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Evidence on haemoderivatives and fluid therapy in haemorrhagic shock in a pre-hospital setting: a systematised review

Carmen Martí Marqués (CMM), degree in Nursing. Faculty of Health Sciences. European University of Valencia. Spain. https://orcid.org/0009-0007-5937-1657
carmenmarti21997@gmail.com

José Vte. Carmona-Simarro (JVC), Phd. Academic Advising Assistant. Faculty of Health Sciences. European University of Valencia. Spain https://orcid.org/0000-0003-4550-0685
josevicente.carmona@universidadeuropea.es

Corresponding author Carmen Martí Marqués, carmenmarti21997@gmail.com

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KEY WORDS: Haemorrhagic shock, Haemoderivatives, Fluid therapy, Red cell concentrate, Plasma, Platelets, Crystalloids, Colloids, Pre-hospital treatment, Emergency medical services.

ABSTRACT

Introduction. Haemorrhagic shock is an emergency that is associated with increased mortality, especially in a pre-hospital setting, caused by road traffic accidents resulting in severe polytrauma. It is a time-dependent situation in the sense that if blood loss is treated quickly the victim's chances of survival increase. Pre-hospital emergency medical services (EMS) do not usually carry blood derivatives in their equipment, especially in urban settings as the time to hospital is usually short, and fluids are used to maintain blood pressure. However, there is evidence of significant side effects from the overuse of certain fluids.

Goal. To analyse the scientific evidence in relation to the treatment of haemorrhagic shock in pre-hospital emergency services, assessing the efficacy of these treatments and the associations made between them.

Method. A Systematised Review of Randomised Clinical Trials (RCTs) published in the last 5 years (2018-2022) was conducted. The PRISMA® system was used to structure each of the different sections in the review. The JADAD scale for RCTs was applied to each of the articles in order to classify them according to their level of scientific quality.

Results. Eleven papers were selected that met the selection criteria and the goals. Five of them were multicentre papers. A flow chart of the search and a table of results of the main variables of interest were drawn up. The JADAD scale scored an average of 5 points.

Discussion. The review reaffirmed the need to show health actions with the highest level of recommendation in order to improve patient prognosis, increase survival and decrease mortality. The treatments used, with statistical significance in the RCTs in this selection were, in the case group, plasma, either fresh or lyophilised. In the control group, crystalloids such as 0.9% sodium chloride, lactated Ringer's, red blood cell concentrate and vasopressin were used.

INTRODUCTION

Haemorrhagic shock is nowadays the leading cause of death in trauma, so it can be said to be a preventable death, predominantly in patients under 44 years of age. The replacement of haemoderivatives in a patient in this situation is the main treatment, but there may be situations in which these products are not available when we are in an out-of-hospital setting. Fluid replacement is important because massive haemorrhage can lead to haemodynamic instability, resulting in decreased tissue perfusion, organ damage and even death. (1)

Hypovolemic shock compared to haemorrhagic shock

Hypovolemic shock is a type of shock that is usually due to external bleeding, internal bleeding, and loss of plasma or interstitial fluid. This type of shock is usually caused by trauma, as with haemorrhagic shock. In this type of shock, before initiating any treatment for improvement, we should take into account that there is no other concomitant aetiology, such as cardiac tamponade, tension pneumothorax or myocardial contusion, among others. Hypovolemic shock can be defined as a situation in which blood flow is insufficient to carry the necessary oxygen to the tissues and organs, and will therefore manifest with hypotension and tachycardia (as a compensatory mechanism). (2)

Major haemorrhage vs. massive haemorrhage

We can define haemorrhage as the outflow of blood from the blood vessels through a break in continuity of the skin and vessels. It is a common sign, but the prognosis and severity changes depending on the volume of blood lost, so it might be the result of a minor injury, in the emergency setting, and even become a life-threatening emergency for the patient. (3) (4)

Major loss of blood leads to insufficient oxygen and glucose reaching the cells, no energy (ATP) is generated and tissue necrosis may occur. (3)

Sudden loss of more than 1 litre of blood at any one time can lead to altered consciousness (coma) and hypovolemic shock. (4)

We can distinguish between severe and massive haemorrhages; the latter has a worse prognosis for the patient's life and recovery. Severe haemorrhage is characterised by an SBP of less than 100 mmHg, as well as a HR between 100-120 beats/min. The most obvious associated manifestations are vasoconstriction (compensatory mechanism), sweating and oliguria, among others. This type of haemorrhage occurs when blood volume has decreased by 25-35% of the total. Massive haemorrhage on the other hand is associated with an SBP of less than 70 mmHg and a HR greater than 120 beats/min (compensatory mechanism); symptoms manifest with intense vasoconstriction and subsequent shock. In massive haemorrhage, blood volume decreases by more than 35% of the total. (3)

Risk factors

The most important risk factor for haemorrhage and therefore the one that can lead to haemorrhagic shock is trauma, as it usually involves significant blood loss. Trauma can be considered a problem worldwide as it is a major cause of mortality, which leads us to try and define the prognosis from the moment it occurs. (5)

