Review Article

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Reviving the Critically Ill: Exploring Effective Fluid Resuscitation Approaches for Diverse Hypovolemic Shock Cases–A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: The present study was performed to investigate the efficacy of different resuscitation fluids in critically ill patients presenting any type of hypovolemic shock.
Methods: We comprehensively searched PubMed, Web of Science, ScienceDirect, Cochrane Library, and Google Scholar for randomized trials published in English from January 1990 to August 2023. The risk of bias and methodological quality assessment was performed using Cochrane's risk of bias tool embedded within the Review Manager software (RevMan 5.4.1). Moreover, this software was used to perform all the statistical analyses in the present study. During these analyses, the random effects model and 95% confidence interval was employed. The overall effect sizes for continuous and dichotomous data were calculated using the Mean Difference (MD) and Risk ratio (RR), respectively.
Results: Our initial database search resulted in 4768 articles, of which only 16 were reviewed and analyzed. A subgroup analysis of data from 4 of these studies showed that hydroxyethyl starches (HES), gelatins and albumins had no significant mortality benefit compared to crystalloids (RR: 0.94; 95% CI: 0.75–1.17; P=0.58, RR: 0.71; 95% 0.46–1.08; P=0.11 and RR: 1.05; 95% CI: 0.77–1.43; P=0.77, respectively). Similarly, a subgroup analysis of data from 9 studies showed that hypertonic saline plus dextran (HSD) had no significant mortality benefit over normal saline (RR: 0.84; 95% CI: 0.62–1.13; P=0.24) or Lactated ringer's solution (RR: 1.03; 95% CI: 0.75–1.42; P=0.87). In addition, we found that hypertonic saline had a similar effect on the overall mortality as isotonic crystalloids (RR: 0.92; 95% CI: 0.68–1.25; P=0.60). Also, our analysis shows that modified fluid gelatins had a similar mortality effect as HES ((RR: 1.02; 95% CI: 0.52–2.02; P=0.95).
Conclusion: Colloids, whether individually or in hypertonic crystalloids (HSD), had no mortality benefit over crystalloids in adult patients with hypovolemic shock.

Keywords: Fluid resuscitation, Hypovolemic shock, Critically ill.

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Introduction

Hypovolemic shock is a potentially life-threatening condition, which when left untreated, may result in ischemic injury of vital organs leading to multiple organ failure (MOF) [1, 2]. Therefore, early recognition of this condition is vital for optimal care. Research has shown that fluid resuscitation effectively restores blood volume and ensures optimal organ perfusion [3, 4]. Fluid resuscitation includes a wide range of products generally classified as crystalloids or colloids. Crystalloids include isotonic and hypertonic solutions, further classified as non-buffered (e.g., isotonic saline) and buffered solutions (e.g., Ringer lactate, acetate, maleate). In addition, the colloid family consists of hypo-oncotic (e.g., gelatins, 4% or 5% of albumin) and hyper-oncotic solutions (e.g., dextran, hydroxyethyl starches, and 20% or 25% albumin). Ideally, colloid solutions are considered more effective than crystalloids in terms of the amount of fluid that remains in the intravascular space [3]; thus, less fluid is required when using colloids as opposed to crystalloids to achieve similar hemodynamic goals [5]. However, these fluids have raised concerns such as altering immune responses to critical illness [3, 4]. In addition, there is concern that hydroxyethyl starches might increase mortality risk and acute kidney injury (AKI) [6].

Although crystalloids and colloids are frequently employed in fluid resuscitation, the ideal fluid for resuscitation is contested. Several previous meta-analyses have tried to investigate the superior fluid resuscitation therapy between colloids and crystalloids. For instance, Choi and colleagues reviewed data from 17 studies with 814 patients and found no considerable difference between colloids and isotonic crystalloids in terms of the overall survival, hospital length of stay, and the incidence of pulmonary edema. However, traumatic patients resuscitated with crystalloids displayed significantly lower mortality rates than those on colloid resuscitation [7]. On the other hand, two previous comprehensive reviews of critically ill patients demonstrated that fluid resuscitation with crystalloids provides no mortality advantage compared to colloids [8, 9]. Based on the evidence in these previous reviews, it is clear that there is still a contention on which resuscitation fluid is superior. Therefore, this systematic review evaluated the effects of various fluid resuscitation strategies on patient outcomes of strictly adult patients presenting with hypovolemic shock.

Material and Methods

A database literature search was performed in PubMed, Web of Science, ScienceDirect, Cochrane Library, and Google Scholar from January 1990 to August 2023. In addition, a manual search was carried out by going through the reference lists of selected articles to identify additional studies. During the search, grey literature and duplicates were eliminated as these articles could undermine the scientific purpose of this research. The search strategy used in the electronic databases was as follows: (Fluid resuscitation OR fluid therapy OR Crystalloid* OR isotonic saline OR Ringer' lactate OR Hartmann's OR saline* OR sodium Chloride OR NaCL OR colloids* OR albumin OR albumen OR dextran OR hydroxyethyl starches OR gelatin*) AND (Hypovolemic shock OR hypovolemia OR shock* OR hemorrhagic shock OR non-hemorrhagic shock) AND (critically ill OR trauma OR traumatic).

Two experienced reviewers were tasked with defining the criteria for the inclusion and exclusion of publications to inform the present review article. After a thorough deliberation between the reviewers, the following inclusion criteria were agreed:

1. Completed Randomized trials (RCTs) with full publications in English.
2. Studies carried out on human subjects.
3. Studies including adult patients only.
4. Studies that compared any fluid resuscitation products in patients with any type of hypovolemic shock or hypovolemia.
5. Studies reporting outcomes related to hemodynamic effects, mortality, amount of transfused blood, and adverse events.

Exclusion criteria included:

1. Studies designed as systematic reviews, conference abstracts, case reports, ongoing clinical trials, and study protocols.
2. Studies in which fluid resuscitation was used to manage severe sepsis, septic shock, and burns.

