Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

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IMPORTANCE Evidence supporting the choice of intravenous colloid vs crystalloid solutions for management of hypovolemic shock remains unclear.

OBJECTIVE To test whether use of colloids compared with crystalloids for fluid resuscitation alters mortality in patients admitted to the intensive care unit (ICU) with hypovolemic shock.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, randomized clinical trial stratified by case mix (sepsis, trauma, or hypovolemic shock without sepsis or trauma). Therapy in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial was open label but outcome assessment was blinded to treatment assignment. Recruitment began in February 2003 and ended in August 2012 of 2857 sequential ICU patients treated at 57 ICUs in France, Belgium, North Africa, and Canada; follow-up ended in November 2012.

INTERVENTIONS Colloids (n = 1414; gelatins, dextrans, hydroxyethyl starches, or 4% or 20% of albumin) or crystalloids (n = 1443; isotonic or hypertonic saline or Ringer lactate solution) for all fluid interventions other than fluid maintenance throughout the ICU stay.

MAIN OUTCOMES AND MEASURES The primary outcome was death within 28 days. Secondary outcomes included 90-day mortality; and days alive and not receiving renal replacement therapy, mechanical ventilation, or vasopressor therapy.

RESULTS Within 28 days, there were 359 deaths (25.4%) in colloids group vs 390 deaths (27.0%) in crystalloids group (relative risk [RR], 0.96 [95% CI, 0.88 to 1.04]; $P = .26$). Within 90 days, there were 434 deaths (30.7%) in colloids group vs 493 deaths (34.2%) in crystalloids group (RR, 0.92 [95% CI, 0.86 to 0.99]; $P = .03$). Renal replacement therapy was used in 156 (11.0%) in colloids group vs 181 (12.5%) in crystalloids group (RR, 0.93 [95% CI, 0.83 to 1.03]; $P = .19$). There were more days alive without mechanical ventilation in the colloids group vs the crystalloids group by 7 days (mean: 2.1 vs 1.8 days, respectively; mean difference, 0.30 [95% CI, 0.09 to 0.48] days; $P = .01$) and by 28 days (mean: 14.6 vs 13.5 days; mean difference, 1.10 [95% CI, 0.14 to 2.06] days; $P = .01$) and alive without vasopressor therapy by 7 days (mean: 5.0 vs 4.7 days; mean difference, 0.30 [95% CI, −0.03 to 0.50] days; $P = .04$) and by 28 days (mean: 16.2 vs 15.2 days; mean difference, 1.04 [95% CI, −0.04 to 2.10] days; $P = .03$).

CONCLUSIONS AND RELEVANCE Among ICU patients with hypovolemia, the use of colloids vs crystalloids did not result in a significant difference in 28-day mortality. Although 90-day mortality was lower among patients receiving colloids, this finding should be considered exploratory and requires further study before reaching conclusions about efficacy.

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Thousands of patients in intensive care units (ICUs) throughout the world are treated with fluid therapy to restore effective blood volume and ensure optimal organ perfusion.[1,2] Fluid therapy includes a broad variety of products that are typically categorized as crystalloids and colloids. Although the goal is to use intravenous fluids to expand the intravascular space, fluid also moves into the extravascular space. Crystalloids are thought to counteract that movement via the osmotic pressure exerted by their solutes, whereas colloids are designed to exploit oncotic pressure gradients for the same effect.[2] Thus, theoretically, expansion of blood volume may be proportional to solute tonicity or oncotic power.

The crystalloid family includes isotonic and hypertonic solutions that are also categorized into nonbuffered (eg, isotonic saline) and buffered solutions (eg, Ringer lactate, acetate, maleate). The colloid family includes hypooncotic (eg, gelatins, 4% or 5% of albumin) and hyperoncotic (eg, dextrans, hydroxyethyl starches, and 20% or 25% of albumin) solutions. Generally, colloid solutions are thought to be more efficient than crystalloids in terms of the amount of fluid that remains in the intravascular space,[2] and so less fluid is required when using colloids vs crystalloids to achieve similar hemodynamic goals.[3,4] However, there are other effects of these fluids, including alterations to the immune response to critical illness.[1,2] Additionally, there is concern that hydroxyethyl starches may increase the risk of death or acute kidney injury.[5,6] Most colloid solutions are also more expensive than crystalloids.

In recent studies of general ICU patient populations, fluid replacement with 5% of albumin[7] or with 6% of hydroxyethyl starch[4] showed similar effects on mortality compared with isotonic saline. Although there was a suggestion that the subset of patients with severe sepsis might benefit from resuscitation with albumin,[8] the current Surviving Sepsis Campaign guidelines recommended crystalloids as the preferred fluid therapy and against the use of hydroxyethyl starches.[9]

The Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial was designed to test whether colloids altered mortality compared with crystalloids for fluid resuscitation in critically ill patients.