Haemorrhage, whether internal or external, is an emergency and tends to be a frequent situation in the out-of-hospital setting; the accidents that cause this haemorrhage are usually traffic or intraoperative accidents, among others. Other factors that can cause haemorrhagic shock are digestive haemorrhages, aneurysmal ruptures of the aorta, complications with anticoagulant treatments, obstetric-gynecological complications, injuries to viscera, tears, fractures in the pelvis and femur, among others. (7)

Clinical manifestations

The clinical manifestations of haemorrhagic shock can be extremely varied and are usually related to the loss of blood. Symptoms and signs include hypotension, tachycardia, a decrease or even disappearance of the pulse. The respiratory rate increases, diuresis decreases and the capillary refill time is greater. The patient's mental state may vary from anxiety/stupor to lethargy or comatose. (7) (8)

Diagnosis

The diagnosis of haemorrhagic shock takes into account various different aspects of the patient's condition, including an anamnesis if the patient is conscious and a complete physical examination.

The anamnesis may include confusion, anxiety, thirst, dyspnoea and pain at the site of injury. (8)

The physical examination should take into account (8):

• BP; a decrease in SBP below 90 mmHg or a reduction of 30 mmHg in the case of a patient with hypertension raises suspicion of this type of shock.

• In the skin, we should look for profuse sweating, cold and clammy skin, pallor and cyanosis of the extremities. Capillary refill time is an important factor that is increased in such cases. In addition, lividity may indicate peripheral vasoconstriction.

• The physical examination should include a rigorous search for visible external bleeding, as well as areas of trauma, wounds and fractures.

• As for the pulse, we should check for the possible presence of tachycardia (this is related to the loss of blood from the haemorrhage). We may also find a weak and thready radial pulse and an absence of peripheral pulse, which suggests a greater severity and may lead to significant haemodynamic deterioration, and even cardiac arrest.

• The patient's respiration may progressively increase due to lack of oxygenation in the cells.

• We should observe the patient's renal function for the possible presence of oliguria or oligoanuria as these are early signs that indicate poor or inappropriate renal perfusion.

• Palpate the abdomen for peritoneal reaction in cases of internal haemorrhage due to intra-abdominal organ injury.

Treatment

The primary goal is to stop the bleeding and restore circulatory volume. In patients in whom bleeding is still active, intravascular fluid recovery should be achieved as soon as possible, as the oxygenation of their currently compromised tissues depends on it. Haemoglobin (Hb) and haematocrit (Hto) concentrations should be determined in order to specify the administration of haemoderivatives. Crystalloids and colloids may also be used, as well as vasoactive drugs. (7). The main haemoderivatives used were: red blood cell concentrates, with the aim of increasing oxygen transport for appropriate tissue perfusion, plasma, in which red blood cells are suspended, platelets, essential in stopping haemorrhages and thus stabilising the patient, and cryoprecipitates ─ coagulation factors (8) (9) (10). In relation to fluids, we should highlight crystalloids, especially sodium chloride 0.9% and lactated Ringer's solution. These crystalloids cause problems when administered in large quantities: for example, sodium chloride 0.9% is associated with metabolic acidosis due to the large amount of chlorine it contains ─ hyperchloremic acidosis ─ and Ringer's Lactate with hyperkalemia, since it contains potassium; in a patient with high blood potassium its concentration would increase even more, with the risk of producing cardiac arrhythmias, especially ventricular arrhythmias. (11). Colloids, as plasma expanders, rapidly increase intravascular pressure, and are reserved for situations in which the administration of crystalloids in large volumes could cause a pulmonary problem, especially in patients who already have underlying acute pulmonary oedema (APO). Patients in whom indiscriminate administration may cause renal and/or hepatic failure in the medium/long term, related to certain types of expanders, should be assessed. In this context, albumin, as a plasma derivative and as a colloid, is administered in situations of hypoalbuminaemia. (11)

Administration of red cell concentrates in critically ill patients

A clinical study showed that transfusion of red cell concentrates in critically ill patients was associated with higher mortality (case group) compared to a control group. It was also associated with a longer stay in the ICU. (12).

Goals

The goals of the present review were to describe and analyse the management of a patient in haemorrhagic shock, especially in relation to haemoderivatives, fluids and drugs, by means of a review of the most current and best-evidenced peer-reviewed literature.

MATERIAL AND METHODS

Study design

Systematised literature review. Through a series of health descriptors with their respective Boolean operators, the search terms were determined: Haemorrhagic shock and Emergency Treatment, Fluid Therapy and haemoderivatives, Haemoderivatives and Erythrocytes, Shock and Crystalloid Solutions, Haemoderivatives and Plasma. The databases used were Pubmed, Cinalhl and IBESC. The selection criteria were: articles published in the last 5 years, in Spanish and/or English, of high methodological quality, especially quasi-experimental articles and RCTs, in patients over 18 years of age, in Full text and related to humans. Once the articles with these criteria had been selected, the title and abstract filters were applied.