Two impartial reviewers scrutinized all the selected research studies and extracted the required information. This information was as follows: Author ID (surname of the first author and publication date), study location/country, the defining traits of participants (i.e., enrolled participants, number of men and women, and mean age), follow-up duration, the type of fluid infused, type of hypovolemic shock, and outcomes of each study. All the disparities experienced throughout this procedure were resolved through dialogue amongst the reviewers or by consulting a third reviewer.

The core objective of our study was the overall mortality rate at the end of each trial's follow-up period, whereas the supplementary endpoints were the amount of transfused blood products in the first 24 hours and adverse events.

The methodological quality and risk of bias assessment of the included studies was performed using Cochrane's risk of bias tool (RoB) embedded within the Review Manager software (RevMan 5.4.1). Using the RoB tool, the studies were appraised based on selection, performance, attrition, reporting, and other risk of bias. A low risk of bias was assigned for every criterion fully addressed in the

study, while a high and unclear risk of bias was assigned to criteria not addressed or with insufficient information, respectively. A summary of the risk of bias assessment is shown in Figure 1.

All the quantitative analyses in the present research were executed with the Review Manager program (RevMan 5.4.1). In all these analyses, the random effects model was applied to combat the projected variability and offer modest pooled effect sizes. For dichotomous data, the effect size was calculated using the Risk Ratio (RR) analyses, while the effect size of continuous data was calculated in terms of the mean difference (MD). Moreover, the degree of variation between studies was assessed using I2 statistics, of which values between 0–25%, 26–50%, and 51–100% were classified as minimal, moderate, and extreme respectively. When suitable, subgroup analyses were undertaken based on the type of fluid resuscitation employed.

Results

Our comprehensive literature search resulted in 4768 articles with predefined MeSH terms and keywords. A duplicate check on these articles led to the exclusion of 1592 records determined to be close or exact duplicates. After that, the titles as well as the abstracts of the remaining records were scrutinized, of which 2188 that did not meet the screening criteria were excluded. Finally, only 16 articles met the inclusion criteria, while 146 were excluded due to the following reasons: 8 studies showed the efficacy of fluid resuscitation strategies in children, 2 were published in languages other than English, 57 included patients with septic shock, burns or severe sepsis only, and 79 were Animal models or experimental studies. The full selection criteria was outlined in the PRISMA flow diagram (Figure 2).

Summary of Study Characteristics

The 16 included studies comprised of 11763 critically ill patients with hypovolemic shock. All the studies were randomized controlled trials (RCTs), of which 3 were conducted in the United States, 2 in the United Kingdom, 3 in Brazil, 1 in China, 1 in Mexico, 1 in Taiwan, 1 in Canada, and 1 in Turkey. The other 2 studies were carried out in multiple countries. Of the 15 studies, 5 reported fluid resuscitation in the intensive care unit (ICU), 8 in the emergency department (ED), and 3 in the prehospital setting (Table 1).

Colloids Versus Crystalloids

Of the 15 trials included in the present study, 4 directly compared different colloids to crystalloids. Out of the 4 trials, 2 compared hydroxyethyl starches (HES) to crystalloids, while one compared gelatin to crystalloids. The other trial compared multiple colloids, including HES, gelatins, and albumin, to crystalloids. Data pooled from the three trials

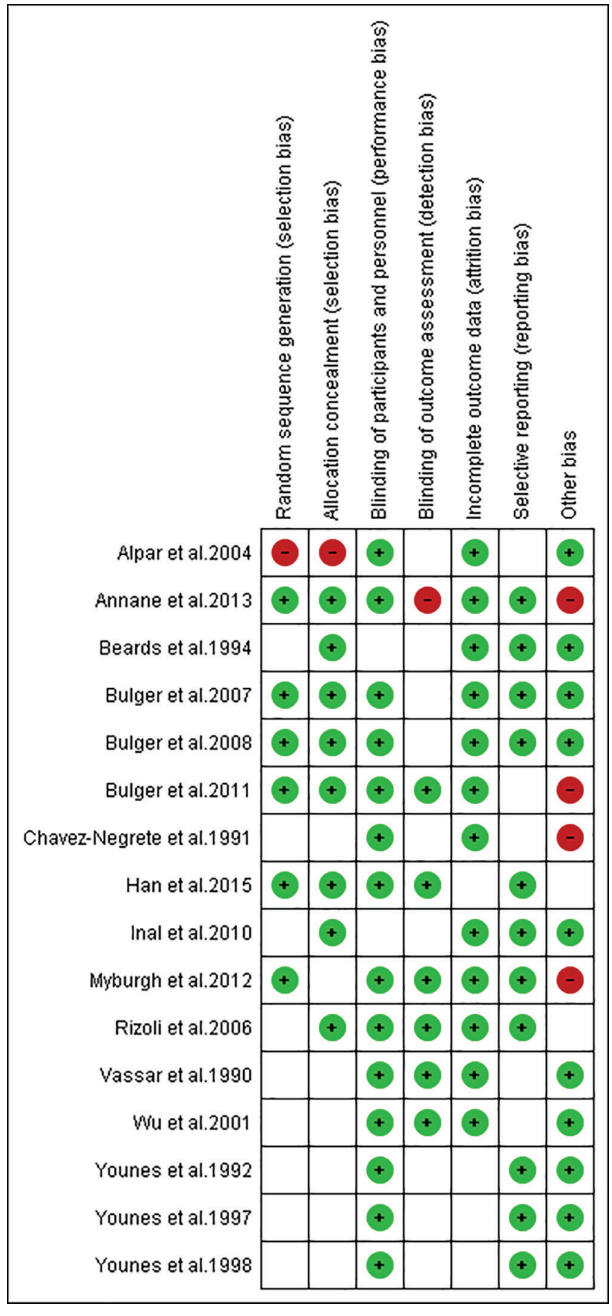

Fig. 1. Risk of bias summary

evaluating the efficacy of HES in fluid resuscitation showed no significant difference in mortality compared to crystalloid (RR: 0.94; 95% CI: 0.75–1.17; P=0.58) (Figure 3). However, the heterogeneity between the studies was high (I^2=72%). Similarly, our meta-analyses did not show any significant difference in mortality for patients resuscitated with gelatins or albumin compared to crystalloids (RR: 0.71; 95% 0.46–1.08; P=0.11 and RR: 1.05; 95% CI: 0.77–1.43; P=0.77, respectively) (Figure 3).