Methods

Study Design

CRISTAL was a pragmatic, international, randomized trial performed in 2 parallel groups. The study protocol was approved by the Committee for the Protection of People of Saint-Germain-en-Laye for French sites and at institutional review boards elsewhere. Waiver of consent was provided from all ethics committees and deferred informed consent was obtained from participants or legally authorized surrogates. The trial investigator committees are listed in the Supplement. The first patients were recruited for the study in February 2003 and the last patients in August 2012. The end of follow-up occurred in November 2012.

Study Participants

Eligible patients were adults admitted to any of 57 participating ICUs in France, Belgium, Canada, Algeria, and Tunisia (additional information appears in the Supplement), accounting for more than 5000 potentially eligible patients. To be eligible, research participants had to have received no prior fluids for resuscitation during their ICU stay and now require fluid resuscitation for acute hypovolemia as defined by the combination of (1) hypotension: systolic arterial pressure of less than 90 mm Hg, mean arterial pressure of less than 60 mm Hg, orthostatic hypotension (ie, a decrease in systolic arterial pressure of at least 20 mm Hg from the supine to the semirecumbent position), or a delta pulse pressure of 13% or higher; (2) evidence for low filling pressures and low cardiac index as assessed either invasively or noninvasively; and (3) signs of tissue hypoperfusion or hypoxia, including at least 2 of the following clinical symptoms: a Glasgow Coma Scale score of less than 12, mottled skin, urinary output of less than 25 mL/h, or capillary refilling time of 3 seconds or longer; and arterial lactate levels higher than 2 mmol/L, blood urea nitrogen higher than 56 mg/dL, or a fractional excretion of sodium of less than 1%. The reasons for exclusion are listed in **Figure 1** and eTable 1 in Supplement.

Randomization

A computer-generated list with fixed-block permutation (n = 4) was used to randomize patients on a 1 to 1 ratio. Randomization was stratified by center and by 3 admission diagnoses: sepsis,[10] multiple trauma, or other causes of hypovolemic shock. Allocation concealment used sealed envelopes at the bedside to allow randomization of eligible patients without any delay and was done blinded to block size.

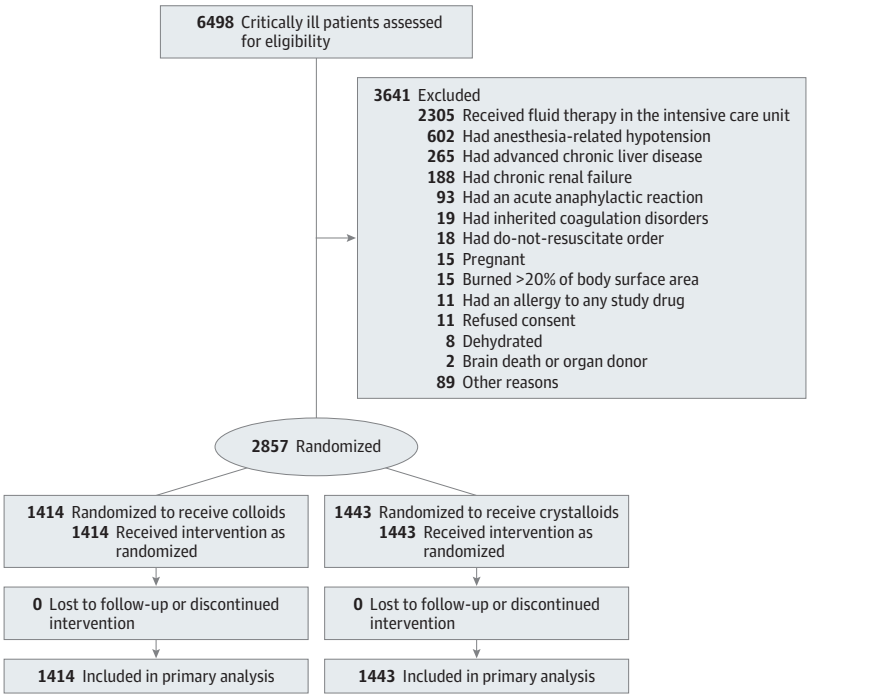
Study Treatments

Eligible patients were randomly allocated to fluid resuscitation with crystalloids (control group) or with colloids (experimental group). In the crystalloids group, allowed treatments included isotonic or hypertonic saline and any buffered solutions. In the colloids group, hypooncotic (eg, gelatins, 4% or 5% of albumin) and hyperoncotic (eg, dextrans, hydroxyethyl starches, and 20% or 25% of albumin) solutions were permitted.