The research question (PICO)

P	Patient or problem. Haemorrhagic shock causes high morbidity and mortality in the hospital setting.
I	Evidence for the use of non-haemoderivative therapy in haemorrhagic shock.
C	Not applicable.
O	Therapy in haemorrhagic shock that is not based on haemoderivatives is expected to be equally effective.

Database-driven selection process

Pudmed

Tesauro	Date of search	Database	Articles found	After criteria and filters
“Haemorrhagic shock and Emergency Treatment”	06 February 2023	Pubmed	16	9
“Fluid Therapy and haemoderivatives”	12 February 2023	Pubmed	8	1
“Shock AND Haemorrhage”	12 February 2023	Pubmed	407	20
“Haemoderivatives AND Erythrocytes”	13 February 2023	Pubmed	7	0
“Shock AND Crystalloid Solutions”	14 February 2023	Pubmed	23	6
“Haemoderivatives AND Plasma”	14 February 2023	Pubmed	115	1

Cinahl

Tesauro	Date of search	Database	Articles found	After criteria and filters
“Haemorrhagic shock and Emergency Treatment”	06 February 2023	Cinahl	324	7
“Fluid Therapy and haemoderivatives”	12 February 2023	Cinahl	523	3
“Shock AND Haemorrhage”	12 February 2023	Cinahl	2100	9
“Haemoderivatives AND Erythrocytes”	13 February 2023	Cinahl	330	2
“Shock AND Crystalloid Solutions”	14 February 2023	Cinahl	96	6
“Haemoderivatives AND Plasma”	14 February 2023	Cinahl	2700	1

IBECS

Tesauro	Date of search	Database	Articles found	After criteria
“Haemorrhagic shock and Emergency Treatment”	06 February 2023	IBECS	4	1
“Fluid Therapy and haemoderivatives”	12 February 2023	IBECS	1	0
“Shock AND Haemorrhage”	12 February 2023	IBECS	118	10
“Haemoderivatives AND Erythrocytes”	13 February 2023	IBECS	2	1
“Shock AND Crystalloid Solutions”	14 February 2023	IBECS	1	1
“Haemoderivatives AND Plasma”	14 February 2023	IBECS	23	4

RESULTS

Flowchart of the article selection process. Designed in-house.