Only one study comparing colloids to crystalloids reported data related to adverse events; therefore, we could not carry out a meta-analysis. According to this study, fluid resuscitation with HES was associated with an increased risk for adverse events than saline (4.6% versus 3.3%; P=0.06). Of these adverse events, the most common were rash and pruritus.

Table 1. Summary of Study Characteristics

Author ID	Location	Participants' characteristics				Fluid (s) infused		Setting of resuscitation	Outcomes
		Sample (n)	M/F	Mean/median age (years)		Intervention	Control		
				Intervention group	Control group				
Alpar et al., 2004 [10]	United Kingdom	180	162/18	28 (21–60)	27 (21–59)	7.5% NaCl plus 4.2% dextran solution (HSD)	Hartmann's solution	ICU	Hemodynamic variables and mortality
Annane et al., 2013 [11]	France, Belgium, Canada, Algeria, and Tunisia	2857	1782/1075	63 (50–76)	63 (50–75)	Hypooncotic colloids (gelatins and 4% or 5% of albumin) and hyperoncotic colloids (dextrans, hydroxyethyl starches, and 20% or 25% of albumin)	Isotonic or hypertonic saline and Ringer's solution.	ICU	Mortality, ICU stay, length of Hospital stay, and Organ failure
Beards et al., 1994 [12]	United Kingdom	28	21/7	61.7	48.3	Rapid infusion (<10 minutes) of 500mL of modified fluid gelatin	Hydroxy-ethyl starch	ICU	Hemodynamic variables and mortality
Bulger et al., 2007[13]	United States	62	47/15	37.8 (15)	36 (16)	250ml of 7.5% saline and 6% dextran 70 (HSD)	250ml of lactated Ringer's solution	Prehospital	Mortality, ICU stay, and complications.
Bulger et al., 2008 [14]	United States	209	137/72	41 (15–84)	35 (13–90)	250mL of 7.5% hypertonic solution and 6% dextran 70 (HSD)	250mL of lactated Ringer solution.	Prehospital	Mortality, ADRS incidence, ICU stay, organ failure, and incidence of nosocomial infections.
Bulger et al., 2011 [15]	United States	853	666/187	37.7 (17.3)	36.8 (16.1)	250mL bolus of 7.5% saline	250mL of 7.5% saline and 6% dextran 70 (HSD) OR 0.9% saline (normal saline)	Prehospital	Mortality, organ failure, incidence of ARDS, nosocomial infections, fluid requirements, ICU stay, and hospital stay.
Chavez-Negrete et al., 1991 [16]	Mexico	49	32/17	42 (22–76)	42 (52–58)	250 ml of 7.5% NaCl and 6% dextran 60 solution (HSD).	Convec-tional lactated Ringer's solution.	ED	Hemodynamic variables and amount of transfused blood products.
Han et al., 2015 [17]	China	246	189/57	45 (0.5)	43 (9.5)	250mL bolus of 3% hypertonic saline solution	250mL bolus of 7.5% hypertonic saline solution OR lactated Ringer's solution.	ED	Hemodynamic variables, adverse reactions, and survival rate.

Author ID	Location	Participants' characteristics				Fluid (s) infused		Setting of resuscitation	Outcomes
		Sample (n)	M/F	Mean/median age (years)		Intervention	Control		
				Intervention group	Control group				
Inal et al., 2010 [18]	Turkey	30	15/15	56 (19.4)	56.4 (16.0)	3.5% polygeline	6% hydroxyethyl starch	ICU	Hemodynamic variables and mortality
Myburgh et al., 2012 [19]	Australia and New Zealand	6742	4071/2671	63.1 (17.0)	62.9 (16.9)	6% hydroxyethyl starch in 0.9% Saline.	0.9% Saline	ICU	Mortality, Organ failure, renal outcomes, ICU, and hospital stay length.
Rizoli et al., 2006 [20]	Canada	27	16/11	47.5 (15.9)	49.3 (16.7)	250mL bolus of 7.5% NaCl and dextran 70 (HSD)	250mL bolus of 0.9% NaCl.	ED	Length of Hospital and ICU stay, incidence of complication, organ failure, mortality, and fluid requirements.
Vassar et al., 1990 [21]	United States	106	NR	NR	NR	250ml bolus of lactated Ringer's solution.	250ml bolus of 7.5% NaCl OR 7.5% NaCl and 6% dextran 70 (HSD)	ED	Hemodynamic variables and mortality
Wu et al., 2001 [22]	Taiwan	34	21/13	41.3 (19.1)	47.8 (19.1)	1000mL infusion of Modified Fluid Gelatin 4% in NaCl,	1000mL infusion of lactated Ringer's solution.	ED	Hemodynamic variables and mortality.
Younes et al., 1992 [23]	Brazil	105	NR	NR	NR	250mL bolus of hypertonic 7.5% NaCl solution.	250mL bolus of hypertonic 7.5% NaCl plus 6% dextran 70 (HSD) OR 250 mL bolus of isotonic 0.9% NaCl solution.	ED	Hemodynamic variables, mortality, and complications.
Younes et al., 1997 [24]	Brazil	212	185/27	29 (16–89)	30 (16–83)	250mL infusion of hypertonic 7.5% NaCl plus 6% dextran 70 (HSD)	250mL infusion of isotonic 0.9% NaCl	ED	Hemodynamic variables, mortality, and complications.
Younes et al., 1998 [25]	Brazil	23	20/3	31.1 (9.5)	34.4 (14.9)	250 mL infusion of isotonic 0.9% NaCl solution	250mL infusion of 10% pentastarch solution	ED	Hemodynamic variables and mortality.

