagic shock were trauma and intestinal bleeding. Protocols for out-of-hospital transfusion differ from country to country. Survival after prehospital blood-component or tranexamic-acid transfusion was associated with better survival than crystalloid transfusion.

CONCLUSIONS. The studies included in this review provided data that support prehospital transfusion of blood components, although research to provide more evidence is needed.

Keywords: Blood transfusion. Hemorrhagic shock. Tranexamic acid. Emergency health services. Ambulance.

El empleo de la transfusión de hemocomponentes en el ámbito extrahospitalario: revisión sistemática

INTRODUCCIÓN. En Europa, la media de transfusiones de concentrados sanguíneos en 2019 fue de 45 por cada 1.000 habitantes, registrándose en ese mismo año en España un total de 1.856.473 concentrados sanguíneos transfundidos. En el medio extrahospitalario, existe un alto porcentaje de hemorragias masivas en pacientes que han sufrido un traumatismo, siendo estos mismos los que reciben la mayor parte de las transfusiones. Por ello, el objetivo de este trabajo es sintetizar la evidencia científica disponible acerca del empleo de hemocomponentes en la atención extrahospitalaria.

METODOLOGÍA. Se llevó a cabo una revisión sistemática de la literatura hasta febrero de 2023, realizando la búsqueda en las bases de datos: Web Of Science (WOS), CINAHL, PubMed y Scopus, incluyendo términos Mesh y Decs. Para valorar la calidad de los artículos se utilizaron diversas listas de verificación (COCHRANE, STROBE, CHEERS y PRISMA).

RESULTADOS. Se incluyeron 32 artículos en la revisión. Las principales causas de *shock* hemorrágico son los traumatismos y las hemorragias intestinales. A nivel internacional, diferentes países cuentan con protocolos o programas de transfusión prehospitalaria. Al evaluar los datos de mortalidad, la supervivencia aumenta en aquellos pacientes que recibieron hemocomponentes prehospitalarios y ácido tranexámico (TXA) en comparación con los que recibieron cristaloides.

CONCLUSIONES. Los estudios incluidos en esta revisión proporcionan datos positivos sobre el uso de la transfusión de hemocomponentes en el ámbito prehospitalario, aunque es necesaria más investigación para poder aportar mayor evidencia.

Palabras clave: Transfusión sanguínea. *Shock* hemorrágico. Ácido tranexámico. Servicios Médicos de Emergencias. Ambulancias.

Introduction

The average number of blood component transfusions in Europe in 2019 was 45 per 1,000 inhabitants, compared to 40 blood components per 1,000 inhabitants administered in Spain.[1]

Blood transfusion is a therapy through which blood components are administered to patients with a specific clinical condition.[2] In the hospital setting, they are used frequently, while in out-of-hospital care, their use is less common and presents a series of obstacles, including a lack of consensus on indications in this care setting.

In out-of-hospital care, one of the indications for admi-

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Article Information: Received: 29-10-2024. Accepted: 25-11-2024. *Online:* 11-2-2025.
Editor in Charge: Rafael Castro Delgado.

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Table 1. DeCS/MESH Descriptors

DeCS Descriptors	MeSH Descriptors
Blood transfusion	Blood transfusion, Blood Transfusions, Transfusion, Blood, Transfusions, Blood
Tranexamic Acid	Tranexamic Acid, AMCHA, trans-4-(Aminomethyl) cyclohexanecarboxylic Acid, t-AMCHA, AMCA, Anvitoff, Cyklokapron, Ugurol, KABI 2161, Spotof, Transamin, Amchafibrin, Exacyl
Hemorrhage	Hemorrhage, Bleeding
Hemorrhagic shock	Emergency Medical Services, Emergency Services Medical, Medical Emergency Service, Medical Emergency Services, Service Medical Emergency, Services Medical Emergency, Emergency Medical Services Emergency, Emergency Medical Service, Medical Service Emergency, Service Emergency Medical, Services Emergency Medical, Emergicenters, Emergicenter, Emergency Care, Emergency Health Services, Emergency Health Service, Health Service Emergency, Health Services Emergency, Service Emergency Health, Services Emergency Health, Pre-hospital, Out-of-Hospital
Transportation of Patients	Transportation of Patients, Patients Transportation, Patients Transportations, Transport of Wounded and Sick, Transport Wounded and Sick, Access to Transportation, Access to Transportations, Accessible Transportation, Accessible Transportations, Transportation Accessible, Transportation Accessibility, Accessibility Transportation, Transportation Accessibilities, Transportation Access, Access Transportation
Ambulances	Ambulances, Ambulance, Emergency Mobile Units, Emergency Mobile Unit, Mobile Unit Emergency, Mobile Units Emergency, Unit Emergency Mobile, Units Emergency Mobile, Mobile Emergency Units, Emergency Unit Mobile, Emergency Units Mobile, Mobile Emergency Unit, Unit Mobile Emergency, Units Mobile Emergency

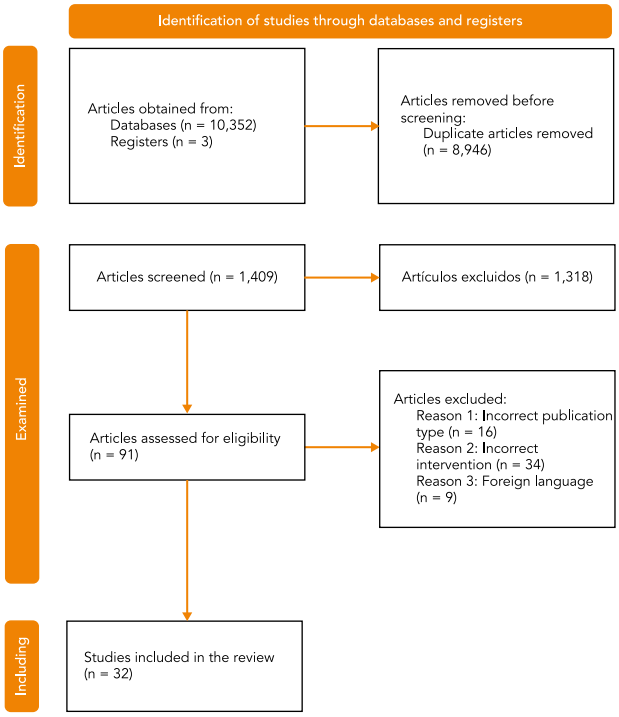

Figure 1. PRISMA flow diagram.

nistering blood components is massive hemorrhage. However, there is great heterogeneity in interpreting the presence or absence of massive hemorrhage, as there is no agreement on the best way to quantify blood loss, assess treatment response, or the effectiveness of recommended hemorrhagic control measures. The Shock Index[3] (SI), defined as the ratio between heart rate and systolic blood pressure, is the most widely implemented prehospital tool that predicts the presence or absence of massive hemorrhage, with a sensitivity of 91% and a specificity of 80%.