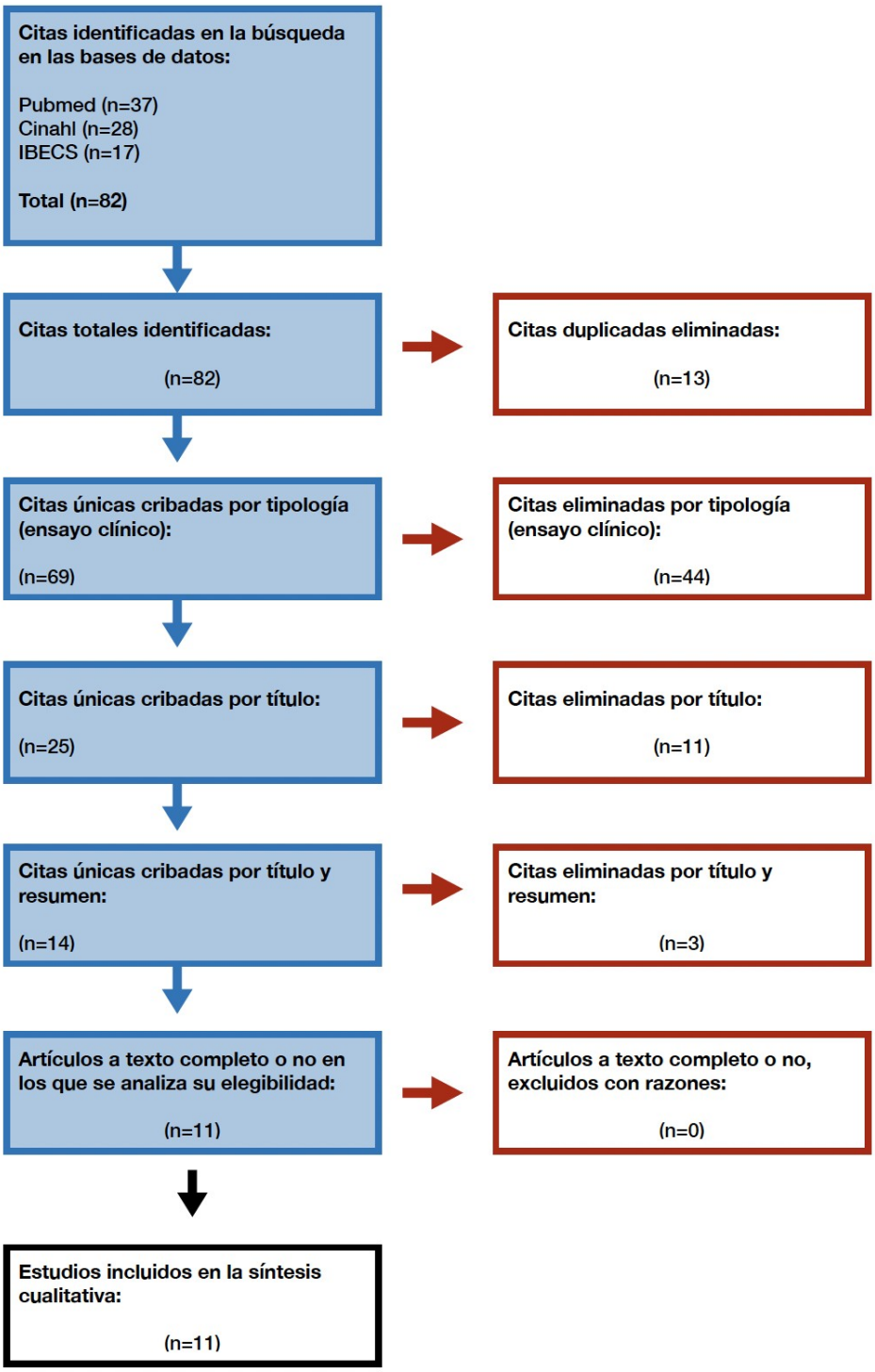


Figura 1: PRISMA. Transparent reporting of systematic Reviews and Meta-analyses. [consultado 5/05/2023] Disponible en: http://www.prisma-statement.org/index.htm

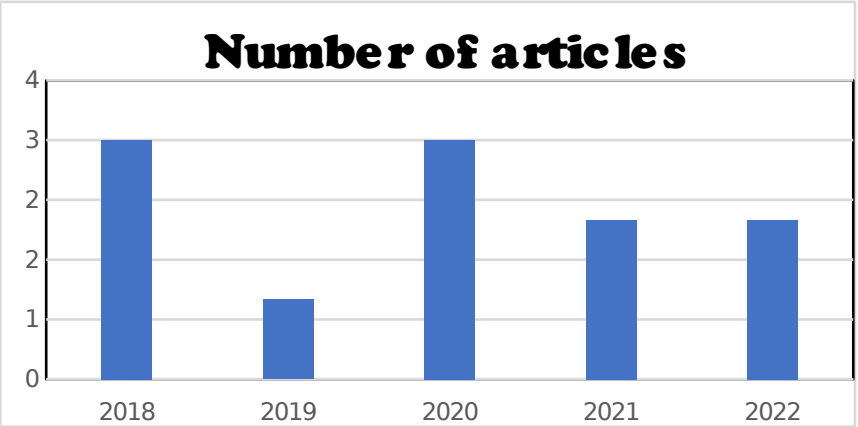
Table of results

Study	Study design	Size of sample (n)	Intervention	Control	Results	Conclusion	Validity (EJ)	Level of evidence (SIGN)	Journal, impact factor, quartile
Moore HB et al.(2018)	Randomised Clinical Trial (RCT)	**125**	Cases = 65 Administration of plasma	Controls = 60 Administration of crystalloids: saline solution	There was no statistically significant difference in mortality between the case and control groups *p=0.37*	The use of pre-hospital plasma was not associated with a survival benefit. Haemoderivatives may be beneficial in settings with longer transport times	5	1++	*Lancet* *202.73* *Q1*
Canton SP et al.	Randomised Clinical Trial (RCT)	**125**	Case group Administration of plasma	Control group Administration of crystalloids	Plasma was associated with lower odds of 30-day mortality (odds ratio [OR], 0.27; 95% CI, 0.08-0.90; p = 0.03).	Pre-hospital plasma is associated with reduced 30-day mortality and lactate in critically injured patients.	5	1++	*J Trauma Acute Care Surg* *3,402* *Q1*
Moore HB et al.(2020)	Randomised Clinical Trial (RCT) Multicentre	**160**	Case group Administration of plasma	Control group Standard administration	The case group had significantly higher rates of hypocalcaemia compared to controls (53% vs 36%; adjusted relative risk, 1.48; 95% confidence interval [CI], 1.03-2.12; *p = 0.03).* Severe **hypocalcaemia** was significantly associated with shorter survival (adjusted hazard ratio, 1.07; 95% CI, 1.02-1.13; *p = 0.01*).	Prehospital plasma is associated with hypocalcaemia, which in turn predicts poorer survival. This data underscores the need for calcium supplementation guidelines in hospital haemotherapy: **sodium citrate** binds to calcium.	5	1++	*J Trauma Acute Care Surg* *3,402* *Q1*
Guyette FX et al. (2021)	Randomised Clinical Trial (RCT) Multicentre	**407**	Three case groups: 1. Administration of red cell concentrate. 2. Administration of plasma. 3. Administration of red cell concentrate with plasma	Administration of crystalloids	Benefits: 1. Administration of red cell concentrate *p = 0.025* 2. Administration of plasma *p = 0.017* 3. Administration of red cell concentrate with plasma *p = 0.01* Mortality was associated with the administration of crystalloids *p = 0.04*	Patients with haemorrhagic shock should receive pre-hospital haemoderivatives when available, preferably red cell concentrate + plasma.	5	1++	*Ann Surg* *13.78* *Q1*
Crombie N et al. (2022)	Randomised Clinical Trial (RCT) Multicentre	**432**	Cases = 209 Administration of lyophilised plasma.	Controls = 223 Administration of crystalloids: sodium chloride 0.9%.	There was no statistically significant difference between plasma and crystalloids. *p = 0,996*	The trial did not show that pre-hospital resuscitation with plasma was superior to 0.9% sodium chloride in adult patients with trauma-related haemorrhagic shock.	5	1++	*Lancet Haematol* *18.96* *Q1*
Pusatori AE et al. (2020)	Randomised Clinical Trial (RCT)	**626**	Transfusion of 2U plasma.	Administration of crystalloids	Significant survival benefit for plasma *p = 0.01*	Prehospital plasma is associated with a survival benefit when transport times are greater than 20 minutes. The benefit-risk ratio is favourable for the use of prehospital plasma.	5	1++	*JAMA Surg* *16.7* *Q1*