ED: Emergency Department; ICU: Intensive care unit; NR: Not Reported; ARDS: Acute respiratory distress syndrome

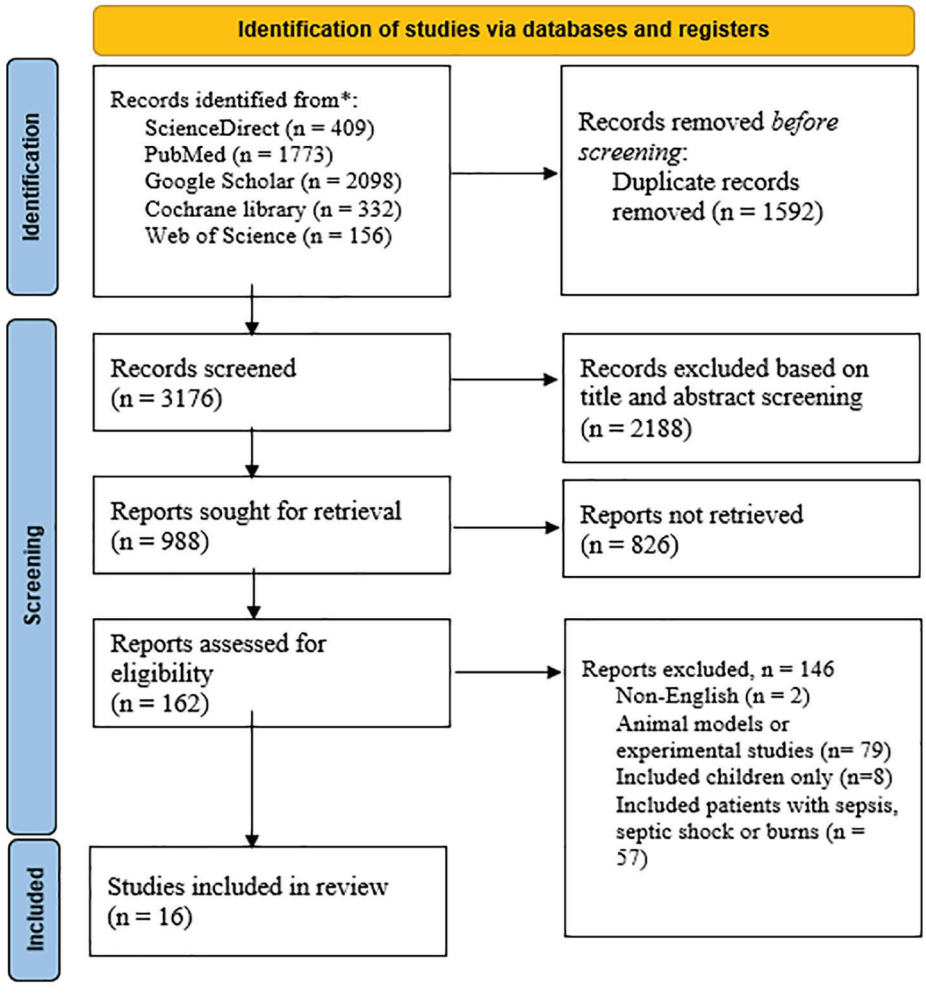

Fig. 2. PRISMA flow diagram for study selection.

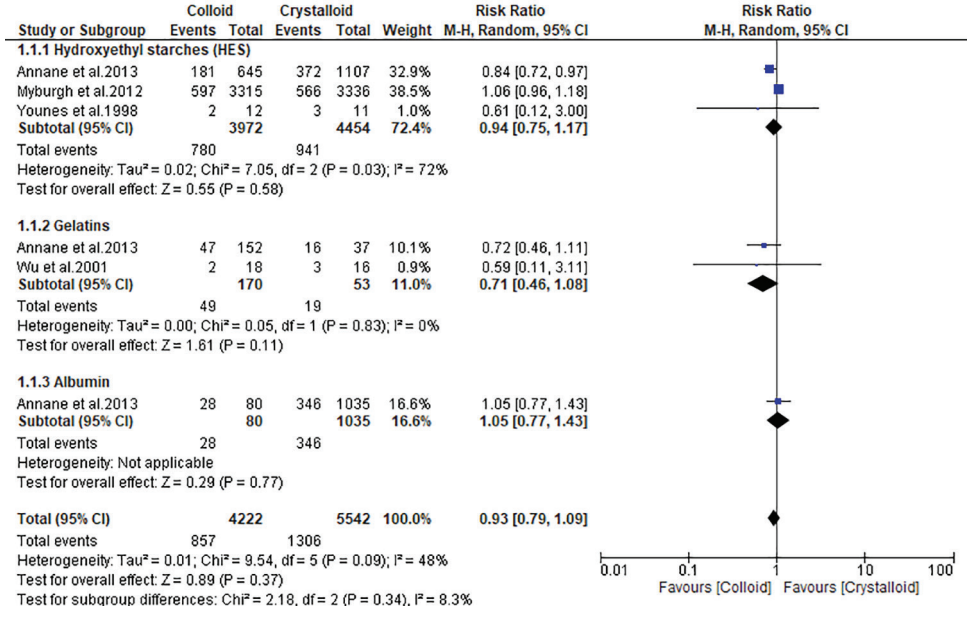

Fig. 3. A forest plot comparing mortality rate when using colloids versus crystalloids

Colloids in Hypertonic Crystalloids Versus Isotonic Crystalloids

Of the 15 trials, 8 compared the efficacy of fluid resuscitation with colloids in hypertonic crystalloids (i.e., HSD) to isotonic crystalloids (i.e., normal saline solution and lactated Ringer's solution). A subgroup analysis of HSD compared to normal saline showed no significant difference in mortality between the two groups (RR: 0.84; 95% CI: 0.62–1.13; P=0.24) (Figure 4). Similarly, HSD had an insignificant effect on mortality compared to lactated Ringer's solution (RR: 1.03; 95% CI: 0.75–1.42; P=0.87) (Figure 4).