Within each treatment group, investigators could use whichever fluids were available at their institution. The amount of fluid and duration of treatment was left at the discretion of the investigators with the following restrictions: (1) the daily total dose of hydroxyethyl starch could not exceed 30 mL/kg of body weight and (2) investigators were required to follow any local regulatory agency recommendations governing use. Adherence to these recommendations was strictly controlled by local pharmacists and regularly checked during random quality audits.

Patients were managed exclusively with the category of fluid to which they were randomized from the time of randomization until discharge from the ICU except for (1) maintenance fluids, which were isotonic crystalloids, regardless of treatment group, and (2) in instances in which physicians wished to administer albumin in response to demonstrated hypoalbuminemia (serum albumin level <20 g/dL).

Figure 1. Patient Enrollment in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) Trial



Blinding

The blinding of the clinicians to the fluid interventions was considered by the study advisors to be inappropriate or infeasible because study treatments had to be available immediately for resuscitation to ensure avoidance of nonstudy fluids in emergent situations. Also, because the intervention would be continued until ICU discharge, and could thus be highly variable, there was no practical way to stock sites with adequate supplies of masked fluid solutions. However, the mortality end points were collected and assessed by study members blinded to treatment assignment. Similarly, the principal investigator, study sponsor, and the members of the data and safety monitoring board remained blinded to the study interventions until all patients were followed up and the final analysis was executed.

Data Collection at Baseline and Follow-up

We systematically recorded demographic and anthropometric data, time of hospital and ICU admission, patient location prior to ICU admission, disability scale score[11] and comorbidity (as measured by McCabe class[12]), vital signs, Simplified Acute Physiology Score II,[13] Sequential Organ Failure Assessment (SOFA) score,[14] Injury Severity Score[15] for trauma patients, any intervention, standard laboratory tests, and a chest x-ray score.[16] Patients were followed up for 90 days.

Study Outcomes

The primary outcome was mortality at 28 days. Secondary outcomes included death rates at 90 days and at ICU and hospital discharge; number of days alive and not receiving renal replacement therapy, mechanical ventilation, or vasopressor therapy; days without organ system failure (ie, SOFA score <6); and days not in the ICU or hospital.

Assessment of Data Quality

As per the French regulation, all individual data were independently checked for accuracy by the Delegation à la Recherche Clinique d'Ile de France. Quality audits included control of the validity of informed consent, compliance to good clinical practices and to the protocol, validity of data recorded in the electronic case report form compared with the original medical charts of patients, and accuracy of reporting of serious adverse events.

Statistical Analysis

We anticipated a mortality rate of 20% at 28 days among patients with acute hypovolemia and treated with crystalloids.[17] Using 2-sided χ^2 tests, assuming a .05 type I error and a statistical power level of 90%, we calculated that 1505 patients per group (ie, a total of 3010 patients) were needed to detect an absolute difference of 5% in 28-day mortality with colloids.

Interim Analyses and Stopping Rules

For safety reasons, a triangular test was planned to sequentially check the difference in 28-day mortality between the 2 randomized groups.[18] The triangular test is a sequential analysis that enables repeated statistical analyses to be performed throughout a trial recruitment period while maintaining a prespecified power and type I error. Thus, the trial could be stopped as soon as the information accumulated was consid-

ered sufficient to reach a conclusion. Accordingly, the accumulated data were inspected at every 100 deaths in a blinded manner by the data and safety monitoring board.

The boundaries of the sequential plan were drawn to demonstrate an absolute difference of 5% in the 28-day mortality rate between the 2 treatment groups, assuming a 20% mortality rate in the crystalloids group with an α and β level of .05 and .10, respectively. At each inspection, 2 statistics were computed, namely, *Z* and *V* (eFigure 1 in Supplement). Briefly, *Z* represents the difference in the main outcome measures between the 2 randomized groups and *V* is related to the number of patients that have been included. When a boundary is crossed, enrollment in the study may be stopped, but the conclusion depends on which boundary has been crossed.

Final Analysis

The final analysis was performed according to the intention-to-treat principle after the enrollment period ended for the study. Categorical variables are expressed as number and percentage and medians and interquartile range (IQR) are given for continuous variables unless otherwise specified. Survival curves have been constructed according to the Kaplan-Meier method. For mortality end points, the analysis was performed using the Mantel-Haenszel test stratified by admission diagnosis (ie, sepsis, trauma, or other causes of hypovolemic shock) and using a Breslow-Day test for the homogeneity of the odds ratios.