When massive hemorrhage occurs, the patient can enter a state of hemorrhagic shock,[4,5] defined as an acute deficit of blood volume. For its management,[6] the cause of the hemorrhage should first be treated, if possible, to then apply treatments to restore the lost volume. Regarding treatment, the action protocol establishes that early fluid resuscitation, mainly isotonic crystalloids, should be conducted to replace the lost volume and thus ensure adequate tissue oxygenation through correct tissue perfusion.[6] The hemorrhagic shock management protocol also includes treatment with tranexamic acid (TXA),[4] whose function is to prevent the breakdown of the clot formed after the injury. Resuscitation with blood components would be the treatment of choice due to its high oxygen-carrying capacity. This type of treatment has been used in several wars and demonstrates increased survival in injured soldiers. However, currently, in prehospital practice, it is difficult to implement due to the storage conditions of blood components.[4]

Therefore, the objective of this review is to synthesize the available scientific evidence on the use of blood components in out-of-hospital care.

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Table 2. Number of patients included in each article

Articles	Sample Size (n)
Pusateri[30], 2019	626
Henriksen[37], 2016	257
Hrebinko[34], 2021	501
Rehn[10], 2019	623
Naumann[24], 2017	729
Griggs[25], 2018	218
Tucker[21], 2023	909
Gruen[31], 2021	501
Hashmi[12], 2022	3,700,000
Crombie[35], 2022	432
Gruen[33], 2020	166
Thies[11], 2020	172
Moore[28], 2018	125
Sperry[29], 2018	501
Zhu[17], 2019	132
Coccolini[32], 2019	626
Sunde[15], 2022	52
Krook[18], 2019	431
Ångerman[8], 2022	36
Yliharju[9], 2022	65
Holcomb[36], 2017	1.058
Vuorinen[14], 2020	62
Jost[23], 2022	134
Hernández[22], 2017	76
Lyon[20], 2017	147
Bjerkvig[16], 2021	24
Roberts[38], 2013	20,211
Colab.Ensayo CRASH-3[39], 2019	12,737
Brown[27], 2015	720
Total	3,742,271
Average	129,044

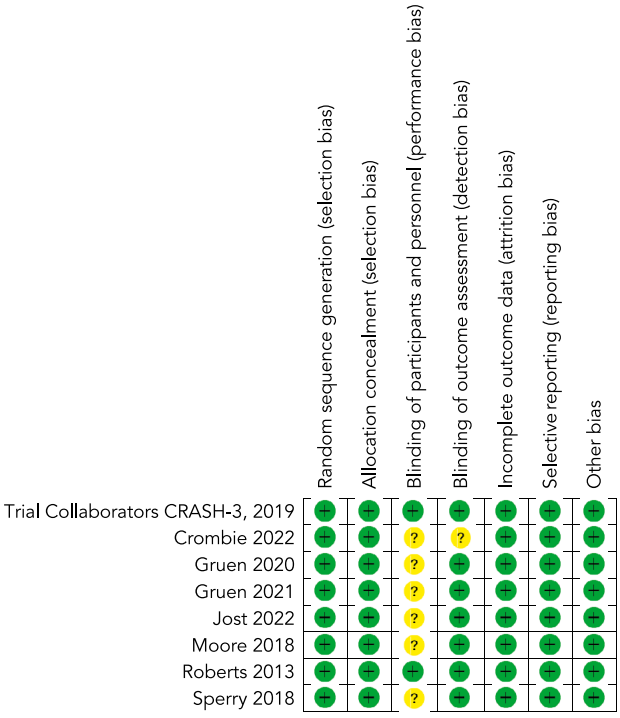

Figure 2. Summary table of risk of bias in clinical trials (n = 8).

Materials and Methods

We conducted a systematic literature review, with no initial time limit until February 2023, following PRISMA recommendations.[7] The search was performed in the WOS, CINAHL, PubMed, and Scopus databases. To formulate the search strategy, different descriptors (Table 1) in English and Spanish, obtained from the DeCS and MeSH thesauri, were selected.

The search strategy used in PubMed was: (("Blood Transfusion"[Mesh] OR "Blood Transfusions" OR "Transfusion, Blood" OR "Transfusions, Blood") OR ("Tranexamic Acid"[Mesh] OR AMCHA OR "trans-4-(Aminomethyl)cyclohexanecarboxylic Acid" OR t-AMCHA OR AMCA OR Anvitoff OR Cyklokapron OR Ugurol OR "KABI 2161" OR Spotof OR Transamin OR Amchafibrin OR Exacyl)) AND ((Hemorrhage [Mesh] OR Bleeding OR "traumatic hemorrhage") OR ("Shock, Hemorrhagic"[Mesh] OR "Hemorrhagic Shock")) AND (("Emergency Medical Services"[Mesh] OR "Emergency Health Service" OR "Emergency Health Services" OR "Prehospital Emergency Care" OR pre-hospital OR "Emergency Care, Prehospital" OR "Out-of-Hospital" OR "Emergency Services, Medical" OR "Medical Emergency Service" OR "Medical Emergency Services" OR "Service, Medical Emergency" OR "Medical Services, Emergency" OR "Emergency Medical Service" OR "Medical Service, Emergency" OR "Service, Emergency Medical" OR "Services, Emergency Medical" OR Emergicenters OR Emergicenter OR "Emergency Care" OR "Health Service, Emergency" OR "Health Services, Emergency" OR "Services, Emergency Health") OR ("Transportation of Patients"[Mesh] OR "Patients Transportation" OR "Patients Transportations" OR "Transport of Wounded and Sick" OR "Access to Transportation" OR "Accessible Transportation" OR "Transportation, Accessible" OR "Transportation Accessibility" OR "Accessibility, Transportation" OR "Transportation Access" OR "Access, Transportation" OR "Ambulances"[Mesh] OR ambulance* OR "Emergency Mobile Units" OR "Emergency Mobile Unit" OR "Mobile Units, Emergency" OR "Mobile Emergency Units" OR "Mobile Emergency Unit")). Similar search strategies were used in the other databases.

For the selection of articles included in this review, a series of selection criteria were established: articles in Spanish or English, focused on patients with massive hemorrhage or hemorrhagic shock requiring blood component treatment during out-of-hospital care. We included all randomized controlled trials, observational studies, and systematic reviews. Exclusion criteria included articles focused on pediatric patients and pregnant women, letters to the editor, or editorials.