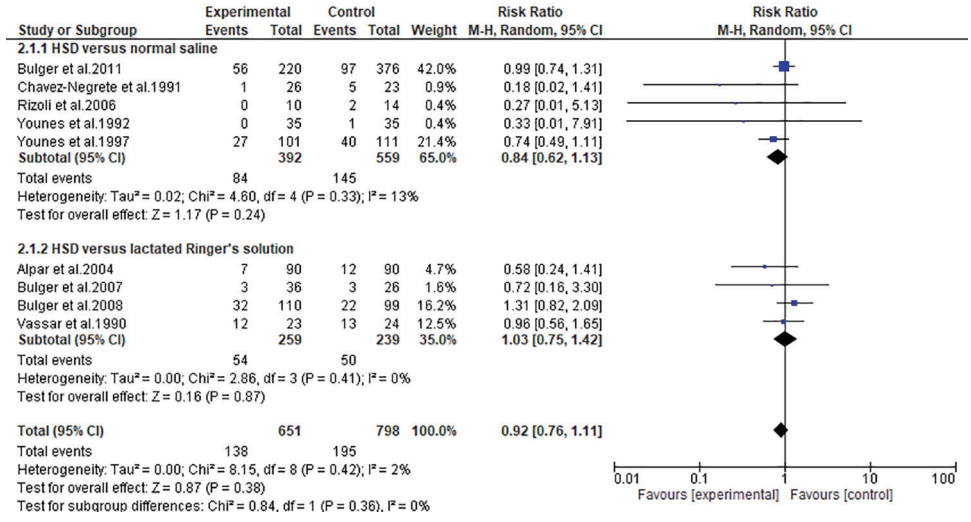

Fig. 4. A forest plot comparing mortality rate when using HSD versus isotonic crystalloids.

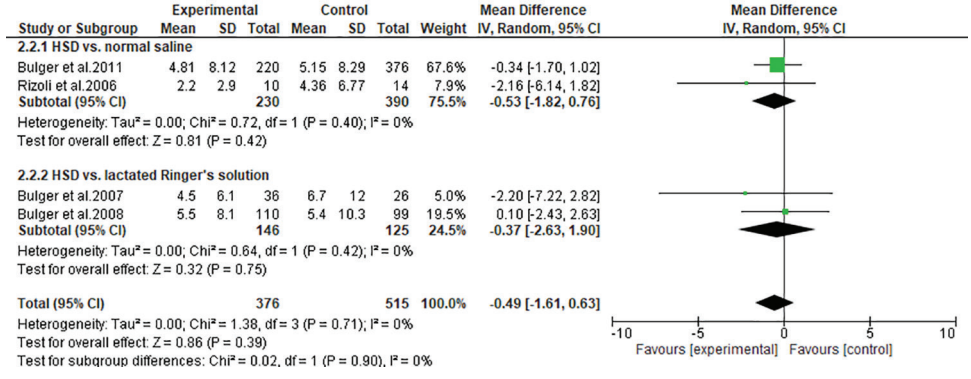

Fig. 5. A forest plot comparing Amount of transfused blood products in the first 24 hours when using HSD versus isotonic crystalloids.

Table 2. Comparison of complication rates when using HSD versus isotonic crystalloids

Type of complication	Number of studies	RR (95% CI)	P value	Heterogeneity (I^2) %
Nosocomial infections				
Pneumonia	2	0.90 (0.62–1.31)	0.59	0
UTI	2	0.77 (0.30–1.94)	0.58	47
Bloodstream infection	2	1.13 (0.66–1.93)	0.67	0
Wound Infection	2	1.32 (0.69–2.52)	0.40	0
ARDS	1	0.94 (0.49–1.80)	0.85	-
Intra-abdominal abscess	1	8.11 (0.44–148.72)	0.16	-
Sinusitis	1	2.70 (0.11–65.59)	0.54	-
Line infection	1	2.70 (0.11–65.59)	0.54	-
Pseudomembranous colitis	1	2.70 (0.11–65.59)	0.54	-
Noninfectious complications				
Renal complications	2	0.61 (0.14–2.66)	0.51	0
Neurological complications	2	1.55 (0.59–4.11)	0.38	0
Cardiac complications	2	0.54 (0.20–1.43)	0.21	0
Deep vein thrombosis	1	0.13 (0.02–1.03)	0.05	-

In addition, our subgroup analyses have shown that the amount of blood products transfused within the first 24 hours did not differ for patients resuscitated with HSD compared to those resuscitated with normal saline (MD: - 0.53; 95% CI: -1.82–0.76; P=0.42) or lactated Ringer's solution (MD: -0.37; 95% CI: -2.63–1.90; P=0.75) (Figure 5). Similarly, we found no significant difference in the risk of nosocomial infections or noninfectious complications between the HSD and isotonic crystalloid groups. However, a subgroup analysis of data from one of the studies showed that isotonic crystalloid (LRS) was associated with an increased risk for deep vein thrombosis. The full list of complications is displayed in Table 2.

Hypertonic Crystalloids Versus Isotonic Crystalloids

Two studies compared fluid resuscitation with

hypertonic crystalloid or isotonic crystalloid. A subgroup analysis showed that although the mortality rate was lower in the 7.5% and 3% hypertonic saline groups compared to normal saline groups, the difference was statistically insignificant (22% vs. 24%; P=0.86 and 9.7% vs. 15%; P=0.60, respectively) (Figure 6). Moreover, our analysis demonstrated no significant difference in the amount of transfused blood products within the first 24 hours between the 7.5% or 3% hypertonic saline groups and the normal saline group (MD: -0.21; 95% CI: -0.47–0.04; P=0.10 and MD: -0.10; 95% CI: -0.39–0.19; P=0.50, respectively) (Figure 7).