SperryJL et al. (2018)	Randomised Clinical Trial (RCT) Multicentre	**501**	Cases = 230 Administration of plasma	Controls = 271 Administration of crystalloids	30-day mortality was significantly lower in the standard care group *p = 0.03* *No significant differences were observed between the two groups in terms of multi-organ failure, acute lung injury, acute respiratory distress syndrome, nosocomial infections, or allergic and transfusion-related reactions.*	Pre-hospital plasma leads to a survival benefit.	5	1++	*N Engl J Med* *176.0* *Q1*
Anto VP et al. (2020)	Randomised Clinical Trial (RCT)	**501**	Cases = 230 Administration of plasma	Controls = 104 Administration of red cell concentrate	Mortality in patients who were given red cell concentrate was higher than in those who were not (MT vs. NO-MT, 42% vs. 26%, *p = 0.01* *The Kaplan-Meier survival curves showed an early separation in cases (log rank p = 0.08) with no survival benefit found in the control group (log rank p = 0.949).*	Survival benefits of pre-hospital plasma were shown only in patients with red blood cell requirements below the transfusion level.	5	1++	*J Trauma Acute Care Surg* *3,402* *Q1*
Sims CA el at. (2019)	Randomised Clinical Trial (RCT)	**100**	Cases = 49 Administration of vasopressin	Controls = 51 Administration of placebo	Patients who were given **vasopressin** required significantly less haemoderivatives (median, 1.4 [IQR, 0.5-2.6] vs. 2.9 [IQR, 1.1-4.8] L; *p = 0.01).*	Low doses of vasopressin during resuscitation of trauma patients in haemorrhagic shock decrease haemoderivative requirements.	5	1++	*JAMA Surg* *16.7* *Q1*
Joel D et al. (2022)	Randomised Clinical Trial (RCT) Multicentre	134	Cases = 68 Administration of lyophilised plasma.	Controls = 66 Administration of saline	The mean values were 1.21 (IQR, 01.12-1.49) in the plasma group and 1.20 (IQR, 1.10-1.39) in the control group (mean difference, -0.01 , [IQR, 0.09 to 0.08) *p = 0.88)*	No significant differences were found between the case and control groups with regard to survival and/or massive transfusion.	5	1++	*JAMA Network* *13.37* *Q1*
Heming N et al. (2018)	Randomised Clinical Trial (RCT) Multicentre	**741**	Cases = 356 Administration of crystalloids	Controls = 385 Administration of colloids	Mortality at day 28 did not differ significantly between crystalloids 84 (23.6%) and colloids 100 (26%, adjusted odds ratio, 0.86, 95% CI, 0.61 to 1.21; *p = 0.768).* *Death at day 90 (111) [31.2%] vs. 122 [31.7%]; adjusted odds ratio.* *0.97, 95% CI, 0.70 to 1.33; p = 0.919) did not differ significantly between groups.*	No statistically significant difference was found in the use of crystalloids vs. colloids.	5	1++	Anesthesiology 9.198 Q1

The most significant aspects of this study are described below based on its goals:

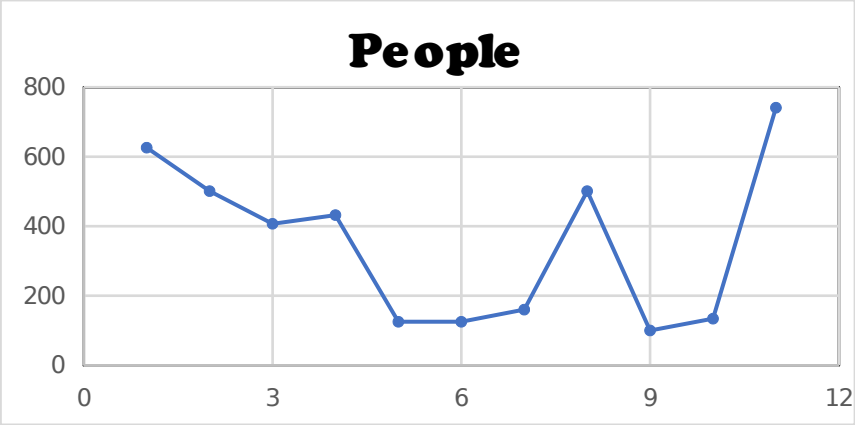
The articles were all published in the last 5 years: 2018 (3), 2019 (1), 2020 (3), 2021 (2) and 2022 (2).



Graph 1: Year of publication of the articles.

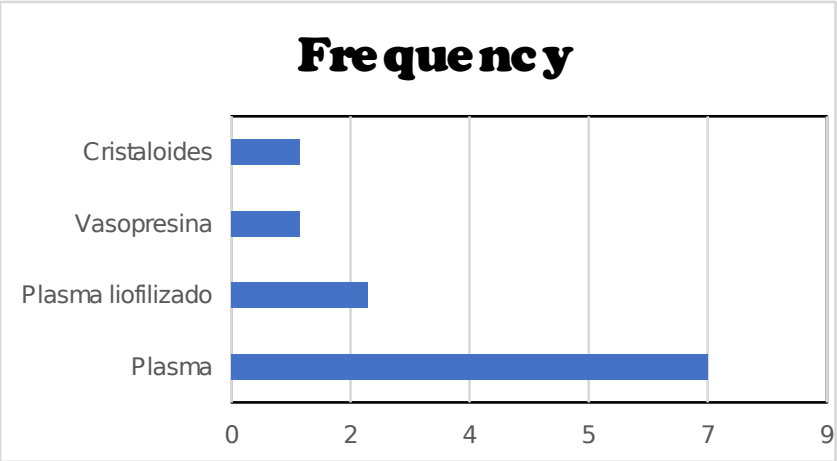
The 11 articles selected are Randomised Clinical Trials (RCTs) : 5 of them are multicentre.

The range of sample size is between 100 and 741 subjects/participants; the mean of all the studies was 350 people.

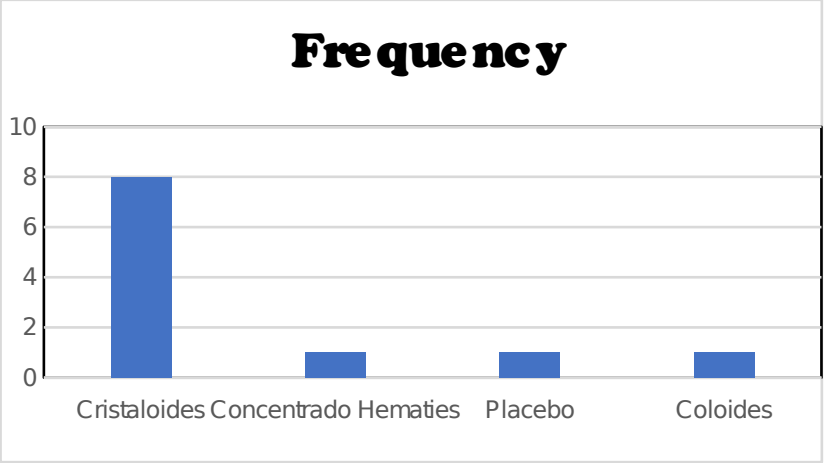


Graph 2: Sample size according to studies

As far as the case (intervention) and control groups are concerned, we could highlight the use of plasma in the intervention group, hence it was the most commonly used haemoderivative for assessing suitability for the treatment of haemorrhage. Lyophilised plasma was used in two cases. In the case of controls we could highlight the use of crystalloids, especially >0.9% sodium chloride (physiological saline solution).