The main outcome measures were hemorrhage-related mortality and overall mortality, evolution after blood component administration, and length of hospital and intensive care unit (ICU) stay.

Results

A total of 10,352 articles were identified in an initial

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Table 3. Synthesis of included articles (n = 32)

Last Name, Year, Country	Study primary endopoint	Study design	Population and sample	Outcome measures	Main results
Pusateri[30], 2019, USA.	To facilitate a combined post hoc analysis of the COMBAT and PAMPer trials to examine questions that could not be answered by either clinical trial alone.	Study based on two clinical trials.	The sample included 626 patients in the 2 clinical trials. Patients who suffered trauma and presented with HS who were randomized to receive standard care or 2 U of thawed plasma followed by standard care in the prehospital setting were included.	Mortality at 28 days.	Mortality differed depending on transport times. In prolonged transport times (> 20 min), mortality decreased in patients who received prehospital plasma transfusion compared to standard care. In short transport times (< 2 min), mortality did not differ.
Van Turenhout[26], 2019, Netherlands.	To describe the effects of PHTRBC on patient outcomes.	Systematic review	55 articles were included. The 55 articles included traumatized patients, in both military and civilian settings, who received PHTRBC. In some cases, it was compared with a control group.	– Mortality. – Shock after transfusion. – Red blood cell requirement. – Signs of TBI upon hospital arrival. – Length of ICU or hospital stay. – Safety or AE.	Regarding mortality, the results are very contradictory, as most articles find a decrease in mortality in patients transfused with red blood cells or red blood cells and plasma, while others indicate no significant differences with patients who did not receive red blood cell transfusion. Regarding the occurrence of shock, in most articles, vital signs improved after red blood cell transfusion, thus reversing the shock state. However, there are also studies that provide contradictory information and found no differences. Regarding the red blood cell requirement, some articles find no clear differences, while others state that the requirement was lower for those who received red blood cells, and still others state it was higher. Regarding the probability of TBI, through INR analysis, study results are also contradictory, as some indicate that this probability decreases in those who received red blood cells, and others show no significant differences. One study even reports a higher probability of suffering coagulopathy in those who had received more units of red blood cells. In studies analyzing the length of ICU and hospital stay, no significant differences are found. Most studies report that no transfusion reactions occurred. The contradictions and differences between articles are attributed to age, ISS, and type of injury.

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search (Figure 1), from which articles were discarded according to the previously mentioned inclusion and exclusion criteria, finally comprising a total of 32 articles in the review.

Of all the selected articles, 56% (n = 18) were conducted in Europe and the remaining 44% (n = 14) in America. Within European countries, studies came from the United Kingdom (44%, n = 8), Finland (17%, n = 3), the Netherlands, France, Norway (11%, n = 2), and Italy (6%, n = 1). As for the type of studies included in this review, out of the total of 32 included studies, 17 are observational studies, 8 clinical trials, 5 systematic reviews, 1 methodological study, and 1 economic evaluation.

The average population for which information has been studied and obtained through all included studies on blood component treatment in out-of-hospital care has been 129,044 patients (Table 2).

Table 3 synthesizes the characteristics of the studies included in this review.

Quality assessment of included studies

Regarding the quality criteria of the different articles, both clinical trials, measured with the Cochrane bias tool (Figure 3), and observational studies, assessed using STROBE, presented a low risk of bias. The study based on an economic evaluation was reviewed using the CHEERS checklist, which met most of the evaluated criteria. Finally, all systematic reviews met the criteria of the PRISMA checklist.

Discussion

Out-of-hospital treatment with blood components is a topic that elicits diverse opinions and specific considerations. Within this therapy, we must consider various aspects

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Table 3. Synthesis of included articles (n = 32) (Continue)

Last Name, Year, Country	Study primary endopoint	Study design	Population and sample	Outcome measures	Main results
Henriksen[37], 2016, USA.	To investigate the influence of prehospital blood products (i.e., plasma and/or red blood cells) on admission hemostatic properties and patient outcomes compared to patients who did not receive prehospital transfusions.	Prospective observational cohort study.	257 trauma patients admitted to a Level I trauma center who had received prehospital or in-hospital blood components within 6 hours of admission were included.	Hemostatic function assessed by rTEG and mortality.	After evaluating the rTEG results, it was concluded that patients who received more prehospital plasma transfusions had better hemostatic outcomes than those who had received fewer units of plasma and better outcomes than those patients who had exclusively received red blood cells. Therefore, prehospital transfusion can lead to the correction of acidosis, thus mitigating coagulopathy. Regarding mortality, although the group that received prehospital transfusions had more severe injuries and a more severe clinical presentation, early and late mortality was very similar to the group that received in-hospital blood components.
Hrebinko[34], 2021, USA.	To evaluate the cost-effectiveness of prehospital thawed plasma transfusion in trauma patients with HS during air medical transport.	Economic evaluation.	501 patients were included. Characteristics for inclusion were prehospital transfusion, short-term hospital care, and healthcare costs and quality of life outcomes.	Relative costs and health-related quality of life were sought, using a cost-effectiveness ratio.	Prehospital thawed plasma transfusion was cost-effective. Therefore, during air medical transport of patients who have suffered trauma and are in HS, prehospital thawed plasma transfusion was cost-effective compared to standard care.
Rehn[10], 2019, UK.	To investigate the effect of red blood cell transfusion on mortality.	Retrospective case-control study of a trauma database.	623 subjects with suspected major hemorrhage.	Mortality before and after the inclusion of prehospital red blood cell transfusion in patients with exsanguinating trauma.	Following the introduction of prehospital red blood cell transfusion, overall survival did not show significant improvement, although prehospital survival was significantly reduced.
Naumann[24], 2017, UK.	To determine how frequently IV fluids were administered during prehospital treatment in hypotensive trauma patients, what types of fluids were most frequently administered, and how these data could affect national resource planning for universal provision of prehospital blood components if the results of ongoing trials show clinical efficacy.	Retrospective observational cohort study, regional survey, standard care, during evacuation resuscitation (RESCUER).	729 patients met the primary inclusion criteria: hypotensive trauma patients (SBP < 90 mmHg or absent radial pulse) attended by a physician. 11 of the 22 air ambulance services in the UK participated.	The primary endpoint was the number of hypotensive trauma patients who received prehospital fluids. Secondary outcomes were types and volumes of fluids. This data was combined with published data to estimate potential national eligibility for prehospital blood components.	Of the 729 patients, 537 received prehospital fluids, with 0.9% saline solution being the most common fluid, administered in a median volume of 750 mL. Approximately 800 patients per year in the UK would receive prehospital blood components if the evidence justifies universal provision. Further studies are required to confirm the estimates.