In addition, the two trials reported varying complications; thus, we could not perform a meta-analysis. Bulger and colleagues investigated incidences of nosocomial infections and found no significant differences between the 7.5% hypertonic and normal saline groups. In contrast, Han and colleagues found that the incidences of coagulopathy, acute renal failure, and pulmonary edema were significantly higher in the LRS group compared to the 7.5% and 3% hypertonic saline groups.

Colloids Versus Other Colloids

In our study, only two trials compared the resuscitation effects of modified fluid gelatin (MFG) to HES. Data pooled from these trials showed no significant difference in mortality incidence among patients resuscitated with MFG or HES (RR: 1.02; 95% CI: 0.52–2.02; P=0.95) (Figure 8).

Discussion

To our knowledge, this is the first systematic review and meta-analysis that has compared various fluid resuscitation strategies in critically ill adult patients with hypovolemic shock. Our meta-analyses have shown that colloids, whether individually or in hypertonic crystalloids, have no mortality benefit compared to crystalloids. Similarly, we found that HES has no mortality benefit compared to MFG. In addition, hypertonic saline solution does not offer any survival benefit compared to isotonic saline.

The debate on colloids versus crystalloids in the resuscitation of critically ill patients has existed for decades. Our study compared various colloids (i.e., HES, albumin, and gelatins) to crystalloids and found that colloids have no mortality benefit over crystalloids in patients with hypovolemic shock. This finding is supported by a previous systematic review that analyzed outcomes in all critically ill

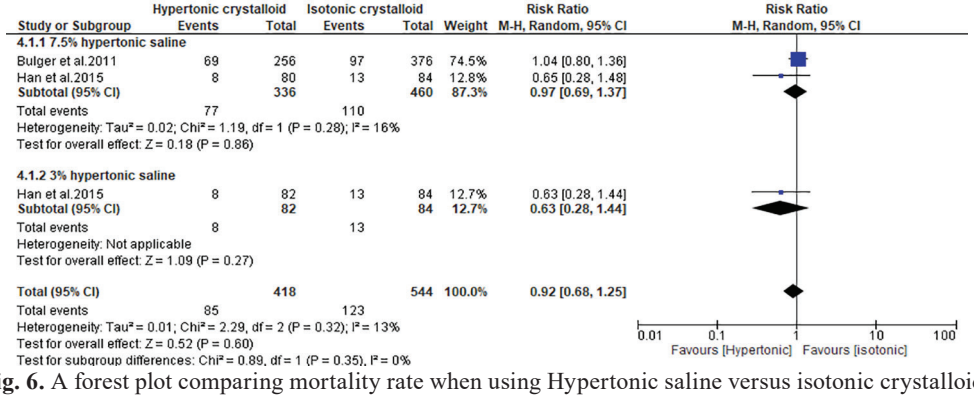

Fig. 6. A forest plot comparing mortality rate when using Hypertonic saline versus isotonic crystalloids

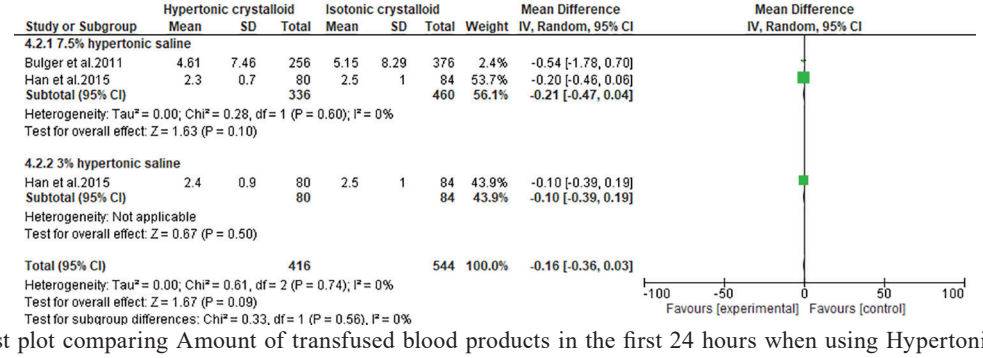

Fig. 7. A forest plot comparing Amount of transfused blood products in the first 24 hours when using Hypertonic saline versus isotonic crystalloids

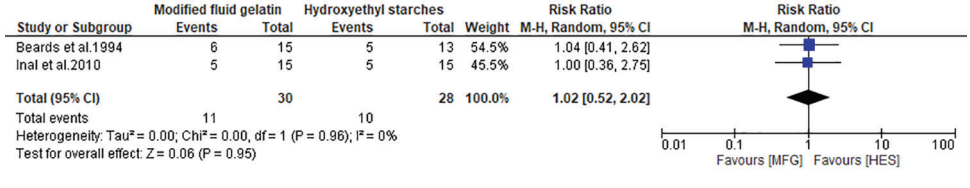

Fig. 8. A forest plot comparing mortality rate when using modified fluid gelatin versus hydroxyethyl starches.

patients, including those in hypovolemic shock [8]. According to that review, HES, albumin, gelatins, and dextrans showed little or no mortality benefit compared with crystalloids. Similarly, experimental and animal studies have recorded no mortality benefit when using colloids. This was evident in a study by Bahrami and colleagues, where the survival rate of hemorrhagic shock in rats did not differ after treatment with either HES or normal saline [26].

Despite the insignificant difference in mortality, our subgroup analysis has shown a high heterogeneity in HES outcomes. After a sensitivity analysis, we found that the CRISTAL study [11] was the primary source of heterogeneity. According to that study, patients receiving HES had significantly lower mortality rates at 90 days than those receiving crystalloids. This finding was unexpected; however, it was unclear why it was observed. Therefore, more randomized trials focused on the mortality benefit of HES in critically ill patients with hypovolemic shock are required to support the findings of this trial. Moreover, due to various limitations, this trial cannot be solely used to guide the clinical care of critically ill patients with hypovolemic shock. First, the study used open-labeled fluids, meaning it lacked the rigor of blinded studies and may have influenced their outcomes. Secondly, the total amount of fluids administered during the ICU stay was not specified. Finally, the physicians were not blinded to the allocation of fluid therapy, meaning that this knowledge may have influenced their outcomes.