Graph 3: Case group

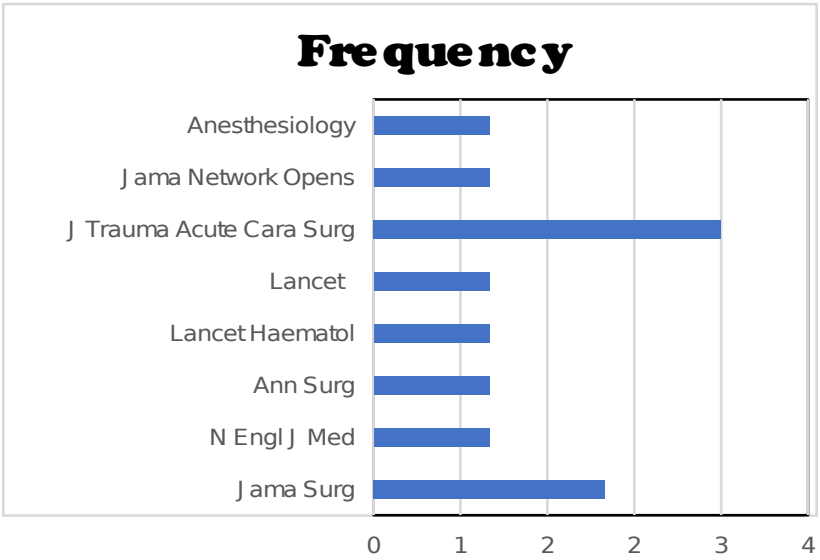


Graph 4: Control group

The JADAD scale was used to assess the methodological quality of the clinical trials: all the trials selected in this systematic review made explicit their randomisation/randomisation, the method of randomisation, the blinding (at least double-blinding), and finally whether there had been any loss/follow-up of subjects in the study, so they all scored 5.

As for the SIGN (level of scientific evidence) scale, all trials scored 1++ (the highest possible score) as they were high-*quality clinical trials with a very low risk of bias*.

The journals > in which the selected articles had been published were as follows (*J Trauma Acute Cara Surge stands out with three article*s):



Graph 5: Journals

All the journals belonging to the Journal Citation Report (JCR) in quartile Q1.

DISCUSSION

Interpretation of the results

This study reaffirms the need to evidence health actions with the highest level of recommendation in order to improve patient prognosis, increase survival and decrease mortality.

The articles were all published in the last 5 years: 2018 (3), 2019 (1), 2020 (3), 2021 (2) y 2022 (2). They are therefore up-to-date articles providing the greatest possible scientific evidence.

The 11 articles selected are Randomised Clinical Trials (RCTs) : 5 of them are multicentre.

The sample size range was between 100 and 701 subjects/participants; the mean of all studies was 350 people.

The JADAD scale was used to assess the methodological quality of the clinical trials: all trials selected in this systematic review made explicit their randomisation/randomisation, the method of randomisation, blinding (at least double-blinding), and finally whether there had been a loss/follow-up of subjects in the study, so they all scored 5.

Regarding the SIGN scale (level of scientific evidence) all the trials scored 1++ (the highest possible score) as they were high quality clinical trials with a very low risk of bias.

As far as the case group (intervention) and controls are concerned, we could highlight the use of plasma in the intervention group, making it the most widely used haemoderivative for assessing suitability in the treatment of haemorrhage. Lyophilised plasma was used in two cases. In the case of controls, we could highlight the use of crystalloids, especially 0.9% sodium chloride (physiological saline solution). We can therefore state that the most commonly used haemoderivative for the study was plasma, and the most commonly used control fluid was 0.9% sodium chloride.

Among the journals in which the selected articles had been published, J Trauma Acute Cara Surge stands out with three articles.

The significant survival benefit found in these articles for plasma is a p-value of 0.01. Mortality after 30 days was found to be significantly lower in the group that received plasma treatment compared to the group that received standard care, with a p-value of 0.03. As the author María García-Uría Santos says, “the administration of plasma during medical transport can improve survival rates; we observed that 30-day mortality is lower in patients who receive plasma and the mean prothrombin time is significantly lower than in patients who are not given this haemoderivative”. (24)

In the articles selected, no significant differences were observed between the two groups in terms of multi-organ failure, acute lung injury, acute respiratory distress syndrome, nosocomial infections, or allergic and transfusion-related reactions.

The benefits of administering each type of haemoderivative were: for red cell concentrate a p-value of 0.025, for plasma a p-value of 0.017 and for red cell concentrate with plasma a p-value of 0.001, showing that the administration of red cell concentrate with plasma is more beneficial for patients in shock. (24) (25)

The mortality associated with the administration of crystalloids was a p-value of 0.004 as stated in the study by Dr Javier Cruz et al. (25). Previously, considerably high amounts of crystalloids were used as an initial treatment for haemorrhagic shock to restore blood pressure, but increased mortality associated with hypothermia, acidosis and coagulopathy, among other factors, was observed. It is therefore recommended to avoid the use of large volumes of both crystalloids and colloids, and to start initial treatment of shock with the early administration of fresh frozen plasma, red blood cells,

cryoprecipitates and, if available and indicated, tranexamic acid and platelets. (25). With regard to the administration of plasma and crystalloids, no statistically significant differences were noted; the p-value was 0.996. Comparing the case group and the control group, we can see that there were no statistically significant differences in mortality either; the p-value was 0.37.

It can be observed that plasma was associated with lower odds of 30-day mortality (odds ratio [OR], 0.27; 95% CI, 0.08-0.90; p=0.03). On the other hand, the case group receiving plasma did have significantly higher rates of hypocalcaemia compared to controls (53% vs 36%; adjusted relative risk, 1.48; 95% confidence interval [CI], 1.03-2.12; p=0.03). Likewise, severe hypocalcaemia was significantly associated with shorter survival (adjusted hazard ratio, 1.07; 95% CI, 1.02-1.13; p=0.01). We can see that the mortality of patients who were given red cell concentrate was higher than those who were not (MT vs. NO-MT, 42% vs. 26%, p = 0.001).