Relative risks (RRs) with 95% confidence intervals (derived by combining strata-specific estimates) were used as the summary measures of treatment effect. For secondary end points, categorical variables were similarly compared. Number of days alive and not receiving mechanical ventilation, vasopressor therapy, and renal replacement therapy and without organ system failure were computed within both 7 days and 28 days from ICU admission, and the numbers of days alive and not in the ICU or hospital were computed for the 28 days following ICU admission and compared between randomized groups using the nonparametric Wilcoxon rank sum test.

Comparisons across randomized groups were then adjusted for prognostic factors (baseline SOFA, McCabe, and Knaus scores) and admission diagnosis using logistic or generalized linear regression models whenever appropriate, whereas center effect was tested using mixed-effects models. There were some missing data for these prognostic factors (range from 0 to 3.1% across variables) so that only a simple imputation method could be used (recoding those values by the sample mode).

To further examine potential interactions of treatment effect on the hazard ratio of death with the diagnosis stratum or the center, separately, forest plots and the Gail and Simon test were used. In addition, exploratory subset analyses of treatment effect on the overall survival within the first 28 or 90 days according to the administered fluid received on the randomization day were performed; only patients who were administered 1 type of fluid were examined.

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc). All statistical tests were 2-sided. A *P* value of .05 was considered statistically significant.

Results

Patients

The lower boundary of the triangular test was crossed at the sixth interim analysis (performed on July 2012) after the observation of 706 deaths in 2612 consecutive patients enrolled up to March 16, 2012 (date of inclusion of the 706th nonsurvivor) (eFigure 1 in Supplement). Because there was no statistical difference in 28-day mortality between the 2 groups, recruitment into the trial was stopped in August 2012 before the fixed sample size of 3010 patients was reached. Between March and August 2012, we recruited an additional 245 patients.

A total of 2857 patients (1414 in the colloids group and 1443 in the crystalloids group) were enrolled in the study (Figure 1). Baseline characteristics were comparable between the 2 groups (**Table 1** and eTable 2 in Supplement). Severe sepsis was the main diagnosis at admission in both groups. Prior to ICU admission, crystalloids were given to 526 patients in the colloids group for a median volume of 1000 mL (IQR, 500-1000 mL) and to 402 patients in the crystalloids group for a median volume of 650 mL (IQR, 500-1000 mL). Colloids were given to 585 patients in the colloids group for a median volume of 1000 mL (IQR, 500-2000 mL) and to 685 patients in the crystalloids group for a median volume of 1000 mL (IQR, 500-2000 mL). The median time from ICU admission to randomization was 0 days (IQR, 0-1 days) in both groups.

Fluid Therapy and Treatment Effects

The median cumulated volume of fluid (except for maintenance therapy) administered for the first 7 days in the ICU was 2000 mL (IQR, 1000-3502 mL) in the colloids group vs 3000 mL (IQR, 500-5200 mL) in the crystalloids group (*P* < .001). The median duration of treatment was 2 days (IQR, 1-3 days) in both the colloids and crystalloids groups (*P* = .93). The total dose and duration of each type of fluids given for both groups appear in eTable 3 in Supplement. A total of 237 patients in the crystalloids group also received albumin supplementation (eTable 3 in Supplement). In the colloids group, protocol violations included administration of normal saline in 252 patients (17.8%), Ringer lactate solution in 88 (6.2%), and hypertonic saline in 19 (1.3%). In the crystalloids group, gelatins were wrongly administered in 24 patients (1.7%) and hydroxyethyl starches in 69 (4.8%).

During the first 24 hours following randomization, mean blood pressure, urinary output, weight, and chest x-ray scores were not significantly different between the 2 groups (eTable 4 in Supplement). There were 377 patients (26.7%) in the colloids group who received blood products at least once during the first 7 days vs 358 (24.8%) in the crystalloids group (*P* = .25). There was no evidence of any difference between groups for the total amount of blood products transfused (mean [SD], 223.5 [495] mL in the colloids group vs 217.4 [517] mL in the crystalloids group; *P* = .75).