Evidence also suggests that colloid solutions are associated with more adverse events than crystalloid solutions. Myburgh and colleagues found that the risk for pruritus and skin rash was elevated when resuscitating patients with HES as opposed to isotonic saline (P=0.006). Moreover, the research indicated that HES corresponded to an elevated risk for AKI, leading to the requirement of renal replacement treatment. Similarly, in studies including patients with severe sepsis and septic shock, HES increases the risk for AKI [27, 28]. However, the CRISTAL study found that colloids did not increase the risk for renal replacement therapy [11]. The discrepancy in this trial was attributed to three reasons. First, the overall amount of starches utilized in this study was within the recommended level by regulatory bodies, and individuals with severe chronic renal failure were excluded. Secondly, colloids in this study were related with a considerable decrease in cardiovascular and respiratory defects, as demonstrated by a decline in the requirement of vasopressor treatment and mechanical ventilators, indicating renal protection could have been obtained. Finally, majority of those enrolled in the crystalloid group had received normal saline, a chloride-rich solution linked with a higher risk for kidney damage compared to chloride-restricted fluids [29].

Although our meta-analysis did not find any mortality benefit of fluid resuscitation with colloids, evidence suggests that colloids have several advantages over crystalloids. First, fluid resuscitation with colloids achieves hemodynamic goals faster than resuscitation with crystalloids. This is evident in a study by Wu and colleagues, who compared hemodynamic responses of MFG to LRS in hypovolemic shock patients and found that mean arterial pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP) significantly increased after 30 and 60 minutes of fluid resuscitation with MFG [22]. However, no significant improvements were observed in the LRS group. Similarly, Younes and colleagues found that SBP significantly increased after 60 minutes of fluid resuscitation with 10% pentastarch compared with isotonic saline [25]. This rapid achievement of hemodynamic goals after fluid resuscitation with colloids means that patients spend less time in a shock state; thus, less organ failure is likely to be observed. Secondly, the volume of intravenous fluids required to achieve similar hemodynamic goals is lower when using colloids. Younes and colleagues found that although the MAP increased at a similar rate, the intravenous volume required to achieve hemodynamic recovery was significantly lower for patients receiving pentastarch than isotonic saline (P<0.001) [25]. Thirdly, colloids are superior to crystalloids in raising circulatory volume since they contain larger molecule sizes that are readily maintained inside the intravascular region and enhance osmotic pressure. Despite these advantages, it should be noted that excessive use of colloids can precipitate cardiac failure and pulmonary and peripheral edema [30]. In addition, fluid resuscitation with colloids might result in anaphylactic shock, leading to a minor increase in the mortality rate [31].

Although earlier trials were focused on the efficacy of colloids compared to crystalloids, more recently, trials have been conducted to study the resuscitation effects of colloids in hypertonic crystalloids. One of the most commonly used hypertonic crystalloid-colloid solutions is hypertonic 7.5% saline plus dextran (HSD). Our meta-analysis did not demonstrate any significant improvement in mortality or the amount of blood products transfused when resuscitating patients with HSD as opposed to isotonic solutions. However, we noticed that the mortality rate in HSD seems to be lower as opposed to isotonic crystalloid (21.2% vs.24.4%), suggesting that HSD might have a significant improvement in mortality in the future with more randomized trials. Contrary to our finding, a previous systematic review comparing HSD to isotonic crystalloids among patients with hypovolemic shock found that HSD was associated with a significant reduction in overall mortality (P=0.01) [32]. The discrepancy between our findings and this systematic review can be attributed to our analysis having more randomized trials, which mostly did not show the mortality benefit of HSD over isotonic crystalloids.

Additionally, our subgroup analysis has shown that HSD is as safe as isotonic crystalloids, as demonstrated by the overall rates of nosocomial and noninfectious complications. However, analysis of data from one of the trials showed that HSD was associated with significantly lower incidences of deep vein thrombosis (DVT). This reduced incidence of DVT with the administration of HSD can be attributed to the antithrombotic effect of dextran due to reduced platelet activity, change in fibrin structure, facilitated lysis of fibrin, and improvement in blood flow [33]. Although we have determined HSD to be safe as an isotonic crystalloid, it is important to note that HSD might have some negative direct effects. First, previous experimental studies have claimed HSD infusion raised Plasma Na^+ concentrations beyond 160 mEq/L [34, 35]. Since this excess concentration is likely to cause acute neurological damage or permanent neurological deficit, there is continued clinical concern about the use of HSD with this risk. Secondly, concern has been raised about the interference of HSD with coagulation when coagulation is most needed. This is evident in previous experimental studies where high doses of high molecular weight dextrans have been shown to interfere with blood coagulation [36, 37]. Finally, like isotonic crystalloids, large doses of HSD are likely to have serious side effects. A study by O'Benar et al. [38] reported that more than 2 doses of 4ml/kg HSD did not improve hemodynamics in situations where an 8% reduction in hematocrit was observed. On the other hand, in a pressure-driven hemorrhage model, Prist and colleagues found that more than two doses of HSD had no hemodynamic advantage and resulted in a reduction in hematocrit to 12.6% [39]. These findings suggest that more than 2 doses of HSD within a short period is not beneficial and can cause harm.

Although we did not perform a meta-analysis on hemodynamic responses, the included studies show that HSD has better hemodynamic effects than isotonic crystalloids. Alpar and colleagues found that HSD administered at a maximum dose of 250 ml was an excellent fluid for resuscitating patients with hypovolemic shock as opposed to Hartmann's solution [10]. According to that study, patients resuscitated with HSD recovered blood pressure (BP) earlier than those resuscitated with Hartmann's solutions, and the BP was well maintained throughout the first 24 hours. Additionally, HSD helped to recover urine output more rapidly than Hartmann's solution. Similarly, Younes (1997) reported a significant increase in MAP within 15 minutes after the infusion of HSD compared to isotonic saline [24]. Moreover, this improvement in hemodynamic variables after infusion of HSD has also been reported in animal and experimental studies [40, 41]. Therefore, it is prudent to say that HSD offers better hemodynamic effects than isotonic crystalloids. However, the evidence is still limited and further research is required to support this conclusion.