The Kaplan-Meier survival curves showed an early separation in cases (log rank p=0.008) with no survival benefit found in the control group (log rank p = 0.949).

Patients given vasopressin required significantly less haemoderivatives (median, 1.4 [IQR, 0.5-2.6] vs. 2.9 [IQR, 1.1-4.8] L; p = 0.01).

The median values were 1.21 (IQR, 1.12-1.49) in the plasma group and 1.20 (IQR, 1.10-1.39) in the control group (median difference, -0.01 [IQR, -0.09 to 0.08]; p = 0.88).

Mortality at day 28 did not differ significantly between crystalloids 84 (23.6%) and colloids 100 (26%; adjusted odds ratio, 0.86; 95% CI, 0.61 to 1.21; p=0.768). Likewise, death at day 90 (111 [31.2%] vs 122 [31.7%]; adjusted odds ratio, 0.97; 95% CI, 0.70 to 1.33; p=0.919) did not differ significantly between groups either.

We can state that pre-hospital plasma is associated with a survival benefit when transport times are longer than 20 minutes. The benefit-risk ratio is favourable for the use of prehospital plasma, and in turn is associated with a benefit in patient survival.

It is advised that patients with haemorrhagic shock should receive pre-hospital haemoderivatives when available, preferably red cell concentrate together with plasma.

The trial did not show that pre-hospital resuscitation with plasma was superior to 0.9% sodium chloride in adult patients with trauma-related haemorrhagic shock. The use of pre-hospital plasma was not directly associated with a survival benefit, but haemoderivatives could be beneficial in settings with longer transport times.

Pre-hospital plasma in trauma is associated with hypocalcaemia, which is a disadvantage because it predicts lower survival.

Pre-hospital plasma in trauma is associated with hypocalcaemia, which is a disadvantage because it predicts lower survival. This data underscores the need for calcium supplementation guidelines in prehospital haemotherapy: sodium nitrate binds to calcium.

Survival benefits of pre-hospital plasma were shown only in patients with red blood cell requirements below the transfusion level.

It can also be observed that low doses of vasopressin during resuscitation of trauma patients in haemorrhagic shock decrease the need for haemoderivatives, and this is beneficial for the patient.

In these studies, no significant differences were found between the case and control groups with regard to survival and/or massive transfusion. Likewise, no statistically significant differences were observed in the use of crystalloids vs. colloids.

As stated by Ander Arnedo Puy et al. It is currently not possible to explain which of the two groups of fluids (colloids and crystalloids) is the most indicated in haemorrhagic shock, and that, although crystalloids are more frequently used, there is a need to evaluate in greater detail the efficacy and safety of these two fluids. (26)

Evidence-based recommendations: Implications for practice

This review shows the benefit of the pre-hospital administration of fresh/lyophilised plasma in haemorrhagic shock over other therapies.

Limitations of the study

Limitations of the study due to biases.

Bias

As in any systematic review, we have highlighted publication bias and selective omission/reporting bias.

Future lines of research

Systematic reviews of Randomised Clinical Trials (RCTs) give us the opportunity to carry out research with other designs such as Meta-analyses that can provide us with new results based on the investigation of all the information contained and with similar characteristics in the studies.

Conflict of interest

This systematised review did not present any conflicts of interest with individuals, companies or institutions.

Ethical considerations

This study was carried out in accordance with universal ethical principles and professional codes of ethics. The personal data in the articles selected was anonymised, as were the names of companies and institutions. It was also taken into account that the subjects in both the case and control groups had signed the informed consent form for the experimentation.

CONCLUSIONS

We analysed the current scientific evidence on fluid therapy treatment in the context of patients in haemorrhage shock in the pre-hospital setting, highlighting plasma as a fundamental haemoderivative for therapy. The level of scientific evidence analysed with the SIGN scale of the articles was very high, as the selection was made up of randomised clinical trials (RCTs). The JADAD scale was also applied to all papers. The treatments used in the RCTs in this selection were, in the case group, plasma, either fresh or lyophilised. In the control group, crystalloids such as 0.9% sodium chloride (physiological saline), lactated Ringer's, red blood cell concentrate and vasopressin were used. The efficacy of the most effective treatment was analysed with a 95% CI for a p-value < 0.05, using hypothesis testing such as the Student's *t*-test and the Wilcoxon test, as has been done in most trials in which plasma has been shown to be effective against other therapies. In the context of pre-hospital care and in the treatment of haemorrhage in patients with haemodynamic instability, the early administration of plasma increases survival and decreases mortality. Once the patient is in hospital, and after further analysis, other parameters of clinical interest such as haemoglobin, haematocrit and coagulation status, among others, can be corrected.

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