Outcomes

At 28 days, there were 359 deaths (25.4%) in the colloids group vs 390 deaths (27.0%) in the crystalloids group (RR, 0.96 [95%

CI, 0.88-1.04]; P = .26) (**Figure 2** and **Table 2**). At 90 days, there were 434 deaths (30.7%) in the colloids group vs 493 deaths (34.2%) in the crystalloids group (RR, 0.92 [95% CI, 0.86-0.99]; P = .03) (eFigure 2A in Supplement). There was no evidence against any proportionality of treatment effect over time (P = .54). There was no significant heterogeneity in the effect of treatment on mortality in any of the predefined strata at 28 days (P = .70; **Figure 3**) or at 90 days (P = .84; eFigure 2B in

Table 1. Baseline Characteristics

	Colloids Group (n = 1414)	Crystalloids Group (n = 1443)
Age, median (IQR), y	63 (50-76)	63 (50-75)
Male sex, No. (%)	880 (62.2)	902 (62.5)
Weight, median (IQR), kg	70 (60-81)	70 (61-81)
Height, median (IQR), cm	170 (161-175)	169 (162-175)
Source of admission to ICU, No. (%)		
Community	674 (48.2)	745 (52.0)
Hospital ward	617 (44.1)	575 (40.1)
Other ICU	57 (4.1)	65 (4.5)
Long-term care facility	50 (3.6)	48 (3.3)
Type of ICU admission, No. (%)	(n = 1399)	(n = 1432)
Medical	991 (70.8)	1040 (72.6)
Emergency surgery	276 (19.7)	267 (18.6)
Scheduled surgery	109 (7.8)	89 (6.2)
Trauma	23 (1.6)	36 (2.5)
McCabe class, No. (%)		
No underlying disease or no fatal disease	903 (63.9)	913 (63.3)
Underlying ultimately fatal disease (>5 y)	429 (30.3)	469 (32.5)
Underlying rapidly fatal disease (<1 y)	82 (5.8)	61 (4.2)
Knaus disability scale, No. (%)		
Prior good health, no functional limitations	342 (24.5)	375 (26.3)
Mild to moderate limitation of activity because of chronic medical problem	439 (31.5)	446 (31.3)
Chronic disease producing serious but not incapacitating restriction of activity	323 (23.2)	325 (22.8)
Severe restriction of activity due to disease, includes persons bedridden or institutionalized due to illness	289 (20.8)	278 (19.5)
Physiology score, median (IQR)		
SAPS II[a]	48 (35-64)	50 (36-65)
SOFA[b]	8 (5-11)	8 (5-11)
Injury Severity[c]	(n = 79) 21 (14-27)	(n = 88) 22 (14-34)
Glasgow Coma Scale score, median (IQR)	(n = 1326) 11 (3-15)	(n = 1353) 11 (3-15)
Systolic blood pressure, median (IQR), mm Hg	(n = 1337) 92 (80-112)	(n = 1372) 94 (80-113)
Heart rate, median (IQR), beats/min	(n = 1335) 105 (86-123)	(n = 1366) 105 (88-21)
Urinary output, median (IQR), mL/h	(n = 1245) 40 (20-70)	(n = 1259) 40 (20-60)
Lactate levels, median (IQR), mmol/L	(n = 1151) 2.3 (1.3-3.8)	(n = 1176) 2.4 (1.4-4.5)
Fluid administration prior ICU admission (within the past 12 h)		
Crystalloids, No. (%)	526 (37.2)	402 (27.9)
Dose, median (IQR), mL	1000 (500-1000)	650 (500-1000)
Colloids, No. (%)	585 (41.4)	685 (47.5)
Dose, median (IQR), mL	1000 (500-2000)	1000 (500-2000)
Mechanical ventilation, No. (%)	1007 (71.2)	1061 (73.5)
Renal replacement therapy, No. (%)	67 (4.7)	73 (5.1)
Predefined strata, No. (%)		
Sepsis	774 (54.7)	779 (54.0)
Trauma	85 (6.0)	92 (6.4)
Hypovolemic shock (without sepsis or trauma)	555 (39.3)	572 (39.6)

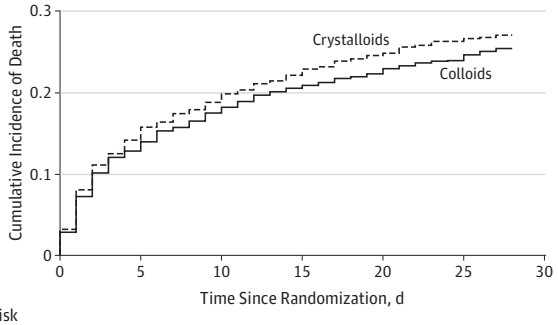
Abbreviations: ICU, intensive care unit; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

[a] Score range from 0 to 163 with higher scores indicating more severe organ dysfunction.

[b] Score range from 0 to 24 with higher scores indicating more severe organ dysfunction.

[c] Score range from 0 to 75 with higher scores indicating more severe injuries.