Previous animal models and clinical studies have shown that hypertonic crystalloids are also effective in resuscitation from hypovolemic shock [42, 43]. Therefore, it is important to investigate their effects in humans. Our meta-analysis has shown that even though the mortality rate was lower in hypertonic crystalloid groups (20% vs. 23%), the difference compared to isotonic crystalloids was statistically insignificant (P=0.60). This finding is supported by a previous systematic review, which found no significant difference among hypovolemic shock patients resuscitated with hypertonic saline or isotonic saline (OR: 0.90; 95% CI: 0.66–1.23; P=0.51) [32]. Moreover, we found no significant difference in the amount of blood products transfused within the first 24 hours, suggesting that hypertonic crystalloids are as effective as isotonic crystalloids in resuscitating hypovolemic shock patients.

While we could not perform any meta-analysis on complications due to heterogeneity in the reported complications, it is important to review the safety of hypertonic crystalloids compared to isotonic crystalloids. Han and colleagues found that LRS was associated with significantly higher incidences of coagulopathy, acute renal failure, and pulmonary edema than 7.5% and 3% hypertonic saline solution [17]. However, the incidence of transient hypotension and sinus tachycardia was significantly higher in the 7.5% hypertonic saline group compared to LRS and 3% hypertonic saline groups. This increased risk for tachycardia may be attributed to the fact that the hypertonic saline solution induced excessive stimulation of cardiac sympathetic nerve activity and reduced vagal excitability. Although these complications were transient and resolved by slowing infusion rate, they can be detrimental in patients in critical conditions. On the other hand, Bulger and colleagues did not find any significant difference in the incidence of nosocomial infections among patients receiving 7.5% hypertonic saline solution or normal saline [15]. Moreover, it is worth noting that isotonic saline solution may have advantages, such as reducing incidences of contrast-induced nephropathy in settings other than resuscitation [44].

In our study, we also compared the resuscitative effects of MFG to HES among patients with hypovolemic shock. Our meta-analysis has shown an insignificant difference in mortality among patients resuscitated with MFG and HES. Therefore, MFG as a fluid for resuscitation in hypovolemic shock patients may be as effective as HES. However, more randomized trials are required to establish this hypothesis fully.

Evidence also suggests that MFG has similar hemodynamic effects as HES. Beard et al. [12] reported that pulmonary artery occlusion pressure (PAOP), stroke volume, and cardiac index significantly increased 15 and 30 minutes after the infusion

of HES and MFG. Similarly, Inal and colleagues showed that SBP, DBP, MAP, and intrathoracic blood volume index increased significantly 30 minutes after polygeline and HES infusion [18]. Despite showing that polygeline (i.e., an MFG) is an effective colloid for intravascular volume expansion, it is subject to more serious allergic reactions compared to HES [45]. Hence, its use should be constantly monitored as a fluid resuscitation agent.

The present systematic review and meta-analysis has some limitations that should be considered while interpreting our findings. First, our eligibility criteria allowed the inclusion of articles with varying types of hypovolemic shock; however, we could not find trials evaluating resuscitation fluids in non-hemorrhagic shock; therefore, we only included studies on hemorrhagic hypovolemic shock. Secondly, we included studies published in English only, meaning that all the relevant data that would have been used to improve the statistical power of our meta-analysis but published in other languages was eliminated. Thirdly, due to a lack of enough data on secondary outcomes such as complications and the amount of blood products transfused, we could not carry out meta-analyses in most cases, and we had to resort to a qualitative review of data. Therefore, it was difficult to generalize these findings. Fourth, a significant heterogeneity persistent in some of the subgroup analyses. This heterogeneity was probably due to variations in sample sizes, patient characteristics and different dosages for the resuscitation fluids. Nonetheless, all our results were pooled using the random-effects model, meaning that the overall effect sizes were conservative. Fifth, due to heterogeneity in the characteristics of resuscitation fluids such as individual composition, dosage, and mode of administration, we were unable to conduct subgroup analyses based on these characteristics. Finally, we could not find any recent trials published within the scope of our topic. Therefore, more randomized trials are needed to support the data from previous articles and findings of the present study.

Our study has shown that colloids offer no mortality benefit over crystalloids during fluid resuscitation of critically ill patients with hypovolemic shock. Furthermore, colloids, especially HES, seem to have more adverse events than crystalloids. Therefore, since colloids are considerably more expensive and offer no mortality benefit over crystalloids, it is hard to see how their continued use in clinical practice is justifiable. As such, we would recommend clinicians continue using crystalloids in resuscitating hypovolemic shock patients. However, this recommendation is bound to change if future trials carefully justify the potential mortality benefit of colloids of over crystalloids.

Additionally, we have found that Colloids in hypertonic crystalloids (i.e., HSD) and hypertonic crystalloids have no mortality benefit compared to isotonic crystalloids; however, we believe that more randomized trials might result in significant differences. Moreover, our meta-analysis has shown that MFG is as effective as HES in the fluid resuscitation of hypovolemic shocked patients. However, evidence suggests polygeline may have more serious allergic reactions than HES. Interestingly, there is evidence suggesting that colloids help patients in hypovolemic shock patients to achieve hemodynamic goals faster than resuscitation with crystalloids. This rapid achievement of hemodynamic goals after fluid resuscitation with colloids means that patients spend less time in a shock state; thus, less organ failure is likely to be observed. However, this finding is shown in few studies. Thus, further research in large-scale randomized trials is required to support this finding. Furthermore, qualitative data review has shown that HSD has better hemodynamic effects than isotonic crystalloids. However, further research is also required to support this finding.

Declaration

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Consent for Publication: As corresponding author and on behalf of all authors I provide the journal full publication rights to this journal.

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