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such as the prehospital pathologies that require this treatment, identify the factors that indicate a situation of hemorrhagic shock, know about the existence of international protocols for prehospital blood administration, and finally, gather data on the impact of said therapy on patient mortality and survival.

Out-of-hospital clinical situations requiring blood component treatment

Comparing two studies carried out in Finland,[8,9] we observe that most of the treated patients had suffered severe trauma resulting in hemorrhage, with a smaller percentage of patients having hemorrhagic shock whose cause was not trauma-related. Blunt traumas, mostly due to traffic accidents, were the most frequent traumatic causes (46%). The main causes of hemorrhage in non-traumatized patients were intestinal hemorrhage (42%), vascular catastrophes (25%), postoperative complications (17%), and gynecological or obstetric hemorrhages (11%).

Current international situation on the use of prehospital blood component transfusion

In 2012, London's Air Ambulance (LAA)[10] became one of the first civilian emergency medical services (EMS) to in-

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Table 3. Synthesis of included articles (n = 32) (Continue)

Last Name, Year, Country	Study primary endopoint	Study design	Population and sample	Outcome measures	Main results
Griggs[25], 2018, UK.	To determine any association between mortality and patients transfused with prehospital PRBCs compared to crystalloids (0.9% sodium chloride) in civilian patients with suspected traumatic hemorrhage.	Retrospective observational cohort study.	218 patients met inclusion criteria: patients who triggered prehospital activation of Code Red (clinical suspicion of major hemorrhage and signs of hemodynamic compromise).	The primary outcomes were the measure of all-cause mortality at 6 hours and 28 days.	Although the data were not statistically significant and more studies are needed, mortality at 6 hours and 28 days in the prehospital red blood cell group was lower than in the group that received fluids. Additionally, patients who received prehospital red blood cell transfusions were less likely to require a massive transfusion in the hospital.
Tucker[21], 2023, England.	To compare prehospital combined RCP (one bag containing red blood cells and plasma) vs RBCs (red blood cells) alone or RBCs and plasma separately (RBC+P) on 24-hour and 30-day mortality in patients with traumatic hemorrhage.	Multicenter cohort study.	909 patients who met the criterion of having received a prehospital transfusion of RBC, RCP, or RBC+P.	Mortality of patients at 24 hours and 30 days.	Patients who received prehospital plasma in addition to red blood cell transfusion were less likely to die at 24 hours compared to those who received red blood cells only. When plasma and red blood cells were administered, the benefit differed according to injury characteristics, being more beneficial in penetrating injuries than in blunt injuries. Regarding 30-day mortality, there were no differences. This may indicate that the effect of plasma transfusion is beneficial in the short term. More future randomized controlled trials are needed to confirm the results.
Gruen[31], 2021, USA.	To characterize unexpected survivors from the PAMPer trial to understand patients who lived despite a high probability of death.	Randomized trial.	501 patients who presented with severe traumatic injuries.	To evaluate 30-day mortality.	Prehospital plasma is associated with an increased number of unexpected survivors after suffering severe traumatic injury and hemorrhage. Those patients with a high predicted mortality, based on injury characteristics, early prehospital, and hospital factors, benefited from an increased probability of survival due to prehospital plasma administration vs standard care.
Hashmi[12], 2022, USA.	To estimate the number of patients who could potentially benefit from prehospital blood component resuscitation after an injury. The secondary objective was to estimate the amount of blood components needed for prehospital resuscitation of injured patients.	Observational cohort study.	3.7 million trauma activations were used for the analysis. Patients with blunt or penetrating injuries were included and classified into 4 cohorts of hemodynamic instability. Cohort 1: SBP < 90. Cohort 2: SBP < 90 and/or HR > 120. Cohort 3: SBP < 90 and HR > 108 or SBP < 70. Cohort 4: SI ≥ 1.	Estimated number of individuals belonging to each cohort who would benefit from blood products. Estimated amount of blood products that would be needed.	The number of patients who benefited was high, and both the utilization of prehospital blood and the collection of blood products should be expanded to broaden the intervention.

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troduce and implement a protocol for transporting red blood cells and thus performing prehospital blood transfusions. From that moment on, EMS in different countries included this treatment.

A survey[11] was conducted in Helicopter Emergency Medical Services (HEMS) across several European countries to identify current European practice regarding the use of prehospital blood transfusion (PHBT) programs. France was the country with the highest acceptance rate for the use of blood components, being the service that implements it the most, highlighting its benefit. It was found that most countries have access to blood components; however, 77% state that they are used less than once a month, although in severe cases of traumatized patients with exsanguinating hemorrhages, it saves lives. The main drawback they express regarding the use of PHBT is that they perceive the need for more scientific evidence to clearly determine the role of blood components in the out-of-hospital setting.

In the United States, Hashmi *et al.*[12] conducted a study to estimate the number of patients who would benefit from this treatment. The data obtained showed that a high percentage of patients could benefit from blood components due to their characteristics. However, in practice, less than 0.4% received this treatment in the out-of-hospital

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Table 3. Synthesis of included articles (n = 32) (Continue)

Last Name, Year, Country	Study primary endopoint	Study design	Population and sample	Outcome measures	Main results
Crombie[35], 2022, UK.	To investigate whether the use of packed red blood cell (PRBC) concentrates was superior to 0.9% sodium chloride for improving tissue perfusion and reducing mortality in trauma-related HS.	Phase 3 multicenter, concealed allocation, open-label, parallel-group, randomized, controlled trial.	432 participants. Patients had to be adults (age ≥ 16 years) with HS and hypotension (defined as SBP <90 mm Hg or absent radial pulse) who had suffered trauma.	Mortality from episodes, decrease in lactate clearance, or both.	Prehospital resuscitation with LyoPlas was not shown to be better than resuscitation with 0.9% sodium chloride and LyoPlas. These results may be a consequence of short transport times. It is concluded that more studies related to this topic are needed.
Gruen[33], 2020, USA.	To evaluate the association between prehospital plasma and survival in TBI patients.	Randomized clinical trial	Randomized trial. This secondary analysis focuses on a predefined subgroup of patients from the PAMPer trial, those with TBI. A total of 166 patients who had suffered TBI were included.	Mortality at 30 days.	When comparing patients who had suffered TBI and had received plasma or standard care, the results obtained were that survival improved at 30 days in those who had received prehospital plasma.
Thies[11], 2020, France.	The primary endpoint is to establish the degree of prehospital use of blood components throughout Europe and discover the main indications. The secondary objective was to evaluate opinions on PHBT and the experience and personal opinions of its users.	Observational cross-sectional study.	Survey conducted on European Helicopter Emergency Medical Services (HEMS) and all French regions of Emergency Medical Assistance Services (SAMU). The sample consisted of 172 responses.	Open-ended and multiple-choice questions to obtain results on the frequency of transfusions, the prehospital blood product used, and the perceived benefit.	Most health services primarily have access to red blood cells, followed by fresh plasma, and finally the smallest percentage has access to LyoPlas. A high percentage stated that prehospital blood components are beneficial and life-saving, although they are infrequently needed. Significant differences in clinical practice opinions are found across different European countries.
Moore[28], 2018, USA.	To investigate the use of prehospital plasma during rapid ground rescue of HS patients before their arrival at an urban Level 1 trauma center.	Randomized COMBAT trial.	Patients who have suffered trauma and consequently HS are included. The sample consisted of a total of 125 patients.	Mortality at 28 days.	Both the group that received plasma and the control group had similar transport times, less than 20 minutes, and it was observed that there was no survival benefit in patients who received prehospital plasma.