Figure 2. Cumulative Incidence of Death Within First 28 Days After Randomization



No. at risk

Colloids	1414	1233	1167	1124	1099	1076
Crystalloids	1443	1239	1172	1124	1089	1064

Supplement). There was significant heterogeneity in mortality rates across centers ($P < .001$; eFigure 3A in Supplement), but no evidence of any interaction with treatment effect (eFigure 3B in Supplement). In addition, estimated treatment effects were not markedly modified when considering fluid subsets (**Table 3** and **Table 4**).

There were 156 patients (11.0%; 9.5%-12.8%) in the colloids group who required renal replacement therapy vs 181 patients (12.5%; 10.9%-14.4%) in the crystalloids group (RR, 0.93 [95% CI, 0.83-1.03]; $P = .19$). In these patients, the number of days alive and not receiving renal replacement therapy was not significantly different between the 2 groups within the first 7 days (mean [SD], 4.8 [2.9] days in the colloids group vs 4.6 [2.9] days in the crystalloids group; $P = .99$) or within 28 days (mean [SD], 13.9 [11.3] days vs 13.1 [11.4] days, respectively; $P = .90$). There was also no difference in SOFA scores between the 2 groups over 28 days (eFigure 4 in

Table 2. Study Outcomes by Treatment Group

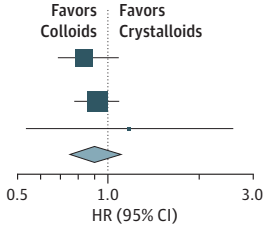
	No. (%) of Patients			
	Colloids (n = 1414)	Crystalloids (n = 1443)	RR (95% CI)	*P* Value[a]
Death				
Within 28 d	359 (25.4)	390 (27.0)	0.96 (0.88 to 1.04)	.26
Within 90 d	434 (30.7)	493 (34.2)	0.92 (0.86 to 0.99)	.03
In ICU	355 (25.1)	405 (28.1)	0.92 (0.85 to 1.00)	.06
In hospital	426 (30.1)	471 (32.6)	0.94 (0.87 to 1.02)	.07
No. of days alive and without the following treatment or condition	**Mean (SD)**		**Mean Difference (95% CI)**	
Mechanical ventilation within the first 7 d	2.1 (2.4)	1.8 (2.3)	0.30 (0.09 to 0.48)	.01
Mechanical ventilation within the first 28 d	14.6 (11.4)	13.5 (11.5)	1.10 (0.14 to 2.06)	.01
Renal replacement therapy within the first 7 d	4.8 (2.9)	4.6 (2.9)	0.2 (−0.4 to 0.8)	.99
Renal replacement therapy within the first 28 d	13.9 (11.3)	13.1 (11.4)	0.8 (−1.6 to 3.3)	.90
Organ failure (SOFA score <6) within the first 7 d	6.2 (1.8)	6.1 (1.8)	0.06 (−0.10 to 0.20)	.31
Organ failure (SOFA score <6) within the first 28 d	21.4 (10.3)	20.9 (10.6)	0.6 (−0.4 to 1.5)	.16
Vasopressor therapy within the first 7 d	5.0 (3.0)	4.7 (3.1)	0.30 (−0.03 to 0.50)	.04
Vasopressor therapy within the first 28 d	16.2 (11.5)	15.2 (11.7)	1.04 (−0.04 to 2.10)	.03
ICU stay within the first 28 d	8.3 (9.0)	8.1 (9.2)	0.2 (−0.5 to 0.9)	.69
Hospital stay within the first 28 d	11.9 (11.1)	11.6 (11.4)	0.3 (−0.5 to 1.1)	.37

Abbreviations: ICU, intensive care unit; RR, relative risk; SOFA, Sequential Organ Failure Assessment.

[a] For mortality end points, the analysis was performed using the Mantel-Haenszel test stratified based on admission diagnosis (ie, sepsis, trauma, or other causes of hypovolemic shock). The number of days alive and not receiving mechanical ventilation, vasopressor therapy, and renal replacement therapy and days alive without organ system failure were compared between randomized groups using the nonparametric Wilcoxon rank sum test.

Figure 3. Assessment of Treatment × Diagnosis Interaction and Death Within First 28 Days

	Colloids Group (n = 1414)		Crystalloids Group (n = 1443)		
Reason for ICU Admission	No. of Patients	No. of Deaths	No. of Patients	No. of Deaths	HR (95% CI)
Other causes of hypovolemic shock	555	131	572	152	0.87 (0.69-1.10)
Sepsis	774	215	779	226	0.95 (0.78-1.10)
Trauma	85	13	92	12	1.19 (0.54-2.60)
All patients	1414	359	1443	390	0.93 (0.80-1.10)



HR indicates hazard ratio; ICU, intensive care unit. $P = .70$ for interaction of homogeneity of HR across the 3 strata, which was calculated using the Gail and Simon statistic test.