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phase. These results indicate that prehospital resuscitation needs to be expanded to ensure increased patient survival.

First, it is essential to know how to recognize that the patient is in hemorrhagic shock, and therefore the authors[12,13] described a series of clinical signs that determine hemodynamic instability and would be indicators for the initiation of prehospital transfusion. Both studies agree on hypotension (systolic blood pressure < 90 mmHg) or tachycardia (heart rate > 120 beats per minute), differing in other indicators such as SI (> 1), altered mental status due to poor perfusion, and type of injury sustained.

These clinical differences show the lack of consensus in current practice for establishing the initiation of prehospital transfusion. To expand the inclusion of this practice in the out-of-hospital setting, the authors deemed it necessary to apply protocols that establish easy availability and storage of blood components, as well as minimize the risk of their waste.

The available protocols for the administration of prehospital blood components were designed primarily for patients who had suffered trauma, in most cases traffic accidents.[14] These patients are at high risk of complications, especially acute traumatic coagulopathy, whose correction is fundamentally based on early blood transfusion.

All programs developed, both in Norway[15,16] and the United States[17] for whole blood, and in Finland[14] and Canada[18] for Red Blood Cells, emphasize the implementation of a light, portable, simple, and small storage device to adapt to the limited storage space of the helicopter.

This box must maintain controlled temperatures for the proper maintenance of blood bags, and these must be replaced in blood banks during specific periods to avoid waste. All of them also establish that the presence of warmers is necessary to infuse blood components at an optimal temperature.[14-18] The programs describe low percentages related to the waste of whole blood or red blood cell units and do not indicate the presence of adverse reactions caused by prehospital transfusion.

These studies agree that, having a developed protocol that determines how logistics for transport should be carried out, this practice is feasible, simple, and safe.[14-18]

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Table 3. Synthesis of included articles (n = 32) (Continue)

Last Name, Year, Country	Study primary endopoint	Study design	Population and sample	Outcome measures	Main results
Sperry[29], 2018, USA.	To determine the efficacy and safety of prehospital administration of thawed plasma in injured patients at risk of HS.	Phase 3 pragmatic, multicenter, cluster-randomized superiority trial (PAMPer).	501 patients who had suffered trauma and were at risk of HS.	30-day mortality.	30-day mortality was lower in the group that received thawed plasma compared to those who received standard resuscitation with crystalloids.
Zhu[17], 2019, USA.	The study aimed to identify adult patients who arrived between January 1st, 2016, and August 31st, 2017, at any Level I trauma center and who required the initiation of an MTP upon arrival.	Review.	132 patients, of whom 109 arrived by ground transport and 21 by HEMS transport. In addition to patients for whom a physician ordered MTP activation, all patients who received 10 or more units of blood products within 24 hours of hospital arrival were included.	Mortalidad general.	Both ground and air transport had high mortality rates, although transport times were short. These rates would be reduced if prehospital blood were administered. In a later initiative carried out by STRAC, low-titer group O whole blood was administered prehospital. After the transport of these patients, it was shown that if resuscitation is initiated early in the prehospital setting, lower overall mortality rates are achieved.
Coccolini[32], 2019, Italy.	To analyze data from two randomized trials to obtain more unequivocal results on the optimal timing for plasma administration in HS patients and the effects of prehospital plasma administration on mortality.	Systematic review with meta-analysis of randomized controlled trials of prehospital plasma versus usual care in HS patients.	The two randomized trials included a total of 626 trauma patients with HS.	24-hour and 30-day mortality. The secondary outcome was morbidity (acute lung injury and multiple organ failure).	24-hour mortality was reduced in the group that received prehospital plasma. However, at 30 days, plasma had no significant effect on mortality, nor on acute lung injury or multiple organ failure rates.
Sunde[15], 2022, Norway.	To describe the implementation and evaluate the safety of a whole blood transfusion program in a civilian helicopter emergency medical service (HEMS).	Prospective observational study.	52 patients who were in HS and received out-of-hospital transfusion of LTOWB or other blood components.	Number of transfused patients, mechanisms of injury/illness, AEs, and survival rates.	The main mechanisms of injury were, first, blunt trauma, with non-traumatic causes being the second reason, and finally penetrating trauma. No data on transfusion reactions, serious complications, or logistical challenges were obtained. A total of 36 out of 52 patients survived the first 24 hours, and of those 36, 28 survived 30 days. These data lead to the conclusion that the implementation of a whole blood transfusion program in civilian HEMS is safe and feasible, and the logistics of transfusions are manageable in the out-of-hospital setting.

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Benefits and survival after prehospital blood component administration

Regarding the health benefits of each type of blood component and whole blood, different studies have been conducted on the different types and comparing the results obtained in patients. A study[10] conducted by the LAA service investigated the effect of prehospital red blood cell administration on patient mortality, resulting in a decrease in prehospital mortality but no improvement in overall mortality. If we compare these data with those provided by Huang *et al.*[19], no improvement in survival is established in most of the reviewed studies, although they indicate that the information may be biased.

With prehospital transfusion, we guarantee early administration of red blood cells, as a delay of > 1 hour could worsen coagulopathy, as stated by Lyon *et al.*[20] Furthermore, they establish that the probabilities of shock decrease with prehospital red blood cell transfusion as it prevents tissue hypoperfusion. In turn, after analyzing their study, they established that administering a 1:1 ratio of red blood cells and plasma in patients with hemorrhagic shock has better benefits in resuscitation.