Table 3. Mortality Outcomes in Patients Who Received Only 1 Type of Fluid

	Colloids Group, No.		Crystalloids Group, No.		
	Patients	Deaths	Patients	Deaths	HR (95% CI)
28-d Mortality					
Entire population	1414	359	1443	390	0.92 (0.80-1.07)
HES vs isotonic saline	645	149	1035	275	0.83 (0.68-1.01)
Gelatins vs isotonic saline	281	69	1035	275	0.90 (0.69-1.17)
HES vs Ringer solution	645	149	72	22	0.71 (0.45-1.11)
Gelatins vs Ringer solution	281	69	72	22	0.78 (0.48-1.26)
Albumin vs isotonic saline	80	24	1035	275	1.10 (0.72-1.68)
90-d Mortality					
Entire population	1414	434	1443	493	0.88 (0.77-0.99)
HES vs isotonic saline	645	181	1035	346	0.79 (0.66-0.95)
Gelatins vs isotonic saline	281	84	1035	346	0.87 (0.68-1.10)
HES vs Ringer solution	645	181	72	26	0.72 (0.48-1.09)
Gelatins vs Ringer solution	281	84	72	26	0.80 (0.51-1.24)
Albumin vs isotonic saline	80	28	1035	346	1.02 (0.69-1.50)

Abbreviations: HES, hydroxyethyl starches; HR, hazard ratio.

Table 4. Mortality Outcomes in Patients With Sepsis

	Colloids Group, No.		Crystalloids Group, No.		
	Patients	Deaths	Patients	Deaths	HR (95% CI)
28-d Mortality					
Entire population	774	215	779	226	0.95 (0.78-1.14)
HES vs isotonic saline	375	105	557	157	0.97 (0.76-1.25)
Gelatins vs isotonic saline	152	40	557	157	0.90 (0.63-1.27)
HES vs Ringer solution	375	105	37	12	0.84 (0.46-1.53)
Gelatins vs Ringer solution	152	40	37	12	0.77 (0.40-1.47)
Albumin vs isotonic saline	59	19	557	157	1.16 (0.72-1.87)
90-d Mortality					
Entire population	774	252	779	286	0.87 (0.73-1.03)
HES vs isotonic saline	375	120	557	197	0.89 (0.71-1.11)
Gelatins vs isotonic saline	152	47	557	197	0.84 (0.61-1.16)
HES vs Ringer solution	375	120	37	16	0.71 (0.42-1.20)
Gelatins vs Ringer solution	152	47	37	16	0.67 (0.38-1.18)
Albumin vs isotonic saline	59	22	557	197	1.07 (0.69-1.67)

Abbreviations: HES, hydroxyethyl starches; HR, hazard ratio.

Supplement) or in the number of days alive without organ failure within 7 days (mean [SD], 6.2 [1.8] days in the colloids group vs 6.1 [1.8] days in the crystalloids group; $P = .31$) or within 28 days (21.4 [10.3] days vs 20.9 [10.6], respectively; $P = .16$).

There was no evidence for a difference between groups for the number of ICU- and hospital-free days (Table 2). There were significantly more days alive without mechanical ventilation within 7 days in patients in the colloids group vs patients in the crystalloids group (mean [SD], 2.1 [2.4] days vs 1.8 [2.3] days; $P = .01$) and within 28 days (mean [SD], 14.6 [11.4] days vs 13.5 [11.5] days, respectively; $P = .01$). There also were more days without vasopressor therapy within 7 days in patients in the colloids group vs patients in the crystalloids group (mean [SD], 5.0 [3.0] days vs 4.7 [3.1] days; $P = .04$) and within 28 days (mean [SD], 16.2 [11.5] days vs 15.2 [11.7] days, respectively; $P = .03$).

Discussion

In a heterogeneous population of patients admitted to ICUs, there was no evidence for a difference in 28-day mortality between patients resuscitated with crystalloids and those resuscitated with colloids. However, there were fewer deaths at 90 days in the patients treated with colloids than in the patients treated with crystalloids.

A large sample size, participation of ICUs from 3 continents (Europe, Canada, and North Africa), and from both university and community hospitals strengthen the generalizability of the CRISTAL trial. We chose to stratify randomization according to admission diagnosis because both the risk of death and the clinical management and responses to fluid therapy may differ in patients with sepsis,

multiple trauma, or hypovolemic shock (without sepsis and nonhemorrhagic).[19]

A computer-generated list of randomization using permutation blocks with allocation concealment minimized the risk of selection bias. The absence of loss to follow-up for vital status up to 90 days postrandomization and the limited proportion of crossover minimized the risk of attrition bias.

Waiver for informed consent and treatment availability at the bedside minimized delays to study initiation and prevented administration of nontrial fluid therapy. In fact, other than maintenance fluids, no other fluids were administered in the ICU prior to to randomization.

Hence, the study population differs from other recent trials[3,4,20] of fluid administration in ICU patients in that it focuses only on patients presenting with hypotension and lactic acidosis. This difference in the hemodynamic status of patients at randomization may at least partly account for the discrepancy in observed effects of colloids on mortality between the CRISTAL trial and previous trials.[3,4,20]

The trial was powered to detect a 5% difference in the risk of death at 28 days with the use of colloids compared with a baseline risk of death of 20% in the crystalloids group, according to information available from a meta-analysis[17] at the time of study design. Note that the stratification of the test on the diagnosis stratum was ignored when computing sample size.

There was no significant difference in mortality rates at 28 days postrandomization. Unexpectedly, there were fewer deaths at 90 days among patients treated with colloids than among patients treated with crystalloids. The observed increase in the magnitude of treatment effect between 28 days and 90 days was previously reported in 2 trials investigating fluid therapies.[3,20] In these trials, as in our trial, separation of survival curves occurred after 3 weeks, resulting in a delayed statistically significant RR of dying without clear explanation.

Notably, there was no evidence of violation of the proportional hazards assumption. In the 2 largest trials comparing a colloid with a crystalloid (ie, isotonic saline), evidence for an increased risk of death was not shown with either 5% of albumin[7] or with 6% of hydroxyethyl starch with a molecular weight of 130 kD and a molar substitution ratio of 0.4.[4] Two small trials suggested an excess risk of death with hydroxyethyl starch compared with buffered crystalloids (ie, Ringer solutions).[3,20] Thus, these findings at 90 days are consistent with other studies suggesting lack of harm with colloids. However, given the null findings at 28 days and the fact that the confidence limit approaches 1, the finding of improved mortality with colloids should be considered exploratory until replicated in a study focusing on this outcome.

In the crystalloids group, about 86% of patients were resuscitated with isotonic saline and about 17% with buffered solutions. In the colloids group, about 70% of patients received hydroxyethyl starches and about 35% received gelatins. These features are in keeping with routine practices in the participating countries.[21] Patients in the crystalloids group received significantly more fluid volumes to achieve the same hemodynamic targets than patients in the colloids group, which was an expected outcome.[2,3,9]

Resuscitation with colloids was associated with more rapid weaning from life-support treatments as shown by significantly more days alive without mechanical ventilation or vasopressor therapy. In this trial, there was no evidence for a colloids-related increase in the risk for renal replacement therapy. These findings are in contrast to previous reports showing increased incidence of acute kidney injury following administration of hydroxyethyl starches.[3-6,20]

There are 3 potential explanations for this discrepancy. First, the total dose of starches in the current trial never exceeded the dose recommended by regulatory agencies, and we excluded patients with severe chronic renal failure. Second, the use of colloids was associated with a significant reduction in cardiovascular and respiratory failures, as suggested by the reduced need for vasopressor therapy and mechanical ventilation that may have contributed to renal protection. Third, the vast majority of patients in the crystalloids group received a chloride-rich solution (ie, normal saline) that may increase the risk of kidney injuries compared with a chloride-restricted fluid therapy.[22]

Study Limitations

Our trial has some limitations, including the use of open-labeled fluids and a recruitment period of 9 years. We deliberately chose to compare 2 therapeutic strategies (ie, fluid therapy with crystalloids vs colloids) rather than comparing 2 molecules because fluid therapy is a more appropriate reflection of routine practice in most countries. Hence, in this pragmatic randomized trial, investigators used fluid solutions available at the bedside in their institution. The broad variety of drugs in each class, and the unpredictable total amount of fluid to be administered during the entire ICU stay, rendered unrealistic the preparation of blinded treatments for the trial. In addition, the robustness of the primary outcome (ie, mortality) and its recording by a blinded outcome assessor minimized the risk of assessment bias. Requirement of renal replacement therapy may have been influenced by knowledge of allocation of the study drugs by physicians. However, this would have likely resulted in an increased use of renal replacement therapy in patients treated with colloids. In addition, adjusting treatment effects by date of enrollment did not modify the direction and size of estimates.

Conclusions

Among ICU patients with hypovolemia, the use of colloids compared with crystalloids did not result in a significant difference in 28-day mortality. Although 90-day mortality was lower among patients receiving colloids, this finding should be considered exploratory and requires further study before reaching conclusions about efficacy.

ARTICLE INFORMATION

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