Based on this last statement, an observational study conducted in England[21] evaluated the effect of administering red blood cells and plasma (RCP) vs only the administration of red blood cells (RBC). Evaluating mortality in the previous assumptions, it was found that if plasma was added in addition to transfusing RBCs, short-term mortality (24 hours) was reduced, but 30-day mortality was not modified. These data are complemented by the results of the

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Table 3. Synthesis of included articles (n = 32) (Continue)

Last Name, Year, Country	Study primary endopoint	Study design	Population and sample	Outcome measures	Main results
Van Turenhout[13], 2020, Netherlands.	To describe the current use and scope of PHTRBC practice and to evaluate the criteria and triggers used to initiate PHTRBC.	Systematic review of the how far current clinical practice goes and transfusion triggering factors	71 articles.	To understand the triggers that initiate PHTRBC.	These triggers are very broad and necessary for determining guidelines on when prehospital transfusion should be initiated. The most commonly used triggers are: hypotension (SBP < 90 mmHg), tachycardia (HR > 120 bpm), clinical signs of deficient perfusion (prolonged capillary refill time or changes in mental status), and type of injury (penetrating, blunt, etc.).
Krook[18], 2019, Canada.	To describe the processes and standard work that ensure the safe storage, administration, and management of red blood cell concentrates.	Observational cohort study.	Data from patients who had received a prehospital transfusion between October 1st, 2013, and October 10th, 2017, were included. Blood was administered to a total of 431 patients.	Analysis of the introduction of a blood program in a Canadian HEMS.	The article describes a process that minimizes blood waste, keeping it available for severely injured patients.
Ångerman[8], 2022, Finland.	To describe and compare traumatized and non-traumatized patients who received PHBT and had similar hemodynamic triggers.	Retrospective observational cohort study.	36 patients who had not suffered trauma and 96 who had suffered trauma; in both groups, massive hemorrhage was suspected, and prehospital transfusion had been administered.	Indications for out-of-hospital transfusion in non-traumatic hemorrhages.	Prehospital transfusion protocols were primarily developed for trauma patients; however, they are also beneficial in non-trauma patients. In fact, laboratory results showed that non-trauma patients had lower hemoglobin levels and were therefore more severely ill. In conclusion, prehospital transfusion protocols should also be evaluated from a non-traumatic perspective and adapted to each patient group.
Yliharju[9], 2022, Finland.	The primary endpoint was to describe patients who received PHBT in ground EMS with prolonged transport times. The second objective was to analyze the effect of PHBT on patient physiology and the need for additional transfusions.	Observational cross-sectional study.	65 patients who received prehospital transfusions of blood products (red blood cells, LyoPlas, or both) from September 2016 to December 2020 in a ground EMS in Finland.	SBP values before and after transfusion, time to first transfusion.	The main patient groups who received prehospital transfusion were those who suffered blunt trauma and gastrointestinal hemorrhages. Mean SBP values increased after the administration of prehospital blood components. Therefore, initiating prehospital transfusion in a ground EMS is a feasible and viable option, as it improves patient physiology and is a safe practice that does not cause a significant amount of AEs
Huang[19], 2017, USA.	To determine the mortality rate of traumatized patients with hemodynamic instability and the benefit of prehospital red blood cell transfusion.	Systematic literature review.	29 studies.	Mortality.	Generally, as patients present with more hemodynamic instability and more severe anatomical injury, the mortality of trauma patients increases. According to this review, there's no improvement in survival with the prehospital availability of red blood cells. There is also information claiming a potential benefit, which is confusing, and additional studies should be conducted to gather stronger evidence.

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observational study by Yliharju *et al.*[9], who state that after the administration of prehospital plasma and red blood cells, vital signs improved considerably and that during the first 24 hours of emergency care, the need to administer blood products at the hospital level decreased.

Among trauma patients, Hernández *et al.*[22] focused on those who suffered traumatic brain injuries and compared the results in patients who received red blood cells or thawed plasma. In terms of mortality, there were no significant differences; however, they did demonstrate better neurological outcomes in patients in the group that received early plasma.

To include platelets in damage control resuscitation, the authors refer to low-titer group O whole blood (LTOWB).[15,16] The implementation of LTOWB programs in Norwegian HEMS claims a benefit in the overall mortality of patients in hemorrhagic shock, as the purpose is to replace lost blood as soon as possible. In addition, it was found that the implementation of this treatment in civilian HEMS is logistically safer and more feasible, although a

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Table 3. Synthesis of included articles (n = 32) (Continue)

Last Name, Year, Country	Study primary endopoint	Study design	Population and sample	Outcome measures	Main results
Holcomb[36], 2017, USA.	To compare two different prehospital resuscitation approaches: crystalloid resuscitation versus red blood cell and/or prehospital plasma resuscitation.	Pragmatic multicenter observational study of prehospital helicopter resuscitation (PROHS).	1,058 trauma patients who were transported by helicopter directly from the injury scene to a Level 1 trauma center, between January 26th, 2015, and November 2nd, 2015.	Mortality at 3 hours, 24 hours, and 30 days.	It's important to note that patients arriving by helicopter had more severe injuries than those arriving by ground ambulance. Among those transported by helicopter, patients who received prehospital blood components also had more severe injuries than those who didn't receive transfusions. Due to this unexpected imbalance in injury severity, specific mortality results couldn't be determined as the analyses were inconclusive. Further studies are needed to detect significant differences in survival.
Vuorinen[14], 2020, Finlandia.	To describe the red blood cell protocol in HEMS and the initial experience with prehospital blood products during the first 3 years after implementation.	Observational study of patients attended by the HEMS unit between 2015 and 2018.	62 patients who received transfusions of red blood cell concentrates, LyoPlas, or both in the HEMS unit.	SBP figures, time to transfusion initiation, waste, and occurrence of adverse transfusion reactions.	SBP values increased during the prehospital phase, and the median time to transfusion initiation was 33 minutes. During the study period, 4 units of red blood cell concentrates were wasted, and no adverse transfusion reactions were reported. Therefore, transporting prehospital blood products by HEMS is a feasible and safe method to initiate transfusion about 30 minutes before reaching the hospital.
Jost[23], 2022, France.	To determine if LyoPlas transfusion can reduce the incidence of trauma-induced coagulopathy (TIC) compared to standard care consisting of normal saline infusion.	Randomized clinical trial.	134 patients who had suffered trauma and were at risk of hemorrhagic shock (HS) and coagulopathy, between April 1st, 2016, and September 30th, 2019.	INR upon hospital arrival. Secondary outcomes included the need for massive transfusion and 30-day survival.	Prehospital LyoPlas transfusion was not associated with significant differences in INR values compared to standard care. The groups also didn't differ in 30-day survival or the need for massive transfusions.

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greater number of studies are needed to obtain firmer conclusions.

Analyzing these data, we can affirm that the use of LTOWB vs red blood cells may be preferable for logistical reasons. Whole blood is more balanced[15] for patients in a critical condition. In this case, by co-administering platelets with red blood cells and plasma, the effectiveness of platelets in coagulation may be greater when administered early.

Effectiveness of blood component treatment compared to other treatments

Different treatments that complement or are administered as alternatives to blood components, such as crystalloids, were compared to determine differences in survival and thus determine the most suitable treatment.

The most frequently administered fluid in cases of hemorrhagic shock is 0.9% saline solution.[24] Studies were conducted to compare the administration of crystalloids with out-of-hospital red blood cells in cases of hemorrhagic shock and to determine if mortality decreased in either of the two groups. Three of the studies performed[25-27] indicate benefits in both short-term and long-term mortality, as early transfusion prevents hemodilution of erythrocytes, which occurs when crystalloids are administered, and oxygen transport is favored. Van Turenhout *et al.*[26] and Brown *et al.*[27] analyzed other secondary outcomes such as the volume of red blood cells transfused after admission, traumatic coagulopathy, and whether the patient was in shock upon admission after transfusion, and all of these were improved in both studies in the group that received red blood cells.

On the other hand, groups that received plasma have also been compared with others that received fluids. The two main trials were the Control of Major Bleeding After Trauma (COMBAT)[28] and Prehospital Air Medical Plasma (PAMPer),[29] conducted in ground ambulances and HEMS, respectively. PAMPer determined that 24-hour and 30-day mortality was reduced in the group that received plasma during prehospital care. COMBAT, however, showed no survival benefit at 28 days but highlighted an important criterion, the transport time until hospital arrival.[28]

Taking this data into account, Pusateri et al.30 conducted a post hoc analysis of these 2 trials and determined that in PAMPer, the prehospital transport time was greater than 20 minutes, and in COMBAT, it was shorter. Therefore, one of the factors influencing mortality would be transport time, as in those cases where it was greater than 20 minutes, survival increased in the group that had received plasma.

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Table 3. Synthesis of included articles (n = 32) (Continue)

Last Name, Year, Country	Study primary endopoint	Study design	Population and sample	Outcome measures	Main results
Hernández[22], 2017, USA.	To determine if there was a difference in neurological and functional outcomes in patients who received thawed plasma or PRBCs in the prehospital setting.	Retrospective observational study.	76 polytrauma patients over 15 years old with head injuries who underwent prehospital resuscitation with blood components (red blood cells or thawed plasma) at a single Level I trauma center, from January 2002 through December 2013.	Neurological and functional outcomes, using the Extended Glasgow Outcome Scale (GOSE) and the Disability Rating Scale (DRS). Secondary endpoints included: length of stay, type and number of transfusion units administered in the prehospital and hospital settings, administration of massive transfusions and critical administration threshold (CAT) status, duration of hospital stay, duration of prehospital transport, vital signs in the emergency department, laboratory data obtained at admission, arrival at the trauma center, GCS, ISS score, radiological diagnosis of intracranial pathology, and AIS score.	There were no significant differences in in-hospital mortality between the plasma group and the red blood cell group. Patients who received plasma showed better functional neurological outcomes, evidenced by a higher median GOSE score compared to those who received red blood cells. At discharge, median DRS scores also indicated better outcomes for patients who received thawed plasma.
Lyon[20], 2017, UK.	To describe the characteristics of patients receiving prehospital red blood cell transfusion in a HEMS and to evaluate their subsequent need for in-hospital transfusion and surgery.	Retrospective observational study.	147 patients transfused with prehospital red blood cells between February 2013 and December 2014.	Injury severity score, vital sign values, and time to hospital arrival.	The ISS was high in patients who received red blood cell transfusions, with a median time of 114 minutes to hospital arrival. PAS significantly improved with red blood cell transfusion, but no differences were observed in HR. Therefore, prehospital red blood cell transfusion potentially improves outcomes for trauma patients with hemorrhage. Prehospital transfusion is crucial due to the extended prehospital patient care time. However, further research is needed to identify which patients are likely to achieve better outcomes.

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Gruen *et al*.[31], for their part, focusing on the PAMPer trial, wanted to characterize patients who unexpectedly survived. Data were analyzed, and it was observed that these survivors were younger, had more severe injuries, and most had received prehospital plasma, so plasma was related to an unexpected increase in survival.

Knowing transport times is important for future studies, as it will help determine which services would be feasible to include this therapy, considering the distance to the reference hospital. It is also fundamental to consider that the administration of prehospital blood will never increase these transport times, without delaying the patient's arrival at the hospital.

Subsequently, the study by Coccolini *et al*.[32] reinforced the benefit in 24-hour mortality if plasma administration occurred within the first hour after injury in patients who had suffered severe traumatic injuries, without influencing long-term mortality.

Two other secondary analyses of PAMPer focused on 2 significant characteristics. On one hand, Gruen *et al*.[33] exclusively selected PAMPer patients who had suffered a traumatic brain injury (TBI) and consequently suffered a brain injury. Within that group, they compared those who had received plasma versus crystalloid solutions and determined that in those patients who received plasma, an even greater benefit in survival was observed.

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Table 3. Synthesis of included articles (n = 32) (Continue)

Last Name, Year, Country	Study primary endopoint	Study design	Population and sample	Outcome measures	Main results
Bjerkvig[16], 2021, Norway.	To describe Norwegian prehospital air ambulance blood transfusion programs, including the rationale and practical aspects of implementing a prehospital low-titer group O whole blood (LTOWB) program, and to present the experience with LTOWB in Norway from the perspective of air ambulance and blood banks.	Observational, cross-sectional study.	The sample included medical directors from 13 HEMS bases, 7 search and rescue (SAR) helicopter bases, and 4 blood banks supporting HEMS with LTOWB, all of whom responded to the survey.	Types of transported blood components and experiences regarding prehospital transfusion administration.	All 20 services transport LyoPlas, 13 transport red blood cells, and 4 transport whole blood. Of the 20 services, 18 preferred whole blood. Most services reported favorable experiences with implementing and using whole blood, indicating that this type of blood transfusion is feasible in Norway.
Roberts[38], 2013, UK.	To determine the effect of early tranexamic acid (ATX) administration on death and the need for transfusions in hemorrhagic trauma patients. Also, to evaluate the effect of ATX on the risk of occlusive vascular events (CRASH-2).	Randomized placebo-controlled trial and economic evaluation.	Adult trauma patients with, or at risk of, significant bleeding who were within 8 hours post-injury. A total of 20,211 patients were randomly assigned to either the ATX group or the placebo group.	The primary outcome was death in the hospital within 4 weeks post-injury, categorized as hemorrhage, vascular occlusion (myocardial infarction, stroke, pulmonary embolism), multiple organ failure, head injury, and others.	The ATX group showed a significant reduction in 28-day mortality. Administering the treatment early, between 1 and 3 hours post-injury, also reduced the risk of hemorrhage-related mortality.
CRASH-3 Collaborators[39], 2019, UK.	To evaluate the effects of tranexamic acid in patients with traumatic brain injury (TBI).	Randomized placebo-controlled trial.	Adult patients with TBI who were within 3 hours post-injury, had a GCS score of < 12, or any intracranial bleeding on rapid rTEG, and no significant extracranial bleeding. The sample consisted of 12,737 TBI patients.	The primary endpoint was death related to a head injury in the hospital within 28 days post-injury in patients treated within 3 hours post-injury.	The risk of death related to TBI, in patients treated within the first 3 hours after injury, was considerably lower in the group that received ATX compared to the placebo group. It was concluded that patients should receive treatment as soon as possible for the benefits to be substantial.
Brown[27], 2015, USA.	To evaluate the association of red blood cell transfusion at pre-trauma centers with outcomes in air medical trauma patients.	Retrospective cohort study.	Trauma patients transported by helicopter to a Level I trauma center. The total sample was 720 patients.	The primary outcome was 24-hour survival. Secondary outcomes included: shock upon admission, volume of in-hospital red blood cell transfusion within 24 hours, trauma-induced coagulopathy (TIC), and in-hospital survival.	In the group that received prehospital red blood cells, there was a higher probability of 24-hour survival. The likelihood of shock and the need for red blood cells at 24 hours were also decreased in the group that received out-of-hospital red blood

SI: Shock Index, HS: Hemorrhagic Shock, TBI: Traumatic Brain Injury, and TIC: Trauma-Induced Coagulopathy. GCS: Glasgow Coma Scale, INR: International Normalized Ratio;ISS: Injury Severity Score; PAS: Systolic Blood Pressure; LyoPlas: Lyophilized Plasma, LTOWB: Low-titer Group O Whole Blood, PHTRBC: Prehospital Red Blood Cell Transfusion, RCP: Red Blood Cells and Plasma, and RCB: Exclusive Administration of Red Blood Cells. Procedures include: MTP: Massive Transfusion Protocol and PHBT: Prehospital Blood Transfusion Programs. Diagnostic imaging is represented by: CT: Computed Tomography; rTEG: Rapid Thromboelastography; ICU: Intensive Care Unit, U: Units; min: Minutes.

On the other hand, knowing the efficiency of prehospital plasma administration becomes especially important to include this treatment in different services. Therefore, an economic evaluation[34] was conducted focusing on the PAMPer study. Through a cost-effectiveness analysis, the relative costs and health-related quality of life of individuals were analyzed, observing that the increase in expenses was due to intra-hospital costs generated by caring for those patients who had survived after out-of-hospital plasma administration. If plasma is further restricted only to polytrauma patients who have suffered brain injuries, the profitability of this strategy may be even greater.

In the RePHILL trial,[35] the combined administration of red blood cells and lyophilized plasma was compared with the administration of crystalloids. No benefit of one group

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over another was seen, a consequence of the transport times mentioned earlier. The same data were obtained in the study by Holcomb *et al.*[36], in this case due to an increase in the severity index of wounds in the group that received blood components. For their part, Henriksen *et al.*[37] focused on hemostatic function and did find benefits of plasma in it. They stated that an increase in studies could lead to an increase in patient survival.

In addition to the administration of blood components, TXA is also included in the resuscitation of patients with hemorrhagic shock. The CRASH-2 trial[38] focused on the early administration of TXA in patients who had suffered trauma to assess its effect on mortality. It was found that in those patients who received TXA within the first 3 hours after injury, along with blood components, 28-day mortality was reduced. It is also stated that with the administration of TXA in patients with traumatic hemorrhagic shock, an average of 100,000 lives per year could be saved worldwide.

Subsequently, the CRASH-3 trial[39] was published, which focused exclusively on CRASH-2 patients who had suffered a TBI. An increase in survival was observed in patients with mild and moderate brain injuries who had received TXA, with no reduction recorded in patients with severe brain injuries. This can be justified because TXA, by reducing intracranial bleeding, improves patient outcomes and increases survival rates.

Conclusions

Strengths and limitations

Regarding the strengths of this review, broad and detailed inclusion criteria were used, reducing the bias of excluding relevant studies. The quality of the evidence from the publications used is also high. Multiple clinical trials investigating the topic, which carry significant weight in the thematic area, have been reviewed. The included studies had a sufficiently high number of participants to obtain consistent results. Additionally, there was no temporal limitation for this review.

Regarding the main limitations of the review, as it is a treatment that is not yet protocolarily established internationally in many countries, many of the obtained results need more research to have even more conclusive scientific evidence. In conclusion, the main clinical situations requiring prehospital treatment with blood products are traumatic pathologies, although there are also non-traumatic pathologies that need such intervention. It is essential to detect the clinical signs that will indicate the initiation of transfusion and to implement protocols to determine the logistics of blood product transport and the actions of professionals for treatment administration. Transfusion of blood components leads to benefits in patient mortality at the out-of-hospital level, compared to the administration of crystalloid solutions, as does the complementary administration of TXA. However, more research is needed as there is a lack of high-quality evidence on the beneficial effects of blood product therapy.

Implication for practice and research

This systematic literature review synthesizes the research available to date to understand the current state of prehospital blood component treatment.

Knowledge about the diverse international practice in the different countries studied could be a first step towards unifying the most important criteria and actions and implementing them in those emergency health services that do not yet have an action protocol, with expert advice. In addition, all considerations that establish the time of initiation of transfusion, as well as transport times to the hospital, can be taken into consideration to know in which services this therapy would be most cost-effective, effective, and practical.

It can influence future research and studies to identify weak points and results that do not yet have sufficient evidence.

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ARTICLE INFORMATION

Conflict of Interest Disclosures: None reported.

Funding: The authors declare the non-existence of funding in relation to this article.

Ethical responsibilities: The authors have confirmed the maintenance of confidentiality and respect for the patient rights, agreement of publication, and transfer of rights to Revista Española de Urgencias y Emergencias.

Article not commissioned by the Editorial Board and with external peer review.

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